(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 October 2013 (10.10.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/151664 A1

(51) International Patent Classification:
A61K 48/00 (2006.01) *C07H 21/04* (2006.01)

(21) International Application Number:
PCT/US2013/030060

(22) International Filing Date:
9 March 2013 (09.03.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/618,862	2 April 2012 (02.04.2012)	US
61/618,866	2 April 2012 (02.04.2012)	US
61/618,868	2 April 2012 (02.04.2012)	US
61/618,870	2 April 2012 (02.04.2012)	US
61/618,873	2 April 2012 (02.04.2012)	US
61/618,878	2 April 2012 (02.04.2012)	US
61/618,885	2 April 2012 (02.04.2012)	US
61/618,896	2 April 2012 (02.04.2012)	US
61/618,911	2 April 2012 (02.04.2012)	US
61/618,922	2 April 2012 (02.04.2012)	US
61/618,935	2 April 2012 (02.04.2012)	US
61/618,945	2 April 2012 (02.04.2012)	US
61/618,953	2 April 2012 (02.04.2012)	US
61/618,961	2 April 2012 (02.04.2012)	US
61/618,957	2 April 2012 (02.04.2012)	US
61/648,286	17 May 2012 (17.05.2012)	US
61/648,244	17 May 2012 (17.05.2012)	US
61/668,157	5 July 2012 (05.07.2012)	US
61/681,667	10 August 2012 (10.08.2012)	US
61/681,648	10 August 2012 (10.08.2012)	US
61/681,675	10 August 2012 (10.08.2012)	US
61/681,654	10 August 2012 (10.08.2012)	US
61/681,687	10 August 2012 (10.08.2012)	US
61/681,647	10 August 2012 (10.08.2012)	US
61/681,696	10 August 2012 (10.08.2012)	US
61/681,658	10 August 2012 (10.08.2012)	US
61/681,704	10 August 2012 (10.08.2012)	US
61/681,720	10 August 2012 (10.08.2012)	US
61/681,742	10 August 2012 (10.08.2012)	US
61/681,649	10 August 2012 (10.08.2012)	US
61/681,645	10 August 2012 (10.08.2012)	US
61/681,661	10 August 2012 (10.08.2012)	US
61/681,650	10 August 2012 (10.08.2012)	US
61/681,712	10 August 2012 (10.08.2012)	US
61/696,381	4 September 2012 (04.09.2012)	US
61/709,303	3 October 2012 (03.10.2012)	US
61/712,490	11 October 2012 (11.10.2012)	US
61/737,168	14 December 2012 (14.12.2012)	US
61/737,203	14 December 2012 (14.12.2012)	US
61/737,155	14 December 2012 (14.12.2012)	US
61/737,213	14 December 2012 (14.12.2012)	US
61/737,134	14 December 2012 (14.12.2012)	US
61/737,174	14 December 2012 (14.12.2012)	US
61/737,139	14 December 2012 (14.12.2012)	US
61/737,152	14 December 2012 (14.12.2012)	US
61/737,184	14 December 2012 (14.12.2012)	US
61/737,160	14 December 2012 (14.12.2012)	US
61/737,135	14 December 2012 (14.12.2012)	US
61/737,191	14 December 2012 (14.12.2012)	US
61/737,130	14 December 2012 (14.12.2012)	US
61/737,147	14 December 2012 (14.12.2012)	US

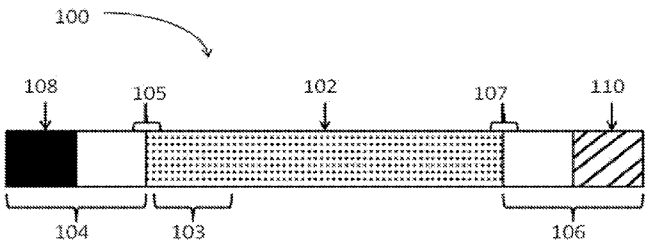
(71) Applicant: **MODERNA THERAPEUTICS** [US/US]; 161 First Street, First Floor, Cambridge, Massachusetts 02142 (US).

(72) Inventors: **BANCEL, Stephane**; 68 Pinckney Road, Boston, Massachusetts 02114 (US). **CHAKRABORTY, Tirtha**; 153 Woburn Street, Medford, Massachusetts 02155 (US). **DE FOUGEROLLES, Antonin**; 66 Summit Avenue, Brookline, Massachusetts 02446 (US). **EL-BASHIR, Sayda M.**; 149 Grove Street, Cambridge, Massachusetts 02138 (US). **JOHN, Matthias**; 338 Harvard St.

[Continued on next page]

(54) Title: MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF PROTEINS

FIGURE 1



(57) Abstract: The invention relates to compositions and methods for the preparation, manufacture and therapeutic use of polynucleotides, primary transcripts and mmRNA molecules.

WO 2013/151664 A1

#5, Cambridge, Massachusetts 02138 (US). **ROY, Atanu**; 115 Hill Street #9, Stoneham, Massachusetts 02180 (US). **WHORISKEY, Susan**; 47 Louise Road, Belmont, Massachusetts 02478 (US). **WOOD, Kristy M.**; 501 Huron Ave, Unit 2, Cambridge, Massachusetts 02138 (US). **HATALA, Paul**; 26 Monument Street #1, Charlestown, Massachusetts 02124 (US). **SCHRUM, Jason P.**; 4601 Flat Rock Road, Apt. 417, Philadelphia, Pennsylvania 19127 (US). **EJEBE, Kenechi**; 208 Pearl Street, Apt. 1, Cambridge, Massachusetts 02139 (US). **ELLSWORTH, Jeff Lynn**; 23 Meriam Street, Lexington, Massachusetts 02420 (US). **GUILD, Justin**; 495 Edgell Rd, Framingham, Massachusetts 01701 (US).

(74) **Agent**: **WARD, Donna T.**; DT WARD, P.C., 142A Main Street, Groton, Massachusetts 01450 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF PROTEINS

REFERENCE TO SEQUENCE LISTING

[0001] The instant application contains a "lengthy" Sequence Listing which has been submitted via CD-R in lieu of a printed paper copy, and is hereby incorporated by reference in its entirety. This contains a sequence listing text file as part of the originally filed subject matter as follows: File name: M309.20-2030.1309PCT_SL.txt; File size: 149,430,208 Bytes; Date created: March 4, 2013. These CD-Rs are labeled "CRF," "Copy 1," and "Copy 2," respectively, and each contain only one identical file, as identified immediately above. The machine-readable format of each CD-R is IBM-PC and the operating system of each compact disc is MS-Windows.

CROSS REFERENCE TO RELATED APPLICATIONS

[0002] This application claims priority to U.S. Provisional Patent Application No 61/681,742, filed, August 10, 2012, entitled Modified Polynucleotides for the Production of Oncology-Related Proteins and Peptides, U.S. Provisional Patent Application No 61/737,224, filed December 14, 2012, entitled Terminally Optimized Modified RNAs, International Application No PCT/US2012/069610, filed December 14, 2012, entitled Modified Nucleoside, Nucleotide, and Nucleic Acid Compositions, U.S. Provisional Patent Application No 61/618,862, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Biologics, U.S. Provisional Patent Application No 61/681,645, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Biologics, U.S. Provisional Patent Application No 61/737,130, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Biologics, U.S. Provisional Patent Application No 61/618,866, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Antibodies, U.S. Provisional Patent Application No 61/681,647, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Antibodies, U.S. Provisional Patent Application No 61/737,134, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Antibodies, U.S. Provisional Patent Application No 61/618,868, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Vaccines, U.S. Provisional Patent Application No 61/681,648, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Vaccines, U.S. Provisional Patent Application No 61/737,135, filed December 14, 2012, entitled

RECTIFIED (RULE 91) - ISA/US

Modified Polynucleotides for the Production of Vaccines, U.S. Provisional Patent Application No 61/618,870, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides, U.S. Provisional Patent Application No 61/681,649, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides, U.S. Provisional Patent Application No 61/737,139, filed December 14, 2012, Modified Polynucleotides for the Production of Therapeutic Proteins and Peptides, U.S. Provisional Patent Application No 61/618,873, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins, U.S. Provisional Patent Application No 61/681,650, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins, U.S. Provisional Patent Application No 61/737,147, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Secreted Proteins, U.S. Provisional Patent Application No 61/618,878, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins, U.S. Provisional Patent Application No 61/681,654, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins, U.S. Provisional Patent Application No 61/737,152, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Plasma Membrane Proteins, U.S. Provisional Patent Application No 61/618,885, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins, U.S. Provisional Patent Application No 61/681,658, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins, U.S. Provisional Patent Application No 61/737,155, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins, U.S. Provisional Patent Application No 61/618,896, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins, U.S. Provisional Patent Application No 61/668,157, filed July 5, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins, U.S. Provisional Patent Application No 61/681,661, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound Proteins, U.S. Provisional Patent Application No 61/737,160, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Intracellular Membrane Bound

Proteins, U.S. Provisional Patent Application No 61/618,911, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins, U.S. Provisional Patent Application No 61/681,667, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins, U.S. Provisional Patent Application No 61/737,168, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Nuclear Proteins, U.S. Provisional Patent Application No 61/618,922, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins, U.S. Provisional Patent Application No 61/681,675, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins, U.S. Provisional Patent Application No 61/737,174, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins, U.S. Provisional Patent Application No 61/618,935, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/681,687, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/737,184, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/618,945, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/681,696, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/737,191, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/618,953, filed April 2, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/681,704, filed August 10, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/737,203, filed December 14, 2012, entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease, U.S. Provisional Patent Application No 61/618,961, filed April 2, 2012, entitled Dosing Methods for Modified mRNA, U.S. Provisional Patent Application No 61/648,286, filed

May 17, 2012, entitled Dosing Methods for Modified mRNA, the contents of each of which are herein incorporated by reference in its entirety.

[0003] This application is also related to International Publication No. PCT/US2012/58519, filed October 3, 2012, entitled Modified Nucleosides, Nucleotides, and Nucleic Acids, and Uses Thereof and International Publication No. PCT/US2012/69610, filed December 14, 2012, entitled Modified Nucleoside, Nucleotide, and Nucleic Acid Compositions.

[0004] The instant application is also related to co-pending applications, each filed concurrently herewith on March 9, 2013 and having Attorney Docket Number M300.20, (PCT/US13/XXXXX) entitled Modified Polynucleotides for the Production of Biologics and Proteins Associated with Human Disease; Attorney Docket Number M304.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Secreted Proteins;, Attorney Docket Number M305.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Membrane Proteins; Attorney Docket Number M306.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Cytoplasmic and Cytoskeletal Proteins; Attorney Docket Number M308.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Nuclear Proteins; Attorney Docket Number M301.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides; Attorney Docket Number M310.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Proteins Associated with Human Disease; Attorney Docket Number MNC1.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Cosmetic Proteins and Peptides and Attorney Docket Number MNC2.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Oncology-Related Proteins and Peptides, the contents of each of which are herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0005] The invention relates to compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of polynucleotides, primary constructs and modified mRNA molecules (mmRNA).

BACKGROUND OF THE INVENTION

[0006] There are multiple problems with prior methodologies of effecting protein expression. For example, introduced DNA can integrate into host cell genomic DNA at some frequency, resulting in alterations and/or damage to the host cell genomic DNA. Alternatively, the heterologous deoxyribonucleic acid (DNA) introduced into a cell can be inherited by daughter cells (whether or not the heterologous DNA has integrated into the chromosome) or by offspring.

[0007] In addition, assuming proper delivery and no damage or integration into the host genome, there are multiple steps which must occur before the encoded protein is made. Once inside the cell, DNA must be transported into the nucleus where it is transcribed into RNA. The RNA transcribed from DNA must then enter the cytoplasm where it is translated into protein. Not only do the multiple processing steps from administered DNA to protein create lag times before the generation of the functional protein, each step represents an opportunity for error and damage to the cell. Further, it is known to be difficult to obtain DNA expression in cells as DNA frequently enters a cell but is not expressed or not expressed at reasonable rates or concentrations. This can be a particular problem when DNA is introduced into primary cells or modified cell lines.

[0008] In the early 1990's Bloom and colleagues successfully rescued vasopressin-deficient rats by injecting in vitro-transcribed vasopressin mRNA into the hypothalamus (Science 255: 996–998; 1992). However, the low levels of translation and the immunogenicity of the molecules hampered the development of mRNA as a therapeutic and efforts have since focused on alternative applications that could instead exploit these pitfalls, i.e. immunization with mRNAs coding for cancer antigens.

[0009] Others have investigated the use of mRNA to deliver a polypeptide of interest and shown that certain chemical modifications of mRNA molecules, particularly pseudouridine and 5-methyl-cytosine, have reduced immunostimulatory effect.

[00010] These studies are disclosed in, for example, Ribostem Limited in United Kingdom patent application serial number 0316089.2 filed on July 9, 2003 now abandoned, PCT application number PCT/GB2004/002981 filed on July 9, 2004 published as WO2005005622, United States patent application national phase entry serial number 10/563,897 filed on June 8, 2006 published as US20060247195 now abandoned,

and European patent application national phase entry serial number EP2004743322 filed on July 9, 2004 published as EP1646714 now withdrawn; Novozymes, Inc. in PCT application number PCT/US2007/88060 filed on December 19, 2007 published as WO2008140615, United States patent application national phase entry serial number 12/520,072 filed on July 2, 2009 published as US20100028943 and European patent application national phase entry serial number EP2007874376 filed on July 7, 2009 published as EP2104739; University of Rochester in PCT application number PCT/US2006/46120 filed on December 4, 2006 published as WO2007064952 and United States patent application serial number 11/606,995 filed on December 1, 2006 published as US20070141030; BioNTech AG in European patent application serial number EP2007024312 filed December 14, 2007 now abandoned, PCT application number PCT/EP2008/01059 filed on December 12, 2008 published as WO2009077134, European patent application national phase entry serial number EP2008861423 filed on June 2, 2010 published as EP2240572, United States patent application national phase entry serial number 12/,735,060 filed November 24, 2010 published as US20110065103, German patent application serial number DE 10 2005 046 490 filed September 28, 2005, PCT application PCT/EP2006/0448 filed September 28, 2006 published as WO2007036366, national phase European patent EP1934345 published March, 21, 2012 and national phase US patent application serial number 11/992,638 filed August 14, 2009 published as 20100129877; Immune Disease Institute Inc. in United States patent application serial number 13/088,009 filed April 15, 2011 published as US20120046346 and PCT application PCT/US2011/32679 filed April 15, 2011 published as WO20110130624; Shire Human Genetic Therapeutics in United States patent application serial number 12/957,340 filed on November 20, 2010 published as US20110244026; Sequitur Inc. in PCT application PCT/US1998/019492 filed on September 18, 1998 published as WO1999014346; The Scripps Research Institute in PCT application number PCT/US2010/00567 filed on February 24, 2010 published as WO2010098861, and United States patent application national phase entry serial number 13/203,229 filed November 3, 2011 published as US20120053333; Ludwig-Maximillians University in PCT application number PCT/EP2010/004681 filed on July 30, 2010 published as WO2011012316; Cellscript Inc. in United States patent number 8,039,214 filed June 30,

2008 and granted October 18, 2011, United States patent application serial numbers 12/962,498 filed on December 7, 2010 published as US20110143436, 12/962,468 filed on December 7, 2010 published as US20110143397, 13/237,451 filed on September 20, 2011 published as US20120009649, and PCT applications PCT/US2010/59305 filed December 7, 2010 published as WO2011071931 and PCT/US2010/59317 filed on December 7, 2010 published as WO2011071936; The Trustees of the University of Pennsylvania in PCT application number PCT/US2006/32372 filed on August 21, 2006 published as WO2007024708, and United States patent application national phase entry serial number 11/990,646 filed on March 27, 2009 published as US20090286852; Curevac GMBH in German patent application serial numbers DE10 2001 027 283.9 filed June 5, 2001, DE10 2001 062 480.8 filed December 19, 2001, and DE 20 2006 051 516 filed October 31, 2006 all abandoned, European patent numbers EP1392341 granted March 30, 2005 and EP1458410 granted January 2, 2008, PCT application numbers PCT/EP2002/06180 filed June 5, 2002 published as WO2002098443, PCT/EP2002/14577 filed on December 19, 2002 published as WO2003051401, PCT/EP2007/09469 filed on December 31, 2007 published as WO2008052770, PCT/EP2008/03033 filed on April 16, 2008 published as WO2009127230, PCT/EP2006/004784 filed on May 19, 2005 published as WO2006122828, PCT/EP2008/00081 filed on January 9, 2007 published as WO2008083949, and United States patent application serial numbers 10/729,830 filed on December 5, 2003 published as US20050032730, 10/870,110 filed on June 18, 2004 published as US20050059624, 11/914,945 filed on July 7, 2008 published as US20080267873, 12/446,912 filed on October 27, 2009 published as US2010047261 now abandoned, 12/522,214 filed on January 4, 2010 published as US20100189729, 12/787,566 filed on May 26, 2010 published as US20110077287, 12/787,755 filed on May 26, 2010 published as US20100239608, 13/185,119 filed on July 18, 2011 published as US20110269950, and 13/106,548 filed on May 12, 2011 published as US20110311472 all of which are herein incorporated by reference in their entirety.

[00011] Notwithstanding these reports which are limited to a selection of chemical modifications including pseudouridine and 5-methyl-cytosine, there remains a need in the art for therapeutic modalities to address the myriad of barriers surrounding the efficacious

modulation of intracellular translation and processing of nucleic acids encoding polypeptides or fragments thereof.

[00012] To this end, the inventors have shown that certain modified mRNA sequences have the potential as therapeutics with benefits beyond just evading, avoiding or diminishing the immune response. Such studies are detailed in published co-pending applications International Application PCT/US2011/046861 filed August 5, 2011 and PCT/US2011/054636 filed October 3, 2011, International Application number PCT/US2011/054617 filed October 3, 2011, the contents of which are incorporated herein by reference in their entirety.

[00013] The present invention addresses this need by providing nucleic acid based compounds or polynucleotides which encode a polypeptide of interest (e.g., modified mRNA or mmRNA) and which have structural and/or chemical features that avoid one or more of the problems in the art, for example, features which are useful for optimizing formulation and delivery of nucleic acid-based therapeutics while retaining structural and functional integrity, overcoming the threshold of expression, improving expression rates, half life and/or protein concentrations, optimizing protein localization, and avoiding deleterious bio-responses such as the immune response and/or degradation pathways.

SUMMARY OF THE INVENTION

[00014] Described herein are compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of modified mRNA (mmRNA) molecules.

[00015] The details of various embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and the drawings, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[00016] The foregoing and other objects, features and advantages will be apparent from the following description of particular embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of various embodiments of the invention.

[00017] FIG. 1 is a schematic of a primary construct of the present invention.

[00018] FIG. 2 illustrates lipid structures in the prior art useful in the present invention. Shown are the structures for 98N12-5 (TETA5-LAP), DLin-DMA, DLin-K-DMA (2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane), DLin-KC2-DMA, DLin-MC3-DMA and C12-200.

[00019] FIG. 3 is a representative plasmid useful in the IVT reactions taught herein. The plasmid contains Insert 64818, designed by the instant inventors.

[00020] FIG. 4 is a gel profile of modified mRNA encapsulated in PLGA microspheres.

[00021] FIG. 5 is a histogram of Factor IX protein production PLGA formulation Factor IX modified mRNA.

[00022] FIG. 6 is a histogram showing VEGF protein production in human keratinocyte cells after transfection of modified mRNA at a range of doses. Figure 6A shows protein production after transfection of modified mRNA comprising natural nucleoside triphosphate (NTP). Figure 6B shows protein production after transfection of modified mRNA fully modified with pseudouridine (Pseudo-U) and 5-methylcytosine (5mC). Figure 6C shows protein production after transfection of modified mRNA fully modified with N1-methyl-pseudouridine (N1-methyl-Pseudo-U) and 5-methylcytosine (5mC).

[00023] FIG. 7 is a histogram of VEGF protein production in HEK293 cells.

[00024] FIG. 8 is a histogram of VEGF expression and IFN-alpha induction after transfection of VEGF modified mRNA in peripheral blood mononuclear cells (PBMC). Figure 8A shows VEGF expression. Figure 8B shows IFN-alpha induction.

[00025] FIG. 9 is a histogram of VEGF protein production in HeLa cells from VEGF modified mRNA.

[00026] FIG. 10 is a histogram of VEGF protein production from lipoplexed VEGF modified mRNA in mice.

[00027] FIG. 11 is a histogram of G-CSF protein production in HeLa cells from G-CSF modified mRNA.

[00028] FIG. 12 is a histogram of Factor IX protein production in HeLa cell supernatant from Factor IX modified mRNA.

DETAILED DESCRIPTION

[00029] It is of great interest in the fields of therapeutics, diagnostics, reagents and for biological assays to be able to deliver a nucleic acid, e.g., a ribonucleic acid (RNA) inside a cell, whether *in vitro*, *in vivo, in situ* or *ex vivo*, such as to cause intracellular translation of the nucleic acid and production of an encoded polypeptide of interest. Of particular importance is the delivery and function of a non-integrative polynucleotide.

[00030] Described herein are compositions (including pharmaceutical compositions) and methods for the design, preparation, manufacture and/or formulation of polynucleotides encoding one or more polypeptides of interest. Also provided are systems, processes, devices and kits for the selection, design and/or utilization of the polynucleotides encoding the polypeptides of interest described herein.

[00031] According to the present invention, these polynucleotides are preferably modified as to avoid the deficiencies of other polypeptide-encoding molecules of the art. Hence these polynucleotides are referred to as modified mRNA or mmRNA.

[00032] The use of modified polynucleotides in the fields of antibodies, viruses, veterinary applications and a variety of *in vivo* settings has been explored by the inventors and these studies are disclosed in for example, co-pending and co-owned United States provisional patent application serial numbers 61/470,451 filed March 31, 2011 teaching in vivo applications of mmRNA; 61/517,784 filed on April 26, 2011 teaching engineered nucleic acids for the production of antibody polypeptides; 61/519,158 filed May 17, 2011 teaching veterinary applications of mmRNA technology; 61/533, 537 filed on September 12, 2011 teaching antimicrobial applications of mmRNA technology; 61/533,554 filed on September 12, 2011 teaching viral applications of mmRNA technology, 61/542,533 filed on October 3, 2011 teaching various chemical modifications for use in mmRNA technology; 61/570,690 filed on December 14, 2011 teaching mobile devices for use in making or using mmRNA technology; 61/570,708 filed on December 14, 2011 teaching the use of mmRNA in acute care situations; 61/576,651 filed on December 16, 2011 teaching terminal modification architecture for mmRNA; 61/576,705 filed on December 16, 2011 teaching delivery methods using lipidoids for mmRNA; 61/578,271 filed on December 21, 2011 teaching methods to increase the viability of organs or tissues using mmRNA; 61/581,322 filed on December

29, 2011 teaching mmRNA encoding cell penetrating peptides; 61/581,352 filed on December 29, 2011 teaching the incorporation of cytotoxic nucleosides in mmRNA and 61/631,729 filed on January 10, 2012 teaching methods of using mmRNA for crossing the blood brain barrier; all of which are herein incorporated by reference in their entirety.

[00033] Provided herein, in part, are polynucleotides, primary constructs and/or mmRNA encoding polypeptides of interest which have been designed to improve one or more of the stability and/or clearance in tissues, receptor uptake and/or kinetics, cellular access by the compositions, engagement with translational machinery, mRNA half-life, translation efficiency, immune evasion, protein production capacity, secretion efficiency (when applicable), accessibility to circulation, protein half-life and/or modulation of a cell's status, function and/or activity.

I. Compositions of the Invention (mmRNA)

[00034] The present invention provides nucleic acid molecules, specifically polynucleotides, primary constructs and/or mmRNA which encode one or more polypeptides of interest. The term "nucleic acid," in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides. These polymers are often referred to as polynucleotides. Exemplary nucleic acids or polynucleotides of the invention include, but are not limited to, ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs, including LNA having a β- D-ribo configuration, α-LNA having an α-L-ribo configuration (a diastereomer of LNA), 2′-amino-LNA having a 2′-amino functionalization, and 2′-amino- α-LNA having a 2′-amino functionalization) or hybrids thereof.

[00035] In preferred embodiments, the nucleic acid molecule is a messenger RNA (mRNA). As used herein, the term "messenger RNA" (mRNA) refers to any polynucleotide which encodes a polypeptide of interest and which is capable of being translated to produce the encoded polypeptide of interest *in vitro, in vivo, in situ* or *ex vivo*.

[00036] Traditionally, the basic components of an mRNA molecule include at least a coding region, a 5′UTR, a 3′UTR, a 5′ cap and a poly-A tail. Building on this wild type modular structure, the present invention expands the scope of functionality of traditional

mRNA molecules by providing polynucleotides or primary RNA constructs which maintain a modular organization, but which comprise one or more structural and/or chemical modifications or alterations which impart useful properties to the polynucleotide including, in some embodiments, the lack of a substantial induction of the innate immune response of a cell into which the polynucleotide is introduced. As such, modified mRNA molecules of the present invention are termed "mmRNA." As used herein, a "structural" feature or modification is one in which two or more linked nucleotides are inserted, deleted, duplicated, inverted or randomized in a polynucleotide, primary construct or mmRNA without significant chemical modification to the nucleotides themselves. Because chemical bonds will necessarily be broken and reformed to effect a structural modification, structural modifications are of a chemical nature and hence are chemical modifications. However, structural modifications will result in a different sequence of nucleotides. For example, the polynucleotide "ATCG" may be chemically modified to "AT-5meC-G". The same polynucleotide may be structurally modified from "ATCG" to "ATCCCG". Here, the dinucleotide "CC" has been inserted, resulting in a structural modification to the polynucleotide.

mmRNA Architecture

[00037] The mmRNA of the present invention are distinguished from wild type mRNA in their functional and/or structural design features which serve to, as evidenced herein, overcome existing problems of effective polypeptide production using nucleic acid-based therapeutics.

[00038] Figure 1 shows a representative polynucleotide primary construct **100** of the present invention. As used herein, the term "primary construct" or "primary mRNA construct" refers to a polynucleotide transcript which encodes one or more polypeptides of interest and which retains sufficient structural and/or chemical features to allow the polypeptide of interest encoded therein to be translated. Primary constructs may be polynucleotides of the invention. When structurally or chemically modified, the primary construct may be referred to as an mmRNA.

[00039] Returning to FIG. **1**, the primary construct **100** here contains a first region of linked nucleotides **102** that is flanked by a first flanking region **104** and a second flaking region **106**. As used herein, the "first region" may be referred to as a "coding region" or

"region encoding" or simply the "first region." This first region may include, but is not limited to, the encoded polypeptide of interest. The polypeptide of interest may comprise at its 5' terminus one or more signal sequences encoded by a signal sequence region **103**. The flanking region **104** may comprise a region of linked nucleotides comprising one or more complete or incomplete 5′ UTRs sequences. The flanking region **104** may also comprise a 5′ terminal cap **108**. The second flanking region **106** may comprise a region of linked nucleotides comprising one or more complete or incomplete 3′ UTRs. The flanking region **106** may also comprise a 3′ tailing sequence **110**.

[00040] Bridging the 5′ terminus of the first region **102** and the first flanking region **104** is a first operational region **105**. Traditionally this operational region comprises a Start codon. The operational region may alternatively comprise any translation initiation sequence or signal including a Start codon.

[00041] Bridging the 3′ terminus of the first region **102** and the second flanking region **106** is a second operational region **107**. Traditionally this operational region comprises a Stop codon. The operational region may alternatively comprise any translation initiation sequence or signal including a Stop codon. According to the present invention, multiple serial stop codons may also be used.

[00042] Generally, the shortest length of the first region of the primary construct of the present invention can be the length of a nucleic acid sequence that is sufficient to encode for a dipeptide, a tripeptide, a tetrapeptide, a pentapeptide, a hexapeptide, a heptapeptide, an octapeptide, a nonapeptide, or a decapeptide. In another embodiment, the length may be sufficient to encode a peptide of 2-30 amino acids, e.g. 5-30, 10-30, 2-25, 5-25, 10-25, or 10-20 amino acids. The length may be sufficient to encode for a peptide of at least 11, 12, 13, 14, 15, 17, 20, 25 or 30 amino acids, or a peptide that is no longer than 40 amino acids, e.g. no longer than 35, 30, 25, 20, 17, 15, 14, 13, 12, 11 or 10 amino acids. Examples of dipeptides that the polynucleotide sequences can encode or include, but are not limited to, carnosine and anserine.

[00043] Generally, the length of the first region encoding the polypeptide of interest of the present invention is greater than about 30 nucleotides in length (e.g., at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500,

1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000, 4,000, 5,000, 6,000, 7,000, 8,000, 9,000, 10,000, 20,000, 30,000, 40,000, 50,000, 60,000, 70,000, 80,000, 90,000 or up to and including 100,000 nucleotides). As used herein, the "first region" may be referred to as a "coding region" or "region encoding" or simply the "first region."

[00044] In some embodiments, the polynucleotide, primary construct, or mmRNA includes from about 30 to about 100,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 1,000, from 30 to 1,500, from 30 to 3,000, from 30 to 5,000, from 30 to 7,000, from 30 to 10,000, from 30 to 25,000, from 30 to 50,000, from 30 to 70,000, from 100 to 250, from 100 to 500, from 100 to 1,000, from 100 to 1,500, from 100 to 3,000, from 100 to 5,000, from 100 to 7,000, from 100 to 10,000, from 100 to 25,000, from 100 to 50,000, from 100 to 70,000, from 100 to 100,000, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 3,000, from 500 to 5,000, from 500 to 7,000, from 500 to 10,000, from 500 to 25,000, from 500 to 50,000, from 500 to 70,000, from 500 to 100,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 3,000, from 1,000 to 5,000, from 1,000 to 7,000, from 1,000 to 10,000, from 1,000 to 25,000, from 1,000 to 50,000, from 1,000 to 70,000, from 1,000 to 100,000, from 1,500 to 3,000, from 1,500 to 5,000, from 1,500 to 7,000, from 1,500 to 10,000, from 1,500 to 25,000, from 1,500 to 50,000, from 1,500 to 70,000, from 1,500 to 100,000, from 2,000 to 3,000, from 2,000 to 5,000, from 2,000 to 7,000, from 2,000 to 10,000, from 2,000 to 25,000, from 2,000 to 50,000, from 2,000 to 70,000, and from 2,000 to 100,000).

[00045] According to the present invention, the first and second flanking regions may range independently from 15-1,000 nucleotides in length (e.g., greater than 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, and 900 nucleotides or at least 30, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, and 1,000 nucleotides).

[00046] According to the present invention, the tailing sequence may range from absent to 500 nucleotides in length (e.g., at least 60, 70, 80, 90, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, or 500 nucleotides). Where the tailing region is a polyA tail, the length may be determined in units of or as a function of polyA Binding Protein binding. In this embodiment, the polyA tail is long enough to bind at least 4 monomers of PolyA

Binding Protein. PolyA Binding Protein monomers bind to stretches of approximately 38 nucleotides. As such, it has been observed that polyA tails of about 80 nucleotides and 160 nucleotides are functional.

[00047] According to the present invention, the capping region may comprise a single cap or a series of nucleotides forming the cap. In this embodiment the capping region may be from 1 to 10, e.g. 2-9, 3-8, 4-7, 1-5, 5-10, or at least 2, or 10 or fewer nucleotides in length. In some embodiments, the cap is absent.

[00048] According to the present invention, the first and second operational regions may range from 3 to 40, e.g., 5-30, 10-20, 15, or at least 4, or 30 or fewer nucleotides in length and may comprise, in addition to a Start and/or Stop codon, one or more signal and/or restriction sequences.

Cyclic mmRNA

[00049] According to the present invention, a primary construct or mmRNA may be cyclized, or concatemerized, to generate a translation competent molecule to assist interactions between poly-A binding proteins and 5′-end binding proteins. The mechanism of cyclization or concatemerization may occur through at least 3 different routes: 1) chemical, 2) enzymatic, and 3) ribozyme catalyzed. The newly formed 5′-/3′-linkage may be intramolecular or intermolecular.

[00050] In the first route, the 5′-end and the 3′-end of the nucleic acid contain chemically reactive groups that, when close together, form a new covalent linkage between the 5′-end and the 3′-end of the molecule. The 5′-end may contain an NHS-ester reactive group and the 3′-end may contain a 3′-amino-terminated nucleotide such that in an organic solvent the 3′-amino-terminated nucleotide on the 3′-end of a synthetic mRNA molecule will undergo a nucleophilic attack on the 5′-NHS-ester moiety forming a new 5′-/3′-amide bond.

[00051] In the second route, T4 RNA ligase may be used to enzymatically link a 5′-phosphorylated nucleic acid molecule to the 3′-hydroxyl group of a nucleic acid forming a new phosphorodiester linkage. In an example reaction, 1μg of a nucleic acid molecule is incubated at 37°C for 1 hour with 1-10 units of T4 RNA ligase (New England Biolabs, Ipswich, MA) according to the manufacturer's protocol. The ligation reaction may occur

in the presence of a split oligonucleotide capable of base-pairing with both the 5′- and 3′-region in juxtaposition to assist the enzymatic ligation reaction.

[00052] In the third route, either the 5′-or 3′-end of the cDNA template encodes a ligase ribozyme sequence such that during *in vitro* transcription, the resultant nucleic acid molecule can contain an active ribozyme sequence capable of ligating the 5′-end of a nucleic acid molecule to the 3′-end of a nucleic acid molecule. The ligase ribozyme may be derived from the Group I Intron, Group I Intron, Hepatitis Delta Virus, Hairpin ribozyme or may be selected by SELEX (systematic evolution of ligands by exponential enrichment). The ribozyme ligase reaction may take 1 to 24 hours at temperatures between 0 and 37°C.

mmRNA Multimers

[00053] According to the present invention, multiple distinct polynucleotides, primary constructs or mmRNA may be linked together through the 3′-end using nucleotides which are modified at the 3′-terminus. Chemical conjugation may be used to control the stoichiometry of delivery into cells. For example, the glyoxylate cycle enzymes, isocitrate lyase and malate synthase, may be supplied into HepG2 cells at a 1:1 ratio to alter cellular fatty acid metabolism. This ratio may be controlled by chemically linking polynucleotides, primary constructs or mmRNA using a 3′-azido terminated nucleotide on one polynucleotide, primary construct or mmRNA species and a C5-ethynyl or alkynyl-containing nucleotide on the opposite polynucleotide, primary construct or mmRNA species. The modified nucleotide is added post-transcriptionally using terminal transferase (New England Biolabs, Ipswich, MA) according to the manufacturer's protocol. After the addition of the 3′-modified nucleotide, the two polynucleotide, primary construct or mmRNA species may be combined in an aqueous solution, in the presence or absence of copper, to form a new covalent linkage via a click chemistry mechanism as described in the literature.

[00054] In another example, more than two polynucleotides may be linked together using a functionalized linker molecule. For example, a functionalized saccharide molecule may be chemically modified to contain multiple chemical reactive groups (SH-, NH_2-, N_3, etc…) to react with the cognate moiety on a 3′-functionalized mRNA molecule (i.e., a 3′-maleimide ester, 3′-NHS-ester, alkynyl). The number of reactive groups on the

modified saccharide can be controlled in a stoichiometric fashion to directly control the stoichiometric ratio of conjugated polynucleotide, primary construct or mmRNA.

mmRNA Conjugates and Combinations

[00055] In order to further enhance protein production, primary constructs or mmRNA of the present invention can be designed to be conjugated to other polynucleotides, dyes, intercalating agents (*e.g.* acridines), cross-linkers (*e.g.* psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (*e.g.*, phenazine, dihydrophenazine), artificial endonucleases (*e.g.* EDTA), alkylating agents, phosphate, amino, mercapto, PEG (*e.g.*, PEG-40K), MPEG, $[MPEG]_2$, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (*e.g.* biotin), transport/absorption facilitators (*e.g.*, aspirin, vitamin E, folic acid), synthetic ribonucleases, proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies *e.g.*, an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell, hormones and hormone receptors, non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, or a drug.

[00056] Conjugation may result in increased stability and/or half life and may be particularly useful in targeting the polynucleotides, primary constructs or mmRNA to specific sites in the cell, tissue or organism.

[00057] According to the present invention, the mmRNA or primary constructs may be administered with, or further encode one or more of RNAi agents, siRNAs, shRNAs, miRNAs, miRNA binding sites, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers or vectors, and the like.

Bifunctional mmRNA

[00058] In one embodiment of the invention are bifunctional polynucleotides (e.g., bifunctional primary constructs or bifunctional mmRNA). As the name implies, bifunctional polynucleotides are those having or capable of at least two functions. These molecules may also by convention be referred to as multi-functional.

[00059] The multiple functionalities of bifunctional polynucleotides may be encoded by the RNA (the function may not manifest until the encoded product is translated) or may be a property of the polynucleotide itself. It may be structural or chemical. Bifunctional modified polynucleotides may comprise a function that is covalently or

electrostatically associated with the polynucleotides. Further, the two functions may be provided in the context of a complex of a mmRNA and another molecule.

[00060] Bifunctional polynucleotides may encode peptides which are anti-proliferative. These peptides may be linear, cyclic, constrained or random coil. They may function as aptamers, signaling molecules, ligands or mimics or mimetics thereof. Anti-proliferative peptides may, as translated, be from 3 to 50 amino acids in length. They may be 5-40, 10-30, or approximately 15 amino acids long. They may be single chain, multichain or branched and may form complexes, aggregates or any multi-unit structure once translated.

Noncoding polynucleotides and primary constructs

[00061] As described herein, provided are polynucleotides and primary constructs having sequences that are partially or substantially not translatable, e.g., having a noncoding region. Such noncoding region may be the "first region" of the primary construct. Alternatively, the noncoding region may be a region other than the first region. Such molecules are generally not translated, but can exert an effect on protein production by one or more of binding to and sequestering one or more translational machinery components such as a ribosomal protein or a transfer RNA (tRNA), thereby effectively reducing protein expression in the cell or modulating one or more pathways or cascades in a cell which in turn alters protein levels. The polynucleotide or primary construct may contain or encode one or more long noncoding RNA (lncRNA, or lincRNA) or portion thereof, a small nucleolar RNA (sno-RNA), micro RNA (miRNA), small interfering RNA (siRNA) or Piwi-interacting RNA (piRNA).

Polypeptides of interest

[00062] According to the present invention, the primary construct is designed to encode one or more polypeptides of interest or fragments thereof. A polypeptide of interest may include, but is not limited to, whole polypeptides, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, a plurality of nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, the term "polypeptides of interest" refer to any polypeptide which is selected to be encoded in the primary construct of the present invention. As used herein, "polypeptide" means a polymer of amino acid residues

(natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. In some instances the polypeptide encoded is smaller than about 50 amino acids and the polypeptide is then termed a peptide. If the polypeptide is a peptide, it will be at least about 2, 3, 4, or at least 5 amino acid residues long. Thus, polypeptides include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments and other equivalents, variants, and analogs of the foregoing. A polypeptide may be a single molecule or may be a multi-molecular complex such as a dimer, trimer or tetramer. They may also comprise single chain or multichain polypeptides such as antibodies or insulin and may be associated or linked. Most commonly disulfide linkages are found in multichain polypeptides. The term polypeptide may also apply to amino acid polymers in which one or more amino acid residues are an artificial chemical analogue of a corresponding naturally occurring amino acid.

[00063] The term "polypeptide variant" refers to molecules which differ in their amino acid sequence from a native or reference sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[00064] In some embodiments "variant mimics" are provided. As used herein, the term "variant mimic" is one which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphoro-threonine and/or phosphoro-serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

[00065] "Homology" as it applies to amino acid sequences is defined as the percentage of residues in the candidate amino acid sequence that are identical with the residues in the amino acid sequence of a second sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. Methods and computer

programs for the alignment are well known in the art. It is understood that homology depends on a calculation of percent identity but may differ in value due to gaps and penalties introduced in the calculation.

[00066] By "homologs" as it applies to polypeptide sequences means the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[00067] "Analogs" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions or deletions of amino acid residues that still maintain one or more of the properties of the parent or starting polypeptide.

[00068] The present invention contemplates several types of compositions which are polypeptide based including variants and derivatives. These include substitutional, insertional, deletion and covalent variants and derivatives. The term "derivative" is used synonymously with the term "variant" but generally refers to a molecule that has been modified and/or changed in any way relative to a reference molecule or starting molecule.

[00069] As such, mmRNA encoding polypeptides containing substitutions, insertions and/or additions, deletions and covalent modifications with respect to reference sequences, in particular the polypeptide sequences disclosed herein, are included within the scope of this invention. For example, sequence tags or amino acids, such as one or more lysines, can be added to the peptide sequences of the invention (e.g., at the N-terminal or C-terminal ends). Sequence tags can be used for peptide purification or localization. Lysines can be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or protein may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[00070] "Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single,

where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[00071] As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[00072] "Insertional variants" when referring to polypeptides are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[00073] "Deletional variants" when referring to polypeptides are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[00074] "Covalent derivatives" when referring to polypeptides include modifications of a native or starting protein with an organic proteinaceous or non-proteinaceous derivatizing agent, and/or post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of the protein with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs

directed at identifying residues important for biological activity, for immunoassays, or for the preparation of anti-protein antibodies for immunoaffinity purification of the recombinant glycoprotein. Such modifications are within the ordinary skill in the art and are performed without undue experimentation.

[00075] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in the polypeptides produced in accordance with the present invention.

[00076] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[00077] "Features" when referring to polypeptides are defined as distinct amino acid sequence-based components of a molecule. Features of the polypeptides encoded by the mmRNA of the present invention include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[00078] As used herein when referring to polypeptides the term "surface manifestation" refers to a polypeptide based component of a protein appearing on an outermost surface.

[00079] As used herein when referring to polypeptides the term "local conformational shape" means a polypeptide based structural manifestation of a protein which is located within a definable space of the protein.

[00080] As used herein when referring to polypeptides the term "fold" refers to the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include

domains and regions formed due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

[00081] As used herein the term "turn" as it relates to protein conformation means a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

[00082] As used herein when referring to polypeptides the term "loop" refers to a structural feature of a polypeptide which may serve to reverse the direction of the backbone of a peptide or polypeptide. Where the loop is found in a polypeptide and only alters the direction of the backbone, it may comprise four or more amino acid residues. Oliva et al. have identified at least 5 classes of protein loops (J. Mol Biol 266 (4): 814-830; 1997). Loops may be open or closed. Closed loops or "cyclic" loops may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids between the bridging moieties. Such bridging moieties may comprise a cysteine-cysteine bridge (Cys-Cys) typical in polypeptides having disulfide bridges or alternatively bridging moieties may be non-protein based such as the dibromozylyl agents used herein.

[00083] As used herein when referring to polypeptides the term "half-loop" refers to a portion of an identified loop having at least half the number of amino acid resides as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to comprise an odd number of amino acids, a half-loop of the odd-numbered loop will comprise the whole number portion or next whole number portion of the loop (number of amino acids of the loop/2+/-0.5 amino acids). For example, a loop identified as a 7 amino acid loop could produce half-loops of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4).

[00084] As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity, serving as a site for protein-protein interactions).

[00085] As used herein when referring to polypeptides the term "half-domain" means a portion of an identified domain having at least half the number of amino acid resides as the domain from which it is derived. It is understood that domains may not always

contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to comprise an odd number of amino acids, a half-domain of the odd-numbered domain will comprise the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids (7/2=3.5+/-0.5 being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids that comprise any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[00086] As used herein when referring to polypeptides the terms "site" as it pertains to amino acid based embodiments is used synonymously with "amino acid residue" and "amino acid side chain." A site represents a position within a peptide or polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide based molecules of the present invention.

[00087] As used herein the terms "termini" or "terminus" when referring to polypeptides refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. The polypeptide based molecules of the present invention may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group (NH2)) and a C-terminus (terminated by an amino acid with a free carboxyl group (COOH)). Proteins of the invention are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

[00088] Once any of the features have been identified or defined as a desired component of a polypeptide to be encoded by the primary construct or mmRNA of the

invention, any of several manipulations and/or modifications of these features may be performed by moving, swapping, inverting, deleting, randomizing or duplicating. Furthermore, it is understood that manipulation of features may result in the same outcome as a modification to the molecules of the invention. For example, a manipulation which involved deleting a domain would result in the alteration of the length of a molecule just as modification of a nucleic acid to encode less than a full length molecule would.

[00089] Modifications and manipulations can be accomplished by methods known in the art such as, but not limited to, site directed mutagenesis. The resulting modified molecules may then be tested for activity using *in vitro* or *in vivo* assays such as those described herein or any other suitable screening assay known in the art.

[00090] According to the present invention, the polypeptides may comprise a consensus sequence which is discovered through rounds of experimentation. As used herein a "consensus" sequence is a single sequence which represents a collective population of sequences allowing for variability at one or more sites.

[00091] As recognized by those skilled in the art, protein fragments, functional protein domains, and homologous proteins are also considered to be within the scope of polypeptides of interest of this invention. For example, provided herein is any protein fragment (meaning a polypeptide sequence at least one amino acid residue shorter than a reference polypeptide sequence but otherwise identical) of a reference protein 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or greater than 100 amino acids in length. In another example, any protein that includes a stretch of about 20, about 30, about 40, about 50, or about 100 amino acids which are about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, or about 100% identical to any of the sequences described herein can be utilized in accordance with the invention. In certain embodiments, a polypeptide to be utilized in accordance with the invention includes 2, 3, 4, 5, 6, 7, 8, 9, 10, or more mutations as shown in any of the sequences provided or referenced herein.

Encoded Polypeptides

[00092] The primary constructs or mmRNA of the present invention may be designed to encode polypeptides of interest selected from any of several target categories including, but not limited to, biologics, antibodies, vaccines, therapeutic proteins or

peptides, cell penetrating peptides, secreted proteins, plasma membrane proteins, cytoplasmic or cytoskeletal proteins, intracellular membrane bound proteins, nuclear proteins, proteins associated with human disease, targeting moieties or those proteins encoded by the human genome for which no therapeutic indication has been identified but which nonetheless have utility in areas of research and discovery.

[00093] In one embodiment primary constructs or mmRNA may encode variant polypeptides which have a certain identity with a reference polypeptide sequence. As used herein, a "reference polypeptide sequence" refers to a starting polypeptide sequence. Reference sequences may be wild type sequences or any sequence to which reference is made in the design of another sequence. A "reference polypeptide sequence" may, e.g., be any one of SEQ ID NOs: 8922-17687 as disclosed herein, e.g., any of SEQ ID NOs 8922, 8923, 8924, 8925, 8926, 8927, 8928, 8929, 8930, 8931, 8932, 8933, 8934, 8935, 8936, 8937, 8938, 8939, 8940, 8941, 8942, 8943, 8944, 8945, 8946, 8947, 8948, 8949, 8950, 8951, 8952, 8953, 8954, 8955, 8956, 8957, 8958, 8959, 8960, 8961, 8962, 8963, 8964, 8965, 8966, 8967, 8968, 8969, 8970, 8971, 8972, 8973, 8974, 8975, 8976, 8977, 8978, 8979, 8980, 8981, 8982, 8983, 8984, 8985, 8986, 8987, 8988, 8989, 8990, 8991, 8992, 8993, 8994, 8995, 8996, 8997, 8998, 8999, 9000, 9001, 9002, 9003, 9004, 9005, 9006, 9007, 9008, 9009, 9010, 9011, 9012, 9013, 9014, 9015, 9016, 9017, 9018, 9019, 9020, 9021, 9022, 9023, 9024, 9025, 9026, 9027, 9028, 9029, 9030, 9031, 9032, 9033, 9034, 9035, 9036, 9037, 9038, 9039, 9040, 9041, 9042, 9043, 9044, 9045, 9046, 9047, 9048, 9049, 9050, 9051, 9052, 9053, 9054, 9055, 9056, 9057, 9058, 9059, 9060, 9061, 9062, 9063, 9064, 9065, 9066, 9067, 9068, 9069, 9070, 9071, 9072, 9073, 9074, 9075, 9076, 9077, 9078, 9079, 9080, 9081, 9082, 9083, 9084, 9085, 9086, 9087, 9088, 9089, 9090, 9091, 9092, 9093, 9094, 9095, 9096, 9097, 9098, 9099, 9100, 9101, 9102, 9103, 9104, 9105, 9106, 9107, 9108, 9109, 9110, 9111, 9112, 9113, 9114, 9115, 9116, 9117, 9118, 9119, 9120, 9121, 9122, 9123, 9124, 9125, 9126, 9127, 9128, 9129, 9130, 9131, 9132, 9133, 9134, 9135, 9136, 9137, 9138, 9139, 9140, 9141, 9142, 9143, 9144, 9145, 9146, 9147, 9148, 9149, 9150, 9151, 9152, 9153, 9154, 9155, 9156, 9157, 9158, 9159, 9160, 9161, 9162, 9163, 9164, 9165, 9166, 9167, 9168, 9169, 9170, 9171, 9172, 9173, 9174, 9175, 9176, 9177, 9178, 9179, 9180, 9181, 9182, 9183, 9184, 9185, 9186, 9187, 9188, 9189, 9190, 9191, 9192, 9193, 9194, 9195, 9196, 9197, 9198, 9199, 9200, 9201,

9202, 9203, 9204, 9205, 9206, 9207, 9208, 9209, 9210, 9211, 9212, 9213, 9214, 9215, 9216, 9217, 9218, 9219, 9220, 9221, 9222, 9223, 9224, 9225, 9226, 9227, 9228, 9229, 9230, 9231, 9232, 9233, 9234, 9235, 9236, 9237, 9238, 9239, 9240, 9241, 9242, 9243, 9244, 9245, 9246, 9247, 9248, 9249, 9250, 9251, 9252, 9253, 9254, 9255, 9256, 9257, 9258, 9259, 9260, 9261, 9262, 9263, 9264, 9265, 9266, 9267, 9268, 9269, 9270, 9271, 9272, 9273, 9274, 9275, 9276, 9277, 9278, 9279, 9280, 9281, 9282, 9283, 9284, 9285, 9286, 9287, 9288, 9289, 9290, 9291, 9292, 9293, 9294, 9295, 9296, 9297, 9298, 9299, 9300, 9301, 9302, 9303, 9304, 9305, 9306, 9307, 9308, 9309, 9310, 9311, 9312, 9313, 9314, 9315, 9316, 9317, 9318, 9319, 9320, 9321, 9322, 9323, 9324, 9325, 9326, 9327, 9328, 9329, 9330, 9331, 9332, 9333, 9334, 9335, 9336, 9337, 9338, 9339, 9340, 9341, 9342, 9343, 9344, 9345, 9346, 9347, 9348, 9349, 9350, 9351, 9352, 9353, 9354, 9355, 9356, 9357, 9358, 9359, 9360, 9361, 9362, 9363, 9364, 9365, 9366, 9367, 9368, 9369, 9370, 9371, 9372, 9373, 9374, 9375, 9376, 9377, 9378, 9379, 9380, 9381, 9382, 9383, 9384, 9385, 9386, 9387, 9388, 9389, 9390, 9391, 9392, 9393, 9394, 9395, 9396, 9397, 9398, 9399, 9400, 9401, 9402, 9403, 9404, 9405, 9406, 9407, 9408, 9409, 9410, 9411, 9412, 9413, 9414, 9415, 9416, 9417, 9418, 9419, 9420, 9421, 9422, 9423, 9424, 9425, 9426, 9427, 9428, 9429, 9430, 9431, 9432, 9433, 9434, 9435, 9436, 9437, 9438, 9439, 9440, 9441, 9442, 9443, 9444, 9445, 9446, 9447, 9448, 9449, 9450, 9451, 9452, 9453, 9454, 9455, 9456, 9457, 9458, 9459, 9460, 9461, 9462, 9463, 9464, 9465, 9466, 9467, 9468, 9469, 9470, 9471, 9472, 9473, 9474, 9475, 9476, 9477, 9478, 9479, 9480, 9481, 9482, 9483, 9484, 9485, 9486, 9487, 9488, 9489, 9490, 9491, 9492, 9493, 9494, 9495, 9496, 9497, 9498, 9499, 9500, 9501, 9502, 9503, 9504, 9505, 9506, 9507, 9508, 9509, 9510, 9511, 9512, 9513, 9514, 9515, 9516, 9517, 9518, 9519, 9520, 9521, 9522, 9523, 9524, 9525, 9526, 9527, 9528, 9529, 9530, 9531, 9532, 9533, 9534, 9535, 9536, 9537, 9538, 9539, 9540, 9541, 9542, 9543, 9544, 9545, 9546, 9547, 9548, 9549, 9550, 9551, 9552, 9553, 9554, 9555, 9556, 9557, 9558, 9559, 9560, 9561, 9562, 9563, 9564, 9565, 9566, 9567, 9568, 9569, 9570, 9571, 9572, 9573, 9574, 9575, 9576, 9577, 9578, 9579, 9580, 9581, 9582, 9583, 9584, 9585, 9586, 9587, 9588, 9589, 9590, 9591, 9592, 9593, 9594, 9595, 9596, 9597, 9598, 9599, 9600, 9601, 9602, 9603, 9604, 9605, 9606, 9607, 9608, 9609, 9610, 9611, 9612, 9613, 9614, 9615, 9616, 9617, 9618, 9619, 9620, 9621, 9622, 9623, 9624, 9625, 9626, 9627, 9628, 9629, 9630, 9631, 9632, 9633, 9634, 9635,

9636, 9637, 9638, 9639, 9640, 9641, 9642, 9643, 9644, 9645, 9646, 9647, 9648, 9649, 9650, 9651, 9652, 9653, 9654, 9655, 9656, 9657, 9658, 9659, 9660, 9661, 9662, 9663, 9664, 9665, 9666, 9667, 9668, 9669, 9670, 9671, 9672, 9673, 9674, 9675, 9676, 9677, 9678, 9679, 9680, 9681, 9682, 9683, 9684, 9685, 9686, 9687, 9688, 9689, 9690, 9691, 9692, 9693, 9694, 9695, 9696, 9697, 9698, 9699, 9700, 9701, 9702, 9703, 9704, 9705, 9706, 9707, 9708, 9709, 9710, 9711, 9712, 9713, 9714, 9715, 9716, 9717, 9718, 9719, 9720, 9721, 9722, 9723, 9724, 9725, 9726, 9727, 9728, 9729, 9730, 9731, 9732, 9733, 9734, 9735, 9736, 9737, 9738, 9739, 9740, 9741, 9742, 9743, 9744, 9745, 9746, 9747, 9748, 9749, 9750, 9751, 9752, 9753, 9754, 9755, 9756, 9757, 9758, 9759, 9760, 9761, 9762, 9763, 9764, 9765, 9766, 9767, 9768, 9769, 9770, 9771, 9772, 9773, 9774, 9775, 9776, 9777, 9778, 9779, 9780, 9781, 9782, 9783, 9784, 9785, 9786, 9787, 9788, 9789, 9790, 9791, 9792, 9793, 9794, 9795, 9796, 9797, 9798, 9799, 9800, 9801, 9802, 9803, 9804, 9805, 9806, 9807, 9808, 9809, 9810, 9811, 9812, 9813, 9814, 9815, 9816, 9817, 9818, 9819, 9820, 9821, 9822, 9823, 9824, 9825, 9826, 9827, 9828, 9829, 9830, 9831, 9832, 9833, 9834, 9835, 9836, 9837, 9838, 9839, 9840, 9841, 9842, 9843, 9844, 9845, 9846, 9847, 9848, 9849, 9850, 9851, 9852, 9853, 9854, 9855, 9856, 9857, 9858, 9859, 9860, 9861, 9862, 9863, 9864, 9865, 9866, 9867, 9868, 9869, 9870, 9871, 9872, 9873, 9874, 9875, 9876, 9877, 9878, 9879, 9880, 9881, 9882, 9883, 9884, 9885, 9886, 9887, 9888, 9889, 9890, 9891, 9892, 9893, 9894, 9895, 9896, 9897, 9898, 9899, 9900, 9901, 9902, 9903, 9904, 9905, 9906, 9907, 9908, 9909, 9910, 9911, 9912, 9913, 9914, 9915, 9916, 9917, 9918, 9919, 9920, 9921, 9922, 9923, 9924, 9925, 9926, 9927, 9928, 9929, 9930, 9931, 9932, 9933, 9934, 9935, 9936, 9937, 9938, 9939, 9940, 9941, 9942, 9943, 9944, 9945, 9946, 9947, 9948, 9949, 9950, 9951, 9952, 9953, 9954, 9955, 9956, 9957, 9958, 9959, 9960, 9961, 9962, 9963, 9964, 9965, 9966, 9967, 9968, 9969, 9970, 9971, 9972, 9973, 9974, 9975, 9976, 9977, 9978, 9979, 9980, 9981, 9982, 9983, 9984, 9985, 9986, 9987, 9988, 9989, 9990, 9991, 9992, 9993, 9994, 9995, 9996, 9997, 9998, 9999, 10000, 10001, 10002, 10003, 10004, 10005, 10006, 10007, 10008, 10009, 10010, 10011, 10012, 10013, 10014, 10015, 10016, 10017, 10018, 10019, 10020, 10021, 10022, 10023, 10024, 10025, 10026, 10027, 10028, 10029, 10030, 10031, 10032, 10033, 10034, 10035, 10036, 10037, 10038, 10039, 10040, 10041, 10042, 10043, 10044, 10045, 10046, 10047, 10048, 10049, 10050, 10051, 10052, 10053, 10054, 10055, 10056, 10057, 10058, 10059,

10060, 10061, 10062, 10063, 10064, 10065, 10066, 10067, 10068, 10069, 10070, 10071, 10072, 10073, 10074, 10075, 10076, 10077, 10078, 10079, 10080, 10081, 10082, 10083, 10084, 10085, 10086, 10087, 10088, 10089, 10090, 10091, 10092, 10093, 10094, 10095, 10096, 10097, 10098, 10099, 10100, 10101, 10102, 10103, 10104, 10105, 10106, 10107, 10108, 10109, 10110, 10111, 10112, 10113, 10114, 10115, 10116, 10117, 10118, 10119, 10120, 10121, 10122, 10123, 10124, 10125, 10126, 10127, 10128, 10129, 10130, 10131, 10132, 10133, 10134, 10135, 10136, 10137, 10138, 10139, 10140, 10141, 10142, 10143, 10144, 10145, 10146, 10147, 10148, 10149, 10150, 10151, 10152, 10153, 10154, 10155, 10156, 10157, 10158, 10159, 10160, 10161, 10162, 10163, 10164, 10165, 10166, 10167, 10168, 10169, 10170, 10171, 10172, 10173, 10174, 10175, 10176, 10177, 10178, 10179, 10180, 10181, 10182, 10183, 10184, 10185, 10186, 10187, 10188, 10189, 10190, 10191, 10192, 10193, 10194, 10195, 10196, 10197, 10198, 10199, 10200, 10201, 10202, 10203, 10204, 10205, 10206, 10207, 10208, 10209, 10210, 10211, 10212, 10213, 10214, 10215, 10216, 10217, 10218, 10219, 10220, 10221, 10222, 10223, 10224, 10225, 10226, 10227, 10228, 10229, 10230, 10231, 10232, 10233, 10234, 10235, 10236, 10237, 10238, 10239, 10240, 10241, 10242, 10243, 10244, 10245, 10246, 10247, 10248, 10249, 10250, 10251, 10252, 10253, 10254, 10255, 10256, 10257, 10258, 10259, 10260, 10261, 10262, 10263, 10264, 10265, 10266, 10267, 10268, 10269, 10270, 10271, 10272, 10273, 10274, 10275, 10276, 10277, 10278, 10279, 10280, 10281, 10282, 10283, 10284, 10285, 10286, 10287, 10288, 10289, 10290, 10291, 10292, 10293, 10294, 10295, 10296, 10297, 10298, 10299, 10300, 10301, 10302, 10303, 10304, 10305, 10306, 10307, 10308, 10309, 10310, 10311, 10312, 10313, 10314, 10315, 10316, 10317, 10318, 10319, 10320, 10321, 10322, 10323, 10324, 10325, 10326, 10327, 10328, 10329, 10330, 10331, 10332, 10333, 10334, 10335, 10336, 10337, 10338, 10339, 10340, 10341, 10342, 10343, 10344, 10345, 10346, 10347, 10348, 10349, 10350, 10351, 10352, 10353, 10354, 10355, 10356, 10357, 10358, 10359, 10360, 10361, 10362, 10363, 10364, 10365, 10366, 10367, 10368, 10369, 10370, 10371, 10372, 10373, 10374, 10375, 10376, 10377, 10378, 10379, 10380, 10381, 10382, 10383, 10384, 10385, 10386, 10387, 10388, 10389, 10390, 10391, 10392, 10393, 10394, 10395, 10396, 10397, 10398, 10399, 10400, 10401, 10402, 10403, 10404, 10405, 10406, 10407, 10408, 10409, 10410, 10411, 10412, 10413, 10414, 10415, 10416, 10417, 10418, 10419, 10420, 10421, 10422, 10423, 10424, 10425, 10426, 10427, 10428, 10429, 10430, 10431,

10432, 10433, 10434, 10435, 10436, 10437, 10438, 10439, 10440, 10441, 10442, 10443, 10444, 10445, 10446, 10447, 10448, 10449, 10450, 10451, 10452, 10453, 10454, 10455, 10456, 10457, 10458, 10459, 10460, 10461, 10462, 10463, 10464, 10465, 10466, 10467, 10468, 10469, 10470, 10471, 10472, 10473, 10474, 10475, 10476, 10477, 10478, 10479, 10480, 10481, 10482, 10483, 10484, 10485, 10486, 10487, 10488, 10489, 10490, 10491, 10492, 10493, 10494, 10495, 10496, 10497, 10498, 10499, 10500, 10501, 10502, 10503, 10504, 10505, 10506, 10507, 10508, 10509, 10510, 10511, 10512, 10513, 10514, 10515, 10516, 10517, 10518, 10519, 10520, 10521, 10522, 10523, 10524, 10525, 10526, 10527, 10528, 10529, 10530, 10531, 10532, 10533, 10534, 10535, 10536, 10537, 10538, 10539, 10540, 10541, 10542, 10543, 10544, 10545, 10546, 10547, 10548, 10549, 10550, 10551, 10552, 10553, 10554, 10555, 10556, 10557, 10558, 10559, 10560, 10561, 10562, 10563, 10564, 10565, 10566, 10567, 10568, 10569, 10570, 10571, 10572, 10573, 10574, 10575, 10576, 10577, 10578, 10579, 10580, 10581, 10582, 10583, 10584, 10585, 10586, 10587, 10588, 10589, 10590, 10591, 10592, 10593, 10594, 10595, 10596, 10597, 10598, 10599, 10600, 10601, 10602, 10603, 10604, 10605, 10606, 10607, 10608, 10609, 10610, 10611, 10612, 10613, 10614, 10615, 10616, 10617, 10618, 10619, 10620, 10621, 10622, 10623, 10624, 10625, 10626, 10627, 10628, 10629, 10630, 10631, 10632, 10633, 10634, 10635, 10636, 10637, 10638, 10639, 10640, 10641, 10642, 10643, 10644, 10645, 10646, 10647, 10648, 10649, 10650, 10651, 10652, 10653, 10654, 10655, 10656, 10657, 10658, 10659, 10660, 10661, 10662, 10663, 10664, 10665, 10666, 10667, 10668, 10669, 10670, 10671, 10672, 10673, 10674, 10675, 10676, 10677, 10678, 10679, 10680, 10681, 10682, 10683, 10684, 10685, 10686, 10687, 10688, 10689, 10690, 10691, 10692, 10693, 10694, 10695, 10696, 10697, 10698, 10699, 10700, 10701, 10702, 10703, 10704, 10705, 10706, 10707, 10708, 10709, 10710, 10711, 10712, 10713, 10714, 10715, 10716, 10717, 10718, 10719, 10720, 10721, 10722, 10723, 10724, 10725, 10726, 10727, 10728, 10729, 10730, 10731, 10732, 10733, 10734, 10735, 10736, 10737, 10738, 10739, 10740, 10741, 10742, 10743, 10744, 10745, 10746, 10747, 10748, 10749, 10750, 10751, 10752, 10753, 10754, 10755, 10756, 10757, 10758, 10759, 10760, 10761, 10762, 10763, 10764, 10765, 10766, 10767, 10768, 10769, 10770, 10771, 10772, 10773, 10774, 10775, 10776, 10777, 10778, 10779, 10780, 10781, 10782, 10783, 10784, 10785, 10786, 10787, 10788, 10789, 10790, 10791, 10792, 10793, 10794, 10795, 10796, 10797, 10798, 10799, 10800, 10801, 10802, 10803,

10804, 10805, 10806, 10807, 10808, 10809, 10810, 10811, 10812, 10813, 10814, 10815, 10816, 10817, 10818, 10819, 10820, 10821, 10822, 10823, 10824, 10825, 10826, 10827, 10828, 10829, 10830, 10831, 10832, 10833, 10834, 10835, 10836, 10837, 10838, 10839, 10840, 10841, 10842, 10843, 10844, 10845, 10846, 10847, 10848, 10849, 10850, 10851, 10852, 10853, 10854, 10855, 10856, 10857, 10858, 10859, 10860, 10861, 10862, 10863, 10864, 10865, 10866, 10867, 10868, 10869, 10870, 10871, 10872, 10873, 10874, 10875, 10876, 10877, 10878, 10879, 10880, 10881, 10882, 10883, 10884, 10885, 10886, 10887, 10888, 10889, 10890, 10891, 10892, 10893, 10894, 10895, 10896, 10897, 10898, 10899, 10900, 10901, 10902, 10903, 10904, 10905, 10906, 10907, 10908, 10909, 10910, 10911, 10912, 10913, 10914, 10915, 10916, 10917, 10918, 10919, 10920, 10921, 10922, 10923, 10924, 10925, 10926, 10927, 10928, 10929, 10930, 10931, 10932, 10933, 10934, 10935, 10936, 10937, 10938, 10939, 10940, 10941, 10942, 10943, 10944, 10945, 10946, 10947, 10948, 10949, 10950, 10951, 10952, 10953, 10954, 10955, 10956, 10957, 10958, 10959, 10960, 10961, 10962, 10963, 10964, 10965, 10966, 10967, 10968, 10969, 10970, 10971, 10972, 10973, 10974, 10975, 10976, 10977, 10978, 10979, 10980, 10981, 10982, 10983, 10984, 10985, 10986, 10987, 10988, 10989, 10990, 10991, 10992, 10993, 10994, 10995, 10996, 10997, 10998, 10999, 11000, 11001, 11002, 11003, 11004, 11005, 11006, 11007, 11008, 11009, 11010, 11011, 11012, 11013, 11014, 11015, 11016, 11017, 11018, 11019, 11020, 11021, 11022, 11023, 11024, 11025, 11026, 11027, 11028, 11029, 11030, 11031, 11032, 11033, 11034, 11035, 11036, 11037, 11038, 11039, 11040, 11041, 11042, 11043, 11044, 11045, 11046, 11047, 11048, 11049, 11050, 11051, 11052, 11053, 11054, 11055, 11056, 11057, 11058, 11059, 11060, 11061, 11062, 11063, 11064, 11065, 11066, 11067, 11068, 11069, 11070, 11071, 11072, 11073, 11074, 11075, 11076, 11077, 11078, 11079, 11080, 11081, 11082, 11083, 11084, 11085, 11086, 11087, 11088, 11089, 11090, 11091, 11092, 11093, 11094, 11095, 11096, 11097, 11098, 11099, 11100, 11101, 11102, 11103, 11104, 11105, 11106, 11107, 11108, 11109, 11110, 11111, 11112, 11113, 11114, 11115, 11116, 11117, 11118, 11119, 11120, 11121, 11122, 11123, 11124, 11125, 11126, 11127, 11128, 11129, 11130, 11131, 11132, 11133, 11134, 11135, 11136, 11137, 11138, 11139, 11140, 11141, 11142, 11143, 11144, 11145, 11146, 11147, 11148, 11149, 11150, 11151, 11152, 11153, 11154, 11155, 11156, 11157, 11158, 11159, 11160, 11161, 11162, 11163, 11164, 11165, 11166, 11167, 11168, 11169, 11170, 11171, 11172, 11173, 11174, 11175,

11176, 11177, 11178, 11179, 11180, 11181, 11182, 11183, 11184, 11185, 11186, 11187, 11188, 11189, 11190, 11191, 11192, 11193, 11194, 11195, 11196, 11197, 11198, 11199, 11200, 11201, 11202, 11203, 11204, 11205, 11206, 11207, 11208, 11209, 11210, 11211, 11212, 11213, 11214, 11215, 11216, 11217, 11218, 11219, 11220, 11221, 11222, 11223, 11224, 11225, 11226, 11227, 11228, 11229, 11230, 11231, 11232, 11233, 11234, 11235, 11236, 11237, 11238, 11239, 11240, 11241, 11242, 11243, 11244, 11245, 11246, 11247, 11248, 11249, 11250, 11251, 11252, 11253, 11254, 11255, 11256, 11257, 11258, 11259, 11260, 11261, 11262, 11263, 11264, 11265, 11266, 11267, 11268, 11269, 11270, 11271, 11272, 11273, 11274, 11275, 11276, 11277, 11278, 11279, 11280, 11281, 11282, 11283, 11284, 11285, 11286, 11287, 11288, 11289, 11290, 11291, 11292, 11293, 11294, 11295, 11296, 11297, 11298, 11299, 11300, 11301, 11302, 11303, 11304, 11305, 11306, 11307, 11308, 11309, 11310, 11311, 11312, 11313, 11314, 11315, 11316, 11317, 11318, 11319, 11320, 11321, 11322, 11323, 11324, 11325, 11326, 11327, 11328, 11329, 11330, 11331, 11332, 11333, 11334, 11335, 11336, 11337, 11338, 11339, 11340, 11341, 11342, 11343, 11344, 11345, 11346, 11347, 11348, 11349, 11350, 11351, 11352, 11353, 11354, 11355, 11356, 11357, 11358, 11359, 11360, 11361, 11362, 11363, 11364, 11365, 11366, 11367, 11368, 11369, 11370, 11371, 11372, 11373, 11374, 11375, 11376, 11377, 11378, 11379, 11380, 11381, 11382, 11383, 11384, 11385, 11386, 11387, 11388, 11389, 11390, 11391, 11392, 11393, 11394, 11395, 11396, 11397, 11398, 11399, 11400, 11401, 11402, 11403, 11404, 11405, 11406, 11407, 11408, 11409, 11410, 11411, 11412, 11413, 11414, 11415, 11416, 11417, 11418, 11419, 11420, 11421, 11422, 11423, 11424, 11425, 11426, 11427, 11428, 11429, 11430, 11431, 11432, 11433, 11434, 11435, 11436, 11437, 11438, 11439, 11440, 11441, 11442, 11443, 11444, 11445, 11446, 11447, 11448, 11449, 11450, 11451, 11452, 11453, 11454, 11455, 11456, 11457, 11458, 11459, 11460, 11461, 11462, 11463, 11464, 11465, 11466, 11467, 11468, 11469, 11470, 11471, 11472, 11473, 11474, 11475, 11476, 11477, 11478, 11479, 11480, 11481, 11482, 11483, 11484, 11485, 11486, 11487, 11488, 11489, 11490, 11491, 11492, 11493, 11494, 11495, 11496, 11497, 11498, 11499, 11500, 11501, 11502, 11503, 11504, 11505, 11506, 11507, 11508, 11509, 11510, 11511, 11512, 11513, 11514, 11515, 11516, 11517, 11518, 11519, 11520, 11521, 11522, 11523, 11524, 11525, 11526, 11527, 11528, 11529, 11530, 11531, 11532, 11533, 11534, 11535, 11536, 11537, 11538, 11539, 11540, 11541, 11542, 11543, 11544, 11545, 11546, 11547,

11548, 11549, 11550, 11551, 11552, 11553, 11554, 11555, 11556, 11557, 11558, 11559, 11560, 11561, 11562, 11563, 11564, 11565, 11566, 11567, 11568, 11569, 11570, 11571, 11572, 11573, 11574, 11575, 11576, 11577, 11578, 11579, 11580, 11581, 11582, 11583, 11584, 11585, 11586, 11587, 11588, 11589, 11590, 11591, 11592, 11593, 11594, 11595, 11596, 11597, 11598, 11599, 11600, 11601, 11602, 11603, 11604, 11605, 11606, 11607, 11608, 11609, 11610, 11611, 11612, 11613, 11614, 11615, 11616, 11617, 11618, 11619, 11620, 11621, 11622, 11623, 11624, 11625, 11626, 11627, 11628, 11629, 11630, 11631, 11632, 11633, 11634, 11635, 11636, 11637, 11638, 11639, 11640, 11641, 11642, 11643, 11644, 11645, 11646, 11647, 11648, 11649, 11650, 11651, 11652, 11653, 11654, 11655, 11656, 11657, 11658, 11659, 11660, 11661, 11662, 11663, 11664, 11665, 11666, 11667, 11668, 11669, 11670, 11671, 11672, 11673, 11674, 11675, 11676, 11677, 11678, 11679, 11680, 11681, 11682, 11683, 11684, 11685, 11686, 11687, 11688, 11689, 11690, 11691, 11692, 11693, 11694, 11695, 11696, 11697, 11698, 11699, 11700, 11701, 11702, 11703, 11704, 11705, 11706, 11707, 11708, 11709, 11710, 11711, 11712, 11713, 11714, 11715, 11716, 11717, 11718, 11719, 11720, 11721, 11722, 11723, 11724, 11725, 11726, 11727, 11728, 11729, 11730, 11731, 11732, 11733, 11734, 11735, 11736, 11737, 11738, 11739, 11740, 11741, 11742, 11743, 11744, 11745, 11746, 11747, 11748, 11749, 11750, 11751, 11752, 11753, 11754, 11755, 11756, 11757, 11758, 11759, 11760, 11761, 11762, 11763, 11764, 11765, 11766, 11767, 11768, 11769, 11770, 11771, 11772, 11773, 11774, 11775, 11776, 11777, 11778, 11779, 11780, 11781, 11782, 11783, 11784, 11785, 11786, 11787, 11788, 11789, 11790, 11791, 11792, 11793, 11794, 11795, 11796, 11797, 11798, 11799, 11800, 11801, 11802, 11803, 11804, 11805, 11806, 11807, 11808, 11809, 11810, 11811, 11812, 11813, 11814, 11815, 11816, 11817, 11818, 11819, 11820, 11821, 11822, 11823, 11824, 11825, 11826, 11827, 11828, 11829, 11830, 11831, 11832, 11833, 11834, 11835, 11836, 11837, 11838, 11839, 11840, 11841, 11842, 11843, 11844, 11845, 11846, 11847, 11848, 11849, 11850, 11851, 11852, 11853, 11854, 11855, 11856, 11857, 11858, 11859, 11860, 11861, 11862, 11863, 11864, 11865, 11866, 11867, 11868, 11869, 11870, 11871, 11872, 11873, 11874, 11875, 11876, 11877, 11878, 11879, 11880, 11881, 11882, 11883, 11884, 11885, 11886, 11887, 11888, 11889, 11890, 11891, 11892, 11893, 11894, 11895, 11896, 11897, 11898, 11899, 11900, 11901, 11902, 11903, 11904, 11905, 11906, 11907, 11908, 11909, 11910, 11911, 11912, 11913, 11914, 11915, 11916, 11917, 11918, 11919,

11920, 11921, 11922, 11923, 11924, 11925, 11926, 11927, 11928, 11929, 11930, 11931, 11932, 11933, 11934, 11935, 11936, 11937, 11938, 11939, 11940, 11941, 11942, 11943, 11944, 11945, 11946, 11947, 11948, 11949, 11950, 11951, 11952, 11953, 11954, 11955, 11956, 11957, 11958, 11959, 11960, 11961, 11962, 11963, 11964, 11965, 11966, 11967, 11968, 11969, 11970, 11971, 11972, 11973, 11974, 11975, 11976, 11977, 11978, 11979, 11980, 11981, 11982, 11983, 11984, 11985, 11986, 11987, 11988, 11989, 11990, 11991, 11992, 11993, 11994, 11995, 11996, 11997, 11998, 11999, 12000, 12001, 12002, 12003, 12004, 12005, 12006, 12007, 12008, 12009, 12010, 12011, 12012, 12013, 12014, 12015, 12016, 12017, 12018, 12019, 12020, 12021, 12022, 12023, 12024, 12025, 12026, 12027, 12028, 12029, 12030, 12031, 12032, 12033, 12034, 12035, 12036, 12037, 12038, 12039, 12040, 12041, 12042, 12043, 12044, 12045, 12046, 12047, 12048, 12049, 12050, 12051, 12052, 12053, 12054, 12055, 12056, 12057, 12058, 12059, 12060, 12061, 12062, 12063, 12064, 12065, 12066, 12067, 12068, 12069, 12070, 12071, 12072, 12073, 12074, 12075, 12076, 12077, 12078, 12079, 12080, 12081, 12082, 12083, 12084, 12085, 12086, 12087, 12088, 12089, 12090, 12091, 12092, 12093, 12094, 12095, 12096, 12097, 12098, 12099, 12100, 12101, 12102, 12103, 12104, 12105, 12106, 12107, 12108, 12109, 12110, 12111, 12112, 12113, 12114, 12115, 12116, 12117, 12118, 12119, 12120, 12121, 12122, 12123, 12124, 12125, 12126, 12127, 12128, 12129, 12130, 12131, 12132, 12133, 12134, 12135, 12136, 12137, 12138, 12139, 12140, 12141, 12142, 12143, 12144, 12145, 12146, 12147, 12148, 12149, 12150, 12151, 12152, 12153, 12154, 12155, 12156, 12157, 12158, 12159, 12160, 12161, 12162, 12163, 12164, 12165, 12166, 12167, 12168, 12169, 12170, 12171, 12172, 12173, 12174, 12175, 12176, 12177, 12178, 12179, 12180, 12181, 12182, 12183, 12184, 12185, 12186, 12187, 12188, 12189, 12190, 12191, 12192, 12193, 12194, 12195, 12196, 12197, 12198, 12199, 12200, 12201, 12202, 12203, 12204, 12205, 12206, 12207, 12208, 12209, 12210, 12211, 12212, 12213, 12214, 12215, 12216, 12217, 12218, 12219, 12220, 12221, 12222, 12223, 12224, 12225, 12226, 12227, 12228, 12229, 12230, 12231, 12232, 12233, 12234, 12235, 12236, 12237, 12238, 12239, 12240, 12241, 12242, 12243, 12244, 12245, 12246, 12247, 12248, 12249, 12250, 12251, 12252, 12253, 12254, 12255, 12256, 12257, 12258, 12259, 12260, 12261, 12262, 12263, 12264, 12265, 12266, 12267, 12268, 12269, 12270, 12271, 12272, 12273, 12274, 12275, 12276, 12277, 12278, 12279, 12280, 12281, 12282, 12283, 12284, 12285, 12286, 12287, 12288, 12289, 12290, 12291,

12292, 12293, 12294, 12295, 12296, 12297, 12298, 12299, 12300, 12301, 12302, 12303, 12304, 12305, 12306, 12307, 12308, 12309, 12310, 12311, 12312, 12313, 12314, 12315, 12316, 12317, 12318, 12319, 12320, 12321, 12322, 12323, 12324, 12325, 12326, 12327, 12328, 12329, 12330, 12331, 12332, 12333, 12334, 12335, 12336, 12337, 12338, 12339, 12340, 12341, 12342, 12343, 12344, 12345, 12346, 12347, 12348, 12349, 12350, 12351, 12352, 12353, 12354, 12355, 12356, 12357, 12358, 12359, 12360, 12361, 12362, 12363, 12364, 12365, 12366, 12367, 12368, 12369, 12370, 12371, 12372, 12373, 12374, 12375, 12376, 12377, 12378, 12379, 12380, 12381, 12382, 12383, 12384, 12385, 12386, 12387, 12388, 12389, 12390, 12391, 12392, 12393, 12394, 12395, 12396, 12397, 12398, 12399, 12400, 12401, 12402, 12403, 12404, 12405, 12406, 12407, 12408, 12409, 12410, 12411, 12412, 12413, 12414, 12415, 12416, 12417, 12418, 12419, 12420, 12421, 12422, 12423, 12424, 12425, 12426, 12427, 12428, 12429, 12430, 12431, 12432, 12433, 12434, 12435, 12436, 12437, 12438, 12439, 12440, 12441, 12442, 12443, 12444, 12445, 12446, 12447, 12448, 12449, 12450, 12451, 12452, 12453, 12454, 12455, 12456, 12457, 12458, 12459, 12460, 12461, 12462, 12463, 12464, 12465, 12466, 12467, 12468, 12469, 12470, 12471, 12472, 12473, 12474, 12475, 12476, 12477, 12478, 12479, 12480, 12481, 12482, 12483, 12484, 12485, 12486, 12487, 12488, 12489, 12490, 12491, 12492, 12493, 12494, 12495, 12496, 12497, 12498, 12499, 12500, 12501, 12502, 12503, 12504, 12505, 12506, 12507, 12508, 12509, 12510, 12511, 12512, 12513, 12514, 12515, 12516, 12517, 12518, 12519, 12520, 12521, 12522, 12523, 12524, 12525, 12526, 12527, 12528, 12529, 12530, 12531, 12532, 12533, 12534, 12535, 12536, 12537, 12538, 12539, 12540, 12541, 12542, 12543, 12544, 12545, 12546, 12547, 12548, 12549, 12550, 12551, 12552, 12553, 12554, 12555, 12556, 12557, 12558, 12559, 12560, 12561, 12562, 12563, 12564, 12565, 12566, 12567, 12568, 12569, 12570, 12571, 12572, 12573, 12574, 12575, 12576, 12577, 12578, 12579, 12580, 12581, 12582, 12583, 12584, 12585, 12586, 12587, 12588, 12589, 12590, 12591, 12592, 12593, 12594, 12595, 12596, 12597, 12598, 12599, 12600, 12601, 12602, 12603, 12604, 12605, 12606, 12607, 12608, 12609, 12610, 12611, 12612, 12613, 12614, 12615, 12616, 12617, 12618, 12619, 12620, 12621, 12622, 12623, 12624, 12625, 12626, 12627, 12628, 12629, 12630, 12631, 12632, 12633, 12634, 12635, 12636, 12637, 12638, 12639, 12640, 12641, 12642, 12643, 12644, 12645, 12646, 12647, 12648, 12649, 12650, 12651, 12652, 12653, 12654, 12655, 12656, 12657, 12658, 12659, 12660, 12661, 12662, 12663,

12664, 12665, 12666, 12667, 12668, 12669, 12670, 12671, 12672, 12673, 12674, 12675, 12676, 12677, 12678, 12679, 12680, 12681, 12682, 12683, 12684, 12685, 12686, 12687, 12688, 12689, 12690, 12691, 12692, 12693, 12694, 12695, 12696, 12697, 12698, 12699, 12700, 12701, 12702, 12703, 12704, 12705, 12706, 12707, 12708, 12709, 12710, 12711, 12712, 12713, 12714, 12715, 12716, 12717, 12718, 12719, 12720, 12721, 12722, 12723, 12724, 12725, 12726, 12727, 12728, 12729, 12730, 12731, 12732, 12733, 12734, 12735, 12736, 12737, 12738, 12739, 12740, 12741, 12742, 12743, 12744, 12745, 12746, 12747, 12748, 12749, 12750, 12751, 12752, 12753, 12754, 12755, 12756, 12757, 12758, 12759, 12760, 12761, 12762, 12763, 12764, 12765, 12766, 12767, 12768, 12769, 12770, 12771, 12772, 12773, 12774, 12775, 12776, 12777, 12778, 12779, 12780, 12781, 12782, 12783, 12784, 12785, 12786, 12787, 12788, 12789, 12790, 12791, 12792, 12793, 12794, 12795, 12796, 12797, 12798, 12799, 12800, 12801, 12802, 12803, 12804, 12805, 12806, 12807, 12808, 12809, 12810, 12811, 12812, 12813, 12814, 12815, 12816, 12817, 12818, 12819, 12820, 12821, 12822, 12823, 12824, 12825, 12826, 12827, 12828, 12829, 12830, 12831, 12832, 12833, 12834, 12835, 12836, 12837, 12838, 12839, 12840, 12841, 12842, 12843, 12844, 12845, 12846, 12847, 12848, 12849, 12850, 12851, 12852, 12853, 12854, 12855, 12856, 12857, 12858, 12859, 12860, 12861, 12862, 12863, 12864, 12865, 12866, 12867, 12868, 12869, 12870, 12871, 12872, 12873, 12874, 12875, 12876, 12877, 12878, 12879, 12880, 12881, 12882, 12883, 12884, 12885, 12886, 12887, 12888, 12889, 12890, 12891, 12892, 12893, 12894, 12895, 12896, 12897, 12898, 12899, 12900, 12901, 12902, 12903, 12904, 12905, 12906, 12907, 12908, 12909, 12910, 12911, 12912, 12913, 12914, 12915, 12916, 12917, 12918, 12919, 12920, 12921, 12922, 12923, 12924, 12925, 12926, 12927, 12928, 12929, 12930, 12931, 12932, 12933, 12934, 12935, 12936, 12937, 12938, 12939, 12940, 12941, 12942, 12943, 12944, 12945, 12946, 12947, 12948, 12949, 12950, 12951, 12952, 12953, 12954, 12955, 12956, 12957, 12958, 12959, 12960, 12961, 12962, 12963, 12964, 12965, 12966, 12967, 12968, 12969, 12970, 12971, 12972, 12973, 12974, 12975, 12976, 12977, 12978, 12979, 12980, 12981, 12982, 12983, 12984, 12985, 12986, 12987, 12988, 12989, 12990, 12991, 12992, 12993, 12994, 12995, 12996, 12997, 12998, 12999, 13000, 13001, 13002, 13003, 13004, 13005, 13006, 13007, 13008, 13009, 13010, 13011, 13012, 13013, 13014, 13015, 13016, 13017, 13018, 13019, 13020, 13021, 13022, 13023, 13024, 13025, 13026, 13027, 13028, 13029, 13030, 13031, 13032, 13033, 13034, 13035,

13036, 13037, 13038, 13039, 13040, 13041, 13042, 13043, 13044, 13045, 13046, 13047, 13048, 13049, 13050, 13051, 13052, 13053, 13054, 13055, 13056, 13057, 13058, 13059, 13060, 13061, 13062, 13063, 13064, 13065, 13066, 13067, 13068, 13069, 13070, 13071, 13072, 13073, 13074, 13075, 13076, 13077, 13078, 13079, 13080, 13081, 13082, 13083, 13084, 13085, 13086, 13087, 13088, 13089, 13090, 13091, 13092, 13093, 13094, 13095, 13096, 13097, 13098, 13099, 13100, 13101, 13102, 13103, 13104, 13105, 13106, 13107, 13108, 13109, 13110, 13111, 13112, 13113, 13114, 13115, 13116, 13117, 13118, 13119, 13120, 13121, 13122, 13123, 13124, 13125, 13126, 13127, 13128, 13129, 13130, 13131, 13132, 13133, 13134, 13135, 13136, 13137, 13138, 13139, 13140, 13141, 13142, 13143, 13144, 13145, 13146, 13147, 13148, 13149, 13150, 13151, 13152, 13153, 13154, 13155, 13156, 13157, 13158, 13159, 13160, 13161, 13162, 13163, 13164, 13165, 13166, 13167, 13168, 13169, 13170, 13171, 13172, 13173, 13174, 13175, 13176, 13177, 13178, 13179, 13180, 13181, 13182, 13183, 13184, 13185, 13186, 13187, 13188, 13189, 13190, 13191, 13192, 13193, 13194, 13195, 13196, 13197, 13198, 13199, 13200, 13201, 13202, 13203, 13204, 13205, 13206, 13207, 13208, 13209, 13210, 13211, 13212, 13213, 13214, 13215, 13216, 13217, 13218, 13219, 13220, 13221, 13222, 13223, 13224, 13225, 13226, 13227, 13228, 13229, 13230, 13231, 13232, 13233, 13234, 13235, 13236, 13237, 13238, 13239, 13240, 13241, 13242, 13243, 13244, 13245, 13246, 13247, 13248, 13249, 13250, 13251, 13252, 13253, 13254, 13255, 13256, 13257, 13258, 13259, 13260, 13261, 13262, 13263, 13264, 13265, 13266, 13267, 13268, 13269, 13270, 13271, 13272, 13273, 13274, 13275, 13276, 13277, 13278, 13279, 13280, 13281, 13282, 13283, 13284, 13285, 13286, 13287, 13288, 13289, 13290, 13291, 13292, 13293, 13294, 13295, 13296, 13297, 13298, 13299, 13300, 13301, 13302, 13303, 13304, 13305, 13306, 13307, 13308, 13309, 13310, 13311, 13312, 13313, 13314, 13315, 13316, 13317, 13318, 13319, 13320, 13321, 13322, 13323, 13324, 13325, 13326, 13327, 13328, 13329, 13330, 13331, 13332, 13333, 13334, 13335, 13336, 13337, 13338, 13339, 13340, 13341, 13342, 13343, 13344, 13345, 13346, 13347, 13348, 13349, 13350, 13351, 13352, 13353, 13354, 13355, 13356, 13357, 13358, 13359, 13360, 13361, 13362, 13363, 13364, 13365, 13366, 13367, 13368, 13369, 13370, 13371, 13372, 13373, 13374, 13375, 13376, 13377, 13378, 13379, 13380, 13381, 13382, 13383, 13384, 13385, 13386, 13387, 13388, 13389, 13390, 13391, 13392, 13393, 13394, 13395, 13396, 13397, 13398, 13399, 13400, 13401, 13402, 13403, 13404, 13405, 13406, 13407,

13408, 13409, 13410, 13411, 13412, 13413, 13414, 13415, 13416, 13417, 13418, 13419, 13420, 13421, 13422, 13423, 13424, 13425, 13426, 13427, 13428, 13429, 13430, 13431, 13432, 13433, 13434, 13435, 13436, 13437, 13438, 13439, 13440, 13441, 13442, 13443, 13444, 13445, 13446, 13447, 13448, 13449, 13450, 13451, 13452, 13453, 13454, 13455, 13456, 13457, 13458, 13459, 13460, 13461, 13462, 13463, 13464, 13465, 13466, 13467, 13468, 13469, 13470, 13471, 13472, 13473, 13474, 13475, 13476, 13477, 13478, 13479, 13480, 13481, 13482, 13483, 13484, 13485, 13486, 13487, 13488, 13489, 13490, 13491, 13492, 13493, 13494, 13495, 13496, 13497, 13498, 13499, 13500, 13501, 13502, 13503, 13504, 13505, 13506, 13507, 13508, 13509, 13510, 13511, 13512, 13513, 13514, 13515, 13516, 13517, 13518, 13519, 13520, 13521, 13522, 13523, 13524, 13525, 13526, 13527, 13528, 13529, 13530, 13531, 13532, 13533, 13534, 13535, 13536, 13537, 13538, 13539, 13540, 13541, 13542, 13543, 13544, 13545, 13546, 13547, 13548, 13549, 13550, 13551, 13552, 13553, 13554, 13555, 13556, 13557, 13558, 13559, 13560, 13561, 13562, 13563, 13564, 13565, 13566, 13567, 13568, 13569, 13570, 13571, 13572, 13573, 13574, 13575, 13576, 13577, 13578, 13579, 13580, 13581, 13582, 13583, 13584, 13585, 13586, 13587, 13588, 13589, 13590, 13591, 13592, 13593, 13594, 13595, 13596, 13597, 13598, 13599, 13600, 13601, 13602, 13603, 13604, 13605, 13606, 13607, 13608, 13609, 13610, 13611, 13612, 13613, 13614, 13615, 13616, 13617, 13618, 13619, 13620, 13621, 13622, 13623, 13624, 13625, 13626, 13627, 13628, 13629, 13630, 13631, 13632, 13633, 13634, 13635, 13636, 13637, 13638, 13639, 13640, 13641, 13642, 13643, 13644, 13645, 13646, 13647, 13648, 13649, 13650, 13651, 13652, 13653, 13654, 13655, 13656, 13657, 13658, 13659, 13660, 13661, 13662, 13663, 13664, 13665, 13666, 13667, 13668, 13669, 13670, 13671, 13672, 13673, 13674, 13675, 13676, 13677, 13678, 13679, 13680, 13681, 13682, 13683, 13684, 13685, 13686, 13687, 13688, 13689, 13690, 13691, 13692, 13693, 13694, 13695, 13696, 13697, 13698, 13699, 13700, 13701, 13702, 13703, 13704, 13705, 13706, 13707, 13708, 13709, 13710, 13711, 13712, 13713, 13714, 13715, 13716, 13717, 13718, 13719, 13720, 13721, 13722, 13723, 13724, 13725, 13726, 13727, 13728, 13729, 13730, 13731, 13732, 13733, 13734, 13735, 13736, 13737, 13738, 13739, 13740, 13741, 13742, 13743, 13744, 13745, 13746, 13747, 13748, 13749, 13750, 13751, 13752, 13753, 13754, 13755, 13756, 13757, 13758, 13759, 13760, 13761, 13762, 13763, 13764, 13765, 13766, 13767, 13768, 13769, 13770, 13771, 13772, 13773, 13774, 13775, 13776, 13777, 13778, 13779,

13780, 13781, 13782, 13783, 13784, 13785, 13786, 13787, 13788, 13789, 13790, 13791, 13792, 13793, 13794, 13795, 13796, 13797, 13798, 13799, 13800, 13801, 13802, 13803, 13804, 13805, 13806, 13807, 13808, 13809, 13810, 13811, 13812, 13813, 13814, 13815, 13816, 13817, 13818, 13819, 13820, 13821, 13822, 13823, 13824, 13825, 13826, 13827, 13828, 13829, 13830, 13831, 13832, 13833, 13834, 13835, 13836, 13837, 13838, 13839, 13840, 13841, 13842, 13843, 13844, 13845, 13846, 13847, 13848, 13849, 13850, 13851, 13852, 13853, 13854, 13855, 13856, 13857, 13858, 13859, 13860, 13861, 13862, 13863, 13864, 13865, 13866, 13867, 13868, 13869, 13870, 13871, 13872, 13873, 13874, 13875, 13876, 13877, 13878, 13879, 13880, 13881, 13882, 13883, 13884, 13885, 13886, 13887, 13888, 13889, 13890, 13891, 13892, 13893, 13894, 13895, 13896, 13897, 13898, 13899, 13900, 13901, 13902, 13903, 13904, 13905, 13906, 13907, 13908, 13909, 13910, 13911, 13912, 13913, 13914, 13915, 13916, 13917, 13918, 13919, 13920, 13921, 13922, 13923, 13924, 13925, 13926, 13927, 13928, 13929, 13930, 13931, 13932, 13933, 13934, 13935, 13936, 13937, 13938, 13939, 13940, 13941, 13942, 13943, 13944, 13945, 13946, 13947, 13948, 13949, 13950, 13951, 13952, 13953, 13954, 13955, 13956, 13957, 13958, 13959, 13960, 13961, 13962, 13963, 13964, 13965, 13966, 13967, 13968, 13969, 13970, 13971, 13972, 13973, 13974, 13975, 13976, 13977, 13978, 13979, 13980, 13981, 13982, 13983, 13984, 13985, 13986, 13987, 13988, 13989, 13990, 13991, 13992, 13993, 13994, 13995, 13996, 13997, 13998, 13999, 14000, 14001, 14002, 14003, 14004, 14005, 14006, 14007, 14008, 14009, 14010, 14011, 14012, 14013, 14014, 14015, 14016, 14017, 14018, 14019, 14020, 14021, 14022, 14023, 14024, 14025, 14026, 14027, 14028, 14029, 14030, 14031, 14032, 14033, 14034, 14035, 14036, 14037, 14038, 14039, 14040, 14041, 14042, 14043, 14044, 14045, 14046, 14047, 14048, 14049, 14050, 14051, 14052, 14053, 14054, 14055, 14056, 14057, 14058, 14059, 14060, 14061, 14062, 14063, 14064, 14065, 14066, 14067, 14068, 14069, 14070, 14071, 14072, 14073, 14074, 14075, 14076, 14077, 14078, 14079, 14080, 14081, 14082, 14083, 14084, 14085, 14086, 14087, 14088, 14089, 14090, 14091, 14092, 14093, 14094, 14095, 14096, 14097, 14098, 14099, 14100, 14101, 14102, 14103, 14104, 14105, 14106, 14107, 14108, 14109, 14110, 14111, 14112, 14113, 14114, 14115, 14116, 14117, 14118, 14119, 14120, 14121, 14122, 14123, 14124, 14125, 14126, 14127, 14128, 14129, 14130, 14131, 14132, 14133, 14134, 14135, 14136, 14137, 14138, 14139, 14140, 14141, 14142, 14143, 14144, 14145, 14146, 14147, 14148, 14149, 14150, 14151,

14152, 14153, 14154, 14155, 14156, 14157, 14158, 14159, 14160, 14161, 14162, 14163, 14164, 14165, 14166, 14167, 14168, 14169, 14170, 14171, 14172, 14173, 14174, 14175, 14176, 14177, 14178, 14179, 14180, 14181, 14182, 14183, 14184, 14185, 14186, 14187, 14188, 14189, 14190, 14191, 14192, 14193, 14194, 14195, 14196, 14197, 14198, 14199, 14200, 14201, 14202, 14203, 14204, 14205, 14206, 14207, 14208, 14209, 14210, 14211, 14212, 14213, 14214, 14215, 14216, 14217, 14218, 14219, 14220, 14221, 14222, 14223, 14224, 14225, 14226, 14227, 14228, 14229, 14230, 14231, 14232, 14233, 14234, 14235, 14236, 14237, 14238, 14239, 14240, 14241, 14242, 14243, 14244, 14245, 14246, 14247, 14248, 14249, 14250, 14251, 14252, 14253, 14254, 14255, 14256, 14257, 14258, 14259, 14260, 14261, 14262, 14263, 14264, 14265, 14266, 14267, 14268, 14269, 14270, 14271, 14272, 14273, 14274, 14275, 14276, 14277, 14278, 14279, 14280, 14281, 14282, 14283, 14284, 14285, 14286, 14287, 14288, 14289, 14290, 14291, 14292, 14293, 14294, 14295, 14296, 14297, 14298, 14299, 14300, 14301, 14302, 14303, 14304, 14305, 14306, 14307, 14308, 14309, 14310, 14311, 14312, 14313, 14314, 14315, 14316, 14317, 14318, 14319, 14320, 14321, 14322, 14323, 14324, 14325, 14326, 14327, 14328, 14329, 14330, 14331, 14332, 14333, 14334, 14335, 14336, 14337, 14338, 14339, 14340, 14341, 14342, 14343, 14344, 14345, 14346, 14347, 14348, 14349, 14350, 14351, 14352, 14353, 14354, 14355, 14356, 14357, 14358, 14359, 14360, 14361, 14362, 14363, 14364, 14365, 14366, 14367, 14368, 14369, 14370, 14371, 14372, 14373, 14374, 14375, 14376, 14377, 14378, 14379, 14380, 14381, 14382, 14383, 14384, 14385, 14386, 14387, 14388, 14389, 14390, 14391, 14392, 14393, 14394, 14395, 14396, 14397, 14398, 14399, 14400, 14401, 14402, 14403, 14404, 14405, 14406, 14407, 14408, 14409, 14410, 14411, 14412, 14413, 14414, 14415, 14416, 14417, 14418, 14419, 14420, 14421, 14422, 14423, 14424, 14425, 14426, 14427, 14428, 14429, 14430, 14431, 14432, 14433, 14434, 14435, 14436, 14437, 14438, 14439, 14440, 14441, 14442, 14443, 14444, 14445, 14446, 14447, 14448, 14449, 14450, 14451, 14452, 14453, 14454, 14455, 14456, 14457, 14458, 14459, 14460, 14461, 14462, 14463, 14464, 14465, 14466, 14467, 14468, 14469, 14470, 14471, 14472, 14473, 14474, 14475, 14476, 14477, 14478, 14479, 14480, 14481, 14482, 14483, 14484, 14485, 14486, 14487, 14488, 14489, 14490, 14491, 14492, 14493, 14494, 14495, 14496, 14497, 14498, 14499, 14500, 14501, 14502, 14503, 14504, 14505, 14506, 14507, 14508, 14509, 14510, 14511, 14512, 14513, 14514, 14515, 14516, 14517, 14518, 14519, 14520, 14521, 14522, 14523,

14524, 14525, 14526, 14527, 14528, 14529, 14530, 14531, 14532, 14533, 14534, 14535, 14536, 14537, 14538, 14539, 14540, 14541, 14542, 14543, 14544, 14545, 14546, 14547, 14548, 14549, 14550, 14551, 14552, 14553, 14554, 14555, 14556, 14557, 14558, 14559, 14560, 14561, 14562, 14563, 14564, 14565, 14566, 14567, 14568, 14569, 14570, 14571, 14572, 14573, 14574, 14575, 14576, 14577, 14578, 14579, 14580, 14581, 14582, 14583, 14584, 14585, 14586, 14587, 14588, 14589, 14590, 14591, 14592, 14593, 14594, 14595, 14596, 14597, 14598, 14599, 14600, 14601, 14602, 14603, 14604, 14605, 14606, 14607, 14608, 14609, 14610, 14611, 14612, 14613, 14614, 14615, 14616, 14617, 14618, 14619, 14620, 14621, 14622, 14623, 14624, 14625, 14626, 14627, 14628, 14629, 14630, 14631, 14632, 14633, 14634, 14635, 14636, 14637, 14638, 14639, 14640, 14641, 14642, 14643, 14644, 14645, 14646, 14647, 14648, 14649, 14650, 14651, 14652, 14653, 14654, 14655, 14656, 14657, 14658, 14659, 14660, 14661, 14662, 14663, 14664, 14665, 14666, 14667, 14668, 14669, 14670, 14671, 14672, 14673, 14674, 14675, 14676, 14677, 14678, 14679, 14680, 14681, 14682, 14683, 14684, 14685, 14686, 14687, 14688, 14689, 14690, 14691, 14692, 14693, 14694, 14695, 14696, 14697, 14698, 14699, 14700, 14701, 14702, 14703, 14704, 14705, 14706, 14707, 14708, 14709, 14710, 14711, 14712, 14713, 14714, 14715, 14716, 14717, 14718, 14719, 14720, 14721, 14722, 14723, 14724, 14725, 14726, 14727, 14728, 14729, 14730, 14731, 14732, 14733, 14734, 14735, 14736, 14737, 14738, 14739, 14740, 14741, 14742, 14743, 14744, 14745, 14746, 14747, 14748, 14749, 14750, 14751, 14752, 14753, 14754, 14755, 14756, 14757, 14758, 14759, 14760, 14761, 14762, 14763, 14764, 14765, 14766, 14767, 14768, 14769, 14770, 14771, 14772, 14773, 14774, 14775, 14776, 14777, 14778, 14779, 14780, 14781, 14782, 14783, 14784, 14785, 14786, 14787, 14788, 14789, 14790, 14791, 14792, 14793, 14794, 14795, 14796, 14797, 14798, 14799, 14800, 14801, 14802, 14803, 14804, 14805, 14806, 14807, 14808, 14809, 14810, 14811, 14812, 14813, 14814, 14815, 14816, 14817, 14818, 14819, 14820, 14821, 14822, 14823, 14824, 14825, 14826, 14827, 14828, 14829, 14830, 14831, 14832, 14833, 14834, 14835, 14836, 14837, 14838, 14839, 14840, 14841, 14842, 14843, 14844, 14845, 14846, 14847, 14848, 14849, 14850, 14851, 14852, 14853, 14854, 14855, 14856, 14857, 14858, 14859, 14860, 14861, 14862, 14863, 14864, 14865, 14866, 14867, 14868, 14869, 14870, 14871, 14872, 14873, 14874, 14875, 14876, 14877, 14878, 14879, 14880, 14881, 14882, 14883, 14884, 14885, 14886, 14887, 14888, 14889, 14890, 14891, 14892, 14893, 14894, 14895,

14896, 14897, 14898, 14899, 14900, 14901, 14902, 14903, 14904, 14905, 14906, 14907, 14908, 14909, 14910, 14911, 14912, 14913, 14914, 14915, 14916, 14917, 14918, 14919, 14920, 14921, 14922, 14923, 14924, 14925, 14926, 14927, 14928, 14929, 14930, 14931, 14932, 14933, 14934, 14935, 14936, 14937, 14938, 14939, 14940, 14941, 14942, 14943, 14944, 14945, 14946, 14947, 14948, 14949, 14950, 14951, 14952, 14953, 14954, 14955, 14956, 14957, 14958, 14959, 14960, 14961, 14962, 14963, 14964, 14965, 14966, 14967, 14968, 14969, 14970, 14971, 14972, 14973, 14974, 14975, 14976, 14977, 14978, 14979, 14980, 14981, 14982, 14983, 14984, 14985, 14986, 14987, 14988, 14989, 14990, 14991, 14992, 14993, 14994, 14995, 14996, 14997, 14998, 14999, 15000, 15001, 15002, 15003, 15004, 15005, 15006, 15007, 15008, 15009, 15010, 15011, 15012, 15013, 15014, 15015, 15016, 15017, 15018, 15019, 15020, 15021, 15022, 15023, 15024, 15025, 15026, 15027, 15028, 15029, 15030, 15031, 15032, 15033, 15034, 15035, 15036, 15037, 15038, 15039, 15040, 15041, 15042, 15043, 15044, 15045, 15046, 15047, 15048, 15049, 15050, 15051, 15052, 15053, 15054, 15055, 15056, 15057, 15058, 15059, 15060, 15061, 15062, 15063, 15064, 15065, 15066, 15067, 15068, 15069, 15070, 15071, 15072, 15073, 15074, 15075, 15076, 15077, 15078, 15079, 15080, 15081, 15082, 15083, 15084, 15085, 15086, 15087, 15088, 15089, 15090, 15091, 15092, 15093, 15094, 15095, 15096, 15097, 15098, 15099, 15100, 15101, 15102, 15103, 15104, 15105, 15106, 15107, 15108, 15109, 15110, 15111, 15112, 15113, 15114, 15115, 15116, 15117, 15118, 15119, 15120, 15121, 15122, 15123, 15124, 15125, 15126, 15127, 15128, 15129, 15130, 15131, 15132, 15133, 15134, 15135, 15136, 15137, 15138, 15139, 15140, 15141, 15142, 15143, 15144, 15145, 15146, 15147, 15148, 15149, 15150, 15151, 15152, 15153, 15154, 15155, 15156, 15157, 15158, 15159, 15160, 15161, 15162, 15163, 15164, 15165, 15166, 15167, 15168, 15169, 15170, 15171, 15172, 15173, 15174, 15175, 15176, 15177, 15178, 15179, 15180, 15181, 15182, 15183, 15184, 15185, 15186, 15187, 15188, 15189, 15190, 15191, 15192, 15193, 15194, 15195, 15196, 15197, 15198, 15199, 15200, 15201, 15202, 15203, 15204, 15205, 15206, 15207, 15208, 15209, 15210, 15211, 15212, 15213, 15214, 15215, 15216, 15217, 15218, 15219, 15220, 15221, 15222, 15223, 15224, 15225, 15226, 15227, 15228, 15229, 15230, 15231, 15232, 15233, 15234, 15235, 15236, 15237, 15238, 15239, 15240, 15241, 15242, 15243, 15244, 15245, 15246, 15247, 15248, 15249, 15250, 15251, 15252, 15253, 15254, 15255, 15256, 15257, 15258, 15259, 15260, 15261, 15262, 15263, 15264, 15265, 15266, 15267,

15268, 15269, 15270, 15271, 15272, 15273, 15274, 15275, 15276, 15277, 15278, 15279, 15280, 15281, 15282, 15283, 15284, 15285, 15286, 15287, 15288, 15289, 15290, 15291, 15292, 15293, 15294, 15295, 15296, 15297, 15298, 15299, 15300, 15301, 15302, 15303, 15304, 15305, 15306, 15307, 15308, 15309, 15310, 15311, 15312, 15313, 15314, 15315, 15316, 15317, 15318, 15319, 15320, 15321, 15322, 15323, 15324, 15325, 15326, 15327, 15328, 15329, 15330, 15331, 15332, 15333, 15334, 15335, 15336, 15337, 15338, 15339, 15340, 15341, 15342, 15343, 15344, 15345, 15346, 15347, 15348, 15349, 15350, 15351, 15352, 15353, 15354, 15355, 15356, 15357, 15358, 15359, 15360, 15361, 15362, 15363, 15364, 15365, 15366, 15367, 15368, 15369, 15370, 15371, 15372, 15373, 15374, 15375, 15376, 15377, 15378, 15379, 15380, 15381, 15382, 15383, 15384, 15385, 15386, 15387, 15388, 15389, 15390, 15391, 15392, 15393, 15394, 15395, 15396, 15397, 15398, 15399, 15400, 15401, 15402, 15403, 15404, 15405, 15406, 15407, 15408, 15409, 15410, 15411, 15412, 15413, 15414, 15415, 15416, 15417, 15418, 15419, 15420, 15421, 15422, 15423, 15424, 15425, 15426, 15427, 15428, 15429, 15430, 15431, 15432, 15433, 15434, 15435, 15436, 15437, 15438, 15439, 15440, 15441, 15442, 15443, 15444, 15445, 15446, 15447, 15448, 15449, 15450, 15451, 15452, 15453, 15454, 15455, 15456, 15457, 15458, 15459, 15460, 15461, 15462, 15463, 15464, 15465, 15466, 15467, 15468, 15469, 15470, 15471, 15472, 15473, 15474, 15475, 15476, 15477, 15478, 15479, 15480, 15481, 15482, 15483, 15484, 15485, 15486, 15487, 15488, 15489, 15490, 15491, 15492, 15493, 15494, 15495, 15496, 15497, 15498, 15499, 15500, 15501, 15502, 15503, 15504, 15505, 15506, 15507, 15508, 15509, 15510, 15511, 15512, 15513, 15514, 15515, 15516, 15517, 15518, 15519, 15520, 15521, 15522, 15523, 15524, 15525, 15526, 15527, 15528, 15529, 15530, 15531, 15532, 15533, 15534, 15535, 15536, 15537, 15538, 15539, 15540, 15541, 15542, 15543, 15544, 15545, 15546, 15547, 15548, 15549, 15550, 15551, 15552, 15553, 15554, 15555, 15556, 15557, 15558, 15559, 15560, 15561, 15562, 15563, 15564, 15565, 15566, 15567, 15568, 15569, 15570, 15571, 15572, 15573, 15574, 15575, 15576, 15577, 15578, 15579, 15580, 15581, 15582, 15583, 15584, 15585, 15586, 15587, 15588, 15589, 15590, 15591, 15592, 15593, 15594, 15595, 15596, 15597, 15598, 15599, 15600, 15601, 15602, 15603, 15604, 15605, 15606, 15607, 15608, 15609, 15610, 15611, 15612, 15613, 15614, 15615, 15616, 15617, 15618, 15619, 15620, 15621, 15622, 15623, 15624, 15625, 15626, 15627, 15628, 15629, 15630, 15631, 15632, 15633, 15634, 15635, 15636, 15637, 15638, 15639,

15640, 15641, 15642, 15643, 15644, 15645, 15646, 15647, 15648, 15649, 15650, 15651, 15652, 15653, 15654, 15655, 15656, 15657, 15658, 15659, 15660, 15661, 15662, 15663, 15664, 15665, 15666, 15667, 15668, 15669, 15670, 15671, 15672, 15673, 15674, 15675, 15676, 15677, 15678, 15679, 15680, 15681, 15682, 15683, 15684, 15685, 15686, 15687, 15688, 15689, 15690, 15691, 15692, 15693, 15694, 15695, 15696, 15697, 15698, 15699, 15700, 15701, 15702, 15703, 15704, 15705, 15706, 15707, 15708, 15709, 15710, 15711, 15712, 15713, 15714, 15715, 15716, 15717, 15718, 15719, 15720, 15721, 15722, 15723, 15724, 15725, 15726, 15727, 15728, 15729, 15730, 15731, 15732, 15733, 15734, 15735, 15736, 15737, 15738, 15739, 15740, 15741, 15742, 15743, 15744, 15745, 15746, 15747, 15748, 15749, 15750, 15751, 15752, 15753, 15754, 15755, 15756, 15757, 15758, 15759, 15760, 15761, 15762, 15763, 15764, 15765, 15766, 15767, 15768, 15769, 15770, 15771, 15772, 15773, 15774, 15775, 15776, 15777, 15778, 15779, 15780, 15781, 15782, 15783, 15784, 15785, 15786, 15787, 15788, 15789, 15790, 15791, 15792, 15793, 15794, 15795, 15796, 15797, 15798, 15799, 15800, 15801, 15802, 15803, 15804, 15805, 15806, 15807, 15808, 15809, 15810, 15811, 15812, 15813, 15814, 15815, 15816, 15817, 15818, 15819, 15820, 15821, 15822, 15823, 15824, 15825, 15826, 15827, 15828, 15829, 15830, 15831, 15832, 15833, 15834, 15835, 15836, 15837, 15838, 15839, 15840, 15841, 15842, 15843, 15844, 15845, 15846, 15847, 15848, 15849, 15850, 15851, 15852, 15853, 15854, 15855, 15856, 15857, 15858, 15859, 15860, 15861, 15862, 15863, 15864, 15865, 15866, 15867, 15868, 15869, 15870, 15871, 15872, 15873, 15874, 15875, 15876, 15877, 15878, 15879, 15880, 15881, 15882, 15883, 15884, 15885, 15886, 15887, 15888, 15889, 15890, 15891, 15892, 15893, 15894, 15895, 15896, 15897, 15898, 15899, 15900, 15901, 15902, 15903, 15904, 15905, 15906, 15907, 15908, 15909, 15910, 15911, 15912, 15913, 15914, 15915, 15916, 15917, 15918, 15919, 15920, 15921, 15922, 15923, 15924, 15925, 15926, 15927, 15928, 15929, 15930, 15931, 15932, 15933, 15934, 15935, 15936, 15937, 15938, 15939, 15940, 15941, 15942, 15943, 15944, 15945, 15946, 15947, 15948, 15949, 15950, 15951, 15952, 15953, 15954, 15955, 15956, 15957, 15958, 15959, 15960, 15961, 15962, 15963, 15964, 15965, 15966, 15967, 15968, 15969, 15970, 15971, 15972, 15973, 15974, 15975, 15976, 15977, 15978, 15979, 15980, 15981, 15982, 15983, 15984, 15985, 15986, 15987, 15988, 15989, 15990, 15991, 15992, 15993, 15994, 15995, 15996, 15997, 15998, 15999, 16000, 16001, 16002, 16003, 16004, 16005, 16006, 16007, 16008, 16009, 16010, 16011,

16012, 16013, 16014, 16015, 16016, 16017, 16018, 16019, 16020, 16021, 16022, 16023, 16024, 16025, 16026, 16027, 16028, 16029, 16030, 16031, 16032, 16033, 16034, 16035, 16036, 16037, 16038, 16039, 16040, 16041, 16042, 16043, 16044, 16045, 16046, 16047, 16048, 16049, 16050, 16051, 16052, 16053, 16054, 16055, 16056, 16057, 16058, 16059, 16060, 16061, 16062, 16063, 16064, 16065, 16066, 16067, 16068, 16069, 16070, 16071, 16072, 16073, 16074, 16075, 16076, 16077, 16078, 16079, 16080, 16081, 16082, 16083, 16084, 16085, 16086, 16087, 16088, 16089, 16090, 16091, 16092, 16093, 16094, 16095, 16096, 16097, 16098, 16099, 16100, 16101, 16102, 16103, 16104, 16105, 16106, 16107, 16108, 16109, 16110, 16111, 16112, 16113, 16114, 16115, 16116, 16117, 16118, 16119, 16120, 16121, 16122, 16123, 16124, 16125, 16126, 16127, 16128, 16129, 16130, 16131, 16132, 16133, 16134, 16135, 16136, 16137, 16138, 16139, 16140, 16141, 16142, 16143, 16144, 16145, 16146, 16147, 16148, 16149, 16150, 16151, 16152, 16153, 16154, 16155, 16156, 16157, 16158, 16159, 16160, 16161, 16162, 16163, 16164, 16165, 16166, 16167, 16168, 16169, 16170, 16171, 16172, 16173, 16174, 16175, 16176, 16177, 16178, 16179, 16180, 16181, 16182, 16183, 16184, 16185, 16186, 16187, 16188, 16189, 16190, 16191, 16192, 16193, 16194, 16195, 16196, 16197, 16198, 16199, 16200, 16201, 16202, 16203, 16204, 16205, 16206, 16207, 16208, 16209, 16210, 16211, 16212, 16213, 16214, 16215, 16216, 16217, 16218, 16219, 16220, 16221, 16222, 16223, 16224, 16225, 16226, 16227, 16228, 16229, 16230, 16231, 16232, 16233, 16234, 16235, 16236, 16237, 16238, 16239, 16240, 16241, 16242, 16243, 16244, 16245, 16246, 16247, 16248, 16249, 16250, 16251, 16252, 16253, 16254, 16255, 16256, 16257, 16258, 16259, 16260, 16261, 16262, 16263, 16264, 16265, 16266, 16267, 16268, 16269, 16270, 16271, 16272, 16273, 16274, 16275, 16276, 16277, 16278, 16279, 16280, 16281, 16282, 16283, 16284, 16285, 16286, 16287, 16288, 16289, 16290, 16291, 16292, 16293, 16294, 16295, 16296, 16297, 16298, 16299, 16300, 16301, 16302, 16303, 16304, 16305, 16306, 16307, 16308, 16309, 16310, 16311, 16312, 16313, 16314, 16315, 16316, 16317, 16318, 16319, 16320, 16321, 16322, 16323, 16324, 16325, 16326, 16327, 16328, 16329, 16330, 16331, 16332, 16333, 16334, 16335, 16336, 16337, 16338, 16339, 16340, 16341, 16342, 16343, 16344, 16345, 16346, 16347, 16348, 16349, 16350, 16351, 16352, 16353, 16354, 16355, 16356, 16357, 16358, 16359, 16360, 16361, 16362, 16363, 16364, 16365, 16366, 16367, 16368, 16369, 16370, 16371, 16372, 16373, 16374, 16375, 16376, 16377, 16378, 16379, 16380, 16381, 16382, 16383,

16384, 16385, 16386, 16387, 16388, 16389, 16390, 16391, 16392, 16393, 16394, 16395, 16396, 16397, 16398, 16399, 16400, 16401, 16402, 16403, 16404, 16405, 16406, 16407, 16408, 16409, 16410, 16411, 16412, 16413, 16414, 16415, 16416, 16417, 16418, 16419, 16420, 16421, 16422, 16423, 16424, 16425, 16426, 16427, 16428, 16429, 16430, 16431, 16432, 16433, 16434, 16435, 16436, 16437, 16438, 16439, 16440, 16441, 16442, 16443, 16444, 16445, 16446, 16447, 16448, 16449, 16450, 16451, 16452, 16453, 16454, 16455, 16456, 16457, 16458, 16459, 16460, 16461, 16462, 16463, 16464, 16465, 16466, 16467, 16468, 16469, 16470, 16471, 16472, 16473, 16474, 16475, 16476, 16477, 16478, 16479, 16480, 16481, 16482, 16483, 16484, 16485, 16486, 16487, 16488, 16489, 16490, 16491, 16492, 16493, 16494, 16495, 16496, 16497, 16498, 16499, 16500, 16501, 16502, 16503, 16504, 16505, 16506, 16507, 16508, 16509, 16510, 16511, 16512, 16513, 16514, 16515, 16516, 16517, 16518, 16519, 16520, 16521, 16522, 16523, 16524, 16525, 16526, 16527, 16528, 16529, 16530, 16531, 16532, 16533, 16534, 16535, 16536, 16537, 16538, 16539, 16540, 16541, 16542, 16543, 16544, 16545, 16546, 16547, 16548, 16549, 16550, 16551, 16552, 16553, 16554, 16555, 16556, 16557, 16558, 16559, 16560, 16561, 16562, 16563, 16564, 16565, 16566, 16567, 16568, 16569, 16570, 16571, 16572, 16573, 16574, 16575, 16576, 16577, 16578, 16579, 16580, 16581, 16582, 16583, 16584, 16585, 16586, 16587, 16588, 16589, 16590, 16591, 16592, 16593, 16594, 16595, 16596, 16597, 16598, 16599, 16600, 16601, 16602, 16603, 16604, 16605, 16606, 16607, 16608, 16609, 16610, 16611, 16612, 16613, 16614, 16615, 16616, 16617, 16618, 16619, 16620, 16621, 16622, 16623, 16624, 16625, 16626, 16627, 16628, 16629, 16630, 16631, 16632, 16633, 16634, 16635, 16636, 16637, 16638, 16639, 16640, 16641, 16642, 16643, 16644, 16645, 16646, 16647, 16648, 16649, 16650, 16651, 16652, 16653, 16654, 16655, 16656, 16657, 16658, 16659, 16660, 16661, 16662, 16663, 16664, 16665, 16666, 16667, 16668, 16669, 16670, 16671, 16672, 16673, 16674, 16675, 16676, 16677, 16678, 16679, 16680, 16681, 16682, 16683, 16684, 16685, 16686, 16687, 16688, 16689, 16690, 16691, 16692, 16693, 16694, 16695, 16696, 16697, 16698, 16699, 16700, 16701, 16702, 16703, 16704, 16705, 16706, 16707, 16708, 16709, 16710, 16711, 16712, 16713, 16714, 16715, 16716, 16717, 16718, 16719, 16720, 16721, 16722, 16723, 16724, 16725, 16726, 16727, 16728, 16729, 16730, 16731, 16732, 16733, 16734, 16735, 16736, 16737, 16738, 16739, 16740, 16741, 16742, 16743, 16744, 16745, 16746, 16747, 16748, 16749, 16750, 16751, 16752, 16753, 16754, 16755,

16756, 16757, 16758, 16759, 16760, 16761, 16762, 16763, 16764, 16765, 16766, 16767, 16768, 16769, 16770, 16771, 16772, 16773, 16774, 16775, 16776, 16777, 16778, 16779, 16780, 16781, 16782, 16783, 16784, 16785, 16786, 16787, 16788, 16789, 16790, 16791, 16792, 16793, 16794, 16795, 16796, 16797, 16798, 16799, 16800, 16801, 16802, 16803, 16804, 16805, 16806, 16807, 16808, 16809, 16810, 16811, 16812, 16813, 16814, 16815, 16816, 16817, 16818, 16819, 16820, 16821, 16822, 16823, 16824, 16825, 16826, 16827, 16828, 16829, 16830, 16831, 16832, 16833, 16834, 16835, 16836, 16837, 16838, 16839, 16840, 16841, 16842, 16843, 16844, 16845, 16846, 16847, 16848, 16849, 16850, 16851, 16852, 16853, 16854, 16855, 16856, 16857, 16858, 16859, 16860, 16861, 16862, 16863, 16864, 16865, 16866, 16867, 16868, 16869, 16870, 16871, 16872, 16873, 16874, 16875, 16876, 16877, 16878, 16879, 16880, 16881, 16882, 16883, 16884, 16885, 16886, 16887, 16888, 16889, 16890, 16891, 16892, 16893, 16894, 16895, 16896, 16897, 16898, 16899, 16900, 16901, 16902, 16903, 16904, 16905, 16906, 16907, 16908, 16909, 16910, 16911, 16912, 16913, 16914, 16915, 16916, 16917, 16918, 16919, 16920, 16921, 16922, 16923, 16924, 16925, 16926, 16927, 16928, 16929, 16930, 16931, 16932, 16933, 16934, 16935, 16936, 16937, 16938, 16939, 16940, 16941, 16942, 16943, 16944, 16945, 16946, 16947, 16948, 16949, 16950, 16951, 16952, 16953, 16954, 16955, 16956, 16957, 16958, 16959, 16960, 16961, 16962, 16963, 16964, 16965, 16966, 16967, 16968, 16969, 16970, 16971, 16972, 16973, 16974, 16975, 16976, 16977, 16978, 16979, 16980, 16981, 16982, 16983, 16984, 16985, 16986, 16987, 16988, 16989, 16990, 16991, 16992, 16993, 16994, 16995, 16996, 16997, 16998, 16999, 17000, 17001, 17002, 17003, 17004, 17005, 17006, 17007, 17008, 17009, 17010, 17011, 17012, 17013, 17014, 17015, 17016, 17017, 17018, 17019, 17020, 17021, 17022, 17023, 17024, 17025, 17026, 17027, 17028, 17029, 17030, 17031, 17032, 17033, 17034, 17035, 17036, 17037, 17038, 17039, 17040, 17041, 17042, 17043, 17044, 17045, 17046, 17047, 17048, 17049, 17050, 17051, 17052, 17053, 17054, 17055, 17056, 17057, 17058, 17059, 17060, 17061, 17062, 17063, 17064, 17065, 17066, 17067, 17068, 17069, 17070, 17071, 17072, 17073, 17074, 17075, 17076, 17077, 17078, 17079, 17080, 17081, 17082, 17083, 17084, 17085, 17086, 17087, 17088, 17089, 17090, 17091, 17092, 17093, 17094, 17095, 17096, 17097, 17098, 17099, 17100, 17101, 17102, 17103, 17104, 17105, 17106, 17107, 17108, 17109, 17110, 17111, 17112, 17113, 17114, 17115, 17116, 17117, 17118, 17119, 17120, 17121, 17122, 17123, 17124, 17125, 17126, 17127,

17128, 17129, 17130, 17131, 17132, 17133, 17134, 17135, 17136, 17137, 17138, 17139, 17140, 17141, 17142, 17143, 17144, 17145, 17146, 17147, 17148, 17149, 17150, 17151, 17152, 17153, 17154, 17155, 17156, 17157, 17158, 17159, 17160, 17161, 17162, 17163, 17164, 17165, 17166, 17167, 17168, 17169, 17170, 17171, 17172, 17173, 17174, 17175, 17176, 17177, 17178, 17179, 17180, 17181, 17182, 17183, 17184, 17185, 17186, 17187, 17188, 17189, 17190, 17191, 17192, 17193, 17194, 17195, 17196, 17197, 17198, 17199, 17200, 17201, 17202, 17203, 17204, 17205, 17206, 17207, 17208, 17209, 17210, 17211, 17212, 17213, 17214, 17215, 17216, 17217, 17218, 17219, 17220, 17221, 17222, 17223, 17224, 17225, 17226, 17227, 17228, 17229, 17230, 17231, 17232, 17233, 17234, 17235, 17236, 17237, 17238, 17239, 17240, 17241, 17242, 17243, 17244, 17245, 17246, 17247, 17248, 17249, 17250, 17251, 17252, 17253, 17254, 17255, 17256, 17257, 17258, 17259, 17260, 17261, 17262, 17263, 17264, 17265, 17266, 17267, 17268, 17269, 17270, 17271, 17272, 17273, 17274, 17275, 17276, 17277, 17278, 17279, 17280, 17281, 17282, 17283, 17284, 17285, 17286, 17287, 17288, 17289, 17290, 17291, 17292, 17293, 17294, 17295, 17296, 17297, 17298, 17299, 17300, 17301, 17302, 17303, 17304, 17305, 17306, 17307, 17308, 17309, 17310, 17311, 17312, 17313, 17314, 17315, 17316, 17317, 17318, 17319, 17320, 17321, 17322, 17323, 17324, 17325, 17326, 17327, 17328, 17329, 17330, 17331, 17332, 17333, 17334, 17335, 17336, 17337, 17338, 17339, 17340, 17341, 17342, 17343, 17344, 17345, 17346, 17347, 17348, 17349, 17350, 17351, 17352, 17353, 17354, 17355, 17356, 17357, 17358, 17359, 17360, 17361, 17362, 17363, 17364, 17365, 17366, 17367, 17368, 17369, 17370, 17371, 17372, 17373, 17374, 17375, 17376, 17377, 17378, 17379, 17380, 17381, 17382, 17383, 17384, 17385, 17386, 17387, 17388, 17389, 17390, 17391, 17392, 17393, 17394, 17395, 17396, 17397, 17398, 17399, 17400, 17401, 17402, 17403, 17404, 17405, 17406, 17407, 17408, 17409, 17410, 17411, 17412, 17413, 17414, 17415, 17416, 17417, 17418, 17419, 17420, 17421, 17422, 17423, 17424, 17425, 17426, 17427, 17428, 17429, 17430, 17431, 17432, 17433, 17434, 17435, 17436, 17437, 17438, 17439, 17440, 17441, 17442, 17443, 17444, 17445, 17446, 17447, 17448, 17449, 17450, 17451, 17452, 17453, 17454, 17455, 17456, 17457, 17458, 17459, 17460, 17461, 17462, 17463, 17464, 17465, 17466, 17467, 17468, 17469, 17470, 17471, 17472, 17473, 17474, 17475, 17476, 17477, 17478, 17479, 17480, 17481, 17482, 17483, 17484, 17485, 17486, 17487, 17488, 17489, 17490, 17491, 17492, 17493, 17494, 17495, 17496, 17497, 17498, 17499,

17500, 17501, 17502, 17503, 17504, 17505, 17506, 17507, 17508, 17509, 17510, 17511, 17512, 17513, 17514, 17515, 17516, 17517, 17518, 17519, 17520, 17521, 17522, 17523, 17524, 17525, 17526, 17527, 17528, 17529, 17530, 17531, 17532, 17533, 17534, 17535, 17536, 17537, 17538, 17539, 17540, 17541, 17542, 17543, 17544, 17545, 17546, 17547, 17548, 17549, 17550, 17551, 17552, 17553, 17554, 17555, 17556, 17557, 17558, 17559, 17560, 17561, 17562, 17563, 17564, 17565, 17566, 17567, 17568, 17569, 17570, 17571, 17572, 17573, 17574, 17575, 17576, 17577, 17578, 17579, 17580, 17581, 17582, 17583, 17584, 17585, 17586, 17587, 17588, 17589, 17590, 17591, 17592, 17593, 17594, 17595, 17596, 17597, 17598, 17599, 17600, 17601, 17602, 17603, 17604, 17605, 17606, 17607, 17608, 17609, 17610, 17611, 17612, 17613, 17614, 17615, 17616, 17617, 17618, 17619, 17620, 17621, 17622, 17623, 17624, 17625, 17626, 17627, 17628, 17629, 17630, 17631, 17632, 17633, 17634, 17635, 17636, 17637, 17638, 17639, 17640, 17641, 17642, 17643, 17644, 17645, 17646, 17647, 17648, 17649, 17650, 17651, 17652, 17653, 17654, 17655, 17656, 17657, 17658, 17659, 17660, 17661, 17662, 17663, 17664, 17665, 17666, 17667, 17668, 17669, 17670, 17671, 17672, 17673, 17674, 17675, 17676, 17677, 17678, 17679, 17680, 17681, 17682, 17683, 17684, 17685, 17686, 17687.

[00094] The term "identity" as known in the art, refers to a relationship between the sequences of two or more peptides, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between peptides, as determined by the number of matches between strings of two or more amino acid residues. Identity measures the percent of identical matches between the smaller of two or more sequences with gap alignments (if any) addressed by a particular mathematical model or computer program (i.e., "algorithms"). Identity of related peptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York, 1991; and Carillo et al., SIAM J. Applied Math. 48, 1073 (1988).

[00095] In some embodiments, the polypeptide variant may have the same or a similar activity as the reference polypeptide. Alternatively, the variant may have an altered activity (e.g., increased or decreased) relative to a reference polypeptide. Generally, variants of a particular polynucleotide or polypeptide of the invention will have at least about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% but less than 100% sequence identity to that particular reference polynucleotide or polypeptide as determined by sequence alignment programs and parameters described herein and known to those skilled in the art. Such tools for alignment include those of the BLAST suite (Stephen F. Altschul, Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.) Other tools are described herein, specifically in the definition of "Identity."

[00096] Default parameters in the BLAST algorithm include, for example, an expect threshold of 10, Word size of 28, Match/Mismatch Scores 1, -2, Gap costs Linear. Any filter can be applied as well as a selection for species specific repeats, e.g., Homo sapiens.

Biologics

[00097] The polynucleotides, primary constructs or mmRNA disclosed herein, may encode one or more biologics. As used herein, a "biologic" is a polypeptide-based molecule produced by the methods provided herein and which may be used to treat, cure, mitigate, prevent, or diagnose a serious or life-threatening disease or medical condition. Biologics, according to the present invention include, but are not limited to, allergenic extracts (e.g. for allergy shots and tests), blood components, gene therapy products, human tissue or cellular products used in transplantation, vaccines, monoclonal antibodies, cytokines, growth factors, enzymes, thrombolytics, and immunomodulators, among others.

[00098] According to the present invention, one or more biologics currently being marketed or in development may be encoded by the polynucleotides, primary constructs or mmRNA of the present invention. While not wishing to be bound by theory, it is believed that incorporation of the encoding polynucleotides of a known biologic into the primary constructs or mmRNA of the invention will result in improved therapeutic

efficacy due at least in part to the specificity, purity and/or selectivity of the construct designs.

Antibodies

[00099] The primary constructs or mmRNA disclosed herein, may encode one or more antibodies or fragments thereof. The term "antibody" includes monoclonal antibodies (including full length antibodies which have an immunoglobulin Fc region), antibody compositions with polyepitopic specificity, multispecific antibodies (e.g., bispecific antibodies, diabodies, and single-chain molecules), as well as antibody fragments. The term "immunoglobulin" (Ig) is used interchangeably with "antibody" herein. As used herein, the term "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (e.g., isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site.

[000100] The monoclonal antibodies herein specifically include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity. Chimeric antibodies of interest herein include, but are not limited to, "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g., Old World Monkey, Ape etc.) and human constant region sequences.

[000101] An "antibody fragment" comprises a portion of an intact antibody, preferably the antigen binding and/or the variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments; diabodies; linear antibodies; nanobodies; single-chain antibody molecules and multispecific antibodies formed from antibody fragments.

[000102] Any of the five classes of immunoglobulins, IgA, IgD, IgE, IgG and IgM, may be encoded by the mmRNA of the invention, including the heavy chains designated alpha, delta, epsilon, gamma and mu, respectively. Also included are polynucleotide sequences encoding the subclasses, gamma and mu. Hence any of the subclasses of antibodies may be encoded in part or in whole and include the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2.

[000103] According to the present invention, one or more antibodies or fragments currently being marketed or in development may be encoded by the polynucleotides, primary constructs or mmRNA of the present invention. While not wishing to be bound by theory, it is believed that incorporation into the primary constructs of the invention will result in improved therapeutic efficacy due at least in part to the specificity, purity and selectivity of the mmRNA designs.

[000104] Antibodies encoded in the polynucleotides, primary constructs or mmRNA of the invention may be utilized to treat conditions or diseases in many therapeutic areas such as, but not limited to, blood, cardiovascular, CNS, poisoning (including antivenoms), dermatology, endocrinology, gastrointestinal, medical imaging, musculoskeletal, oncology, immunology, respiratory, sensory and anti-infective.

[000105] In one embodiment, primary constructs or mmRNA disclosed herein may encode monoclonal antibodies and/or variants thereof. Variants of antibodies may also include, but are not limited to, substitutional variants, conservative amino acid substitution, insertional variants, deletional variants and/or covalent derivatives. In one embodiment, the primary construct and/or mmRNA disclosed herein may encode an immunoglobulin Fc region. In another embodiment, the primary constructs and/or mmRNA may encode a variant immunoglobulin Fc region. As a non-limiting example, the primary constructs and/or mmRNA may encode an antibody having a variant immunoglobulin Fc region as described in U.S. Pat. No. 8,217,147 herein incorporated by reference in its entirety.

Vaccines

[000106] The primary constructs or mmRNA disclosed herein, may encode one or more vaccines. As used herein, a "vaccine" is a biological preparation that improves immunity to a particular disease or infectious agent. According to the present invention, one or

more vaccines currently being marketed or in development may be encoded by the polynucleotides, primary constructs or mmRNA of the present invention. While not wishing to be bound by theory, it is believed that incorporation into the primary constructs or mmRNA of the invention will result in improved therapeutic efficacy due at least in part to the specificity, purity and selectivity of the construct designs.

[000107] Vaccines encoded in the polynucleotides, primary constructs or mmRNA of the invention may be utilized to treat conditions or diseases in many therapeutic areas such as, but not limited to, cardiovascular, CNS, dermatology, endocrinology, oncology, immunology, respiratory, and anti-infective.

Therapeutic proteins or peptides

[000108] The primary constructs or mmRNA disclosed herein, may encode one or more validated or "in testing" therapeutic proteins or peptides.

[000109] According to the present invention, one or more therapeutic proteins or peptides currently being marketed or in development may be encoded by the polynucleotides, primary constructs or mmRNA of the present invention. While not wishing to be bound by theory, it is believed that incorporation into the primary constructs or mmRNA of the invention will result in improved therapeutic efficacy due at least in part to the specificity, purity and selectivity of the construct designs.

[000110] Therapeutic proteins and peptides encoded in the polynucleotides, primary constructs or mmRNA of the invention may be utilized to treat conditions or diseases in many therapeutic areas such as, but not limited to, blood, cardiovascular, CNS, poisoning (including antivenoms), dermatology, endocrinology, genetic, genitourinary, gastrointestinal, musculoskeletal, oncology, and immunology, respiratory, sensory and anti-infective.

Cell-Penetrating Polypeptides

[000111] The primary constructs or mmRNA disclosed herein, may encode one or more cell-penetrating polypeptides. As used herein, "cell-penetrating polypeptide" or CPP refers to a polypeptide which may facilitate the cellular uptake of molecules. A cell-penetrating polypeptide of the present invention may contain one or more detectable labels. The polypeptides may be partially labeled or completely labeled throughout. The polynucleotide, primary construct or mmRNA may encode the detectable label

completely, partially or not at all. The cell-penetrating peptide may also include a signal sequence. As used herein, a "signal sequence" refers to a sequence of amino acid residues bound at the amino terminus of a nascent protein during protein translation. The signal sequence may be used to signal the secretion of the cell-penetrating polypeptide.

[000112] In one embodiment, the polynucleotides, primary constructs or mmRNA may also encode a fusion protein. The fusion protein may be created by operably linking a charged protein to a therapeutic protein. As used herein, "operably linked" refers to the therapeutic protein and the charged protein being connected in such a way to permit the expression of the complex when introduced into the cell. As used herein, "charged protein" refers to a protein that carries a positive, negative or overall neutral electrical charge. Preferably, the therapeutic protein may be covalently linked to the charged protein in the formation of the fusion protein. The ratio of surface charge to total or surface amino acids may be approximately 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8 or 0.9.

[000113] The cell-penetrating polypeptide encoded by the polynucleotides, primary constructs or mmRNA may form a complex after being translated. The complex may comprise a charged protein linked, e.g. covalently linked, to the cell-penetrating polypeptide. "Therapeutic protein" refers to a protein that, when administered to a cell has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[000114] In one embodiment, the cell-penetrating polypeptide may comprise a first domain and a second domain. The first domain may comprise a supercharged polypeptide. The second domain may comprise a protein-binding partner. As used herein, "protein-binding partner" includes, but is not limited to, antibodies and functional fragments thereof, scaffold proteins, or peptides. The cell-penetrating polypeptide may further comprise an intracellular binding partner for the protein-binding partner. The cell-penetrating polypeptide may be capable of being secreted from a cell where the polynucleotide, primary construct or mmRNA may be introduced. The cell-penetrating polypeptide may also be capable of penetrating the first cell.

[000115] In a further embodiment, the cell-penetrating polypeptide is capable of penetrating a second cell. The second cell may be from the same area as the first cell, or

it may be from a different area. The area may include, but is not limited to, tissues and organs. The second cell may also be proximal or distal to the first cell.

[000116] In one embodiment, the polynucleotides, primary constructs or mmRNA may encode a cell-penetrating polypeptide which may comprise a protein-binding partner. The protein binding partner may include, but is not limited to, an antibody, a supercharged antibody or a functional fragment. The polynucleotides, primary constructs or mmRNA may be introduced into the cell where a cell-penetrating polypeptide comprising the protein-binding partner is introduced.

Secreted proteins

[000117] Human and other eukaryotic cells are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

[000118] One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER).

[000119] Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane. While not wishing to be bound by theory, the molecules of the present invention may be used to exploit the cellular trafficking described above. As such, in some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a secreted protein. The secreted proteins may be selected from those described herein or those in US Patent Publication, 20100255574, the contents of which are incorporated herein by reference in their entirety.

[000120] In one embodiment, these may be used in the manufacture of large quantities of valuable human gene products.

Plasma membrane proteins

[000121] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a protein of the plasma membrane.

Cytoplasmic or cytoskeletal proteins

[000122] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a cytoplasmic or cytoskeletal protein.

Intracellular membrane bound proteins

[000123] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express an intracellular membrane bound protein.

Nuclear proteins

[000124] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a nuclear protein.

Proteins associated with human disease

[000125] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a protein associated with human disease.

Miscellaneous proteins

[000126] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a protein with a presently unknown therapeutic function.

Targeting Moieties

[000127] In some embodiments of the invention, polynucleotides, primary constructs or mmRNA are provided to express a targeting moiety. These include a protein-binding partner or a receptor on the surface of the cell, which functions to target the cell to a specific tissue space or to interact with a specific moiety, either *in vivo* or *in vitro*. Suitable protein-binding partners include, but are not limited to, antibodies and functional fragments thereof, scaffold proteins, or peptides. Additionally, polynucleotide, primary construct or mmRNA can be employed to direct the synthesis and extracellular localization of lipids, carbohydrates, or other biological moieties or biomolecules.

Polypeptide Libraries

[000128] In one embodiment, the polynucleotides, primary constructs or mmRNA may be used to produce polypeptide libraries. These libraries may arise from the production of a population of polynucleotides, primary constructs or mmRNA, each containing various structural or chemical modification designs. In this embodiment, a population of polynucleotides, primary constructs or mmRNA may comprise a plurality of encoded

polypeptides, including but not limited to, an antibody or antibody fragment, protein binding partner, scaffold protein, and other polypeptides taught herein or known in the art. In a preferred embodiment, the polynucleotides are primary constructs of the present invention, including mmRNA which may be suitable for direct introduction into a target cell or culture which in turn may synthesize the encoded polypeptides.

[000129] In certain embodiments, multiple variants of a protein, each with different amino acid modification(s), may be produced and tested to determine the best variant in terms of pharmacokinetics, stability, biocompatibility, and/or biological activity, or a biophysical property such as expression level. Such a library may contain 10, 10^2, 10^3, 10^4, 10^5, 10^6, 10^7, 10^8, 10^9, or over 10^9 possible variants (including, but not limited to, substitutions, deletions of one or more residues, and insertion of one or more residues).

Anti-Microbial and Anti-viral Polypeptides

[000130] The polynucleotides, primary constructs and mmRNA of the present invention may be designed to encode on or more antimicrobial peptides (AMP) or antiviral peptides (AVP). AMPs and AVPs have been isolated and described from a wide range of animals such as, but not limited to, microorganisms, invertebrates, plants, amphibians, birds, fish, and mammals (Wang *et al.*, *Nucleic Acids Res.* 2009; 37 (Database issue):D933-7). For example, anti-microbial polypeptides are described in Antimicrobial Peptide Database (http://aps.unmc.edu/AP/main.php; Wang *et al., Nucleic Acids Res.* 2009; 37 (Database issue):D933-7), CAMP: Collection of Anti-Microbial Peptides (http://www.bicnirrh.res.in/antimicrobial/); Thomas *et al., Nucleic Acids Res.* 2010; 38 (Database issue):D774-80), US 5221732, US 5447914, US 5519115, US 5607914, US 5714577, US 5734015, US 5798336, US 5821224, US 5849490, US 5856127, US 5905187, US 5994308, US 5998374, US 6107460, US 6191254, US 6211148, US 6300489, US 6329504, US 6399370, US 6476189, US 6478825, US 6492328, US 6514701, US 6573361, US 6573361, US 6576755, US 6605698, US 6624140, US 6638531, US 6642203, US 6653280, US 6696238, US 6727066, US 6730659, US 6743598, US 6743769, US 6747007, US 6790833, US 6794490, US 6818407, US 6835536, US 6835713, US 6838435, US 6872705, US 6875907, US 6884776, US 6887847, US 6906035, US 6911524, US 6936432, US 7001924, US 7071293, US

7078380, US 7091185, US 7094759, US 7166769, US 7244710, US 7314858, and US 7582301, the contents of which are incorporated by reference in their entirety.

[000131] The anti-microbial polypeptides described herein may block cell fusion and/or viral entry by one or more enveloped viruses (*e.g.*, HIV, HCV). For example, the anti-microbial polypeptide can comprise or consist of a synthetic peptide corresponding to a region, *e.g.*, a consecutive sequence of at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 amino acids of the transmembrane subunit of a viral envelope protein, *e.g.*, HIV-1 gp120 or gp41. The amino acid and nucleotide sequences of HIV-1 gp120 or gp41 are described in, *e.g.*, Kuiken *et al.*, (2008). *"HIV Sequence Compendium,"* Los Alamos National Laboratory.

[000132] In some embodiments, the anti-microbial polypeptide may have at least about 75%, 80%, 85%, 90%, 95%, 100% sequence homology to the corresponding viral protein sequence. In some embodiments, the anti-microbial polypeptide may have at least about 75%, 80%, 85%, 90%, 95%, or 100% sequence homology to the corresponding viral protein sequence.

[000133] In other embodiments, the anti-microbial polypeptide may comprise or consist of a synthetic peptide corresponding to a region, *e.g.*, a consecutive sequence of at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 amino acids of the binding domain of a capsid binding protein. In some embodiments, the anti-microbial polypeptide may have at least about 75%, 80%, 85%, 90%, 95%, or 100% sequence homology to the corresponding sequence of the capsid binding protein.

[000134] The anti-microbial polypeptides described herein may block protease dimerization and inhibit cleavage of viral proproteins (*e.g.*, HIV Gag-pol processing) into functional proteins thereby preventing release of one or more enveloped viruses (*e.g.*, HIV, HCV). In some embodiments, the anti-microbial polypeptide may have at least about 75%, 80%, 85%, 90%, 95%, 100% sequence homology to the corresponding viral protein sequence.

[000135] In other embodiments, the anti-microbial polypeptide can comprise or consist of a synthetic peptide corresponding to a region, *e.g.*, a consecutive sequence of at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 amino acids of the binding domain of a protease binding protein. In some embodiments, the anti-microbial polypeptide may

have at least about 75%, 80%, 85%, 90%, 95%, 100% sequence homology to the corresponding sequence of the protease binding protein.

[000136] The anti-microbial polypeptides described herein can include an *in vitro*-evolved polypeptide directed against a viral pathogen.

Anti-Microbial Polypeptides

[000137] Anti-microbial polypeptides (AMPs) are small peptides of variable length, sequence and structure with broad spectrum activity against a wide range of microorganisms including, but not limited to, bacteria, viruses, fungi, protozoa, parasites, prions, and tumor/cancer cells. (See, *e.g.*, Zaiou, J Mol Med, 2007; 85:317; herein incorporated by reference in its entirety). It has been shown that AMPs have broad-spectrum of rapid onset of killing activities, with potentially low levels of induced resistance and concomitant broad anti-inflammatory effects.

[000138] In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be under 10kDa, *e.g.*, under 8kDa, 6kDa, 4kDa, 2kDa, or 1kDa. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) consists of from about 6 to about 100 amino acids, *e.g.*, from about 6 to about 75 amino acids, about 6 to about 50 amino acids, about 6 to about 25 amino acids, about 25 to about 100 amino acids, about 50 to about 100 amino acids, or about 75 to about 100 amino acids. In certain embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may consist of from about 15 to about 45 amino acids. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) is substantially cationic.

[000139] In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be substantially amphipathic. In certain embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be substantially cationic and amphipathic. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be cytostatic to a Gram-positive bacterium. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be cytotoxic to a Gram-positive bacterium. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be cytostatic and cytotoxic to a Gram-positive bacterium. In some embodiments, the anti-microbial polypeptide (*e.g.*, an

anti-bacterial polypeptide) may be cytostatic to a Gram-negative bacterium. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be cytotoxic to a Gram-negative bacterium. In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be cytostatic and cytotoxic to a Gram-positive bacterium. In some embodiments, the anti-microbial polypeptide may be cytostatic to a virus, fungus, protozoan, parasite, prion, or a combination thereof. In some embodiments, the anti-microbial polypeptide may be cytotoxic to a virus, fungus, protozoan, parasite, prion, or a combination thereof. In certain embodiments, the anti-microbial polypeptide may be cytostatic and cytotoxic to a virus, fungus, protozoan, parasite, prion, or a combination thereof. In some embodiments, the anti-microbial polypeptide may be cytotoxic to a tumor or cancer cell (*e.g.*, a human tumor and/or cancer cell). In some embodiments, the anti-microbial polypeptide may be cytostatic to a tumor or cancer cell (*e.g.*, a human tumor and/or cancer cell). In certain embodiments, the anti-microbial polypeptide may be cytotoxic and cytostatic to a tumor or cancer cell (*e.g.*, a human tumor or cancer cell). In some embodiments, the anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide) may be a secreted polypeptide.

[000140] In some embodiments, the anti-microbial polypeptide comprises or consists of a defensin. Exemplary defensins include, but are not limited to, α-defensins (*e.g.*, neutrophil defensin 1, defensin alpha 1, neutrophil defensin 3, neutrophil defensin 4, defensin 5, defensin 6), β-defensins (*e.g.*, beta-defensin 1, beta-defensin 2, beta-defensin 103, beta-defensin 107, beta-defensin 110, beta-defensin 136), and θ-defensins. In other embodiments, the anti-microbial polypeptide comprises or consists of a cathelicidin (*e.g.*, hCAP18).

Anti-Viral Polypeptides

[000141] Anti-viral polypeptides (AVPs) are small peptides of variable length, sequence and structure with broad spectrum activity against a wide range of viruses. See, *e.g.*, Zaiou, J Mol Med, 2007; 85:317. It has been shown that AVPs have a broad-spectrum of rapid onset of killing activities, with potentially low levels of induced resistance and concomitant broad anti-inflammatory effects. In some embodiments, the anti-viral polypeptide is under 10kDa, *e.g.*, under 8kDa, 6kDa, 4kDa, 2kDa, or 1kDa. In some embodiments, the anti-viral polypeptide comprises or consists of from about 6 to

about 100 amino acids, *e.g.*, from about 6 to about 75 amino acids, about 6 to about 50 amino acids, about 6 to about 25 amino acids, about 25 to about 100 amino acids, about 50 to about 100 amino acids, or about 75 to about 100 amino acids. In certain embodiments, the anti-viral polypeptide comprises or consists of from about 15 to about 45 amino acids. In some embodiments, the anti-viral polypeptide is substantially cationic. In some embodiments, the anti-viral polypeptide is substantially amphipathic. In certain embodiments, the anti-viral polypeptide is substantially cationic and amphipathic. In some embodiments, the anti-viral polypeptide is cytostatic to a virus. In some embodiments, the anti-viral polypeptide is cytotoxic to a virus. In some embodiments, the anti-viral polypeptide is cytostatic and cytotoxic to a virus. In some embodiments, the anti-viral polypeptide is cytostatic to a bacterium, fungus, protozoan, parasite, prion, or a combination thereof. In some embodiments, the anti-viral polypeptide is cytotoxic to a bacterium, fungus, protozoan, parasite, prion or a combination thereof. In certain embodiments, the anti-viral polypeptide is cytostatic and cytotoxic to a bacterium, fungus, protozoan, parasite, prion, or a combination thereof. In some embodiments, the anti-viral polypeptide is cytotoxic to a tumor or cancer cell (*e.g.*, a human cancer cell). In some embodiments, the anti-viral polypeptide is cytostatic to a tumor or cancer cell (*e.g.*, a human cancer cell). In certain embodiments, the anti-viral polypeptide is cytotoxic and cytostatic to a tumor or cancer cell (*e.g.*, a human cancer cell). In some embodiments, the anti-viral polypeptide is a secreted polypeptide.

Cytotoxic Nucleosides

[000142] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may incorporate one or more cytotoxic nucleosides. For example, cytotoxic nucleosides may be incorporated into polynucleotides, primary constructs or mmRNA such as bifunctional modified RNAs or mRNAs. Cytotoxic nucleoside anti-cancer agents include, but are not limited to, adenosine arabinoside, cytarabine, cytosine arabinoside, 5-fluorouracil, fludarabine, floxuridine, FTORAFUR® (a combination of tegafur and uracil), tegafur ((RS)-5-fluoro-1-(tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione), and 6-mercaptopurine.

[000143] A number of cytotoxic nucleoside analogues are in clinical use, or have been the subject of clinical trials, as anticancer agents. Examples of such analogues include,

but are not limited to, cytarabine, gemcitabine, troxacitabine, decitabine, tezacitabine, 2′-deoxy-2′-methylidenecytidine (DMDC), cladribine, clofarabine, 5-azacytidine, 4'-thio-aracytidine, cyclopentenylcytosine and 1-(2-C-cyano-2-deoxy-beta-D-arabino-pentofuranosyl)-cytosine. Another example of such a compound is fludarabine phosphate. These compounds may be administered systemically and may have side effects which are typical of cytotoxic agents such as, but not limited to, little or no specificity for tumor cells over proliferating normal cells.

[000144] A number of prodrugs of cytotoxic nucleoside analogues are also reported in the art. Examples include, but are not limited to, N4-behenoyl-1-beta-D-arabinofuranosylcytosine, N4-octadecyl-1-beta-D-arabinofuranosylcytosine, N4-palmitoyl-1-(2-C-cyano-2-deoxy-beta-D-arabino-pentofuranosyl) cytosine, and P-4055 (cytarabine 5'-elaidic acid ester). In general, these prodrugs may be converted into the active drugs mainly in the liver and systemic circulation and display little or no selective release of active drug in the tumor tissue. For example, capecitabine, a prodrug of 5'-deoxy-5-fluorocytidine (and eventually of 5-fluorouracil), is metabolized both in the liver and in the tumor tissue. A series of capecitabine analogues containing "an easily hydrolysable radical under physiological conditions" has been claimed by Fujiu et al. (U.S. Pat. No. 4,966,891) and is herein incorporated by reference. The series described by Fujiu includes N4 alkyl and aralkyl carbamates of 5'-deoxy-5-fluorocytidine and the implication that these compounds will be activated by hydrolysis under normal physiological conditions to provide 5'-deoxy-5-fluorocytidine.

[000145] A series of cytarabine N4-carbamates has been by reported by Fadl et al (Pharmazie. 1995, 50, 382-7, herein incorporated by reference) in which compounds were designed to convert into cytarabine in the liver and plasma. WO 2004/041203, herein incorporated by reference, discloses prodrugs of gemcitabine, where some of the prodrugs are N4-carbamates. These compounds were designed to overcome the gastrointestinal toxicity of gemcitabine and were intended to provide gemcitabine by hydrolytic release in the liver and plasma after absorption of the intact prodrug from the gastrointestinal tract. Nomura et al (Bioorg Med. Chem. 2003, 11, 2453-61, herein incorporated by reference) have described acetal derivatives of 1-(3-C-ethynyl-β-D-ribo-

pentofaranosyl) cytosine which, on bioreduction, produced an intermediate that required further hydrolysis under acidic conditions to produce a cytotoxic nucleoside compound.

[000146] Cytotoxic nucleotides which may be chemotherapeutic also include, but are not limited to, pyrazolo [3,4-D]-pyrimidines, allopurinol, azathioprine, capecitabine, cytosine arabinoside, fluorouracil, mercaptopurine, 6-thioguanine, acyclovir, ara-adenosine, ribavirin, 7-deaza-adenosine, 7-deaza-guanosine, 6-aza-uracil, 6-aza-cytidine, thymidine ribonucleotide, 5-bromodeoxyuridine, 2-chloro-purine, and inosine, or combinations thereof.

Flanking Regions: Untranslated Regions (UTRs)

[000147] Untranslated regions (UTRs) of a gene are transcribed but not translated. The 5′UTR starts at the transcription start site and continues to the start codon but does not include the start codon; whereas, the 3′UTR starts immediately following the stop codon and continues until the transcriptional termination signal. There is growing body of evidence about the regulatory roles played by the UTRs in terms of stability of the nucleic acid molecule and translation. The regulatory features of a UTR can be incorporated into the polynucleotides, primary constructs and/or mmRNA of the present invention to enhance the stability of the molecule. The specific features can also be incorporated to ensure controlled down-regulation of the transcript in case they are misdirected to undesired organs sites.

5′ UTR and Translation Initiation

[000148] Natural 5′UTRs bear features which play roles in for translation initiation. They harbor signatures like Kozak sequences which are commonly known to be involved in the process by which the ribosome initiates translation of many genes. Kozak sequences have the consensus CCR(A/G)CCAUGG, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another 'G'. 5′UTR also have been known to form secondary structures which are involved in elongation factor binding.

[000149] By engineering the features typically found in abundantly expressed genes of specific target organs, one can enhance the stability and protein production of the polynucleotides, primary constructs or mmRNA of the invention. For example, introduction of 5′ UTR of liver-expressed mRNA, such as albumin, serum amyloid A,

Apolipoprotein A/B/E, transferrin, alpha fetoprotein, erythropoietin, or Factor VIII, could be used to enhance expression of a nucleic acid molecule, such as a mmRNA, in hepatic cell lines or liver. Likewise, use of 5′ UTR from other tissue-specific mRNA to improve expression in that tissue is possible for muscle (MyoD, Myosin, Myoglobin, Myogenin, Herculin), for endothelial cells (Tie-1, CD36), for myeloid cells (C/EBP, AML1, G-CSF, GM-CSF, CD11b, MSR, Fr-1, i-NOS), for leukocytes (CD45, CD18), for adipose tissue (CD36, GLUT4, ACRP30, adiponectin) and for lung epithelial cells (SP-A/B/C/D).

[000150] Other non-UTR sequences may be incorporated into the 5′ (or 3′ UTR) UTRs. For example, introns or portions of introns sequences may be incorporated into the flanking regions of the polynucleotides, primary constructs or mmRNA of the invention. Incorporation of intronic sequences may increase protein production as well as mRNA levels.

3′ UTR and the AU Rich Elements

[000151] 3′ UTRs are known to have stretches of Adenosines and Uridines embedded in them. These AU rich signatures are particularly prevalent in genes with high rates of turnover. Based on their sequence features and functional properties, the AU rich elements (AREs) can be separated into three classes (Chen et al, 1995): Class I AREs contain several dispersed copies of an AUUUA motif within U-rich regions. C-Myc and MyoD contain class I AREs. Class II AREs possess two or more overlapping UUAUUUA(U/A)(U/A) nonamers. Molecules containing this type of AREs include GM-CSF and TNF-a. Class III ARES are less well defined. These U rich regions do not contain an AUUUA motif. c-Jun and Myogenin are two well-studied examples of this class. Most proteins binding to the AREs are known to destabilize the messenger, whereas members of the ELAV family, most notably HuR, have been documented to increase the stability of mRNA. HuR binds to AREs of all the three classes. Engineering the HuR specific binding sites into the 3′ UTR of nucleic acid molecules will lead to HuR binding and thus, stabilization of the message *in vivo*.

[000152] Introduction, removal or modification of 3′ UTR AU rich elements (AREs) can be used to modulate the stability of polynucleotides, primary constructs or mmRNA of the invention. When engineering specific polynucleotides, primary constructs or mmRNA, one or more copies of an ARE can be introduced to make polynucleotides,

primary constructs or mmRNA of the invention less stable and thereby curtail translation and decrease production of the resultant protein. Likewise, AREs can be identified and removed or mutated to increase the intracellular stability and thus increase translation and production of the resultant protein. Transfection experiments can be conducted in relevant cell lines, using polynucleotides, primary constructs or mmRNA of the invention and protein production can be assayed at various time points post-transfection. For example, cells can be transfected with different ARE-engineering molecules and by using an ELISA kit to the relevant protein and assaying protein produced at 6 hour, 12 hour, 24 hour, 48 hour, and 7 days post-transfection.

Incorporating microRNA Binding Sites

[000153] microRNAs (or miRNA) are 19-25 nucleotide long noncoding RNAs that bind to the 3′UTR of nucleic acid molecules and down-regulate gene expression either by reducing nucleic acid molecule stability or by inhibiting translation. The polynucleotides, primary constructs or mmRNA of the invention may comprise one or more microRNA target sequences, microRNA seqences, or microRNA seeds. Such sequences may correspond to any known microRNA such as those taught in US Publication US2005/0261218 and US Publication US2005/0059005, the contents of which are incorporated herein by reference in their entirety.

[000154] A microRNA sequence comprises a "seed" region, i.e., a sequence in the region of positions 2-8 of the mature microRNA, which sequence has perfect Watson-Crick complementarity to the miRNA target sequence. A microRNA seed may comprise positions 2-8 or 2-7 of the mature microRNA. In some embodiments, a microRNA seed may comprise 7 nucleotides (e.g., nucleotides 2-8 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked by an adenine (A) opposed to microRNA position 1. In some embodiments, a microRNA seed may comprise 6 nucleotides (e.g., nucleotides 2-7 of the mature microRNA), wherein the seed-complementary site in the corresponding miRNA target is flanked byan adenine (A) opposed to microRNA position 1. See for example, Grimson A, Farh KK, Johnston WK, Garrett-Engele P, Lim LP, Bartel DP; Mol Cell. 2007 Jul 6;27(1):91-105; each of which is herein incorporated by reference in their entirety. The bases of the microRNA seed have complete complementarity with the target sequence. By engineering microRNA

target sequences into the 3′UTR of polynucleotides, primary constructs or mmRNA of the invention one can target the molecule for degradation or reduced translation, provided the microRNA in question is available. This process will reduce the hazard of off target effects upon nucleic acid molecule delivery. Identification of microRNA, microRNA target regions, and their expression patterns and role in biology have been reported (Bonauer et al., Curr Drug Targets 2010 11:943-949; Anand and Cheresh Curr Opin Hematol 2011 18:171-176; Contreras and Rao Leukemia 2012 26:404-413 (2011 Dec 20. doi: 10.1038/leu.2011.356); Bartel Cell 2009 136:215-233; Landgraf et al, Cell, 2007 129:1401-1414; each of which is herein incorporated by reference in its entirety).

[000155] For example, if the nucleic acid molecule is an mRNA and is not intended to be delivered to the liver but ends up there, then miR-122, a microRNA abundant in liver, can inhibit the expression of the gene of interest if one or multiple target sites of miR-122 are engineered into the 3′ UTR of the polynucleotides, primary constructs or mmRNA. Introduction of one or multiple binding sites for different microRNA can be engineered to further decrease the longevity, stability, and protein translation of a polynucleotides, primary constructs or mmRNA.

[000156] As used herein, the term "microRNA site" refers to a microRNA target site or a microRNA recognition site, or any nucleotide sequence to which a microRNA binds or associates. It should be understood that "binding" may follow traditional Watson-Crick hybridization rules or may reflect any stable association of the microRNA with the target sequence at or adjacent to the microRNA site.

[000157] Conversely, for the purposes of the polynucleotides, primary constructs or mmRNA of the present invention, microRNA binding sites can be engineered out of (i.e. removed from) sequences in which they naturally occur in order to increase protein expression in specific tissues. For example, miR-122 binding sites may be removed to improve protein expression in the liver. Regulation of expression in multiple tissues can be accomplished through introduction or removal or one or several microRNA binding sites.

[000158] Examples of tissues where microRNA are known to regulate mRNA, and thereby protein expression, include, but are not limited to, liver (miR-122), muscle (miR-133, miR-206, miR-208), endothelial cells (miR-17-92, miR-126), myeloid cells (miR-

142-3p, miR-142-5p, miR-16, miR-21, miR-223, miR-24, miR-27), adipose tissue (let-7, miR-30c), heart (miR-1d, miR-149), kidney (miR-192, miR-194, miR-204), and lung epithelial cells (let-7, miR-133, miR-126). MicroRNA can also regulate complex biological processes such as angiogenesis (miR-132) (Anand and Cheresh Curr Opin Hematol 2011 18:171-176; herein incorporated by reference in its entirety). In the polynucleotides, primary constructs or mmRNA of the present invention, binding sites for microRNAs that are involved in such processes may be removed or introduced, in order to tailor the expression of the polynucleotides, primary constructs or mmRNA expression to biologically relevant cell types or to the context of relevant biological processes. A listing of MicroRNA, miR sequences and miR binding sites is listed in Table 9 of U.S. Provisional Application No. 61/753,661 filed January 17, 2013, in Table 9 of U.S. Provisional Application No. 61/754,159 filed January 18, 2013, and in Table 7 of U.S. Provisional Application No. 61/758,921 filed January 31, 2013, each of which are herein incorporated by reference in their entireties.

[000159] Examples of use of microRNA to drive tissue or disease-specific gene expression are listed (Getner and Naldini, Tissue Antigens. 2012, 80:393-403; herein incoroporated by reference in its entirety). In addition, microRNA seed sites can be incorporated into mRNA to decrease expression in certain cells which results in a biological improvement. An example of this is incorporation of miR-142 sites into a UGT1A1-expressing lentiviral vector. The presence of miR-142 seed sites reduced expression in hematopoietic cells, and as a consequence reduced expression in antigen-presentating cells, leading to the absence of an immune response against the virally expressed UGT1A1 (Schmitt et al., Gastroenterology 2010; 139:999-1007; Gonzalez-Asequinolaza et al. Gastroenterology 2010, 139:726-729; both herein incorporated by reference in its entirety) . Incorporation of miR-142 sites into modified mRNA could not only reduce expression of the encoded protein in hematopoietic cells, but could also reduce or abolish immune responses to the mRNA-encoded protein. Incorporation of miR-142 seed sites (one or multiple) into mRNA would be important in the case of treatment of patients with complete protein deficiencies (UGT1A1 type I, LDLR-deficient patients, CRIM-negative Pompe patients, etc.) .

[000160] Lastly, through an understanding of the expression patterns of microRNA in different cell types, polynucleotides, primary constructs or mmRNA can be engineered for more targeted expression in specific cell types or only under specific biological conditions. Through introduction of tissue-specific microRNA binding sites, polynucleotides, primary constructs or mmRNA could be designed that would be optimal for protein expression in a tissue or in the context of a biological condition.

[000161] Transfection experiments can be conducted in relevant cell lines, using engineered polynucleotides, primary constructs or mmRNA and protein production can be assayed at various time points post-transfection. For example, cells can be transfected with different microRNA binding site-engineering polynucleotides, primary constructs or mmRNA and by using an ELISA kit to the relevant protein and assaying protein produced at 6 hour, 12 hour, 24 hour, 48 hour, 72 hour and 7 days post-transfection. *In vivo* experiments can also be conducted using microRNA-binding site-engineered molecules to examine changes in tissue-specific expression of formulated polynucleotides, primary constructs or mmRNA.

5′ Capping

[000162] The 5′ cap structure of an mRNA is involved in nuclear export, increasing mRNA stability and binds the mRNA Cap Binding Protein (CBP), which is responsibile for mRNA stability in the cell and translation competency through the association of CBP with poly(A) binding protein to form the mature cyclic mRNA species. The cap further assists the removal of 5′ proximal introns removal during mRNA splicing.

[000163] Endogenous mRNA molecules may be 5′-end capped generating a 5′-ppp-5′-triphosphate linkage between a terminal guanosine cap residue and the 5′-terminal transcribed sense nucleotide of the mRNA molecule. This 5′-guanylate cap may then be methylated to generate an N7-methyl-guanylate residue. The ribose sugars of the terminal and/or anteterminal transcribed nucleotides of the 5′ end of the mRNA may optionally also be 2′-O-methylated. 5′-decapping through hydrolysis and cleavage of the guanylate cap structure may target a nucleic acid molecule, such as an mRNA molecule, for degradation.

[000164] Modifications to the polynucleotides, primary constructs, and mmRNA of the present invention may generate a non-hydrolyzable cap structure preventing decapping

and thus increasing mRNA half-life. Because cap structure hydrolysis requires cleavage of 5′-ppp-5′ phosphorodiester linkages, modified nucleotides may be used during the capping reaction. For example, a Vaccinia Capping Enzyme from New England Biolabs (Ipswich, MA) may be used with α-thio-guanosine nucleotides according to the manufacturer's instructions to create a phosphorothioate linkage in the 5′-ppp-5′ cap. Additional modified guanosine nucleotides may be used such as α-methyl-phosphonate and seleno-phosphate nucleotides.

[000165] Additional modifications include, but are not limited to, 2′-O-methylation of the ribose sugars of 5′-terminal and/or 5′-anteterminal nucleotides of the mRNA (as mentioned above) on the 2′-hydroxyl group of the sugar ring. Multiple distinct 5′-cap structures can be used to generate the 5′-cap of a nucleic acid molecule, such as an mRNA molecule.

[000166] Cap analogs, which herein are also referred to as synthetic cap analogs, chemical caps, chemical cap analogs, or structural or functional cap analogs, differ from natural (i.e. endogenous, wild-type or physiological) 5′-caps in their chemical structure, while retaining cap function. Cap analogs may be chemically (i.e. non-enzymatically) or enzymatically synthesized and/or linked to a nucleic acid molecule.

[000167] For example, the Anti-Reverse Cap Analog (ARCA) cap contains two guanines linked by a 5′-5′-triphosphate group, wherein one guanine contains an N7 methyl group as well as a 3′-O-methyl group (i.e., N7,3′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine (m^7G-3′mppp-G; which may equivaliently be designated 3′ O-Me-m7G(5')ppp(5')G). The 3′-O atom of the other, unmodified, guanine becomes linked to the 5′-terminal nucleotide of the capped nucleic acid molecule (e.g. an mRNA or mmRNA). The N7- and 3′-O-methlyated guanine provides the terminal moiety of the capped nucleic acid molecule (e.g. mRNA or mmRNA).

[000168] Another exemplary cap is mCAP, which is similar to ARCA but has a 2′-O-methyl group on guanosine (i.e., N7,2′-O-dimethyl-guanosine-5′-triphosphate-5′-guanosine, m^7Gm-ppp-G).

[000169] While cap analogs allow for the concomitant capping of a nucleic acid molecule in an in vitro transcription reaction, up to 20% of transcripts can remain uncapped. This, as well as the structural differences of a cap analog from an endogenous

5′-cap structures of nucleic acids produced by the endogenous, cellular transcription machinery, may lead to reduced translational competency and reduced cellular stability.

[000170] Polynucleotides, primary constructs and mmRNA of the invention may also be capped post-transcriptionally, using enzymes, in order to generate more authentic 5′-cap structures. As used herein, the phrase "more authentic" refers to a feature that closely mirrors or mimics, either structurally or functionally, an endogenous or wild type feature. That is, a "more authentic" feature is better representative of an endogenous, wild-type, natural or physiological cellular function and/or structure as compared to synthetic features or analogs, etc., of the prior art, or which outperforms the corresponding endogenous, wild-type, natural or physiological feature in one or more respects. Non-limiting examples of more authentic 5′cap structures of the present invention are those which, among other things, have enhanced binding of cap binding proteins, increased half life, reduced susceptibility to 5′ endonucleases and/or reduced 5′decapping, as compared to synthetic 5′cap structures known in the art (or to a wild-type, natural or physiological 5′cap structure). For example, recombinant Vaccinia Virus Capping Enzyme and recombinant 2′-O-methyltransferase enzyme can create a canonical 5′-5′-triphosphate linkage between the 5′-terminal nucleotide of an mRNA and a guanine cap nucleotide wherein the cap guanine contains an N7 methylation and the 5′-terminal nucleotide of the mRNA contains a 2′-O-methyl. Such a structure is termed the Cap1 structure. This cap results in a higher translational-competency and cellular stability and a reduced activation of cellular pro-inflammatory cytokines, as compared, e.g., to other 5′cap analog structures known in the art. Cap structures include, but are not limited to, 7mG(5')ppp(5')N,pN2p (cap 0), 7mG(5')ppp(5')NlmpNp (cap 1), and 7mG(5')-ppp(5')NlmpN2mp (cap 2).

[000171] Because the polynucleotides, primary constructs or mmRNA may be capped post-transcriptionally, and because this process is more efficient, nearly 100% of the polynucleotides, primary constructs or mmRNA may be capped. This is in contrast to ~80% when a cap analog is linked to an mRNA in the course of an in vitro transcription reaction.

[000172] According to the present invention, 5′ terminal caps may include endogenous caps or cap analogs. According to the present invention, a 5′ terminal cap may comprise

a guanine analog. Useful guanine analogs include, but are not limited to, inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

Viral Sequences

[000173] Additional viral sequences such as, but not limited to, the translation enhancer sequence of the barley yellow dwarf virus (BYDV-PAV), the Jaagsiekte sheep retrovirus (JSRV) and/or the Enzootic nasal tumor virus (See e.g., International Pub. No. WO2012129648; herein incorporated by reference in its entirety) can be engineered and inserted in the 3′ UTR of the polynucleotides, primary constructs or mmRNA of the invention and can stimulate the translation of the construct *in vitro* and *in vivo*. Transfection experiments can be conducted in relevant cell lines at and protein production can be assayed by ELISA at 12hr, 24hr, 48hr, 72 hr and day 7 post-transfection.

IRES Sequences

[000174] Further, provided are polynucleotides, primary constructs or mmRNA which may contain an internal ribosome entry site (IRES). First identified as a feature Picorna virus RNA, IRES plays an important role in initiating protein synthesis in absence of the 5′ cap structure. An IRES may act as the sole ribosome binding site, or may serve as one of multiple ribosome binding sites of an mRNA. Polynucleotides, primary constructs or mmRNA containing more than one functional ribosome binding site may encode several peptides or polypeptides that are translated independently by the ribosomes ("multicistronic nucleic acid molecules"). When polynucleotides, primary constructs or mmRNA are provided with an IRES, further optionally provided is a second translatable region. Examples of IRES sequences that can be used according to the invention include without limitation, those from picornaviruses (e.g. FMDV), pest viruses (CFFV), polio viruses (PV), encephalomyocarditis viruses (ECMV), foot-and-mouth disease viruses (FMDV), hepatitis C viruses (HCV), classical swine fever viruses (CSFV), murine leukemia virus (MLV), simian immune deficiency viruses (SIV) or cricket paralysis viruses (CrPV).

Poly-A tails

[000175] During RNA processing, a long chain of adenine nucleotides (poly-A tail) may be added to a polynucleotide such as an mRNA molecules in order to increase stability. Immediately after transcription, the 3' end of the transcript may be cleaved to free a 3' hydroxyl. Then poly-A polymerase adds a chain of adenine nucleotides to the RNA. The process, called polyadenylation, adds a poly-A tail that can be between, for example, approximately 100 and 250 residues long.

[000176] It has been discovered that unique poly-A tail lengths provide certain advantages to the polynucleotides, primary constructs or mmRNA of the present invention.

[000177] Generally, the length of a poly-A tail of the present invention is greater than 30 nucleotides in length. In another embodiment, the poly-A tail is greater than 35 nucleotides in length (e.g., at least or greater than about 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, 1,200, 1,300, 1,400, 1,500, 1,600, 1,700, 1,800, 1,900, 2,000, 2,500, and 3,000 nucleotides). In some embodiments, the polynucleotide, primary construct, or mmRNA includes from about 30 to about 3,000 nucleotides (e.g., from 30 to 50, from 30 to 100, from 30 to 250, from 30 to 500, from 30 to 750, from 30 to 1,000, from 30 to 1,500, from 30 to 2,000, from 30 to 2,500, from 50 to 100, from 50 to 250, from 50 to 500, from 50 to 750, from 50 to 1,000, from 50 to 1,500, from 50 to 2,000, from 50 to 2,500, from 50 to 3,000, from 100 to 500, from 100 to 750, from 100 to 1,000, from 100 to 1,500, from 100 to 2,000, from 100 to 2,500, from 100 to 3,000, from 500 to 750, from 500 to 1,000, from 500 to 1,500, from 500 to 2,000, from 500 to 2,500, from 500 to 3,000, from 1,000 to 1,500, from 1,000 to 2,000, from 1,000 to 2,500, from 1,000 to 3,000, from 1,500 to 2,000, from 1,500 to 2,500, from 1,500 to 3,000, from 2,000 to 3,000, from 2,000 to 2,500, and from 2,500 to 3,000).

[000178] In one embodiment, the poly-A tail is designed relative to the length of the overall polynucleotides, primary constructs or mmRNA. This design may be based on the length of the coding region, the length of a particular feature or region (such as the first or flanking regions), or based on the length of the ultimate product expressed from the polynucleotides, primary constructs or mmRNA.

[000179] In this context the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100% greater in length than the polynucleotides, primary constructs or mmRNA or feature thereof. The poly-A tail may also be designed as a fraction of polynucleotides, primary constructs or mmRNA to which it belongs. In this context, the poly-A tail may be 10, 20, 30, 40, 50, 60, 70, 80, or 90% or more of the total length of the construct or the total length of the construct minus the poly-A tail. Further, engineered binding sites and conjugation of polynucleotides, primary constructs or mmRNA for Poly-A binding protein may enhance expression.

[000180] Additionally, multiple distinct polynucleotides, primary constructs or mmRNA may be linked together to the PABP (Poly-A binding protein) through the 3′-end using modified nucleotides at the 3′-terminus of the poly-A tail. Transfection experiments can be conducted in relevant cell lines at and protein production can be assayed by ELISA at 12hr, 24hr, 48hr, 72 hr and day 7 post-transfection.

[000181] In one embodiment, the polynucleotide primary constructs of the present invention are designed to include a polyA-G Quartet. The G-quartet is a cyclic hydrogen bonded array of four guanine nucleotides that can be formed by G-rich sequences in both DNA and RNA. In this embodiment, the G-quartet is incorporated at the end of the poly-A tail. The resultant mmRNA construct is assayed for stability, protein production and other parameters including half-life at various time points. It has been discovered that the polyA-G quartet results in protein production equivalent to at least 75% of that seen using a poly-A tail of 120 nucleotides alone.

Quantification

[000182] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may be quantified in exosomes derived from one or more bodily fluid. As used herein "bodily fluids" include peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from sinus cavities, bronchopulmonary aspirates, blastocyl

cavity fluid, and umbilical cord blood. Alternatively, exosomes may be retrieved from an organ selected from the group consisting of lung, heart, pancreas, stomach, intestine, bladder, kidney, ovary, testis, skin, colon, breast, prostate, brain, esophagus, liver, and placenta.

[000183] In the quantification method, a sample of not more than 2mL is obtained from the subject and the exosomes isolated by size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof. In the analysis, the level or concentration of a polynucleotide, primary construct or mmRNA may be an expression level, presence, absence, truncation or alteration of the administered construct. It is advantageous to correlate the level with one or more clinical phenotypes or with an assay for a human disease biomarker. The assay may be performed using construct specific probes, cytometry, qRT-PCR, real-time PCR, PCR, flow cytometry, electrophoresis, mass spectrometry, or combinations thereof while the exosomes may be isolated using immunohistochemical methods such as enzyme linked immunosorbent assay (ELISA) methods. Exosomes may also be isolated by size exclusion chromatography, density gradient centrifugation, differential centrifugation, nanomembrane ultrafiltration, immunoabsorbent capture, affinity purification, microfluidic separation, or combinations thereof.

[000184] These methods afford the investigator the ability to monitor, in real time, the level of polynucleotides, primary constructs or mmRNA remaining or delivered. This is possible because the polynucleotides, primary constructs or mmRNA of the present invention differ from the endogenous forms due to the structural or chemical modifications.

II. Design and synthesis of mmRNA

[000185] Polynucleotides, primary constructs or mmRNA for use in accordance with the invention may be prepared according to any available technique including, but not limited to chemical synthesis, enzymatic synthesis, which is generally termed *in vitro* transcription (IVT) or enzymatic or chemical cleavage of a longer precursor, etc. Methods of synthesizing RNAs are known in the art (see, *e.g.*, Gait, M.J. (ed.) *Oligonucleotide synthesis: a practical approach*, Oxford [Oxfordshire], Washington, DC:

IRL Press, 1984; and Herdewijn, P. (ed.) *Oligonucleotide synthesis: methods and applications*, Methods in Molecular Biology, v. 288 (Clifton, N.J.) Totowa, N.J.: Humana Press, 2005; both of which are incorporated herein by reference).

[000186] The process of design and synthesis of the primary constructs of the invention generally includes the steps of gene construction, mRNA production (either with or without modifications) and purification. In the enzymatic synthesis method, a target polynucleotide sequence encoding the polypeptide of interest is first selected for incorporation into a vector which will be amplified to produce a cDNA template. Optionally, the target polynucleotide sequence and/or any flanking sequences may be codon optimized. The cDNA template is then used to produce mRNA through *in vitro* transcription (IVT). After production, the mRNA may undergo purification and clean-up processes. The steps of which are provided in more detail below.

Gene Construction

[000187] The step of gene construction may include, but is not limited to gene synthesis, vector amplification, plasmid purification, plasmid linearization and clean-up, and cDNA template synthesis and clean-up.

Gene Synthesis

[000188] Once a polypeptide of interest, or target, is selected for production, a primary construct is designed. Within the primary construct, a first region of linked nucleosides encoding the polypeptide of interest may be constructed using an open reading frame (ORF) of a selected nucleic acid (DNA or RNA) transcript. The ORF may comprise the wild type ORF, an isoform, variant or a fragment thereof. As used herein, an "open reading frame" or "ORF" is meant to refer to a nucleic acid sequence (DNA or RNA) which is capable of encoding a polypeptide of interest. ORFs often begin with the start codon, ATG and end with a nonsense or termination codon or signal.

[000189] Further, the nucleotide sequence of the first region may be codon optimized. Codon optimization methods are known in the art and may be useful in efforts to achieve one or more of several goals. These goals include to match codon frequencies in target and host organisms to ensure proper folding, bias GC content to increase mRNA stability or reduce secondary structures, minimize tandem repeat codons or base runs that may impair gene construction or expression, customize transcriptional and translational

control regions, insert or remove protein trafficking sequences, remove/add post translation modification sites in encoded protein (e.g. glycosylation sites), add, remove or shuffle protein domains, insert or delete restriction sites, modify ribosome binding sites and mRNA degradation sites, to adjust translational rates to allow the various domains of the protein to fold properly, or to reduce or eliminate problem secondary structures within the mRNA. Codon optimization tools, algorithms and services are known in the art, non-limiting examples include services from GeneArt (Life Technologies), DNA2.0 (Menlo Park CA) and/or proprietary methods. In one embodiment, the ORF sequence is optimized using optimization algorithms. Codon options for each amino acid are given in Table 1.

Table 1. Codon Options

Amino Acid	Single Letter Code	Codon Options
Isoleucine	I	ATT, ATC, ATA
Leucine	L	CTT, CTC, CTA, CTG, TTA, TTG
Valine	V	GTT, GTC, GTA, GTG
Phenylalanine	F	TTT, TTC
Methionine	M	ATG
Cysteine	C	TGT, TGC
Alanine	A	GCT, GCC, GCA, GCG
Glycine	G	GGT, GGC, GGA, GGG
Proline	P	CCT, CCC, CCA, CCG
Threonine	T	ACT, ACC, ACA, ACG
Serine	S	TCT, TCC, TCA, TCG, AGT, AGC
Tyrosine	Y	TAT, TAC
Tryptophan	W	TGG
Glutamine	Q	CAA, CAG
Asparagine	N	AAT, AAC
Histidine	H	CAT, CAC
Glutamic acid	E	GAA, GAG
Aspartic acid	D	GAT, GAC
Lysine	K	AAA, AAG
Arginine	R	CGT, CGC, CGA, CGG, AGA, AGG
Selenocysteine	Sec	UGA in mRNA in presence of Selenocystein insertion element (SECIS)
Stop codons	Stop	TAA, TAG, TGA

[000190] Features, which may be considered beneficial in some embodiments of the present invention, may be encoded by the primary construct and may flank the ORF as a first or second flanking region. The flanking regions may be incorporated into the primary construct before and/or after optimization of the ORF. It is not required that a

primary construct contain both a 5′ and 3′ flanking region. Examples of such features include, but are not limited to, untranslated regions (UTRs), Kozak sequences, an oligo(dT) sequence, and detectable tags and may include multiple cloning sites which may have XbaI recognition.

[000191] In some embodiments, a 5′ UTR and/or a 3′ UTR may be provided as flanking regions. Multiple 5′ or 3′ UTRs may be included in the flanking regions and may be the same or of different sequences. Any portion of the flanking regions, including none, may be codon optimized and any may independently contain one or more different structural or chemical modifications, before and/or after codon optimization. Combinations of features may be included in the first and second flanking regions and may be contained within other features. For example, the ORF may be flanked by a 5' UTR which may contain a strong Kozak translational initiation signal and/or a 3' UTR which may include an oligo(dT) sequence for templated addition of a poly-A tail. 5'UTR may comprise a first polynucleotide fragment and a second polynucleotide fragment from the same and/or different genes such as the 5'UTRs described in US Patent Application Publication No. 20100293625, herein incorporated by reference in its entirety.

[000192] Tables 2 and 3 provide a listing of exemplary UTRs which may be utilized in the primary construct of the present invention as flanking regions. Shown in Table 2 is a listing of a 5′-untranslated region of the invention. Variants of 5' UTRs may be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

Table 2. 5′-Untranslated Regions

5′ UTR Identifier	Name/Description	Sequence	SEQ ID NO.
5UTR-001	Upstream UTR	GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCACC	1
5UTR-002	Upstream UTR	GGGAGATCAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCACC	2
5UTR-003	Upstream UTR	GGAATAAAAGTCTCAACACAACATATACAAAACAAACGAATCTCAAGCAATCAAGCATTCTACTTCTATTGCAGCAATTTAAATCATTTCTTTTAAAGCAAAAGCAATTTTCTGAAAATTTTCACCATTTACGAACGATAGCAAC	3
5UTR-	Upstream UTR	GGGAGACAAGCUUGGCAUUCCGGUACUGU	4

004		UGGUAAAGCCACC	

[000193] Shown in Table 3 is a representative listing of 3′-untranslated regions of the invention. Variants of 3' UTRs may be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

Table 3. 3′-Untranslated Regions

3′ UTR Identifier	Name/Description	Sequence	SEQ ID NO.
3UTR-001	Creatine Kinase	GCGCCTGCCCACCTGCCACCGACTGCTGGAA CCCAGCCAGTGGGAGGGCCTGGCCCACCAGA GTCCTGCTCCCTCACTCCTCGCCCCGCCCCCT GTCCCAGAGTCCCACCTGGGGGCTCTCTCCA CCCTTCTCAGAGTTCCAGTTTCAACCAGAGTT CCAACCAATGGGCTCCATCCTCTGGATTCTG GCCAATGAAATATCTCCCTGGCAGGGTCCTC TTCTTTTCCCAGAGCTCCACCCCAACCAGGA GCTCTAGTTAATGGAGAGCTCCCAGCACACT CGGAGCTTGTGCTTTGTCTCCACGCAAAGCG ATAAATAAAAGCATTGGTGGCCTTTGGTCTT TGAATAAAGCCTGAGTAGGAAGTCTAGA	5
3UTR-002	Myoglobin	GCCCCTGCCGCTCCCACCCCCACCCATCTGG GCCCCGGGTTCAAGAGAGAGCGGGGTCTGAT CTCGTGTAGCCATATAGAGTTTGCTTCTGAGT GTCTGCTTTGTTTAGTAGAGGTGGGCAGGAG GAGCTGAGGGGCTGGGGCTGGGGTGTTGAA GTTGGCTTTGCATGCCCAGCGATGCGCCTCC CTGTGGGATGTCATCACCCTGGGAACCGGGA GTGGCCCTTGGCTCACTGTGTTCTGCATGGTT TGGATCTGAATTAATTGTCCTTTCTTCTAAAT CCCAACCGAACTTCTTCCAACCTCCAAACTG GCTGTAACCCCAAATCCAAGCCATTAACTAC ACCTGACAGTAGCAATTGTCTGATTAATCAC TGGCCCCTTGAAGACAGCAGAATGTCCCTTT GCAATGAGGAGGAGATCTGGGCTGGGCGGG CCAGCTGGGGAAGCATTTGACTATCTGGAAC TTGTGTGTGCCTCCTCAGGTATGGCAGTGACT CACCTGGTTTTAATAAAACAACCTGCAACAT CTCATGGTCTTTGAATAAAGCCTGAGTAGGA AGTCTAGA	6
3UTR-003	α-actin	ACACACTCCACCTCCAGCACGCGACTTCTCA GGACGACGAATCTTCTCAATGGGGGGGCGGC TGAGCTCCAGCCACCCCGCAGTCACTTTCTTT GTAACAACTTCCGTTGCTGCCATCGTAAACT GACACAGTGTTTATAACGTGTACATACATTA	7

		ACTTATTACCTCATTTTGTTATTTTTCGAAAC AAAGCCCTGTGGAAGAAAATGGAAAACTTG AAGAAGCATTAAAGTCATTCTGTTAAGCTGC GTAAATGGTCTTTGAATAAAGCCTGAGTAGG AAGTCTAGA	
3UTR-004	Albumin	CATCACATTTAAAAGCATCTCAGCCTACCAT GAGAATAAGAGAAAGAAAATGAAGATCAAA AGCTTATTCATCTGTTTTTCTTTTTCGTTGGTG TAAAGCCAACACCCTGTCTAAAAAACATAAA TTTCTTTAATCATTTTGCCTCTTTTCTCTGTGC TTCAATTAATAAAAAATGGAAAGAATCTAAT AGAGTGGTACAGCACTGTTATTTTTCAAAGA TGTGTTGCTATCCTGAAAATTCTGTAGGTTCT GTGGAAGTTCCAGTGTTCTCTCTTATTCCACT TCGGTAGAGGATTTCTAGTTTCTTGTGGGCTA ATTAAATAAATCATTAATACTCTTCTAATGGT CTTTGAATAAAGCCTGAGTAGGAAGTCTAGA	8
3UTR-005	α-globin	GCTGCCTTCTGCGGGGCTTGCCTTCTGGCCAT GCCCTTCTTCTCTCCCTTGCACCTGTACCTCT TGGTCTTTGAATAAAGCCTGAGTAGGAAGGC GGCCGCTCGAGCATGCATCTAGA	9
3UTR-006	G-CSF	GCCAAGCCCTCCCCATCCCATGTATTTATCTC TATTTAATATTTATGTCTATTTAAGCCTCATA TTTAAAGACAGGGAAGAGCAGAACGGAGCC CCAGGCCTCTGTGTCCTTCCCTGCATTTCTGA GTTTCATTCTCCTGCCTGTAGCAGTGAGAAA AAGCTCCTGTCCTCCCATCCCCTGGACTGGG AGGTAGATAGGTAAATACCAAGTATTTATTA CTATGACTGCTCCCCAGCCCTGGCTCTGCAAT GGGCACTGGGATGAGCCGCTGTGAGCCCCTG GTCCTGAGGGTCCCCACCTGGGACCCTTGAG AGTATCAGGTCTCCCACGTGGGAGACAAGAA ATCCCTGTTTAATATTTAAACAGCAGTGTTCC CCATCTGGGTCCTTGCACCCCTCACTCTGGCC TCAGCCGACTGCACAGCGGCCCCTGCATCCC CTTGGCTGTGAGGCCCCTGGACAAGCAGAGG TGGCCAGAGCTGGGAGGCATGGCCCTGGGGT CCCACGAATTTGCTGGGGAATCTCGTTTTTCT TCTTAAGACTTTTGGGACATGGTTTGACTCCC GAACATCACCGACGCGTCTCCTGTTTTTCTGG GTGGCCTCGGGACACCTGCCCTGCCCCCACG AGGGTCAGGACTGTGACTCTTTTTAGGGCCA GGCAGGTGCCTGGACATTTGCCTTGCTGGAC GGGGACTGGGGATGTGGGAGGGAGCAGACA GGAGGAATCATGTCAGGCCTGTGTGTGAAAG GAAGCTCCACTGTCACCCTCCACCTCTTCACC CCCCACTCACCAGTGTCCCCTCCACTGTCACA TTGTAACTGAACTTCAGGATAATAAAGTGTT TGCCTCCATGGTCTTTGAATAAAGCCTGAGT AGGAAGGCGGCCGCTCGAGCATGCATCTAGA	10

3UTR-007	Col1a2; collagen, type I, alpha 2	ACTCAATCTAAATTAAAAAAGAAAGAAATTT GAAAAAACTTTCTCTTTGCCATTTCTTCTTCT TCTTTTTTAACTGAAAGCTGAATCCTTCCATT TCTTCTGCACATCTACTTGCTTAAATTGTGGG CAAAAGAGAAAAAGAAGGATTGATCAGAGC ATTGTGCAATACAGTTTCATTAACTCCTTCCC CCGCTCCCCCAAAAATTTGAATTTTTTTTTCA ACACTCTTACACCTGTTATGGAAAATGTCAA CCTTTGTAAGAAAACCAAAATAAAAATTGAA AAATAAAAACCATAAACATTTGCACCACTTG TGGCTTTTGAATATCTTCCACAGAGGGAAGT TTAAAACCCAAACTTCCAAAGGTTTAAACTA CCTCAAAACACTTTCCCATGAGTGTGATCCA CATTGTTAGGTGCTGACCTAGACAGAGATGA ACTGAGGTCCTTGTTTTGTTTTGTTCATAATA CAAAGGTGCTAATTAATAGTATTTCAGATAC TTGAAGAATGTTGATGGTGCTAGAAGAATTT GAGAAGAAATACTCCTGTATTGAGTTGTATC GTGTGGTGTATTTTTTAAAAAATTTGATTTAG CATTCATATTTTCCATCTTATTCCCAATTAAA AGTATGCAGATTATTTGCCCAAATCTTCTTCA GATTCAGCATTTGTTCTTTGCCAGTCTCATTT TCATCTTCTTCCATGGTTCCACAGAAGCTTTG TTTCTTGGGCAAGCAGAAAAATTAAATTGTA CCTATTTTGTATATGTGAGATGTTTAAATAAA TTGTGAAAAAAATGAAATAAAGCATGTTTGG TTTTCCAAAAGAACATAT	11
3UTR-008	Col6a2; collagen, type VI, alpha 2	CGCCGCCGCCCGGGCCCCGCAGTCGAGGGTC GTGAGCCCACCCCGTCCATGGTGCTAAGCGG GCCCGGGTCCCACACGGCCAGCACCGCTGCT CACTCGGACGACGCCCTGGGCCTGCACCTCT CCAGCTCCTCCCACGGGGTCCCCGTAGCCCC GGCCCCCGCCCAGCCCCAGGTCTCCCCAGGC CCTCCGCAGGCTGCCCGGCCTCCCTCCCCCTG CAGCCATCCCAAGGCTCCTGACCTACCTGGC CCCTGAGCTCTGGAGCAAGCCCTGACCCAAT AAAGGCTTTGAACCCAT	12
3UTR-009	RPN1; ribophorin I	GGGGCTAGAGCCCTCTCCGCACAGCGTGGAG ACGGGGCAAGGAGGGGGGTTATTAGGATTG GTGGTTTTGTTTTGCTTTGTTTAAAGCCGTGG GAAAATGGCACAACTTTACCTCTGTGGGAGA TGCAACACTGAGAGCCAAGGGGTGGGAGTT GGGATAATTTTTATATAAAAGAAGTTTTTCC ACTTTGAATTGCTAAAAGTGGCATTTTTCCTA TGTGCAGTCACTCCTCTCATTTCTAAAATAGG GACGTGGCCAGGCACGGTGGCTCATGCCTGT AATCCCAGCACTTTGGGAGGCCGAGGCAGGC GGCTCACGAGGTCAGGAGATCGAGACTATCC TGGCTAACACGGTAAAACCCTGTCTCTACTA AAAGTACAAAAAATTAGCTGGGCGTGGTGGT GGGCACCTGTAGTCCCAGCTACTCGGGAGGC	13

		TGAGGCAGGAGAAAGGCATGAATCCAAGAG GCAGAGCTTGCAGTGAGCTGAGATCACGCCA TTGCACTCCAGCCTGGGCAACAGTGTTAAGA CTCTGTCTCAAATATAAATAAATAAATAAAT AAATAAATAAATAAATAAAAATAAAGCGAG ATGTTGCCCTCAAA	
3UTR-010	LRP1; low density lipoprotein receptor-related protein 1	GGCCCTGCCCCGTCGGACTGCCCCCAGAAAG CCTCCTGCCCCCTGCCAGTGAAGTCCTTCAGT GAGCCCCTCCCCAGCCAGCCCTTCCCTGGCC CCGCCGGATGTATAAATGTAAAAATGAAGGA ATTACATTTTATATGTGAGCGAGCAAGCCGG CAAGCGAGCACAGTATTATTTCTCCATCCCCT CCCTGCCTGCTCCTTGGCACCCCCATGCTGCC TTCAGGGAGACAGGCAGGGAGGGCTTGGGG CTGCACCTCCTACCCTCCCACCAGAACGCAC CCCACTGGGAGAGCTGGTGGTGCAGCCTTCC CCTCCCTGTATAAGACACTTTGCCAAGGCTCT CCCCTCTCGCCCCATCCCTGCTTGCCCGCTCC CACAGCTTCCTGAGGGCTAATTCTGGGAAGG GAGAGTTCTTTGCTGCCCCTGTCTGGAAGAC GTGGCTCTGGGTGAGGTAGGCGGGAAAGGA TGGAGTGTTTTAGTTCTTGGGGGAGGCCACC CCAAACCCCAGCCCCAACTCCAGGGGCACCT ATGAGATGGCCATGCTCAACCCCCCTCCCAG ACAGGCCCTCCCTGTCTCCAGGGCCCCCACC GAGGTTCCCAGGGCTGGAGACTTCCTCTGGT AAACATTCCTCCAGCCTCCCCTCCCCTGGGG ACGCCAAGGAGGTGGGCCACACCCAGGAAG GGAAAGCGGGCAGCCCCGTTTTGGGGACGTG AACGTTTTAATAATTTTTGCTGAATTCCTTTA CAACTAAATAACACAGATATTGTTATAAATA AAATTGT	14
3UTR-011	Nnt1; cardiotrophin-like cytokine factor 1	ATATTAAGGATCAAGCTGTTAGCTAATAATG CCACCTCTGCAGTTTTGGGAACAGGCAAATA AAGTATCAGTATACATGGTGATGTACATCTG TAGCAAAGCTCTTGGAGAAAATGAAGACTGA AGAAAGCAAAGCAAAAACTGTATAGAGAGA TTTTTCAAAAGCAGTAATCCCTCAATTTTAAA AAAGGATTGAAAATTCTAAATGTCTTTCTGT GCATATTTTTTGTGTTAGGAATCAAAAGTATT TTATAAAAGGAGAAAGAACAGCCTCATTTTA GATGTAGTCCTGTTGGATTTTTTATGCCTCCT CAGTAACCAGAAATGTTTTAAAAAACTAAGT GTTTAGGATTTCAAGACAACATTATACATGG CTCTGAAATATCTGACACAATGTAAACATTG CAGGCACCTGCATTTTATGTTTTTTTTTTCAA CAAATGTGACTAATTTGAAACTTTTATGAAC TTCTGAGCTGTCCCCTTGCAATTCAACCGCAG TTTGAATTAATCATATCAAATCAGTTTTAATT TTTTAAATTGTACTTCAGAGTCTATATTTCAA GGGCACATTTTCTCACTACTATTTTAATACAT	15

		TAAAGGACTAAATAATCTTTCAGAGATGCTG GAAACAAATCATTTGCTTTATATGTTTCATTA GAATACCAATGAAACATACAACTTGAAAATT AGTAATAGTATTTTTGAAGATCCCATTTCTAA TTGGAGATCTCTTTAATTTCGATCAACTTATA ATGTGTAGTACTATATTAAGTGCACTTGAGT GGAATTCAACATTTGACTAATAAAATGAGTT CATCATGTTGGCAAGTGATGTGGCAATTATC TCTGGTGACAAAAGAGTAAAATCAAATATTT CTGCCTGTTACAAATATCAAGGAAGACCTGC TACTATGAAATAGATGACATTAATCTGTCTTC ACTGTTTATAATACGGATGGATTTTTTTTCAA ATCAGTGTGTGTTTTGAGGTCTTATGTAATTG ATGACATTTGAGAGAAATGGTGGCTTTTTTT AGCTACCTCTTTGTTCATTTAAGCACCAGTAA AGATCATGTCTTTTTATAGAAGTGTAGATTTT CTTTGTGACTTTGCTATCGTGCCTAAAGCTCT AAATATAGGTGAATGTGTGATGAATACTCAG ATTATTTGTCTCTCTATATAATTAGTTTGGTA CTAAGTTTCTCAAAAAATTATTAACACATGA AAGACAATCTCTAAACCAGAAAAAGAAGTA GTACAAATTTTGTTACTGTAATGCTCGCGTTT AGTGAGTTTAAAACACACAGTATCTTTTGGT TTTATAATCAGTTTCTATTTTGCTGTGCCTGA GATTAAGATCTGTGTATGTGTGTGTGTGTGTG TGTGCGTTTGTGTGTTAAAGCAGAAAAGACT TTTTTAAAAGTTTTAAGTGATAAATGCAATTT GTTAATTGATCTTAGATCACTAGTAAACTCA GGGCTGAATTATACCATGTATATTCTATTAG AAGAAAGTAAACACCATCTTTATTCCTGCCC TTTTTCTTCTCTCAAAGTAGTTGTAGTTATAT CTAGAAAGAAGCAATTTTGATTTCTTGAAAA GGTAGTTCCTGCACTCAGTTTAAACTAAAAA TAATCATACTTGGATTTTATTTATTTTTGTCA TAGTAAAAATTTTAATTTATATATATTTTTAT TTAGTATTATCTTATTCTTTGCTATTTGCCAA TCCTTTGTCATCAATTGTGTTAAATGAATTGA AAATTCATGCCCTGTTCATTTTATTTTACTTT ATTGGTTAGGATATTTAAAGGATTTTTGTATA TATAATTTCTTAAATTAATATTCCAAAAGGTT AGTGGACTTAGATTATAAATTATGGCAAAAA TCTAAAAACAACAAAAATGATTTTTATACAT TCTATTTCATTATTCCTCTTTTTCCAATAAGTC ATACAATTGGTAGATATGACTTATTTTATTTT TGTATTATTCACTATATCTTTATGATATTTAA GTATAAATAATTAAAAAAATTTATTGTACCT TATAGTCTGTCACCAAAAAAAAAAAATTATC TGTAGGTAGTGAAATGCTAATGTTGATTTGT CTTTAAGGGCTTGTTAACTATCCTTTATTTTC TCATTTGTCTTAAATTAGGAGTTTGTGTTTAA ATTACTCATCTAAGCAAAAAATGTATATAAA	

		TCCCATTACTGGGTATATACCCAAAGGATTA TAAATCATGCTGCTATAAAGACACATGCACA CGTATGTTTATTGCAGCACTATTCACAATAGC AAAGACTTGGAACCAACCCAAATGTCCATCA ATGATAGACTTGATTAAGAAAATGTGCACAT ATACACCATGGAATACTATGCAGCCATAAAA AAGGATGAGTTCATGTCCTTTGTAGGGACAT GGATAAAGCTGGAAACCATCATTCTGAGCAA ACTATTGCAAGGACAGAAAACCAAACACTGC ATGTTCTCACTCATAGGTGGGAATTGAACAA TGAGAACACTTGGACACAAGGTGGGGAACA CCACACACCAGGGCCTGTCATGGGGTGGGGG GAGTGGGGAGGGATAGCATTAGGAGATATA CCTAATGTAAATGATGAGTTAATGGGTGCAG CACACCAACATGGCACATGTATACATATGTA GCAAACCTGCACGTTGTGCACATGTACCCTA GAACTTAAAGTATAATTAAAAAAAAAAAGA AAACAGAAGCTATTTATAAAGAAGTTATTTG CTGAAATAAATGTGATCTTTCCCATTAAAAA AATAAAGAAATTTTGGGGTAAAAAAACACA ATATATTGTATTCTTGAAAAATTCTAAGAGA GTGGATGTGAAGTGTTCTCACCACAAAAGTG ATAACTAATTGAGGTAATGCACATATTAATT AGAAAGATTTTGTCATTCCACAATGTATATA TACTTAAAAATATGTTATACACAATAAATAC ATACATTAAAAAATAAGTAAATGTA	
3UTR-012	Col6a1; collagen, type VI, alpha 1	CCCACCCTGCACGCCGGCACCAAACCCTGTC CTCCCACCCCTCCCCACTCATCACTAAACAG AGTAAAATGTGATGCGAATTTTCCCGACCAA CCTGATTCGCTAGATTTTTTTTAAGGAAAAGC TTGGAAAGCCAGGACACAACGCTGCTGCCTG CTTTGTGCAGGGTCCTCCGGGGCTCAGCCCT GAGTTGGCATCACCTGCGCAGGGCCCTCTGG GGCTCAGCCCTGAGCTAGTGTCACCTGCACA GGGCCCTCTGAGGCTCAGCCCTGAGCTGGCG TCACCTGTGCAGGGCCCTCTGGGGCTCAGCC CTGAGCTGGCCTCACCTGGGTTCCCCACCCC GGGCTCTCCTGCCCTGCCCTCCTGCCCGCCCT CCCTCCTGCCTGCGCAGCTCCTTCCCTAGGCA CCTCTGTGCTGCATCCCACCAGCCTGAGCAA GACGCCCTCTCGGGGCCTGTGCCGCACTAGC CTCCCTCTCCTCTGTCCCCATAGCTGGTTTTT CCCACCAATCCTCACCTAACAGTTACTTTACA ATTAAACTCAAAGCAAGCTCTTCTCCTCAGC TTGGGGCAGCCATTGGCCTCTGTCTCGTTTTG GGAAACCAAGGTCAGGAGGCCGTTGCAGAC ATAAATCTCGGCGACTCGGCCCCGTCTCCTG AGGGTCCTGCTGGTGACCGGCCTGGACCTTG GCCCTACAGCCCTGGAGGCCGCTGCTGACCA GCACTGACCCCGACCTCAGAGAGTACTCGCA GGGGCGCTGGCTGCACTCAAGACCCTCGAGA	16

		TTAACGGTGCTAACCCCGTCTGCTCCTCCCTC CCGCAGAGACTGGGGCCTGGACTGGACATGA GAGCCCCTTGGTGCCACAGAGGGCTGTGTCT TACTAGAAACAACGCAAACCTCTCCTTCCTC AGAATAGTGATGTGTTCGACGTTTTATCAAA GGCCCCCTTTCTATGTTCATGTTAGTTTTGCT CCTTCTGTGTTTTTTTCTGAACCATATCCATG TTGCTGACTTTTCCAAATAAAGGTTTTCACTC CTCTC	
3UTR-013	Calr; calreticulin	AGAGGCCTGCCTCCAGGGCTGGACTGAGGCC TGAGCGCTCCTGCCGCAGAGCTGGCCGCGCC AAATAATGTCTCTGTGAGACTCGAGAACTTT CATTTTTTTCCAGGCTGGTTCGGATTTGGGGT GGATTTTGGTTTTGTTCCCCTCCTCCACTCTC CCCCACCCCCTCCCCGCCCTTTTTTTTTTTTT TTTTAAACTGGTATTTTATCTTTGATTCTCCTT CAGCCCTCACCCCTGGTTCTCATCTTTCTTGA TCAACATCTTTTCTTGCCTCTGTCCCCTTCTCT CATCTCTTAGCTCCCCTCCAACCTGGGGGGC AGTGGTGTGGAGAAGCCACAGGCCTGAGATT TCATCTGCTCTCCTTCCTGGAGCCCAGAGGA GGGCAGCAGAAGGGGGTGGTGTCTCCAACCC CCCAGCACTGAGGAAGAACGGGGCTCTTCTC ATTTCACCCCTCCCTTTCTCCCCTGCCCCCAG GACTGGGCCACTTCTGGGTGGGGCAGTGGGT CCCAGATTGGCTCACACTGAGAATGTAAGAA CTACAAACAAAATTTCTATTAAATTAAATTTT GTGTCTCC	17
3UTR-014	Col1a1; collagen, type I, alpha 1	CTCCCTCCATCCCAACCTGGCTCCCTCCCACC CAACCAACTTTCCCCCCAACCCGGAAACAGA CAAGCAACCCAAACTGAACCCCCTCAAAAGC CAAAAAATGGGAGACAATTTCACATGGACTT TGGAAAATATTTTTTTCCTTTGCATTCATCTC TCAAACTTAGTTTTTATCTTTGACCAACCGAA CATGACCAAAAACCAAAAGTGCATTCAACCT TACCAAAAAAAAAAAAAAAAAAAGAATAAA TAAATAACTTTTTAAAAAAGGAAGCTTGGTC CACTTGCTTGAAGACCCATGCGGGGGTAAGT CCCTTTCTGCCCGTTGGGCTTATGAAACCCCA ATGCTGCCCTTTCTGCTCCTTTCTCCACACCC CCCTTGGGGCCTCCCCTCCACTCCTTCCCAAA TCTGTCTCCCCAGAAGACACAGGAAACAATG TATTGTCTGCCCAGCAATCAAAGGCAATGCT CAAACACCCAAGTGGCCCCCACCCTCAGCCC GCTCCTGCCCGCCCAGCACCCCCAGGCCCTG GGGGACCTGGGGTTCTCAGACTGCCAAAGAA GCCTTGCCATCTGGCGCTCCCATGGCTCTTGC AACATCTCCCCTTCGTTTTTGAGGGGGTCATG CCGGGGGAGCCACCAGCCCCTCACTGGGTTC GGAGGAGAGTCAGGAAGGGCCACGACAAAG CAGAAACATCGGATTTGGGGAACGCGTGTCA	18

		ATCCCTTGTGCCGCAGGGCTGGGCGGGAGAG ACTGTTCTGTTCCTTGTGTAACTGTGTTGCTG AAAGACTACCTCGTTCTTGTCTTGATGTGTCA CCGGGGCAACTGCCTGGGGGCGGGGATGGG GGCAGGGTGGAAGCGGCTCCCCATTTTATAC CAAAGGTGCTACATCTATGTGATGGGTGGGG TGGGGAGGGAATCACTGGTGCTATAGAAATT GAGATGCCCCCCCAGGCCAGCAAATGTTCCT TTTTGTTCAAAGTCTATTTTTATTCCTTGATAT TTTTCTTTTTTTTTTTTTTTTTTTGTGGATGGG GACTTGTGAATTTTTCTAAAGGTGCTATTTAA CATGGGAGGAGAGCGTGTGCGGCTCCAGCCC AGCCCGCTGCTCACTTTCCACCCTCTCTCCAC CTGCCTCTGGCTTCTCAGGCCTCTGCTCTCCG ACCTCTCTCCTCTGAAACCCTCCTCCACAGCT GCAGCCCATCCTCCCGGCTCCCTCCTAGTCTG TCCTGCGTCCTCTGTCCCCGGGTTTCAGAGAC AACTTCCCAAAGCACAAAGCAGTTTTTCCCC CTAGGGGTGGGAGGAAGCAAAAGACTCTGT ACCTATTTTGTATGTGTATAATAATTTGAGAT GTTTTTAATTATTTTGATTGCTGGAATAAAGC ATGTGGAAATGACCCAAACATAATCCGCAGT GGCCTCCTAATTTCCTTCTTTGGAGTTGGGGG AGGGGTAGACATGGGGAAGGGGCTTTGGGG TGATGGGCTTGCCTTCCATTCCTGCCCTTTCC CTCCCCACTATTCTCTTCTAGATCCCTCCATA ACCCCACTCCCCTTTCTCTCACCCTTCTTATA CCGCAAACCTTTCTACTTCCTCTTTCATTTTCT ATTCTTGCAATTTCCTTGCACCTTTTCCAAAT CCTCTTCTCCCCTGCAATACCATACAGGCAAT CCACGTGCACAACACACACACACACTCTTCA CATCTGGGGTTGTCCAAACCTCATACCCACT CCCCTTCAAGCCCATCCACTCTCCACCCCCTG GATGCCCTGCACTTGGTGGCGGTGGGATGCT CATGGATACTGGGAGGGTGAGGGGAGTGGA ACCCGTGAGGAGGACCTGGGGGCCTCTCCTT GAACTGACATGAAGGGTCATCTGGCCTCTGC TCCCTTCTCACCCACGCTGACCTCCTGCCGAA GGAGCAACGCAACAGGAGAGGGGTCTGCTG AGCCTGGCGAGGGTCTGGGAGGGACCAGGA GGAAGGCGTGCTCCCTGCTCGCTGTCCTGGC CCTGGGGGAGTGAGGGAGACAGACACCTGG GAGAGCTGTGGGGAAGGCACTCGCACCGTGC TCTTGGGAAGGAAGGAGACCTGGCCCTGCTC ACCACGGACTGGGTGCCTCGACCTCCTGAAT CCCCAGAACACAACCCCCCTGGGCTGGGGTG GTCTGGGGAACCATCGTGCCCCCGCCTCCCG CCTACTCCTTTTTAAGCTT	
3UTR-015	Plod1; procollagen-lysine, 2-	TTGGCCAGGCCTGACCCTCTTGGACCTTTCTT CTTTGCCGACAACCACTGCCCAGCAGCCTCT GGGACCTCGGGGTCCCAGGGAACCCAGTCCA	19

	oxoglutarate 5-dioxygenase 1	GCCTCCTGGCTGTTGACTTCCCATTGCTCTTG GAGCCACCAATCAAAGAGATTCAAAGAGATT CCTGCAGGCCAGAGGCGGAACACACCTTTAT GGCTGGGGCTCTCCGTGGTGTTCTGGACCCA GCCCCTGGAGACACCATTCACTTTTACTGCTT TGTAGTGACTCGTGCTCTCCAACCTGTCTTCC TGAAAAACCAAGGCCCCCTTCCCCCACCTCT TCCATGGGGTGAGACTTGAGCAGAACAGGG GCTTCCCCAAGTTGCCCAGAAAGACTGTCTG GGTGAGAAGCCATGGCCAGAGCTTCTCCCAG GCACAGGTGTTGCACCAGGGACTTCTGCTTC AAGTTTTGGGGTAAAGACACCTGGATCAGAC TCCAAGGGCTGCCCTGAGTCTGGGACTTCTG CCTCCATGGCTGGTCATGAGAGCAAACCGTA GTCCCCTGGAGACAGCGACTCCAGAGAACCT CTTGGGAGACAGAAGAGGCATCTGTGCACAG CTCGATCTTCTACTTGCCTGTGGGGAGGGGA GTGACAGGTCCACACACCACACTGGGTCACC CTGTCCTGGATGCCTCTGAAGAGAGGGACAG ACCGTCAGAAACTGGAGAGTTTCTATTAAAG GTCATTTAAACCA	
3UTR-016	Nucb1; nucleobindin 1	TCCTCCGGGACCCCAGCCCTCAGGATTCCTG ATGCTCCAAGGCGACTGATGGGCGCTGGATG AAGTGGCACAGTCAGCTTCCCTGGGGGCTGG TGTCATGTTGGGCTCCTGGGGCGGGGGCACG GCCTGGCATTTCACGCATTGCTGCCACCCCA GGTCCACCTGTCTCCACTTTCACAGCCTCCAA GTCTGTGGCTCTTCCCTTCTGTCCTCCGAGGG GCTTGCCTTCTCTCGTGTCCAGTGAGGTGCTC AGTGATCGGCTTAACTTAGAGAAGCCCGCCC CCTCCCCTTCTCCGTCTGTCCCAAGAGGGTCT GCTCTGAGCCTGCGTTCCTAGGTGGCTCGGC CTCAGCTGCCTGGGTTGTGGCCGCCCTAGCA TCCTGTATGCCCACAGCTACTGGAATCCCCG CTGCTGCTCCGGGCCAAGCTTCTGGTTGATTA ATGAGGGCATGGGGTGGTCCCTCAAGACCTT CCCCTACCTTTTGTGGAACCAGTGATGCCTCA AAGACAGTGTCCCCTCCACAGCTGGGTGCCA GGGGCAGGGGATCCTCAGTATAGCCGGTGAA CCCTGATACCAGGAGCCTGGGCCTCCCTGAA CCCCTGGCTTCCAGCCATCTCATCGCCAGCCT CCTCCTGGACCTCTTGGCCCCCAGCCCCTTCC CCACACAGCCCCAGAAGGGTCCCAGAGCTGA CCCCACTCCAGGACCTAGGCCCAGCCCCTCA GCCTCATCTGGAGCCCCTGAAGACCAGTCCC ACCCACCTTTCTGGCCTCATCTGACACTGCTC CGCATCCTGCTGTGTGTCCTGTTCCATGTTCC GGTTCCATCCAAATACACTTTCTGGAACAAA	20
3UTR-017	α-globin	GCTGGAGCCTCGGTGGCCATGCTTCTTGCCC CTTGGGCCTCCCCCCAGCCCCTCCTCCCCTTC CTGCACCCGTACCCCCGTGGTCTTTGAATAA	21

		AGTCTGAGTGGGCGGC	

[000194] It should be understood that those listed in the previous tables are examples and that any UTR from any gene may be incorporated into the respective first or second flanking region of the primary construct. Furthermore, multiple wild-type UTRs of any known gene may be utilized. It is also within the scope of the present invention to provide artificial UTRs which are not variants of wild type genes. These UTRs or portions thereof may be placed in the same orientation as in the transcript from which they were selected or may be altered in orientation or location. Hence a 5′ or 3′ UTR may be inverted, shortened, lengthened, made chimeric with one or more other 5′ UTRs or 3′ UTRs. As used herein, the term "altered" as it relates to a UTR sequence, means that the UTR has been changed in some way in relation to a reference sequence. For example, a 3′ or 5′ UTR may be altered relative to a wild type or native UTR by the change in orientation or location as taught above or may be altered by the inclusion of additional nucleotides, deletion of nucleotides, swapping or transposition of nucleotides. Any of these changes producing an "altered" UTR (whether 3′ or 5′) comprise a variant UTR.

[000195] In one embodiment, a double, triple or quadruple UTR such as a 5′ or 3′ UTR may be used. As used herein, a "double" UTR is one in which two copies of the same UTR are encoded either in series or substantially in series. For example, a double beta-globin 3′ UTR may be used as described in US Patent publication 20100129877, the contents of which are incorporated herein by reference in its entirety.

[000196] It is also within the scope of the present invention to have patterned UTRs. As used herein "patterned UTRs" are those UTRs which reflect a repeating or alternating pattern, such as ABABAB or AABBAABBAABB or ABCABCABC or variants thereof repeated once, twice, or more than 3 times. In these patterns, each letter, A, B, or C represent a different UTR at the nucleotide level.

[000197] In one embodiment, flanking regions are selected from a family of transcripts whose proteins share a common function, structure, feature of property. For example, polypeptides of interest may belong to a family of proteins which are expressed in a particular cell, tissue or at some time during development. The UTRs from any of these genes may be swapped for any other UTR of the same or different family of proteins to

create a new chimeric primary transcript. As used herein, a "family of proteins" is used in the broadest sense to refer to a group of two or more polypeptides of interest which share at least one function, structure, feature, localization, origin, or expression pattern.

[000198] After optimization (if desired), the primary construct components are reconstituted and transformed into a vector such as, but not limited to, plasmids, viruses, cosmids, and artificial chromosomes. For example, the optimized construct may be reconstituted and transformed into chemically competent *E. coli,* yeast, neurospora, maize, drosophila, etc. where high copy plasmid-like or chromosome structures occur by methods described herein.

[000199] The untranslated region may also include translation enhancer elements (TEE). As a non-limiting example, the TEE may include those described in US Application No. 20090226470, herein incorporated by reference in its entirety, and those known in the art.

Stop Codons

[000200] In one embodiment, the primary constructs of the present invention may include at least two stop codons before the 3' untranslated region (UTR). The stop codon may be selected from TGA, TAA and TAG. In one embodiment, the primary constructs of the present invention include the stop codon TGA and one additional stop codon. In a further embodiment the addition stop codon may be TAA. In another embodiment, the primary constructs of the present invention include three stop codons.

Vector Amplification

[000201] The vector containing the primary construct is then amplified and the plasmid isolated and purified using methods known in the art such as, but not limited to, a maxi prep using the Invitrogen PURELINK™ HiPure Maxiprep Kit (Carlsbad, CA).

Plasmid Linearization

[000202] The plasmid may then be linearized using methods known in the art such as, but not limited to, the use of restriction enzymes and buffers. The linearization reaction may be purified using methods including, for example Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA), and HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC) and Invitrogen's standard

PURELINK™ PCR Kit (Carlsbad, CA). The purification method may be modified depending on the size of the linearization reaction which was conducted. The linearized plasmid is then used to generate cDNA for *in vitro* transcription (IVT) reactions.

cDNA Template Synthesis

[000203] A cDNA template may be synthesized by having a linearized plasmid undergo polymerase chain reaction (PCR). Table 4 is a listing of primers and probes that may be usefully in the PCR reactions of the present invention. It should be understood that the listing is not exhaustive and that primer-probe design for any amplification is within the skill of those in the art. Probes may also contain chemically modified bases to increase base-pairing fidelity to the target molecule and base-pairing strength. Such modifications may include 5-methyl-Cytidine, 2, 6-di-amino-purine, 2′-fluoro, phosphoro-thioate, or locked nucleic acids.

Table 4. Primers and Probes

Primer/ Probe Identifier	Sequence (5′-3′)	Hybridization target	SEQ ID NO.
UFP	TTGGACCCTCGTACAGAAGCTAA TACG	cDNA Template	22
URP	T_{x160}CTTCCTACTCAGGCTTTATTC AAAGACCA	cDNA Template	23
GBA1	CCTTGACCTTCTGGAACTTC	Acid glucocerebrosidase	24
GBA2	CCAAGCACTGAAACGGATAT	Acid glucocerebrosidase	25
LUC1	GATGAAAAGTGCTCCAAGGA	Luciferase	26
LUC2	AACCGTGATGAAAAGGTACC	Luciferase	27
LUC3	TCATGCAGATTGGAAAGGTC	Luciferase	28
GCSF1	CTTCTTGGACTGTCCAGAGG	G-CSF	29
GCSF2	GCAGTCCCTGATACAAGAAC	G-CSF	30
GCSF3	GATTGAAGGTGGCTCGCTAC	G-CSF	31

*UFP is universal forward primer; URP is universal reverse primer.

[000204] In one embodiment, the cDNA may be submitted for sequencing analysis before undergoing transcription.

mRNA Production

[000205] The process of mRNA or mmRNA production may include, but is not limited to, *in vitro* transcription, cDNA template removal and RNA clean-up, and mRNA capping and/or tailing reactions.

In Vitro Transcription

[000206] The cDNA produced in the previous step may be transcribed using an *in vitro* transcription (IVT) system. The system typically comprises a transcription buffer, nucleotide triphosphates (NTPs), an RNase inhibitor and a polymerase. The NTPs may be manufactured in house, may be selected from a supplier, or may be synthesized as described herein. The NTPs may be selected from, but are not limited to, those described herein including natural and unnatural (modified) NTPs. The polymerase may be selected from, but is not limited to, T7 RNA polymerase, T3 RNA polymerase and mutant polymerases such as, but not limited to, polymerases able to incorporate modified nucleic acids.

RNA Polymerases

[000207] Any number of RNA polymerases or variants may be used in the design of the primary constructs of the present invention.

[000208] RNA polymerases may be modified by inserting or deleting amino acids of the RNA polymerase sequence. As a non-limiting example, the RNA polymerase may be modified to exhibit an increased ability to incorporate a 2'-modified nucleotide triphosphate compared to an unmodified RNA polymerase (see International Publication WO2008078180 and U.S. Patent 8,101,385; herein incorporated by reference in their entireties).

[000209] Variants may be obtained by evolving an RNA polymerase, optimizing the RNA polymerase amino acid and/or nucleic acid sequence and/or by using other methods known in the art. As a non-limiting example, T7 RNA polymerase variants may be evolved using the continuous directed evolution system set out by Esvelt *et al.* (Nature (2011) 472(7344):499-503; herein incorporated by reference in its entirety) where clones of T7 RNA polymerase may encode at least one mutation such as, but not limited to, lysine at position 93 substituted for threonine (K93T), I4M, A7T, E63V, V64D, A65E, D66Y, T76N, C125R, S128R, A136T, N165S, G175R, H176L, Y178H, F182L, L196F, G198V, D208Y, E222K, S228A, Q239R, T243N, G259D, M267I, G280C, H300R,

D351A, A354S, E356D, L360P, A383V, Y385C, D388Y, S397R, M401T, N410S, K450R, P451T, G452V, E484A, H523L, H524N, G542V, E565K, K577E, K577M, N601S, S684Y, L699I, K713E, N748D, Q754R, E775K, A827V, D851N or L864F. As another non-limiting example, T7 RNA polymerase variants may encode at least mutation as described in U.S. Pub. Nos. 20100120024 and 20070117112; herein incorporated by reference in their entireties. Variants of RNA polymerase may also include, but are not limited to, substitutional variants, conservative amino acid substitution, insertional variants, deletional variants and/or covalent derivatives.

[000210] In one embodiment, the primary construct may be designed to be recognized by the wild type or variant RNA polymerases. In doing so, the primary construct may be modified to contain sites or regions of sequence changes from the wild type or parent primary construct.

[000211] In one embodiment, the primary construct may be designed to include at least one substitution and/or insertion upstream of an RNA polymerase binding or recognition site, downstream of the RNA polymerase binding or recognition site, upstream of the TATA box sequence, downstream of the TATA box sequence of the primary construct but upstream of the coding region of the primary construct, within the 5'UTR, before the 5'UTR and/or after the 5'UTR.

[000212] In one embodiment, the 5'UTR of the primary construct may be replaced by the insertion of at least one region and/or string of nucleotides of the same base. The region and/or string of nucleotides may include, but is not limited to, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 nucleotides and the nucleotides may be natural and/or unnatural. As a non-limiting example, the group of nucleotides may include 5-8 adenine, cytosine, thymine, a string of any of the other nucleotides disclosed herein and/or combinations thereof.

[000213] In one embodiment, the 5'UTR of the primary construct may be replaced by the insertion of at least two regions and/or strings of nucleotides of two different bases such as, but not limited to, adenine, cytosine, thymine, any of the other nucleotides disclosed herein and/or combinations thereof. For example, the 5'UTR may be replaced by inserting 5-8 adenine bases followed by the insertion of 5-8 cytosine bases. In another

example, the 5'UTR may be replaced by inserting 5-8 cytosine bases followed by the insertion of 5-8 adenine bases.

[000214] In one embodiment, the primary construct may include at least one substitution and/or insertion downstream of the transcription start site which may be recognized by an RNA polymerase. As a non-limiting example, at least one substitution and/or insertion may occur downstream the transcription start site by substituting at least one nucleic acid in the region just downstream of the transcription start site (such as, but not limited to, +1 to +6). Changes to region of nucleotides just downstream of the transcription start site may affect initiation rates, increase apparent nucleotide triphosphate (NTP) reaction constant values, and increase the dissociation of short transcripts from the transcription complex curing initial transcription (Brieba et al, Biochemistry (2002) 41: 5144-5149; herein incorporated by reference in its entirety). The modification, substitution and/or insertion of at least one nucleic acid may cause a silent mutation of the nucleic acid sequence or may cause a mutation in the amino acid sequence.

[000215] In one embodiment, the primary construct may include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12 or at least 13 guanine bases downstream of the transcription start site.

[000216] In one embodiment, the primary construct may include the substitution of at least 1, at least 2, at least 3, at least 4, at least 5 or at least 6 guanine bases in the region just downstream of the transcription start site. As a non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be substituted by at least 1, at least 2, at least 3 or at least 4 adenine nucleotides. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be substituted by at least 1, at least 2, at least 3 or at least 4 cytosine bases. In another non-limiting example, if the nucleotides in the region are GGGAGA the guanine bases may be substituted by at least 1, at least 2, at least 3 or at least 4 thymine, and/or any of the nucleotides described herein.

[000217] In one embodiment, the primary construct may include at least one substitution and/or insertion upstream of the start codon. For the purpose of clarity, one

of skill in the art would appreciate that the start codon is the first codon of the protein coding region whereas the transcription start site is the site where transcription begins. The primary construct may include, but is not limited to, at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7 or at least 8 substitutions and/or insertions of nucleotide bases. The nucleotide bases may be inserted or substituted at 1, at least 1, at least 2, at least 3, at least 4 or at least 5 locations upstream of the start codon. The nucleotides inserted and/or substituted may be the same base (e.g., all A or all C or all T or all G), two different bases (e.g., A and C, A and T, or C and T), three different bases (e.g., A, C and T or A, C and T) or at least four different bases. As a non-limiting example, the guanine base upstream of the coding region in the primary construct may be substituted with adenine, cytosine, thymine, or any of the nucleotides described herein. In another non-limiting example the substitution of guanine bases in the primary construct may be designed so as to leave one guanine base in the region downstream of the transcription start site and before the start codon (see Esvelt *et al.* Nature (2011) 472(7344):499-503; herein incorporated by reference in its entirety). As a non-limiting example, at least 5 nucleotides may be inserted at 1 location downstream of the transcription start site but upstream of the start codon and the at least 5 nucleotides may be the same base type.

cDNA Template Removal and Clean-Up

[000218] The cDNA template may be removed using methods known in the art such as, but not limited to, treatment with Deoxyribonuclease I (DNase I). RNA clean-up may also include a purification method such as, but not limited to, AGENCOURT® CLEANSEQ® system from Beckman Coulter (Danvers, MA), HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC) .

Capping and/or Tailing Reactions

[000219] The primary construct or mmRNA may also undergo capping and/or tailing reactions. A capping reaction may be performed by methods known in the art to add a 5′ cap to the 5′ end of the primary construct. Methods for capping include, but are not limited to, using a Vaccinia Capping enzyme (New England Biolabs, Ipswich, MA).

[000220] A poly-A tailing reaction may be performed by methods known in the art, such as, but not limited to, 2′ O-methyltransferase and by methods as described herein. If the primary construct generated from cDNA does not include a poly-T, it may be beneficial to perform the poly-A-tailing reaction before the primary construct is cleaned.

mRNA Purification

[000221] Primary construct or mmRNA purification may include, but is not limited to, mRNA or mmRNA clean-up, quality assurance and quality control. mRNA or mmRNA clean-up may be performed by methods known in the arts such as, but not limited to, AGENCOURT® beads (Beckman Coulter Genomics, Danvers, MA), poly-T beads, LNA™ oligo-T capture probes (EXIQON® Inc, Vedbaek, Denmark) or HPLC based purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC). The term "purified" when used in relation to a polynucleotide such as a "purified mRNA or mmRNA" refers to one that is separated from at least one contaminant. As used herein, a "contaminant" is any substance which makes another unfit, impure or inferior. Thus, a purified polynucleotide (e.g., DNA and RNA) is present in a form or setting different from that in which it is found in nature, or a form or setting different from that which existed prior to subjecting it to a treatment or purification method.

[000222] A quality assurance and/or quality control check may be conducted using methods such as, but not limited to, gel electrophoresis, UV absorbance, or analytical HPLC.

[000223] In another embodiment, the mRNA or mmRNA may be sequenced by methods including, but not limited to reverse-transcriptase-PCR.

[000224] In one embodiment, the mRNA or mmRNA may be quantified using methods such as, but not limited to, ultraviolet visible spectroscopy (UV/Vis). A non-limiting example of a UV/Vis spectrometer is a NANODROP® spectrometer (ThermoFisher, Waltham, MA). The quantified mRNA or mmRNA may be analyzed in order to determine if the mRNA or mmRNA may be of proper size, check that no degradation of the mRNA or mmRNA has occurred. Degradation of the mRNA and/or mmRNA may be checked by methods such as, but not limited to, agarose gel electrophoresis, HPLC based

purification methods such as, but not limited to, strong anion exchange HPLC, weak anion exchange HPLC, reverse phase HPLC (RP-HPLC), and hydrophobic interaction HPLC (HIC-HPLC), liquid chromatography-mass spectrometry (LCMS), capillary electrophoresis (CE) and capillary gel electrophoresis (CGE).

Signal Sequences

[000225] The primary constructs or mmRNA may also encode additional features which facilitate trafficking of the polypeptides to therapeutically relevant sites. One such feature which aids in protein trafficking is the signal sequence. As used herein, a "signal sequence" or "signal peptide" is a polynucleotide or polypeptide, respectively, which is from about 9 to 200 nucleotides (3-60 amino acids) in length which is incorporated at the 5′ (or N-terminus) of the coding region or polypeptide encoded, respectively. Addition of these sequences result in trafficking of the encoded polypeptide to the endoplasmic reticulum through one or more secretory pathways. Some signal peptides are cleaved from the protein by signal peptidase after the proteins are transported.

[000226] Table 5 is a representative listing of protein signal sequences which may be incorporated for encoding by the polynucleotides, primary constructs or mmRNA of the invention.

Table 5. Signal Sequences

ID	Description	NUCLEOTIDE SEQUENCE (5′-3′)	SEQ ID NO.	ENCODED PEPTIDE	SEQ ID NO.
SS-001	α-1-antitrypsin	ATGATGCCATCCTCAGTCTCATGGGGTATTTTGCTCTTGGCGGGTCTGTGCTGTCTCGTGCCGGTGTCGCTCGCA	32	MMPSSVSWGILLAGLCCLVPVSLA	94
SS-002	G-CSF	ATGGCCGGACCGGCGACTCAGTCGCCCATGAAACTCATGGCCCTGCAGTTGTTGCTTTGGCACTCAGCCCTCTGGACCGTCCAAGAGGCG	33	MAGPATQSPMKLMALQLLLWHSALWTVQEA	95
SS-003	Factor IX	ATGCAGAGAGTGAACATGATTATGGCCGAGTCCCCATCGCTCATCACAATCTGCCTGCTTGGTACCTGCTTTCCGCCGAATGCACTGTCTTTCTGGATCACGAGAATGCGAATAAGATCTTGAACCGACCCAAACGG	34	MQRVNMIMAESPSLITICLLGYLLSAECTVFLDHENANKILNRPKR	96

SS-004	Prolactin	ATGAAAGGATCATTGCTGTTGCTCCTCGTGTCGAACCTTCTGCTTTGCCAGTCCGTAGCCCCC	35	MKGSLLLLLVSNLLLCQSVAP	97
SS-005	Albumin	ATGAAATGGGTGACGTTCATCTCACTGTTGTTTTTGTTCTCGTCCGCCTACTCCAGGGGAGTATTCCGCCGA	36	MKWVTFISLLFLFSSAYSRG VFRR	98
SS-006	HMMSP38	ATGTGGTGGCGGCTCTGGTGGCTGCTCCTGTTGCTCCTCTTGCTGTGGCCCATGGTGTGGGCA	37	MWWRLWWLLLLLLLLPMWA	99
MLS-001	ornithine carbamoyl transferase	TGCTCTTTAACCTCCGCATCCTGTTGAATAACGCTGCGTTCCGAAATGGGCATAACTTCATGGTACGCAACTTCAGATGCGGCCAGCCACTCCAG	38	MLFNLRILLNNAAFRNGHNFMVRNFRCGQPLQ	100
MLS-002	Cytochrome C Oxidase subunit 8A	ATGTCCGTCTTGACACCCCTGCTCTTGAGAGGGCTGACGGGGTCCGCTAGACGCCTGCCGGTACCGCGAGCGAAGATCCACTCCCTG	39	MSVLTPLLLRGLTGSARRLPVPRAKIHSL	101
MLS-003	Cytochrome C Oxidase subunit 8A	ATGAGCGTGCTCACTCCGTTGCTTCTTCGAGGGCTTACGGGATCGGCTCGGAGGTTGCCCGTCCCGAGAGCGAAGATCCATTCGTTG	40	MSVLTPLLLRGLTGSARRLPVPRAKIHSL	102
SS-007	Type III, bacterial	TGACAAAAATAACTTTATCTCCCCAGAATTTTAGAATCCAAAAACAGGAAACCACACTACTAAAAGAAAAATCAACCGAGAAAAATTCTTTAGCAAAAAGTATTCTCGCAGTAAAAATCACTTCATCGAATTAAGGTCAAAATTATCGGAACGTTTTATTTCGCATAAGAACACT	41	MVTKITLSPQNFRIQKQETTLLKEKSTEKNSLAKSILAVKNHFIELRSKLSERFISHKNT	103
SS-008	Viral	ATGCTGAGCTTTGTGGATACCCGCACCCTGCTGCTGCTGGCGGTGACCAGCTGCCTGGCGACCTGCCAG	42	MLSFVDTRTLLLLAVTSCLATCQ	104
SS-009	viral	ATGGGCAGCAGCCAGGCGCCGCGCATGGGCAGCGTGGGCGGCCATGGCCTGATGGCGCTGCTGATGGCGGGCCTGATTCTGCCGGGCATTCTGGCG	43	MGSSQAPRMGSVGGHGLMALLMAGLILPGILA	105
SS-010	Viral	ATGGCGGGCATTTTTTATTTTCTGTTTAGCTTTCTGT	44	MAGIFYFLFSFLFGICD	106

		TTGGCATTTGCGAT			
SS-011	Viral	ATGGAAAACCGCCTGCTGCGCGTGTTTCTGGTGTGGGCGGCGCTGACCATGGATGGCGCGAGCGCG	45	MENRLLRVFLVWAALTMDGASA	107
SS-012	Viral	ATGGCGCGCCAGGGCTGCTTTGGCAGCTATCAGGTGATTAGCCTGTTTACCTTTGCGATTGGCGTGAACCTGTGCCTGGGC	46	MARQGCFGSYQVISLFTFAIGVNLCLG	108
SS-013	*Bacillus*	ATGAGCCGCCTGCCGGTGCTGCTGCTGCTGCAGCTGCTGGTGCGCCCGGGCCTGCAG	47	MSRLPVLLLLQLLVRPGLQ	109
SS-014	*Bacillus*	ATGAAACAGCAGAAACGCCTGTATGCGCGCCTGCTGACCCTGCTGTTTGCGCTGATTTTTCTGCTGCCGCATAGCAGCGCGAGCGCG	48	MKQQKRLYARLLTLLFALIFLLPHSSASA	110
SS-015	Secretion signal	ATGGCGACGCCGCTGCCTCCGCCCTCCCCGCGGCACCTGCGGCTGCTGCGGCTGCTGCTCTCCGCCCTCGTCCTCGGC	49	MATPLPPPSPRHLRLLRLLLSG	111
SS-016	Secretion signal	ATGAAGGCTCCGGGTCGGCTCGTGCTCATCATCCTGTGCTCCGTGGTCTTCTCT	50	MKAPGRLVLIILCSVVFS	112
SS-017	Secretion signal	ATGCTTCAGCTTTGGAAACTTGTTCTCCTGTGCGGCGTGCTCACT	51	MLQLWKLLCGVLT	113
SS-018	Secretion signal	ATGCTTTATCTCCAGGGTTGGAGCATGCCTGCTGTGGCA	52	MLYLQGWSMPAVA	114
SS-019	Secretion signal	ATGGATAACGTGCAGCCGAAAATAAAACATCGCCCCTTCTGCTTCAGTGTGAAAGGCCACGTGAAGATGCTGCGGCTGGATATTATCAACTCACTGGTAACAACAGTATTCATGCTCATCGTATCTGTGTTGGCACTGATACCA	53	MDNVQPKIKHRPFCFSVKGHVKMLRLDIINSLVTTVFMLIVSVLALIP	115
SS-020	Secretion signal	ATGCCCTGCCTAGACCAACAGCTCACTGTTCATGCCCTACCCTGCCCTGCCCAGCCCTCCTCTCTGGCCTTCTGCCAAGTGGGGTTCTTAACAGCA	54	MPCLDQQLTVHALPCPAQPSSLAFCQVGFLTA	116
SS-021	Secretion signal	ATGAAAACCTTGTTCAATCCAGCCCCTGCCATTGCTGACCTGGATCCCCAGTTC	55	MKTLFNPAPAIADLDPQFYTLSDV	117

		TACACCCTCTCAGATGTG TTCTGCTGCAATGAAAGT GAGGCTGAGATTTTAACT GGCCTCACGGTGGGCAGC GCTGCAGATGCT		FCCNESEA EILTGLTVG SAADA	
SS-022	Secretion signal	ATGAAGCCTCTCCTTGTT GTGTTTGTCTTTCTTTTCC TTTGGGATCCAGTGCTGG CA	56	MKPLLVVF VFLFLWDP VLA	118
SS-023	Secretion signal	ATGTCCTGTTCCCTAAAG TTTACTTTGATTGTAATTT TTTTTTACTGTTGGCTTTC ATCCAGC	57	MSCSLKFT LIVIFFTCT LSSS	119
SS-024	Secretion signal	ATGGTTCTTACTAAACCT CTTCAAAGAAATGGCAGC ATGATGAGCTTTGAAAAT GTGAAAGAAAAGAGCAG AGAAGGAGGGCCCCATG CACACACACCCGAAGAA GAATTGTGTTTCGTGGTA ACACACTACCCTCAGGTT CAGACCACACTCAACCTG TTTTTCCATATATTCAAG GTTCTTACTCAACCACTTT CCCTTCTGTGGGGT	58	MVLTKPLQ RNGSMMSF ENVKEKSR EGGPHAHT PEEELCFV VTHTPQVQ TTLNLFFHI FKVLTQPL SLLWG	120
SS-025	Secretion signal	ATGGCCACCCCGCCATTC CGGCTGATAAGGAAGAT GTTTTCCTTCAAGGTGAG CAGATGGATGGGGCTTGC CTGCTTCCGGTCCCTGGC GGCATCC	59	MATPPFRLI RKMFSFKV SRWMGLA CFRSLAAS	121
SS-026	Secretion signal	ATGAGCTTTTTCCAACTC CTGATGAAAAGGAAGGA ACTCATTCCCTTGGTGGT GTTCATGACTGTGGCGGC GGGTGGAGCCTCATCT	60	MSFFQLLM KRKELIPLV VFMTVAA GGASS	122
SS-027	Secretion signal	ATGGTCTCAGCTCTGCGG GGAGCACCCCTGATCAGG GTGCACTCAAGCCCTGTT TCTTCTCCTTCTGTGAGTG GACCACGGAGGCTGGTG AGCTGCCTGTCATCCCAA AGCTCAGCTCTGAGC	61	MVSALRG APLIRVHSS PVSSPSVSG PAALVSCL SSQSSALS	123
SS-028	Secretion signal	ATGATGGGGTCCCCAGTG AGTCATCTGCTGGCCGGC TTCTGTGTGTGGGTCGTC TTGGGC	62	MMGSPVS HLLAGFCV WVVLG	124
SS-029	Secretion signal	ATGGCAAGCATGGCTGCC GTGCTCACCTGGGCTCTG GCTCTTCTTTCAGCGTTTT	63	MASMAAV LTWALALL SAFSATQA	125

		CGGCCACCCAGGCA			
SS-030	Secretion signal	ATGGTGCTCATGTGGACC AGTGGTGACGCCTTCAAG ACGGCCTACTTCCTGCTG AAGGGTGCCCCTCTGCAG TTCTCCGTGTGCGGCCTG CTGCAGGTGCTGGTGGAC CTGGCCATCCTGGGGCAG GCCTACGCC	64	MVLMWTS GDAFKTAY FLLKGAPL QFSVCGLL QVLVDLAI LGQATA	126
SS-031	Secretion signal	ATGGATTTTGTCGCTGGA GCCATCGGAGGCGTCTGC GGTGTTGCTGTGGGCTAC CCCCTGGACACGGTGAAG GTCAGGATCCAGACGGA GCCAAAGTACACAGGCAT CTGGCACTGCGTCCGGGA TACGTATCACCGAGAGCG CGTGTGGG GCTTCTACCGGGGCCTCT CGCTGCCCGTGTGCACGG TGTCCCTGGTATCTTCC	65	MDFVAGAI GGVCGVA VGYPLDTV KVRIQTEPL YTGIWHCV RDTYHRER VWGFYRG LSLPVCTV SLVSS	127
SS-032	Secretion signal	ATGGAGAAGCCCCTCTTC CCATTAGTGCCTTTGCAT TGGTTTGGCTTTGGCTAC ACAGCACTGGTTGTTTCT GGTGGGATCGTTGGCTAT GTAAAAACAGGCAGCGT GCCGTCCCTGGCTGCAGG GCTGCTCTTCGGCAGTCT AGCC	66	MEKPLFPL VPLHWFGF GYTALVVS GGIVGYVK TGSVPSLA AGLLFGSL A	128
SS-033	Secretion signal	ATGGGTCTGCTCCTTCCC CTGGCACTCTGCATCCTA GTCCTGTGC	67	MGLLLPLA LCILVLC	129
SS-034	Secretion signal	ATGGGGATCCAGACGAG CCCCGTCCTGCTGGCCTC CCTGGGGGTGGGGCTGGT CACTCTGCTCGGCCTGGC TGTGGGC	68	MGIQTSPV LLASLGVG LVTLLGLA VG	130
SS-035	Secretion signal	ATGTCGGACCTGCTACTA CTGGGCCTGATTGGGGGC CTGACTCTCTTACTGCTG CTGACGCTGCTAGCCTTT GCC	69	MSDLLLLG LIGGLTLLL LLTLLAFA	131
SS-036	Secretion signal	ATGGAGACTGTGGTGATT GTTGCCATAGGTGTGCTG GCCACCATGTTTCTGGCT TCGTTTGCAGCCTTGGTG CTGGTTTGCAGGCAG	70	METVVIVA IGVLATIFL ASFAALVL VCRQ	132
SS-037	Secretion signal	ATGCGCGGCTCTGTGGAG TGCACCTGGGGTTGGGGG	71	MAGSVECT WGWGHCA	133

		CACTGTGCCCCCAGCCCC CTGCTCCTTTGGACTCTA CTTCTGTTTGCAGCCCCA TTTGGCCTGCTGGGG		PSPLLLWT LLLFAAPF GLLG	
SS-038	Secretion signal	ATGATGCCGTCCCGTACC AACCTGGCTACTGGAATC CCCAGTAGTAAAGTGAAA TATTCAAGGCTCTCCAGC ACAGACGATGGCTACATT GACCTTCAGTTTAAGAAA ACCCCTCCTAAGATCCCT TATAAGGCCATCGCACTT GCCACTGTGCTGTTTTTG ATTGGCGCC	72	MMPSRTNL ATGIPSSKV KYSRLSST DDGYIDLQ FKKTPPKIP YKAIALAT VLFLIGA	134
SS-039	Secretion signal	ATGGCCCTGCCCCAGATG TGTGACGGGAGCCACTTG GCCTCCACCCTCCGCTAT TGCATGACAGTCAGCGGC ACAGTGGTTCTGGTGGCC GGGACGCTCTGCTTCGCT	73	MALPQMC DGSHLAST LRYCMTVS GTVVLVAG TLCFA	135
SS-041	Vrg-6	TGAAAAAGTGGTTCGTTG CTGCCGGCATCGGCGCTG CCGGACTCATGCTCTCCA GCGCCGCCA	74	MKKWFVA AGIGAGLL MLSSAA	136
SS-042	PhoA	ATGAAACAGAGCACCATT GCGCTGGCGCTGCTGCCG CTGCTGTTTACCCCGGTG ACCAAAGCG	75	MKQSTIAL ALLPLLFTP VTKA	137
SS-043	OmpA	ATGAAAAAAACCGCGATT GCGATTGCGGTGGCGCTG GCGGGCTTTGCGACCGTG GCGCAGGCG	76	MKKTAIAI AVALAGFA TVAQA	138
SS-044	STI	ATGAAAAAACTGATGCTG GCGATTTTTTTTAGCGTG CTGAGCTTTCCGAGCTTT AGCCAGAGC	77	MKKLMLAI FFSVLSFPS FSQS	139
SS-045	STII	ATGAAAAAAAACATTGC GTTTCTGCTGGCGAGCAT GTTTGTGTTTAGCATTGC GACCAACGCGTATGCG	78	MKKNIAFL LASMFVFSI ATNAYA	140
SS-046	Amylase	ATGTTTGCGAAACGCTTT AAAACCAGCCTGCTGCCG CTGTTTGCGGGCTTTCTG CTGCTGTTTCATCTGGTG CTGGCGGGCCCGGCGGCG GCGAGC	79	MFAKRFKT SLLPLFAGF LLLFHLVL AGPAAAS	141
SS-047	Alpha Factor	ATGCGCTTTCCGAGCATT TTTACCGCGGTGCTGTTT GCGGCGAGCAGCGCGCT GGCG	80	MRFPSIFTA VLFAASSA LA	142

SS-048	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCACCGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	81	MRFPSIFTTVLFAASSALA	143
SS-049	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCAGCGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	82	MRFPSIFTSVLFAASSALA	144
SS-050	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCCATGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	83	MRFPSIFTHVLFAASSALA	145
SS-051	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCATTGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	84	MRFPSIFTIVLFAASSALA	146
SS-052	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCTTTGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	85	MRFPSIFTFVLFAASSALA	147
SS-053	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCGAAGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	86	MRFPSIFTEVLFAASSALA	148
SS-054	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCGGCGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	87	MRFPSIFTGVLFAASSALA	149
SS-055	Endoglucanase V	ATGCGTTCCTCCCCCCTCCTCCGCTCCGCCGTTGTGGCCGCCCTGCCGGTGTTGGCCCTTGCC	88	MRSSPLLRSAVVAALPVLALA	150
SS-056	Secretion signal	ATGGGCGCGGCGGCCGTGCGCTGGCACTTGTGCGTGCTGCTGGCCCTGGGCACACGCGGGCGGCTG	89	MGAAAVRWHLCVLLALGTRGRL	151
SS-057	Fungal	ATGAGGAGCTCCCTTGTGCTGTTCTTTGTCTCTGCGTGGACGGCCTTGGCCAG	90	MRSSLVLFFVSAWTALA	152
SS-058	Fibronectin	ATGCTCAGGGGTCCGGGACCCGGGCGGCTGCTGCTGCTAGCAGTCCTGTGCCTGGGGACATCGGTGCGCTGCACCGAAACCGGGAAGAGCAAGAGG	91	MLRGPGPGRLLLLAVLCLGTSVRCTETGKSKR	153
SS-059	Fibronectin	ATGCTTAGGGGTCCGGGGCCCGGGCTGCTGCTGCTGGCCGTCCAGCTGGGGACAGCGGTGCCCTCCACG	92	MLRGPGPGLLLLAVQCLGTAVPSTGA	154

SS-060	Fibronectin	ATGCGCCGGGGGGCCCTGACCGGGCTGCTCCTGGTCCTGTGCCTGAGTGTTGTGCTACGTGCAGCCCCCTCTGCAACAAGCAAGAAGCGCAGG	93	MRRGALTGLLLVLCLSVVLRAAPSATSKKRR	155

[000227] In the table, SS is secretion signal and MLS is mitochondrial leader signal. The primary constructs or mmRNA of the present invention may be designed to encode any of the signal sequences of SEQ ID NOs 94-155, or fragments or variants thereof. These sequences may be included at the beginning of the polypeptide coding region, in the middle or at the terminus or alternatively into a flanking region. Further, any of the polynucleotide primary constructs of the present invention may also comprise one or more of the sequences defined by SEQ ID NOs 32-93. These may be in the first region or either flanking region.

[000228] Additional signal sequences which may be utilized in the present invention include those taught in, for example, databases such as those found at http://www.signalpeptide.de/ or http://proline.bic.nus.edu.sg/spdb/. Those described in US Patents 8,124,379; 7,413,875 and 7,385,034 are also within the scope of the invention and the contents of each are incorporated herein by reference in their entirety.

Target Selection

[000229] According to the present invention, the primary constructs comprise at least a first region of linked nucleosides encoding at least one polypeptide of interest. The polypeptides of interest or "Targets" of the present invention are listed in Table 6. Shown in Table 6, in addition to the name and description of the gene encoding the polypeptide of interest (Target Description) are the ENSEMBL Transcript ID (ENST), the ENSEMBL Protein ID (ENSP) and when available the optimized open reading frame sequence ID (Optimized ORF SEQ ID). For any particular gene there may exist one or more variants or isoforms. Where these exist, they are shown in the table as well. It will be appreciated by those of skill in the art that disclosed in the Table are potential flanking regions. These are encoded in each ENST transcript either to the 5′ (upstream) or 3′ (downstream) of the ORF or coding region. The coding region is definitively and specifically disclosed by teaching the ENSP sequence. Consequently, the sequences

taught flanking that encoding the protein are considered flanking regions. It is also possible to further characterize the 5′ and 3′ flanking regions by utilizing one or more available databases or algorithms. Databases have annotated the features contained in the flanking regions of the ENST transcripts and these are available in the art.

Table 6. Targets

Target No	Target Description	ENST	Trans SEQ ID NO	ENSP	Peptide SEQ ID NO	Optimized ORF SEQ ID
1	15 kDa selenoprotein	331835	156	328729	8922	17688, 26454, 35220, 43986, 52752
2	15 kDa selenoprotein	370554	157	359585	8923	17689, 26455, 35221, 43987, 52753
3	15 kDa selenoprotein	401030	158	383810	8924	17690, 26456, 35222, 43988, 52754
4	1-aminocyclopropane-1-carboxylate synthase homolog (Arabidopsis)(non-functional)-like	378832	159	368109	8925	17691, 26457, 35223, 43989, 52755
5	28S ribosomal protein S21 mitochondrial	581066	160	461930	8926	17692, 26458, 35224, 43990, 52756
6	2-oxoglutarate and iron-dependent oxygenase domain containing 1	336111	161	337196	8927	17693, 26459, 35225, 43991, 52757
7	2-oxoglutarate and iron-dependent oxygenase domain containing 1	540727	162	443875	8928	17694, 26460, 35226, 43992, 52758
8	2-oxoglutarate and iron-dependent oxygenase domain containing 1	566157	163	457258	8929	17695, 26461, 35227, 43993, 52759
9	2-oxoglutarate and iron-dependent oxygenase domain containing 2	228922	164	228922	8930	17696, 26462, 35228, 43994, 52760
10	2-oxoglutarate and iron-dependent oxygenase domain containing 2	397389	165	380544	8931	17697, 26463, 35229, 43995, 52761
11	3-hydroxymethyl-3-methylglutaryl-CoA lyase-like 1	274901	166	274901	8932	17698, 26464, 35230, 43996, 52762
12	3-hydroxymethyl-3-methylglutaryl-CoA lyase-like 1	358072	167	350779	8933	17699, 26465, 35231, 43997, 52763

13	3-hydroxymethyl-3-methylglutaryl-CoA lyase-like 1	398661	168	381654	8934	17700, 26466, 35232, 43998, 52764
14	4-hydroxyphenylpyruvate dioxygenase-like	334815	169	335060	8935	17701, 26467, 35233, 43999, 52765
15	5'-nucleotidase domain containing 1	319550	170	326858	8936	17702, 26468, 35234, 44000, 52766
16	5'-nucleotidase domain containing 1	368618	171	357607	8937	17703, 26469, 35235, 44001, 52767
17	5'-nucleotidase domain containing 1	417846	172	404419	8938	17704, 26470, 35236, 44002, 52768
18	5'-nucleotidase domain containing 1	419791	173	393578	8939	17705, 26471, 35237, 44003, 52769
19	5'-nucleotidase domain containing 2	307076	174	302468	8940	17706, 26472, 35238, 44004, 52770
20	5'-nucleotidase domain containing 2	307092	175	306017	8941	17707, 26473, 35239, 44005, 52771
21	5'-nucleotidase domain containing 2	422318	176	406933	8942	17708, 26474, 35240, 44006, 52772
22	A kinase (PRKA) anchor protein 4	594184	177	472101	8943	17709, 26475, 35241, 44007, 52773
23	abhydrolase domain containing 12B	337334	178	336693	8944	17710, 26476, 35242, 44008, 52774
24	abhydrolase domain containing 12B	353130	179	343951	8945	17711, 26477, 35243, 44009, 52775
25	abhydrolase domain containing 12B	395752	180	379101	8946	17712, 26478, 35244, 44010, 52776
26	abhydrolase domain containing 16B	369916	181	358932	8947	17713, 26479, 35245, 44011, 52777
27	abhydrolase domain containing 4	428304	182	414558	8948	17714, 26480, 35246, 44012, 52778
28	abhydrolase domain containing 8	247706	183	247706	8949	17715, 26481, 35247, 44013, 52779
29	abhydrolase domain containing 8	544788	184	438984	8950	17716, 26482, 35248, 44014,

						52780
30	absent in melanoma 1-like	308182	185	310435	8951	17717, 26483, 35249, 44015, 52781
31	absent in melanoma 1-like	449629	186	416093	8952	17718, 26484, 35250, 44016, 52782
32	absent in melanoma 1-like	527815	187	433931	8953	17719, 26485, 35251, 44017, 52783
33	absent in melanoma 1-like	538018	188	442623	8954	17720, 26486, 35252, 44018, 52784
34	actin gamma 1	598366	189	470446	8955	17721, 26487, 35253, 44019, 52785
35	actin gamma 1	601845	190	469093	8956	17722, 26488, 35254, 44020, 52786
36	acyl-CoA binding domain containing 4	321854	191	314440	8957	17723, 26489, 35255, 44021, 52787
37	acyl-CoA binding domain containing 4	376955	192	366154	8958	17724, 26490, 35256, 44022, 52788
38	acyl-CoA binding domain containing 4	398322	193	381367	8959	17725, 26491, 35257, 44023, 52789
39	acyl-CoA binding domain containing 4	431281	194	405969	8960	17726, 26492, 35258, 44024, 52790
40	acyl-CoA binding domain containing 7	356189	195	367453	8961	17727, 26493, 35259, 44025, 52791
41	acyl-CoA dehydrogenase family, member 10	313698	196	325137	8962	17728, 26494, 35260, 44026, 52792
42	acyl-CoA dehydrogenase family, member 10	392636	197	376411	8963	17729, 26495, 35261, 44027, 52793
43	acyl-CoA dehydrogenase family, member 10	413681	198	405390	8964	17730, 26496, 35262, 44028, 52794
44	acyl-CoA dehydrogenase family, member 10	455480	199	389813	8965	17731, 26497, 35263, 44029, 52795
45	acyl-CoA dehydrogenase family, member 10	514615	200	421527	8966	17732, 26498, 35264, 44030, 52796
46	ADAM metallopeptidase	575175	201	459941	8967	17733, 26499,

	with thrombospondin type 1 motif 10					35265, 44031, 52797
47	adenosine deaminase domain containing 2	268624	202	268624	8968	17734, 26500, 35266, 44032, 52798
48	adenosine deaminase domain containing 2	315906	203	325153	8969	17735, 26501, 35267, 44033, 52799
49	adenosine deaminase, tRNA-specific 2	237283	204	237283	8970	17736, 26502, 35268, 44034, 52800
50	adenosine deaminase, tRNA-specific 2	367593	205	356565	8971	17737, 26503, 35269, 44035, 52801
51	adenosine deaminase, tRNA-specific 2	367594	206	356566	8972	17738, 26504, 35270, 44036, 52802
52	adenosine deaminase, tRNA-specific 3	329478	207	332448	8973	17739, 26505, 35271, 44037, 52803
53	adenosine deaminase, tRNA-specific 3	454697	208	404502	8974	17740, 26506, 35272, 44038, 52804
54	adenosine deaminase-like	389651	209	374302	8975	17741, 26507, 35273, 44039, 52805
55	adenosine deaminase-like	422466	210	398744	8976	17742, 26508, 35274, 44040, 52806
56	adenosine deaminase-like	428046	211	413074	8977	17743, 26509, 35275, 44041, 52807
57	adenosylhomocysteinase-like 2	325006	212	315931	8978	17744, 26510, 35276, 44042, 52808
58	adenosylhomocysteinase-like 2	446212	213	405267	8979	17745, 26511, 35277, 44043, 52809
59	adenosylhomocysteinase-like 2	446544	214	413639	8980	17746, 26512, 35278, 44044, 52810
60	adenosylhomocysteinase-like 2	460109	215	419717	8981	17747, 26513, 35279, 44045, 52811
61	adenosylhomocysteinase-like 2	474594	216	420459	8982	17748, 26514, 35280, 44046, 52812
62	adenosylhomocysteinase-like 2	531335	217	431787	8983	17749, 26515, 35281, 44047, 52813

63	adenosylhomocysteinase-like 2	490911	218	420801	8984	17750, 26516, 35282, 44048, 52814
64	adenylate kinase domain containing 1	285397	219	285397	8985	17751, 26517, 35283, 44049, 52815
65	adenylate kinase domain containing 1	341338	220	344637	8986	17752, 26518, 35284, 44050, 52816
66	adenylate kinase domain containing 1	368948	221	357944	8987	17753, 26519, 35285, 44051, 52817
67	adenylate kinase domain containing 1	424296	222	410186	8988	17754, 26520, 35286, 44052, 52818
68	adenylate kinase domain containing 1	448084	223	407510	8989	17755, 26521, 35287, 44053, 52819
69	ADP-ribosylarginine hydrolase	357003	224	349496	8990	17756, 26522, 35288, 44054, 52820
70	ADP-ribosylarginine hydrolase	465513	225	417430	8991	17757, 26523, 35289, 44055, 52821
71	ADP-ribosylarginine hydrolase	478399	226	420200	8992	17758, 26524, 35290, 44056, 52822
72	ADP-ribosylarginine hydrolase	478927	227	417528	8993	17759, 26525, 35291, 44057, 52823
73	ADP-ribosylarginine hydrolase	481816	228	419703	8994	17760, 26526, 35292, 44058, 52824
74	ADP-ribosylation factor-like 10	310389	229	308496	8995	17761, 26527, 35293, 44059, 52825
75	ADP-ribosylation factor-like 13A	450049	230	398637	8996	17762, 26528, 35294, 44060, 52826
76	ADP-ribosylation factor-like 13A	450457	231	414757	8997	17763, 26529, 35295, 44061, 52827
77	ADP-ribosylation factor-like 16	397498	232	380635	8998	17764, 26530, 35296, 44062, 52828
78	ADP-ribosylation factor-like 5C	269586	233	269586	8999	17765, 26531, 35297, 44063, 52829
79	ADP-ribosylation factor-like 5C	444555	234	387615	9000	17766, 26532, 35298, 44064,

						52830
80	AF4/FMR2 family member 2	595230	235	472279	9001	17767, 26533, 35299, 44065, 52831
81	AF4/FMR2 family member 2	600198	236	469697	9002	17768, 26534, 35300, 44066, 52832
82	AKNA domain containing 1	357393	237	349968	9003	17769, 26535, 35301, 44067, 52833
83	AKNA domain containing 1	369994	238	359011	9004	17770, 26536, 35302, 44068, 52834
84	AKNA domain containing 1	369995	239	359012	9005	17771, 26537, 35303, 44069, 52835
85	AKNA domain containing 1	370001	240	359018	9006	17772, 26538, 35304, 44070, 52836
86	aldo-keto reductase family 1 member B15	457545	241	389289	9007	17773, 26539, 35305, 44071, 52837
87	aldo-keto reductase family 1 member C1 (dihydrodiol dehydrogenase 1; 20-alpha (3-alpha)-hydroxysteroid dehydrogenase)	582412	242	462966	9008	17774, 26540, 35306, 44072, 52838
88	aldo-keto reductase family 1 member C2 (dihydrodiol dehydrogenase 2; bile acid binding protein; 3-alpha hydroxysteroid dehydrogenase type III)	580545	243	464045	9009	17775, 26541, 35307, 44073, 52839
89	aldo-keto reductase family 1 member C3 (3-alpha hydroxysteroid dehydrogenase type II)	583876	244	464178	9010	17776, 26542, 35308, 44074, 52840
90	aldo-keto reductase family 1 member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase type I; dihydrodiol dehydrogenase 4)	579965	245	463709	9011	17777, 26543, 35309, 44075, 52841
91	aldo-keto reductase family 1 member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase type I; dihydrodiol dehydrogenase	583238	246	464270	9012	17778, 26544, 35310, 44076, 52842

	4)					
92	aldo-keto reductase family 1, member B15	423958	247	397009	9013	17779, 26545, 35311, 44077, 52843
93	aldo-keto reductase family 1, member C-like 1	445191	248	394055	9014	17780, 26546, 35312, 44078, 52844
94	aldo-keto reductase family 7-like	420396	249	406430	9015	17781, 26547, 35313, 44079, 52845
95	alpha tubulin acetyltransferase 1	318999	250	324222	9016	17782, 26548, 35314, 44080, 52846
96	alpha tubulin acetyltransferase 1	319027	251	324459	9017	17783, 26549, 35315, 44081, 52847
97	alpha tubulin acetyltransferase 1	329992	252	332374	9018	17784, 26550, 35316, 44082, 52848
98	alpha tubulin acetyltransferase 1	330083	253	327832	9019	17785, 26551, 35317, 44083, 52849
99	alpha tubulin acetyltransferase 1	376478	254	365661	9020	17786, 26552, 35318, 44084, 52850
100	alpha tubulin acetyltransferase 1	376483	255	365666	9021	17787, 26553, 35319, 44085, 52851
101	alpha tubulin acetyltransferase 1	376485	256	365668	9022	17788, 26554, 35320, 44086, 52852
102	alpha tubulin acetyltransferase 1	383582	257	373076	9023	17789, 26555, 35321, 44087, 52853
103	alpha tubulin acetyltransferase 1	383583	258	373077	9024	17790, 26556, 35322, 44088, 52854
104	alpha tubulin acetyltransferase 1	383584	259	373078	9025	17791, 26557, 35323, 44089, 52855
105	alpha tubulin acetyltransferase 1	383585	260	373079	9026	17792, 26558, 35324, 44090, 52856
106	alpha tubulin acetyltransferase 1	400575	261	383419	9027	17793, 26559, 35325, 44091, 52857
107	alpha tubulin acetyltransferase 1	400576	262	383420	9028	17794, 26560, 35326, 44092, 52858
108	alpha tubulin	411724	263	388617	9029	17795, 26561,

	acetyltransferase 1					35327, 44093, 52859
109	alpha tubulin acetyltransferase 1	416435	264	412993	9030	17796, 26562, 35328, 44094, 52860
110	alpha tubulin acetyltransferase 1	416917	265	402998	9031	17797, 26563, 35329, 44095, 52861
111	alpha tubulin acetyltransferase 1	417183	266	393868	9032	17798, 26564, 35330, 44096, 52862
112	alpha tubulin acetyltransferase 1	418248	267	411362	9033	17799, 26565, 35331, 44097, 52863
113	alpha tubulin acetyltransferase 1	420586	268	411050	9034	17800, 26566, 35332, 44098, 52864
114	alpha tubulin acetyltransferase 1	423338	269	415000	9035	17801, 26567, 35333, 44099, 52865
115	alpha tubulin acetyltransferase 1	423654	270	403142	9036	17802, 26568, 35334, 44100, 52866
116	alpha tubulin acetyltransferase 1	424121	271	412198	9037	17803, 26569, 35335, 44101, 52867
117	alpha tubulin acetyltransferase 1	425448	272	391244	9038	17804, 26570, 35336, 44102, 52868
118	alpha tubulin acetyltransferase 1	428764	273	399509	9039	17805, 26571, 35337, 44103, 52869
119	alpha tubulin acetyltransferase 1	430611	274	409296	9040	17806, 26572, 35338, 44104, 52870
120	alpha tubulin acetyltransferase 1	432356	275	416994	9041	17807, 26573, 35339, 44105, 52871
121	alpha tubulin acetyltransferase 1	432643	276	416925	9042	17808, 26574, 35340, 44106, 52872
122	alpha tubulin acetyltransferase 1	442844	277	394914	9043	17809, 26575, 35341, 44107, 52873
123	alpha tubulin acetyltransferase 1	443114	278	405656	9044	17810, 26576, 35342, 44108, 52874
124	alpha tubulin acetyltransferase 1	443391	279	406071	9045	17811, 26577, 35343, 44109, 52875

125	alpha tubulin acetyltransferase 1	445486	280	398422	9046	17812, 26578, 35344, 44110, 52876
126	alpha tubulin acetyltransferase 1	445973	281	415408	9047	17813, 26579, 35345, 44111, 52877
127	alpha tubulin acetyltransferase 1	446100	282	393269	9048	17814, 26580, 35346, 44112, 52878
128	alpha tubulin acetyltransferase 1	448670	283	389129	9049	17815, 26581, 35347, 44113, 52879
129	alpha tubulin acetyltransferase 1	449905	284	399529	9050	17816, 26582, 35348, 44114, 52880
130	alpha tubulin acetyltransferase 1	450003	285	406421	9051	17817, 26583, 35349, 44115, 52881
131	alpha tubulin acetyltransferase 1	450220	286	405036	9052	17818, 26584, 35350, 44116, 52882
132	alpha tubulin acetyltransferase 1	454794	287	409067	9053	17819, 26585, 35351, 44117, 52883
133	alpha tubulin acetyltransferase 1	454987	288	410415	9054	17820, 26586, 35352, 44118, 52884
134	alpha tubulin acetyltransferase 1	456215	289	399452	9055	17821, 26587, 35353, 44119, 52885
135	alpha tubulin acetyltransferase 1	456704	290	394357	9056	17822, 26588, 35354, 44120, 52886
136	alpha tubulin acetyltransferase 1	457161	291	388171	9057	17823, 26589, 35355, 44121, 52887
137	alpha tubulin acetyltransferase 1	457334	292	398374	9058	17824, 26590, 35356, 44122, 52888
138	alpha tubulin acetyltransferase 1	546440	293	449304	9059	17825, 26591, 35357, 44123, 52889
139	alpha tubulin acetyltransferase 1	547124	294	449503	9060	17826, 26592, 35358, 44124, 52890
140	alpha tubulin acetyltransferase 1	550031	295	449729	9061	17827, 26593, 35359, 44125, 52891
141	alpha tubulin acetyltransferase 1	551737	296	448247	9062	17828, 26594, 35360, 44126,

						52892
142	alpha tubulin acetyltransferase 1	553018	297	448905	9063	17829, 26595, 35361, 44127, 52893
143	alpha tubulin acetyltransferase 1	553093	298	449160	9064	17830, 26596, 35362, 44128, 52894
144	Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase-like protein LOC641515	330493	299	446921	9065	17831, 26597, 35363, 44129, 52895
145	Alpha-1,3-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase-like protein LOC641515	549576	300	450079	9066	17832, 26598, 35364, 44130, 52896
146	alpha-kinase 2	361673	301	354991	9067	17833, 26599, 35365, 44131, 52897
147	amidohydrolase domain containing 2	293971	302	293971	9068	17834, 26600, 35366, 44132, 52898
148	amidohydrolase domain containing 2	302956	303	307481	9069	17835, 26601, 35367, 44133, 52899
149	amidohydrolase domain containing 2	413459	304	391596	9070	17836, 26602, 35368, 44134, 52900
150	AMME chromosomal region gene 1-like	272647	305	272647	9071	17837, 26603, 35369, 44135, 52901
151	AMME chromosomal region gene 1-like	393001	306	376726	9072	17838, 26604, 35370, 44136, 52902
152	amyloid beta (A4) precursor protein-binding, family A, member 3	316757	307	315136	9073	17839, 26605, 35371, 44137, 52903
153	angel homolog 1 (Drosophila)	251089	308	251089	9074	17840, 26606, 35372, 44138, 52904
154	angel homolog 2 (Drosophila)	310246	309	309755	9075	17841, 26607, 35373, 44139, 52905
155	angel homolog 2 (Drosophila)	360506	310	353696	9076	17842, 26608, 35374, 44140, 52906
156	angel homolog 2 (Drosophila)	366962	311	355929	9077	17843, 26609, 35375, 44141, 52907
157	angel homolog 2 (Drosophila)	535388	312	438141	9078	17844, 26610, 35376, 44142,

						52908
158	angel homolog 2 (Drosophila)	540642	313	446124	9079	17845, 26611, 35377, 44143, 52909
159	angel homolog 2 (Drosophila)	544555	314	443193	9080	17846, 26612, 35378, 44144, 52910
160	ankyrin repeat and BTB (POZ) domain containing 2	298992	315	298992	9081	17847, 26613, 35379, 44145, 52911
161	ankyrin repeat and BTB (POZ) domain containing 2	435224	316	410157	9082	17848, 26614, 35380, 44146, 52912
162	ankyrin repeat and death domain containing 1A	319580	317	325895	9083	17849, 26615, 35381, 44147, 52913
163	ankyrin repeat and death domain containing 1A	319597	318	326203	9084	17850, 26616, 35382, 44148, 52914
164	ankyrin repeat and death domain containing 1A	357698	319	350329	9085	17851, 26617, 35383, 44149, 52915
165	ankyrin repeat and death domain containing 1A	380230	320	369579	9086	17852, 26618, 35384, 44150, 52916
166	ankyrin repeat and death domain containing 1A	395720	321	379070	9087	17853, 26619, 35385, 44151, 52917
167	ankyrin repeat and death domain containing 1A	395723	322	379073	9088	17854, 26620, 35386, 44152, 52918
168	ankyrin repeat and death domain containing 1A	496660	323	420999	9089	17855, 26621, 35387, 44153, 52919
169	ankyrin repeat and GTPase domain Arf GTPase activating protein 11	444180	324	417034	9090	17856, 26622, 35388, 44154, 52920
170	ankyrin repeat and IBR domain containing 1	265742	325	265742	9091	17857, 26623, 35389, 44155, 52921
171	ankyrin repeat and IBR domain containing 1	442183	326	407002	9092	17858, 26624, 35390, 44156, 52922
172	ankyrin repeat and LEM domain containing 2	337516	327	337651	9093	17859, 26625, 35391, 44157, 52923
173	ankyrin repeat and LEM domain containing 2	357997	328	350686	9094	17860, 26626, 35392, 44158, 52924
174	ankyrin repeat and LEM	539605	329	446268	9095	17861, 26627,

	domain containing 2					35393, 44159, 52925
175	ankyrin repeat and MYND domain containing 1	272972	330	272972	9096	17862, 26628, 35394, 44160, 52926
176	ankyrin repeat and MYND domain containing 1	361678	331	355097	9097	17863, 26629, 35395, 44161, 52927
177	ankyrin repeat and MYND domain containing 1	373320	332	362417	9098	17864, 26630, 35396, 44162, 52928
178	ankyrin repeat and MYND domain containing 1	391987	333	375847	9099	17865, 26631, 35397, 44163, 52929
179	ankyrin repeat and MYND domain containing 1	405523	334	385635	9100	17866, 26632, 35398, 44164, 52930
180	ankyrin repeat and MYND domain containing 1	411765	335	404337	9101	17867, 26633, 35399, 44165, 52931
181	ankyrin repeat and MYND domain containing 1	418708	336	407015	9102	17868, 26634, 35400, 44166, 52932
182	ankyrin repeat and MYND domain containing 1	536462	337	444707	9103	17869, 26635, 35401, 44167, 52933
183	ankyrin repeat and MYND domain containing 1	539830	338	444166	9104	17870, 26636, 35402, 44168, 52934
184	ankyrin repeat and MYND domain containing 2	306999	339	303570	9105	17871, 26637, 35403, 44169, 52935
185	ankyrin repeat and SOCS box containing 10	275838	340	275838	9106	17872, 26638, 35404, 44170, 52936
186	ankyrin repeat and SOCS box containing 10	377867	341	367098	9107	17873, 26639, 35405, 44171, 52937
187	ankyrin repeat and SOCS box containing 10	420175	342	391137	9108	17874, 26640, 35406, 44172, 52938
188	ankyrin repeat and SOCS box containing 10	422024	343	401369	9109	17875, 26641, 35407, 44173, 52939
189	ankyrin repeat and SOCS box containing 10	434669	344	398247	9110	17876, 26642, 35408, 44174, 52940
190	ankyrin repeat and SOCS box containing 12	361287	345	354626	9111	17877, 26643, 35409, 44175, 52941

191	ankyrin repeat and SOCS box containing 12	362002	346	355195	9112	17878, 26644, 35410, 44176, 52942
192	ankyrin repeat and SOCS box containing 12	396130	347	379435	9113	17879, 26645, 35411, 44177, 52943
193	ankyrin repeat and SOCS box containing 14	389601	348	374252	9114	17880, 26646, 35412, 44178, 52944
194	ankyrin repeat and SOCS box containing 14	438870	349	403878	9115	17881, 26647, 35413, 44179, 52945
195	ankyrin repeat and SOCS box containing 14	487349	350	419199	9116	17882, 26648, 35414, 44180, 52946
196	ankyrin repeat and SOCS box containing 15	275699	351	275699	9117	17883, 26649, 35415, 44181, 52947
197	ankyrin repeat and SOCS box containing 15	434204	352	390963	9118	17884, 26650, 35416, 44182, 52948
198	ankyrin repeat and SOCS box containing 15	437535	353	406163	9119	17885, 26651, 35417, 44183, 52949
199	ankyrin repeat and SOCS box containing 15	447789	354	401166	9120	17886, 26652, 35418, 44184, 52950
200	ankyrin repeat and SOCS box containing 15	451215	355	416433	9121	17887, 26653, 35419, 44185, 52951
201	ankyrin repeat and SOCS box containing 15	451558	356	397655	9122	17888, 26654, 35420, 44186, 52952
202	ankyrin repeat and SOCS box containing 15	540573	357	438643	9123	17889, 26655, 35421, 44187, 52953
203	ankyrin repeat and SOCS box containing 15	542545	358	445415	9124	17890, 26656, 35422, 44188, 52954
204	ankyrin repeat and SOCS box containing 16	293414	359	293414	9125	17891, 26657, 35423, 44189, 52955
205	ankyrin repeat and SOCS box containing 17	284142	360	284142	9126	17892, 26658, 35424, 44190, 52956
206	ankyrin repeat and SOCS box containing 18	330842	361	329970	9127	17893, 26659, 35425, 44191, 52957
207	ankyrin repeat and SOCS box containing 18	409749	362	386532	9128	17894, 26660, 35426, 44192,

						52958
208	ankyrin repeat and SOCS box containing 5	296525	363	296525	9129	17895, 26661, 35427, 44193, 52959
209	ankyrin repeat and SOCS box containing 5	505299	364	423232	9130	17896, 26662, 35428, 44194, 52960
210	ankyrin repeat and SOCS box containing 7	332783	365	328327	9131	17897, 26663, 35429, 44195, 52961
211	ankyrin repeat and SOCS box containing 7	343276	366	339819	9132	17898, 26664, 35430, 44196, 52962
212	ankyrin repeat and SOCS box containing 9	380483	367	369850	9133	17899, 26665, 35431, 44197, 52963
213	ankyrin repeat and SOCS box containing 9	380485	368	369852	9134	17900, 26666, 35432, 44198, 52964
214	ankyrin repeat and SOCS box containing 9	380488	369	369855	9135	17901, 26667, 35433, 44199, 52965
215	ankyrin repeat and SOCS box containing 9	546332	370	438943	9136	17902, 26668, 35434, 44200, 52966
216	ankyrin repeat and sterile alpha motif domain containing 3	304283	371	304586	9137	17903, 26669, 35435, 44201, 52967
217	ankyrin repeat and sterile alpha motif domain containing 3	446014	372	406796	9138	17904, 26670, 35436, 44202, 52968
218	ankyrin repeat and sterile alpha motif domain containing 3	450067	373	388270	9139	17905, 26671, 35437, 44203, 52969
219	ankyrin repeat and ubiquitin domain containing 1	383050	374	372522	9140	17906, 26672, 35438, 44204, 52970
220	ankyrin repeat and ubiquitin domain containing 1	446160	375	387907	9141	17907, 26673, 35439, 44205, 52971
221	ankyrin repeat and zinc finger domain containing 1	323348	376	321617	9142	17908, 26674, 35440, 44206, 52972
222	ankyrin repeat and zinc finger domain containing 1	410034	377	386337	9143	17909, 26675, 35441, 44207, 52973
223	ankyrin repeat and zinc finger domain containing 1	436226	378	394652	9144	17910, 26676, 35442, 44208, 52974
224	ankyrin repeat and zinc	447157	379	399667	9145	17911, 26677,

	finger domain containing 1					35443, 44209, 52975
225	ankyrin repeat domain 10	267339	380	267339	9146	17912, 26678, 35444, 44210, 52976
226	ankyrin repeat domain 10	375758	381	364911	9147	17913, 26679, 35445, 44211, 52977
227	ankyrin repeat domain 13 family, member D	308440	382	310874	9148	17914, 26680, 35446, 44212, 52978
228	ankyrin repeat domain 13 family, member D	447274	383	402616	9149	17915, 26681, 35447, 44213, 52979
229	ankyrin repeat domain 13 family, member D	511455	384	427130	9150	17916, 26682, 35448, 44214, 52980
230	ankyrin repeat domain 13 family, member D	514166	385	444404	9151	17917, 26683, 35449, 44215, 52981
231	ankyrin repeat domain 13 family, member D	515828	386	443977	9152	17918, 26684, 35450, 44216, 52982
232	ankyrin repeat domain 13A	261738	387	261738	9153	17919, 26685, 35451, 44217, 52983
233	ankyrin repeat domain 13A	261739	388	261739	9154	17920, 26686, 35452, 44218, 52984
234	ankyrin repeat domain 13B	394859	389	378328	9155	17921, 26687, 35453, 44219, 52985
235	ankyrin repeat domain 16	191063	390	352361	9156	17922, 26688, 35454, 44220, 52986
236	ankyrin repeat domain 16	380092	391	369434	9157	17923, 26689, 35455, 44221, 52987
237	ankyrin repeat domain 16	380094	392	369436	9158	17924, 26690, 35456, 44222, 52988
238	ankyrin repeat domain 18A	313339	393	326555	9159	17925, 26691, 35457, 44223, 52989
239	ankyrin repeat domain 18A	357072	394	349583	9160	17926, 26692, 35458, 44224, 52990
240	ankyrin repeat domain 18A	399703	395	382610	9161	17927, 26693, 35459, 44225, 52991

241	ankyrin repeat domain 18B	290943	396	290943	9162	17928, 26694, 35460, 44226, 52992
242	ankyrin repeat domain 18B	357927	397	350607	9163	17929, 26695, 35461, 44227, 52993
243	ankyrin repeat domain 20 family, member A2	377601	398	366826	9164	17930, 26696, 35462, 44228, 52994
244	ankyrin repeat domain 20 family, member A3	254835	399	254835	9165	17931, 26697, 35463, 44229, 52995
245	ankyrin repeat domain 20 family, member A4	357336	400	349891	9166	17932, 26698, 35464, 44230, 52996
246	ankyrin repeat domain 22	371930	401	360998	9167	17933, 26699, 35465, 44231, 52997
247	ankyrin repeat domain 24	262970	402	262970	9168	17934, 26700, 35466, 44232, 52998
248	ankyrin repeat domain 24	318934	403	321731	9169	17935, 26701, 35467, 44233, 52999
249	ankyrin repeat domain 24	600132	404	471252	9170	17936, 26702, 35468, 44234, 53000
250	ankyrin repeat domain 29	284207	405	284207	9171	17937, 26703, 35469, 44235, 53001
251	ankyrin repeat domain 29	322980	406	323387	9172	17938, 26704, 35470, 44236, 53002
252	ankyrin repeat domain 29	592179	407	468354	9173	17939, 26705, 35471, 44237, 53003
253	ankyrin repeat domain 30B	277669	408	277669	9174	17940, 26706, 35472, 44238, 53004
254	ankyrin repeat domain 30B	320584	409	317892	9175	17941, 26707, 35473, 44239, 53005
255	ankyrin repeat domain 30B	358984	410	351875	9176	17942, 26708, 35474, 44240, 53006
256	ankyrin repeat domain 30B	447268	411	399031	9177	17943, 26709, 35475, 44241, 53007
257	ankyrin repeat domain 31	274361	412	274361	9178	17944, 26710, 35476, 44242,

						53008
258	ankyrin repeat domain 33	340970	413	344690	9179	17945, 26711, 35477, 44243, 53009
259	ankyrin repeat domain 33	538991	414	443722	9180	17946, 26712, 35478, 44244, 53010
260	ankyrin repeat domain 33B	296657	415	296657	9181	17947, 26713, 35479, 44245, 53011
261	ankyrin repeat domain 34A	323397	416	314103	9182	17948, 26714, 35480, 44246, 53012
262	ankyrin repeat domain 34C	421388	417	401089	9183	17949, 26715, 35481, 44247, 53013
263	ankyrin repeat domain 35	355594	418	347802	9184	17950, 26716, 35482, 44248, 53014
264	ankyrin repeat domain 35	453670	419	392211	9185	17951, 26717, 35483, 44249, 53015
265	ankyrin repeat domain 35	544626	420	442671	9186	17952, 26718, 35484, 44250, 53016
266	ankyrin repeat domain 36	289105	421	289105	9187	17953, 26719, 35485, 44251, 53017
267	ankyrin repeat domain 36	357042	422	349546	9188	17954, 26720, 35486, 44252, 53018
268	ankyrin repeat domain 36	393513	423	377149	9189	17955, 26721, 35487, 44253, 53019
269	ankyrin repeat domain 36	420699	424	391950	9190	17956, 26722, 35488, 44254, 53020
270	ankyrin repeat domain 36	455519	425	398703	9191	17957, 26723, 35489, 44255, 53021
271	ankyrin repeat domain 36	461153	426	419530	9192	17958, 26724, 35490, 44256, 53022
272	ankyrin repeat domain 36	461694	427	443316	9193	17959, 26725, 35491, 44257, 53023
273	ankyrin repeat domain 36C	295246	428	295246	9194	17960, 26726, 35492, 44258, 53024
274	ankyrin repeat domain 36C	419039	429	407838	9195	17961, 26727,

						35493, 44259, 53025
275	ankyrin repeat domain 36C	420871	430	415231	9196	17962, 26728, 35494, 44260, 53026
276	ankyrin repeat domain 36C	456556	431	403302	9197	17963, 26729, 35495, 44261, 53027
277	ankyrin repeat domain 39	393537	432	377170	9198	17964, 26730, 35496, 44262, 53028
278	ankyrin repeat domain 40	285243	433	285243	9199	17965, 26731, 35497, 44263, 53029
279	ankyrin repeat domain 42	342658	434	345328	9200	17966, 26732, 35498, 44264, 53030
280	ankyrin repeat domain 42	393389	435	377049	9201	17967, 26733, 35499, 44265, 53031
281	ankyrin repeat domain 42	393392	436	377051	9202	17968, 26734, 35500, 44266, 53032
282	ankyrin repeat domain 42	545672	437	445153	9203	17969, 26735, 35501, 44267, 53033
283	ankyrin repeat domain 43	378693	438	367965	9204	17970, 26736, 35502, 44268, 53034
284	ankyrin repeat domain 44	282272	439	282272	9205	17971, 26737, 35503, 44269, 53035
285	ankyrin repeat domain 44	328737	440	331516	9206	17972, 26738, 35504, 44270, 53036
286	ankyrin repeat domain 44	337207	441	338794	9207	17973, 26739, 35505, 44271, 53037
287	ankyrin repeat domain 44	409153	442	387141	9208	17974, 26740, 35506, 44272, 53038
288	ankyrin repeat domain 44	409919	443	387233	9209	17975, 26741, 35507, 44273, 53039
289	ankyrin repeat domain 44	450567	444	402420	9210	17976, 26742, 35508, 44274, 53040
290	ankyrin repeat domain 44	539527	445	437825	9211	17977, 26743, 35509, 44275, 53041

291	ankyrin repeat domain 45	333279	446	331268	9212	17978, 26744, 35510, 44276, 53042
292	ankyrin repeat domain 5	378380	447	367631	9213	17979, 26745, 35511, 44277, 53043
293	ankyrin repeat domain 5	378392	448	367644	9214	17980, 26746, 35512, 44278, 53044
294	ankyrin repeat domain 50	504087	449	425658	9215	17981, 26747, 35513, 44279, 53045
295	ankyrin repeat domain 50	515641	450	425355	9216	17982, 26748, 35514, 44280, 53046
296	ankyrin repeat domain 52	267116	451	267116	9217	17983, 26749, 35515, 44281, 53047
297	ankyrin repeat domain 52	417002	452	416967	9218	17984, 26750, 35516, 44282, 53048
298	ankyrin repeat domain 53	272421	453	272421	9219	17985, 26751, 35517, 44283, 53049
299	ankyrin repeat domain 53	360589	454	353796	9220	17986, 26752, 35518, 44284, 53050
300	ankyrin repeat domain 55	341048	455	342295	9221	17987, 26753, 35519, 44285, 53051
301	ankyrin repeat domain 55	434982	456	429421	9222	17988, 26754, 35520, 44286, 53052
302	ankyrin repeat domain 55	507283	457	423180	9223	17989, 26755, 35521, 44287, 53053
303	ankyrin repeat domain 56	334306	458	334879	9224	17990, 26756, 35522, 44288, 53054
304	ankyrin repeat domain 57	356454	459	365830	9225	17991, 26757, 35523, 44289, 53055
305	ankyrin repeat domain 58	343905	460	340975	9226	17992, 26758, 35524, 44290, 53056
306	ankyrin repeat domain 60	371167	461	360209	9227	17993, 26759, 35525, 44291, 53057
307	ankyrin repeat domain 60	457363	462	396747	9228	17994, 26760, 35526, 44292,

						53058
308	ankyrin repeat domain 62	314074	463	326572	9229	17995, 26761, 35527, 44293, 53059
309	ankyrin repeat domain 62	418274	464	405628	9230	17996, 26762, 35528, 44294, 53060
310	ankyrin repeat domain 63	434396	465	399547	9231	17997, 26763, 35529, 44295, 53061
311	ankyrin repeat domain 65	537107	466	445688	9232	17998, 26764, 35530, 44296, 53062
312	ankyrin repeat domain 65	427211	467	428419	9233	17999, 26765, 35531, 44297, 53063
313	ankyrin repeat domain 65	520296	468	429035	9234	18000, 26766, 35532, 44298, 53064
314	ankyrin repeat domain 9	286918	469	286918	9235	18001, 26767, 35533, 44299, 53065
315	ankyrin repeat domain 9	557902	470	454080	9236	18002, 26768, 35534, 44300, 53066
316	ankyrin repeat domain 9	559404	471	453417	9237	18003, 26769, 35535, 44301, 53067
317	ankyrin repeat domain 9	559651	472	454100	9238	18004, 26770, 35536, 44302, 53068
318	ankyrin repeat domain 9	560748	473	453650	9239	18005, 26771, 35537, 44303, 53069
319	ankyrin-repeat and fibronectin type III domain containing 1	318698	474	321627	9240	18006, 26772, 35538, 44304, 53070
320	annexin A8-like 1	358140	475	350859	9241	18007, 26773, 35539, 44305, 53071
321	annexin A8-like 1	359178	476	352101	9242	18008, 26774, 35540, 44306, 53072
322	annexin A8-like 1	414655	477	415523	9243	18009, 26775, 35541, 44307, 53073
323	annexin A8-like 1	545298	478	442198	9244	18010, 26776, 35542, 44308, 53074
324	annexin A8-like 2	340243	479	339264	9245	18011, 26777,

						35543, 44309, 53075
325	annexin A8-like 2	374277	480	363395	9246	18012, 26778, 35544, 44310, 53076
326	annexin A8-like 2	449464	481	407079	9247	18013, 26779, 35545, 44311, 53077
327	annexin A8-like 2	538825	482	440742	9248	18014, 26780, 35546, 44312, 53078
328	anoctamin 7-like 1	442385	483	409166	9249	18015, 26781, 35547, 44313, 53079
329	antagonist of mitotic exit network 1 homolog (S. cerevisiae)	281471	484	281471	9250	18016, 26782, 35548, 44314, 53080
330	anterior pharynx defective 1 homolog A (C. elegans)	582205	485	463082	9251	18017, 26783, 35549, 44315, 53081
331	APITD1-CORT readthrough	400900	486	383692	9252	18018, 26784, 35550, 44316, 53082
332	APITD1-CORT readthrough	470413	487	433615	9253	18019, 26785, 35551, 44317, 53083
333	apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3A	570508	488	461288	9254	18020, 26786, 35552, 44318, 53084
334	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D	216099	489	216099	9255	18021, 26787, 35553, 44319, 53085
335	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D	381568	490	370980	9256	18022, 26788, 35554, 44320, 53086
336	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3D	427494	491	388017	9257	18023, 26789, 35555, 44321, 53087
337	apolipoprotein B receptor	328423	492	327669	9258	18024, 26790, 35556, 44322, 53088
338	apolipoprotein B receptor	431282	493	416094	9259	18025, 26791, 35557, 44323, 53089
339	apolipoprotein B receptor	564831	494	457539	9260	18026, 26792, 35558, 44324, 53090
340	apolipoprotein C-IV	592954	495	468236	9261	18027, 26793, 35559, 44325, 53091

341	aquaporin 12B	407834	496	384894	9262	18028, 26794, 35560, 44326, 53092
342	archaelysin family metallopeptidase 1	312371	497	308149	9263	18029, 26795, 35561, 44327, 53093
343	archaelysin family metallopeptidase 2	359783	498	352831	9264	18030, 26796, 35562, 44328, 53094
344	archaelysin family metallopeptidase 2	359904	499	352976	9265	18031, 26797, 35563, 44329, 53095
345	archaelysin family metallopeptidase 2	392720	500	376481	9266	18032, 26798, 35564, 44330, 53096
346	archaelysin family metallopeptidase 2	573646	501	458752	9267	18033, 26799, 35565, 44331, 53097
347	archaelysin family metallopeptidase 2	575682	502	461778	9268	18034, 26800, 35566, 44332, 53098
348	archaelysin family metallopeptidase 2	583572	503	462911	9269	18035, 26801, 35567, 44333, 53099
349	ArfGAP with coiled-coil ankyrin repeat and PH domains 3	354700	504	346733	9270	18036, 26802, 35568, 44334, 53100
350	ArfGAP with coiled-coil, ankyrin repeat and PH domains 3	353662	505	321139	9271	18037, 26803, 35569, 44335, 53101
351	ArfGAP with FG repeats 2	262935	506	262935	9272	18038, 26804, 35570, 44336, 53102
352	ArfGAP with FG repeats 2	300176	507	300176	9273	18039, 26805, 35571, 44337, 53103
353	ArfGAP with GTPase domain, ankyrin repeat and PH domain 10	355232	508	347372	9274	18040, 26806, 35572, 44338, 53104
354	ArfGAP with GTPase domain, ankyrin repeat and PH domain 10	413193	509	407436	9275	18041, 26807, 35573, 44339, 53105
355	ArfGAP with GTPase domain, ankyrin repeat and PH domain 10	452145	510	392206	9276	18042, 26808, 35574, 44340, 53106
356	ArfGAP with GTPase domain, ankyrin repeat and PH domain 4	342551	511	343438	9277	18043, 26809, 35575, 44341, 53107
357	ArfGAP with GTPase domain, ankyrin repeat and	448048	512	392513	9278	18044, 26810, 35576, 44342,

	PH domain 4					53108
358	ArfGAP with GTPase domain, ankyrin repeat and PH domain 5	374094	513	363207	9279	18045, 26811, 35577, 44343, 53109
359	ArfGAP with GTPase domain, ankyrin repeat and PH domain 5	443782	514	402792	9280	18046, 26812, 35578, 44344, 53110
360	ArfGAP with GTPase domain, ankyrin repeat and PH domain 6	374056	515	363168	9281	18047, 26813, 35579, 44345, 53111
361	ArfGAP with GTPase domain, ankyrin repeat and PH domain 6	412531	516	400972	9282	18048, 26814, 35580, 44346, 53112
362	ArfGAP with GTPase domain, ankyrin repeat and PH domain 7	374095	517	363208	9283	18049, 26815, 35581, 44347, 53113
363	ArfGAP with GTPase domain, ankyrin repeat and PH domain 8	311652	518	309985	9284	18050, 26816, 35582, 44348, 53114
364	ArfGAP with GTPase domain, ankyrin repeat and PH domain 8	425119	519	415452	9285	18051, 26817, 35583, 44349, 53115
365	ArfGAP with GTPase domain, ankyrin repeat and PH domain 9	354954	520	347040	9286	18052, 26818, 35584, 44350, 53116
366	ArfGAP with GTPase domain, ankyrin repeat and PH domain 9	432490	521	412127	9287	18053, 26819, 35585, 44351, 53117
367	ArfGAP with GTPase domain, ankyrin repeat and PH domain 9	453919	522	396454	9288	18054, 26820, 35586, 44352, 53118
368	ArfGAP with GTPase domain, ankyrin repeat and PH domain 9	456984	523	403270	9289	18055, 26821, 35587, 44353, 53119
369	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3	239440	524	239440	9290	18056, 26822, 35588, 44354, 53120
370	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3	504448	525	421148	9291	18057, 26823, 35589, 44355, 53121
371	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3	508305	526	421826	9292	18058, 26824, 35590, 44356, 53122
372	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3	513878	527	421468	9293	18059, 26825, 35591, 44357, 53123
373	arginine vasopressin receptor 2	596997	528	469472	9294	18060, 26826, 35592, 44358, 53124
374	arginine vasopressin-	370626	529	359660	9295	18061, 26827,

	induced 1					35593, 44359, 53125
375	arginine/serine-rich coiled-coil 2	331738	530	330188	9296	18062, 26828, 35594, 44360, 53126
376	arginine/serine-rich coiled-coil 2	354654	531	346678	9297	18063, 26829, 35595, 44361, 53127
377	arginine/serine-rich coiled-coil 2	418773	532	398858	9298	18064, 26830, 35596, 44362, 53128
378	ARL17 protein	547659	533	448038	9299	18065, 26831, 35597, 44363, 53129
379	armadillo repeat containing 12	288065	534	288065	9300	18066, 26832, 35598, 44364, 53130
380	armadillo repeat containing 12	373866	535	362973	9301	18067, 26833, 35599, 44365, 53131
381	armadillo repeat containing 12	373869	536	362976	9302	18068, 26834, 35600, 44366, 53132
382	armadillo repeat containing 2	237512	537	237512	9303	18069, 26835, 35601, 44367, 53133
383	armadillo repeat containing 2	368972	538	357968	9304	18070, 26836, 35602, 44368, 53134
384	armadillo repeat containing 2	392644	539	376417	9305	18071, 26837, 35603, 44369, 53135
385	armadillo repeat containing 3	298032	540	298032	9306	18072, 26838, 35604, 44370, 53136
386	armadillo repeat containing 3	376528	541	365711	9307	18073, 26839, 35605, 44371, 53137
387	armadillo repeat containing 3	409049	542	387288	9308	18074, 26840, 35606, 44372, 53138
388	armadillo repeat containing 3	409983	543	386943	9309	18075, 26841, 35607, 44373, 53139
389	armadillo repeat containing 4	239715	544	239715	9310	18076, 26842, 35608, 44374, 53140
390	armadillo repeat containing 4	305242	545	306410	9311	18077, 26843, 35609, 44375, 53141

391	armadillo repeat containing 4	434029	546	398155	9312	18078, 26844, 35610, 44376, 53142
392	armadillo repeat containing 4	537573	547	438427	9313	18079, 26845, 35611, 44377, 53143
393	armadillo repeat containing 4	537576	548	443208	9314	18080, 26846, 35612, 44378, 53144
394	armadillo repeat containing 4	545014	549	441076	9315	18081, 26847, 35613, 44379, 53145
395	armadillo repeat containing 5	268314	550	268314	9316	18082, 26848, 35614, 44380, 53146
396	armadillo repeat containing 5	408912	551	386125	9317	18083, 26849, 35615, 44381, 53147
397	armadillo repeat containing 5	412665	552	400183	9318	18084, 26850, 35616, 44382, 53148
398	armadillo repeat containing 5	457010	553	399561	9319	18085, 26851, 35617, 44383, 53149
399	armadillo repeat containing 5	538189	554	443995	9320	18086, 26852, 35618, 44384, 53150
400	armadillo repeat containing 6	269932	555	269932	9321	18087, 26853, 35619, 44385, 53151
401	armadillo repeat containing 6	379532	556	368847	9322	18088, 26854, 35620, 44386, 53152
402	armadillo repeat containing 6	392335	557	376147	9323	18089, 26855, 35621, 44387, 53153
403	armadillo repeat containing 6	392336	558	376148	9324	18090, 26856, 35622, 44388, 53154
404	armadillo repeat containing 6	535612	559	444156	9325	18091, 26857, 35623, 44389, 53155
405	armadillo repeat containing 6	536098	560	439038	9326	18092, 26858, 35624, 44390, 53156
406	armadillo repeat containing 6	537263	561	441948	9327	18093, 26859, 35625, 44391, 53157
407	armadillo repeat containing 6	538663	562	438369	9328	18094, 26860, 35626, 44392,

						53158
408	armadillo repeat containing 6	540634	563	443719	9329	18095, 26861, 35627, 44393, 53159
409	armadillo repeat containing 6	540707	564	442263	9330	18096, 26862, 35628, 44394, 53160
410	armadillo repeat containing 6	540792	565	439269	9331	18097, 26863, 35629, 44395, 53161
411	armadillo repeat containing 6	541725	566	446209	9332	18098, 26864, 35630, 44396, 53162
412	armadillo repeat containing 6	541898	567	446037	9333	18099, 26865, 35631, 44397, 53163
413	armadillo repeat containing 7	245543	568	245543	9334	18100, 26866, 35632, 44398, 53164
414	armadillo repeat containing 8	358441	569	351221	9335	18101, 26867, 35633, 44399, 53165
415	armadillo repeat containing 8	393058	570	376778	9336	18102, 26868, 35634, 44400, 53166
416	armadillo repeat containing 8	461600	571	418074	9337	18103, 26869, 35635, 44401, 53167
417	armadillo repeat containing 8	466749	572	417699	9338	18104, 26870, 35636, 44402, 53168
418	armadillo repeat containing 8	468560	573	418457	9339	18105, 26871, 35637, 44403, 53169
419	armadillo repeat containing 8	469044	574	419413	9340	18106, 26872, 35638, 44404, 53170
420	armadillo repeat containing 8	471453	575	420440	9341	18107, 26873, 35639, 44405, 53171
421	armadillo repeat containing 8	481646	576	420333	9342	18108, 26874, 35640, 44406, 53172
422	armadillo repeat containing 8	491704	577	417304	9343	18109, 26875, 35641, 44407, 53173
423	armadillo repeat containing 8	538260	578	441592	9344	18110, 26876, 35642, 44408, 53174
424	armadillo repeat containing	539459	579	443861	9345	18111, 26877,

	8					35643, 44409, 53175
425	armadillo repeat containing 9	349938	580	258417	9346	18112, 26878, 35644, 44410, 53176
426	armadillo repeat containing 9	359743	581	352781	9347	18113, 26879, 35645, 44411, 53177
427	armadillo repeat containing 9	440107	582	387391	9348	18114, 26880, 35646, 44412, 53178
428	armadillo repeat containing X-linked 3	598606	583	472666	9349	18115, 26881, 35647, 44413, 53179
429	armadillo repeat containing X-linked 3	601244	584	471433	9350	18116, 26882, 35648, 44414, 53180
430	armadillo repeat containing X-linked 4	600986	585	470552	9351	18117, 26883, 35649, 44415, 53181
431	armadillo repeat containing X-linked 6	593478	586	468835	9352	18118, 26884, 35650, 44416, 53182
432	armadillo repeat containing X-linked 6	595156	587	472946	9353	18119, 26885, 35651, 44417, 53183
433	armadillo repeat containing X-linked 6	597206	588	471050	9354	18120, 26886, 35652, 44418, 53184
434	armadillo repeat containing, X-linked 5	246174	589	246174	9355	18121, 26887, 35653, 44419, 53185
435	armadillo repeat containing, X-linked 5	372742	590	361827	9356	18122, 26888, 35654, 44420, 53186
436	armadillo repeat containing, X-linked 5	536530	591	445851	9357	18123, 26889, 35655, 44421, 53187
437	armadillo repeat containing, X-linked 5	537008	592	439001	9358	18124, 26890, 35656, 44422, 53188
438	armadillo repeat containing, X-linked 5	541409	593	446385	9359	18125, 26891, 35657, 44423, 53189
439	ARP3 actin-related protein 3 homolog C (yeast)	252071	594	252071	9360	18126, 26892, 35658, 44424, 53190
440	ARP3 actin-related protein 3 homolog C (yeast)	477367	595	417997	9361	18127, 26893, 35659, 44425, 53191

441	ARP3 actin-related protein 3 homolog C (yeast)	539352	596	440990	9362	18128, 26894, 35660, 44426, 53192
442	ARPC4-TTLL3 readthrough	397256	597	380427	9363	18129, 26895, 35661, 44427, 53193
443	arrestin domain containing 2	222250	598	222250	9364	18130, 26896, 35662, 44428, 53194
444	arrestin domain containing 2	379656	599	368977	9365	18131, 26897, 35663, 44429, 53195
445	arrestin domain containing 4	268042	600	268042	9366	18132, 26898, 35664, 44430, 53196
446	arrestin domain containing 4	538249	601	443774	9367	18133, 26899, 35665, 44431, 53197
447	arrestin domain containing 5	381781	602	371200	9368	18134, 26900, 35666, 44432, 53198
448	arylacetamide deacetylase-like 3	332530	603	333352	9369	18135, 26901, 35667, 44433, 53199
449	arylacetamide deacetylase-like 3	359318	604	352268	9370	18136, 26902, 35668, 44434, 53200
450	arylsulfatase G	570630	605	459720	9371	18137, 26903, 35669, 44435, 53201
451	asparagine synthetase domain containing 1	260952	606	260952	9372	18138, 26904, 35670, 44436, 53202
452	asparagine synthetase domain containing 1	420250	607	406790	9373	18139, 26905, 35671, 44437, 53203
453	asparagine synthetase domain containing 1	425590	608	398129	9374	18140, 26906, 35672, 44438, 53204
454	asparagine-linked glycosylation 1-like	340333	609	340009	9375	18141, 26907, 35673, 44439, 53205
455	aspartate dehydrogenase domain containing	376916	610	366114	9376	18142, 26908, 35674, 44440, 53206
456	aspartate dehydrogenase domain containing	389208	611	373860	9377	18143, 26909, 35675, 44441, 53207
457	aspartyl aminopeptidase	273075	612	273075	9378	18144, 26910, 35676, 44442,

						53208
458	aspartyl aminopeptidase	337010	613	337776	9379	18145, 26911, 35677, 44443, 53209
459	aspartyl aminopeptidase	535056	614	444067	9380	18146, 26912, 35678, 44444, 53210
460	astacin-like metallo-endopeptidase (M12 family)	342380	615	343674	9381	18147, 26913, 35679, 44445, 53211
461	asteroid homolog 1 (Drosophila)	264992	616	264992	9382	18148, 26914, 35680, 44446, 53212
462	asteroid homolog 1 (Drosophila)	446270	617	396981	9383	18149, 26915, 35681, 44447, 53213
463	asteroid homolog 1 (Drosophila)	504725	618	422851	9384	18150, 26916, 35682, 44448, 53214
464	asteroid homolog 1 (Drosophila)	505545	619	425683	9385	18151, 26917, 35683, 44449, 53215
465	asteroid homolog 1 (Drosophila)	509060	620	427303	9386	18152, 26918, 35684, 44450, 53216
466	asunder, spermatogenesis regulator homolog (Drosphila)	261190	621	261190	9387	18153, 26919, 35685, 44451, 53217
467	asunder, spermatogenesis regulator homolog (Drosphila)	261191	622	261191	9388	18154, 26920, 35686, 44452, 53218
468	asunder, spermatogenesis regulator homolog (Drosphila)	335745	623	336713	9389	18155, 26921, 35687, 44453, 53219
469	asunder, spermatogenesis regulator homolog (Drosphila)	537336	624	443066	9390	18156, 26922, 35688, 44454, 53220
470	asunder, spermatogenesis regulator homolog (Drosphila)	538727	625	448467	9391	18157, 26923, 35689, 44455, 53221
471	asunder, spermatogenesis regulator homolog (Drosphila)	539625	626	443724	9392	18158, 26924, 35690, 44456, 53222
472	asunder, spermatogenesis regulator homolog (Drosphila)	544548	627	446183	9393	18159, 26925, 35691, 44457, 53223
473	AT hook, DNA binding motif, containing 1	247087	628	247087	9394	18160, 26926, 35692, 44458, 53224
474	AT hook, DNA binding	374011	629	363123	9395	18161, 26927,

	motif, containing 1					35693, 44459, 53225
475	AT hook, DNA binding motif, containing 1	407475	630	384021	9396	18162, 26928, 35694, 44460, 53226
476	AT rich interactive domain 3C (BRIGHT-like)	378909	631	368189	9397	18163, 26929, 35695, 44461, 53227
477	ataxin 7-like 1	318724	632	326344	9398	18164, 26930, 35696, 44462, 53228
478	ataxin 7-like 1	388807	633	373459	9399	18165, 26931, 35697, 44463, 53229
479	ataxin 7-like 1	419735	634	410759	9400	18166, 26932, 35698, 44464, 53230
480	ataxin 7-like 1	477775	635	418476	9401	18167, 26933, 35699, 44465, 53231
481	ataxin 7-like 2	369869	636	358885	9402	18168, 26934, 35700, 44466, 53232
482	ataxin 7-like 2	369870	637	358886	9403	18169, 26935, 35701, 44467, 53233
483	ataxin 7-like 2	541125	638	442752	9404	18170, 26936, 35702, 44468, 53234
484	ataxin 7-like 3B	519948	639	430000	9405	18171, 26937, 35703, 44469, 53235
485	ATG2 autophagy related 2 homolog A (S. cerevisiae)	227459	640	227459	9406	18172, 26938, 35704, 44470, 53236
486	ATG2 autophagy related 2 homolog A (S. cerevisiae)	377262	641	366473	9407	18173, 26939, 35705, 44471, 53237
487	ATG2 autophagy related 2 homolog A (S. cerevisiae)	377264	642	366475	9408	18174, 26940, 35706, 44472, 53238
488	ATG2 autophagy related 2 homolog A (S. cerevisiae)	421419	643	410522	9409	18175, 26941, 35707, 44473, 53239
489	ATG2 autophagy related 2 homolog B (S. cerevisiae)	359933	644	353010	9410	18176, 26942, 35708, 44474, 53240
490	ATH1, acid trehalase-like 1 (yeast)	409548	645	387185	9411	18177, 26943, 35709, 44475, 53241

491	ATP binding domain 4	256538	646	256538	9412	18178, 26944, 35710, 44476, 53242
492	ATP binding domain 4	440392	647	406976	9413	18179, 26945, 35711, 44477, 53243
493	ATP citrate lyase	564506	648	455275	9414	18180, 26946, 35712, 44478, 53244
494	ATP1A1 opposite strand	369491	649	358503	9415	18181, 26947, 35713, 44479, 53245
495	ATP1A1 opposite strand	369492	650	358504	9416	18182, 26948, 35714, 44480, 53246
496	ATP5S-like	221943	651	221943	9417	18183, 26949, 35715, 44481, 53247, 61518, 61576
497	ATP5S-like	301183	652	301183	9418	18184, 26950, 35716, 44482, 53248
498	ATP5S-like	417807	653	403910	9419	18185, 26951, 35717, 44483, 53249
499	ATP5S-like	438807	654	397413	9420	18186, 26952, 35718, 44484, 53250
500	ATP5S-like	507129	655	441484	9421	18187, 26953, 35719, 44485, 53251
501	ATP5S-like	592922	656	467205	9422	18188, 26954, 35720, 44486, 53252
502	ATPase Ca++ transporting plasma membrane 3	602058	657	468854	9423	18189, 26955, 35721, 44487, 53253
503	ATPase family, AAA domain containing 2B	238789	658	238789	9424	18190, 26956, 35722, 44488, 53254
504	ATPase family, AAA domain containing 2B	442596	659	400808	9425	18191, 26957, 35723, 44489, 53255
505	ATPase family, AAA domain containing 2B	546030	660	439969	9426	18192, 26958, 35724, 44490, 53256
506	ATPase family, AAA domain containing 3C	378785	661	368062	9427	18193, 26959, 35725, 44491, 53257
507	ATP-binding cassette, sub-	292808	662	292808	9428	18194, 26960,

	family F (GCN20), member 3					35726, 44492, 53258
508	ATP-binding cassette, sub-family F (GCN20), member 3	429586	663	411471	9429	18195, 26961, 35727, 44493, 53259
509	atrophin 1	594779	664	469054	9430	18196, 26962, 35728, 44494, 53260
510	atrophin 1	599184	665	469977	9431	18197, 26963, 35729, 44495, 53261
511	autism susceptibility candidate 2	342771	666	344087	9432	18198, 26964, 35730, 44496, 53262
512	autism susceptibility candidate 2	403018	667	385572	9433	18199, 26965, 35731, 44497, 53263
513	autism susceptibility candidate 2	406775	668	385263	9434	18200, 26966, 35732, 44498, 53264
514	axonemal dynein light chain domain containing 1	359183	669	352107	9435	18201, 26967, 35733, 44499, 53265
515	axonemal dynein light chain domain containing 1	360322	670	353471	9436	18202, 26968, 35734, 44500, 53266
516	axonemal dynein light chain domain containing 1	367618	671	356590	9437	18203, 26969, 35735, 44501, 53267
517	axonemal dynein light chain domain containing 1	457238	672	416712	9438	18204, 26970, 35736, 44502, 53268
518	axonemal dynein light chain domain containing 1	508229	673	422992	9439	18205, 26971, 35737, 44503, 53269
519	axonemal dynein light chain domain containing 1	508285	674	424337	9440	18206, 26972, 35738, 44504, 53270
520	B melanoma antigen family member 5	602027	675	472450	9441	18207, 26973, 35739, 44505, 53271
521	B melanoma antigen family, member 4	540061	676	444145	9442	18208, 26974, 35740, 44506, 53272
522	baculoviral IAP repeat containing 7	395306	677	378717	9443	18209, 26975, 35741, 44507, 53273
523	BAH domain and coiled-coil containing 1	307745	678	303486	9444	18210, 26976, 35742, 44508, 53274

524	basic leucine zipper and W2 domains 2	258761	679	258761	9445	18211, 26977, 35743, 44509, 53275
525	basic leucine zipper and W2 domains 2	415365	680	403481	9446	18212, 26978, 35744, 44510, 53276
526	basic leucine zipper and W2 domains 2	430000	681	416531	9447	18213, 26979, 35745, 44511, 53277
527	basic leucine zipper and W2 domains 2	433922	682	397249	9448	18214, 26980, 35746, 44512, 53278
528	basic leucine zipper and W2 domains 2	438834	683	415924	9449	18215, 26981, 35747, 44513, 53279
529	basic leucine zipper and W2 domains 2	446596	684	412750	9450	18216, 26982, 35748, 44514, 53280
530	basic leucine zipper and W2 domains 2	452975	685	411715	9451	18217, 26983, 35749, 44515, 53281
531	basic transcription factor 3-like 4	313334	686	360664	9452	18218, 26984, 35750, 44516, 53282
532	basic transcription factor 3-like 4	472944	687	436712	9453	18219, 26985, 35751, 44517, 53283
533	BBSome interacting protein 1	436562	688	431936	9454	18220, 26986, 35752, 44518, 53284
534	BBSome interacting protein 1	447005	689	432849	9455	18221, 26987, 35753, 44519, 53285
535	BBSome interacting protein 1	448814	690	436622	9456	18222, 26988, 35754, 44520, 53286
536	BBSome interacting protein 1	423273	691	432274	9457	18223, 26989, 35755, 44521, 53287
537	BBSome interacting protein 1	454061	692	433157	9458	18224, 26990, 35756, 44522, 53288
538	BCDIN3 domain containing	333924	693	335201	9459	18225, 26991, 35757, 44523, 53289
539	B-cell receptor-associated protein 31	596601	694	473146	9460	18226, 26992, 35758, 44524, 53290
540	B-cell receptor-associated protein 31	600824	695	472405	9461	18227, 26993, 35759, 44525,

						53291
541	BCL2-associated athanogene 2	370693	696	359727	9462	18228, 26994, 35760, 44526, 53292
542	BCL2-associated athanogene 2	438730	697	401851	9463	18229, 26995, 35761, 44527, 53293
543	BCL2-associated athanogene 2	545080	698	441795	9464	18230, 26996, 35762, 44528, 53294
544	BEN domain containing 2	380030	699	369369	9465	18231, 26997, 35763, 44529, 53295
545	BEN domain containing 2	380033	700	369372	9466	18232, 26998, 35764, 44530, 53296
546	BEN domain containing 3	369042	701	358038	9467	18233, 26999, 35765, 44531, 53297
547	BEN domain containing 3	429433	702	411268	9468	18234, 27000, 35766, 44532, 53298
548	BEN domain containing 4	411720	703	412495	9469	18235, 27001, 35767, 44533, 53299
549	BEN domain containing 4	502486	704	421169	9470	18236, 27002, 35768, 44534, 53300
550	BEN domain containing 4	504360	705	421160	9471	18237, 27003, 35769, 44535, 53301
551	BEN domain containing 6	322055	706	322773	9472	18238, 27004, 35770, 44536, 53302
552	BEN domain containing 6	370745	707	359781	9473	18239, 27005, 35771, 44537, 53303
553	BEN domain containing 6	370746	708	359782	9474	18240, 27006, 35772, 44538, 53304
554	BEN domain containing 6	370748	709	359784	9475	18241, 27007, 35773, 44539, 53305
555	BEN domain containing 6	370750	710	359786	9476	18242, 27008, 35774, 44540, 53306
556	BEN domain containing 6	545789	711	439320	9477	18243, 27009, 35775, 44541, 53307
557	BEN domain containing 7	341083	712	345773	9478	18244, 27010,

						35776, 44542, 53308
558	BEN domain containing 7	378605	713	367868	9479	18245, 27011, 35777, 44543, 53309
559	BEN domain containing 7	396898	714	380107	9480	18246, 27012, 35778, 44544, 53310
560	BEN domain containing 7	396900	715	380108	9481	18247, 27013, 35779, 44545, 53311
561	BEN domain containing 7	440282	716	401256	9482	18248, 27014, 35780, 44546, 53312
562	beta-gamma crystallin domain containing 3	182096	717	182096	9483	18249, 27015, 35781, 44547, 53313
563	beta-gamma crystallin domain containing 3	389622	718	374273	9484	18250, 27016, 35782, 44548, 53314
564	beta-gamma crystallin domain containing 3	495403	719	418420	9485	18251, 27017, 35783, 44549, 53315
565	biorientation of chromosomes in cell division 1-like	40738	720	40738	9486	18252, 27018, 35784, 44550, 53316, 61519, 61577
566	biorientation of chromosomes in cell division 1-like 2	585477	721	467843	9487	18253, 27019, 35785, 44551, 53317
567	bolA homolog 1 (E. coli)	581429	722	462736	9488	18254, 27020, 35786, 44552, 53318
568	bolA homolog 2B (E. coli)	305321	723	306752	9489	18255, 27021, 35787, 44553, 53319
569	bone morphogenetic protein receptor, type II (serine/threonine kinase)	374574	724	363702	9490	18256, 27022, 35788, 44554, 53320
570	bora, aurora kinase A activator	377815	725	367046	9491	18257, 27023, 35789, 44555, 53321
571	bora, aurora kinase A activator	390667	726	375082	9492	18258, 27024, 35790, 44556, 53322
572	BR serine/threonine kinase 2	308219	727	310697	9493	18259, 27025, 35791, 44557, 53323
573	BR serine/threonine kinase 2	308230	728	310805	9494	18260, 27026, 35792, 44558,

						53324
574	BR serine/threonine kinase 2	382179	729	371614	9495	18261, 27027, 35793, 44559, 53325
575	BR serine/threonine kinase 2	526678	730	433370	9496	18262, 27028, 35794, 44560, 53326
576	BR serine/threonine kinase 2	528841	731	432000	9497	18263, 27029, 35795, 44561, 53327
577	BR serine/threonine kinase 2	531197	732	431152	9498	18264, 27030, 35796, 44562, 53328
578	BR serine/threonine kinase 2	544817	733	445168	9499	18265, 27031, 35797, 44563, 53329
579	brain expressed X-linked 5	594094	734	469862	9500	18266, 27032, 35798, 44564, 53330
580	brain expressed X-linked 5	602137	735	469622	9501	18267, 27033, 35799, 44565, 53331
581	breast cancer anti-estrogen resistance 3	260502	736	260502	9502	18268, 27034, 35800, 44566, 53332
582	breast cancer anti-estrogen resistance 3	370243	737	359263	9503	18269, 27035, 35801, 44567, 53333
583	breast cancer anti-estrogen resistance 3	370244	738	359264	9504	18270, 27036, 35802, 44568, 53334
584	breast cancer anti-estrogen resistance 3	370247	739	359267	9505	18271, 27037, 35803, 44569, 53335
585	breast cancer anti-estrogen resistance 3	539242	740	441343	9506	18272, 27038, 35804, 44570, 53336
586	bromodomain adjacent to zinc finger domain 1B	575505	741	460410	9507	18273, 27039, 35805, 44571, 53337
587	bromodomain containing 9	323510	742	323557	9508	18274, 27040, 35806, 44572, 53338
588	bromodomain containing 9	323547	743	325200	9509	18275, 27041, 35807, 44573, 53339
589	bromodomain containing 9	388890	744	373542	9510	18276, 27042, 35808, 44574, 53340
590	bromodomain containing 9	435709	745	402984	9511	18277, 27043,

						35809, 44575, 53341
591	bromodomain containing 9	467963	746	419765	9512	18278, 27044, 35810, 44576, 53342
592	bromodomain containing 9	483173	747	419845	9513	18279, 27045, 35811, 44577, 53343
593	BRWD1 intronic transcript 2 (non-protein coding)	539811	748	443539	9514	18280, 27046, 35812, 44578, 53344
594	BSD domain containing 1	325745	749	317670	9515	18281, 27047, 35813, 44579, 53345
595	BSD domain containing 1	341071	750	344816	9516	18282, 27048, 35814, 44580, 53346
596	BSD domain containing 1	413080	751	409114	9517	18283, 27049, 35815, 44581, 53347
597	BSD domain containing 1	419121	752	405752	9518	18284, 27050, 35816, 44582, 53348
598	BSD domain containing 1	446293	753	397759	9519	18285, 27051, 35817, 44583, 53349
599	BSD domain containing 1	449308	754	391762	9520	18286, 27052, 35818, 44584, 53350
600	BSD domain containing 1	455895	755	412173	9521	18287, 27053, 35819, 44585, 53351
601	BSD domain containing 1	526031	756	432382	9522	18288, 27054, 35820, 44586, 53352
602	BTB (POZ) domain containing 1	379403	757	368713	9523	18289, 27055, 35821, 44587, 53353
603	BTB (POZ) domain containing 16	260723	758	260723	9524	18290, 27056, 35822, 44588, 53354
604	BTB (POZ) domain containing 16	368994	759	357990	9525	18291, 27057, 35823, 44589, 53355
605	BTB (POZ) domain containing 18	422652	760	394472	9526	18292, 27058, 35824, 44590, 53356
606	BTB (POZ) domain containing 18	436147	761	397020	9527	18293, 27059, 35825, 44591, 53357

607	BTB (POZ) domain containing 18	527995	762	432341	9528	18294, 27060, 35826, 44592, 53358
608	BTB (POZ) domain containing 19	450269	763	395461	9529	18295, 27061, 35827, 44593, 53359
609	BTB (POZ) domain containing 19	453418	764	405193	9530	18296, 27062, 35828, 44594, 53360
610	BTB (POZ) domain containing 3	254977	765	254977	9531	18297, 27063, 35829, 44595, 53361
611	BTB (POZ) domain containing 3	378226	766	367471	9532	18298, 27064, 35830, 44596, 53362
612	BTB (POZ) domain containing 3	399006	767	381971	9533	18299, 27065, 35831, 44597, 53363
613	BTB (POZ) domain containing 3	405977	768	384545	9534	18300, 27066, 35832, 44598, 53364
614	BTB (POZ) domain containing 3	422390	769	397809	9535	18301, 27067, 35833, 44599, 53365
615	BTB (POZ) domain containing 3	450368	770	404268	9536	18302, 27068, 35834, 44600, 53366
616	BUD13 homolog (S. cerevisiae)	260210	771	260210	9537	18303, 27069, 35835, 44601, 53367
617	BUD13 homolog (S. cerevisiae)	375445	772	364594	9538	18304, 27070, 35836, 44602, 53368
618	C15orf37 protein	542003	773	440412	9539	18305, 27071, 35837, 44603, 53369
619	C15orf38-AP3S2 readthrough	398333	774	381377	9540	18306, 27072, 35838, 44604, 53370
620	C19orf29 antisense RNA 1 (non-protein coding)	447295	775	412459	9541	18307, 27073, 35839, 44605, 53371
621	C2 calcium-dependent domain containing 4D	454109	776	389554	9542	18308, 27074, 35840, 44606, 53372
622	C2CD2-like	336702	777	338885	9543	18309, 27075, 35841, 44607, 53373
623	cadherin-related family member 3	343407	778	341510	9544	18310, 27076, 35842, 44608,

						53374
624	cadherin-related family member 3	466045	779	419017	9545	18311, 27077, 35843, 44609, 53375
625	cadherin-related family member 3	541203	780	443733	9546	18312, 27078, 35844, 44610, 53376
626	cadherin-related family member 3	542731	781	439766	9547	18313, 27079, 35845, 44611, 53377
627	calcineurin-like phosphoesterase domain containing 1	381774	782	371193	9548	18314, 27080, 35846, 44612, 53378
628	calcineurin-like phosphoesterase domain containing 1	433677	783	411127	9549	18315, 27081, 35847, 44613, 53379
629	calcitonin-related polypeptide alpha	571711	784	459971	9550	18316, 27082, 35848, 44614, 53380
630	calcium and integrin binding family member 2	258930	785	258930	9551	18317, 27083, 35849, 44615, 53381
631	calcium and integrin binding family member 3	269878	786	269878	9552	18318, 27084, 35850, 44616, 53382
632	calcium and integrin binding family member 3	379859	787	369188	9553	18319, 27085, 35851, 44617, 53383
633	calcium and integrin binding family member 3	541493	788	444490	9554	18320, 27086, 35852, 44618, 53384
634	calcium and integrin binding family member 4	288861	789	288861	9555	18321, 27087, 35853, 44619, 53385
635	calmodulin-like 4	448060	790	400755	9556	18322, 27088, 35854, 44620, 53386
636	calmodulin-like 4	467889	791	419081	9557	18323, 27089, 35855, 44621, 53387
637	calmodulin-like 4	540479	792	438177	9558	18324, 27090, 35856, 44622, 53388
638	calmodulin-like 5	380332	793	369689	9559	18325, 27091, 35857, 44623, 53389
639	calpain 13	295055	794	295055	9560	18326, 27092, 35858, 44624, 53390
640	calpain 13	534090	795	431298	9561	18327, 27093,

						35859, 44625, 53391
641	calpain 14	403897	796	385247	9562	18328, 27094, 35860, 44626, 53392
642	calpain 14	444918	797	398670	9563	18329, 27095, 35861, 44627, 53393
643	calpain 8	366872	798	355837	9564	18330, 27096, 35862, 44628, 53394
644	calpain 8	366873	799	355838	9565	18331, 27097, 35863, 44629, 53395
645	calpain 8	419193	800	401665	9566	18332, 27098, 35864, 44630, 53396
646	cancer susceptibility candidate 1	320267	801	313141	9567	18333, 27099, 35865, 44631, 53397
647	cancer susceptibility candidate 1	354189	802	346126	9568	18334, 27100, 35866, 44632, 53398
648	cancer susceptibility candidate 1	389246	803	373898	9569	18335, 27101, 35867, 44633, 53399
649	cancer susceptibility candidate 1	395987	804	379310	9570	18336, 27102, 35868, 44634, 53400
650	cancer susceptibility candidate 1	395990	805	379313	9571	18337, 27103, 35869, 44635, 53401
651	cancer susceptibility candidate 1	395992	806	379314	9572	18338, 27104, 35870, 44636, 53402
652	cancer susceptibility candidate 1	537577	807	444715	9573	18339, 27105, 35871, 44637, 53403
653	cancer susceptibility candidate 1	554347	808	451232	9574	18340, 27106, 35872, 44638, 53404
654	cancer susceptibility candidate 1	545133	809	437373	9575	18341, 27107, 35873, 44639, 53405
655	cancer/testis antigen 62	449977	810	399356	9576	18342, 27108, 35874, 44640, 53406
656	cancer/testis antigen family 45 member A3	596640	811	471090	9577	18343, 27109, 35875, 44641, 53407

657	cancer/testis antigen family 47, member A12	416816	812	414509	9578	18344, 27110, 35876, 44642, 53408
658	cancer/testis antigen family 47, member A12	419982	813	391318	9579	18345, 27111, 35877, 44643, 53409
659	cannabinoid receptor interacting protein 1	263655	814	263655	9580	18346, 27112, 35878, 44644, 53410
660	cannabinoid receptor interacting protein 1	409559	815	386883	9581	18347, 27113, 35879, 44645, 53411
661	canopy 1 homolog (zebrafish)	321736	816	317439	9582	18348, 27114, 35880, 44646, 53412
662	CAP-GLY domain containing linker protein 2	575893	817	461219	9583	18349, 27115, 35881, 44647, 53413
663	CAP-GLY domain containing linker protein family, member 4	320081	818	327009	9584	18350, 27116, 35882, 44648, 53414
664	CAP-GLY domain containing linker protein family, member 4	379543	819	368859	9585	18351, 27117, 35883, 44649, 53415
665	CAP-GLY domain containing linker protein family, member 4	402240	820	384533	9586	18352, 27118, 35884, 44650, 53416
666	CAP-GLY domain containing linker protein family, member 4	404424	821	385594	9587	18353, 27119, 35885, 44651, 53417
667	CAP-GLY domain containing linker protein family, member 4	449202	822	393354	9588	18354, 27120, 35886, 44652, 53418
668	CAP-GLY domain containing linker protein family, member 4	530644	823	434609	9589	18355, 27121, 35887, 44653, 53419
669	carbohydrate kinase domain containing	309957	824	311984	9590	18356, 27122, 35888, 44654, 53420
670	carbohydrate kinase domain containing	397191	825	380375	9591	18357, 27123, 35889, 44655, 53421
671	carbohydrate kinase domain containing	424185	826	413191	9592	18358, 27124, 35890, 44656, 53422
672	carbohydrate kinase domain containing	439607	827	412002	9593	18359, 27125, 35891, 44657, 53423
673	carbohydrate kinase domain containing	458711	828	412789	9594	18360, 27126, 35892, 44658,

						53424
674	carbonic anhydrase XIII	321764	829	318912	9595	18361, 27127, 35893, 44659, 53425
675	carboxypeptidase A5	583967	830	464290	9596	18362, 27128, 35894, 44660, 53426
676	carboxypeptidase A5	584427	831	461972	9597	18363, 27129, 35895, 44661, 53427
677	carboxypeptidase X (M14 family), member 2	418782	832	395006	9598	18364, 27130, 35896, 44662, 53428
678	carboxypeptidase X (M14 family), member 2	540123	833	440929	9599	18365, 27131, 35897, 44663, 53429
679	carcinoembryonic antigen-related cell adhesion molecule 16	396750	834	379974	9600	18366, 27132, 35898, 44664, 53430
680	carcinoembryonic antigen-related cell adhesion molecule 16	587331	835	466561	9601	18367, 27133, 35899, 44665, 53431
681	carcinoembryonic antigen-related cell adhesion molecule 18	451086	836	415509	9602	18368, 27134, 35900, 44666, 53432
682	carcinoembryonic antigen-related cell adhesion molecule 18	451626	837	402203	9603	18369, 27135, 35901, 44667, 53433
683	casein kinase 2, beta polypeptide	375885	838	365046	9604	18370, 27136, 35902, 44668, 53434
684	caspase recruitment domain family, member 16	375704	839	364856	9605	18371, 27137, 35903, 44669, 53435
685	caspase recruitment domain family, member 16	375706	840	364858	9606	18372, 27138, 35904, 44670, 53436
686	caspase recruitment domain family, member 16	525374	841	433700	9607	18373, 27139, 35905, 44671, 53437
687	caspase recruitment domain family, member 18	530950	842	436691	9608	18374, 27140, 35906, 44672, 53438
688	cat eye syndrome chromosome region candidate 6	399875	843	382764	9609	18375, 27141, 35907, 44673, 53439
689	cat eye syndrome chromosome region, candidate 6	331437	844	329318	9610	18376, 27142, 35908, 44674, 53440
690	CCR4-NOT transcription	572852	845	459928	9611	18377, 27143,

	complex subunit 3					35909, 44675, 53441
691	CCR4-NOT transcription complex subunit 3	575585	846	458908	9612	18378, 27144, 35910, 44676, 53442
692	CCR4-NOT transcription complex subunit 3	597534	847	471389	9613	18379, 27145, 35911, 44677, 53443
693	CCR4-NOT transcription complex subunit 3	598781	848	473141	9614	18380, 27146, 35912, 44678, 53444
694	CCR4-NOT transcription complex subunit 3	599520	849	470121	9615	18381, 27147, 35913, 44679, 53445
695	CCR4-NOT transcription complex subunit 3	599679	850	469789	9616	18382, 27148, 35914, 44680, 53446
696	CCR4-NOT transcription complex subunit 3	601223	851	470678	9617	18383, 27149, 35915, 44681, 53447
697	CD200 molecule	315711	852	312766	9618	18384, 27150, 35916, 44682, 53448
698	CD200 molecule	473539	853	420298	9619	18385, 27151, 35917, 44683, 53449
699	CD4 molecule	594128	854	469397	9620	18386, 27152, 35918, 44684, 53450
700	CD99 molecule-like 2	597984	855	473060	9621	18387, 27153, 35919, 44685, 53451
701	Cdk5 and Abl enzyme substrate 2	279101	856	279101	9622	18388, 27154, 35920, 44686, 53452
702	Cdk5 and Abl enzyme substrate 2	370560	857	359591	9623	18389, 27155, 35921, 44687, 53453
703	Cdk5 and Abl enzyme substrate 2	453274	858	398535	9624	18390, 27156, 35922, 44688, 53454
704	CDKN2A interacting protein N-terminal like	395009	859	378456	9625	18391, 27157, 35923, 44689, 53455
705	CDKN2A interacting protein N-terminal like	458198	860	394183	9626	18392, 27158, 35924, 44690, 53456
706	CDNA FLJ20147 fis, clone COL07954HCG1781466Un characterized protein	451472	861	394135	9627	18393, 27159, 35925, 44691, 53457

707	CDNA FLJ20464 fis, clone KAT06158HCG1777549Uncharacterized protein	504184	862	438213	9628	18394, 27160, 35926, 44692, 53458
708	CDNA FLJ25552 fis, clone JTH02127HBV preS1-transactivated protein 5Sulfiredoxin 1 homolog (S. cerevisiae), isoform CRA_aUncharacterized protein	427916	863	411734	9629	18395, 27161, 35927, 44693, 53459
709	CDNA FLJ26134 fis, clone TMS03713Uncharacterized protein	399242	864	382186	9630	18396, 27162, 35928, 44694, 53460
710	CDNA FLJ26432 fis, clone KDN01418Uncharacterized protein	544076	865	442192	9631	18397, 27163, 35929, 44695, 53461
711	cDNA FLJ34843 fis, clone NT2NE2011119, highly similar to C-TERMINAL BINDING PROTEIN 2	391571	866	375413	9632	18398, 27164, 35930, 44696, 53462
712	CDNA: FLJ21031 fis, clone CAE07336HCG1780521Uncharacterized protein	536061	867	438279	9633	18399, 27165, 35931, 44697, 53463
713	cell division cycle 20 homolog B (S. cerevisiae)	296733	868	296733	9634	18400, 27166, 35932, 44698, 53464
714	cell division cycle 20 homolog B (S. cerevisiae)	322374	869	315720	9635	18401, 27167, 35933, 44699, 53465
715	cell division cycle 20 homolog B (S. cerevisiae)	331730	870	330566	9636	18402, 27168, 35934, 44700, 53466
716	cell division cycle 20 homolog B (S. cerevisiae)	334206	871	335664	9637	18403, 27169, 35935, 44701, 53467
717	cell division cycle 20 homolog B (S. cerevisiae)	381375	872	370781	9638	18404, 27170, 35936, 44702, 53468
718	cell division cycle associated 3	598882	873	469847	9639	18405, 27171, 35937, 44703, 53469
719	cell growth regulator with ring finger domain 1	216420	874	216420	9640	18406, 27172, 35938, 44704, 53470
720	Cell growth-inhibiting protein 7HCG1784586Uncharacterized protein	439873	875	405722	9641	18407, 27173, 35939, 44705, 53471
721	centrosomal protein 135kDa	422247	876	412799	9642	18408, 27174, 35940, 44706,

						53472
722	centrosomal protein 41kDa	580536	877	462047	9643	18409, 27175, 35941, 44707, 53473
723	ceramide synthase 4	561053	878	452910	9644	18410, 27176, 35942, 44708, 53474
724	cerebellar degeneration-related protein 2-like	337231	879	336587	9645	18411, 27177, 35943, 44709, 53475
725	ChaC, cation transport regulator homolog 2 (E. coli)	295304	880	295304	9646	18412, 27178, 35944, 44710, 53476
726	chemokine (C-C motif) ligand 26	576539	881	461652	9647	18413, 27179, 35945, 44711, 53477
727	chibby homolog 3 (Drosophila)	376974	882	366173	9648	18414, 27180, 35946, 44712, 53478
728	chondrosarcoma associated gene 1	370287	883	359310	9649	18415, 27181, 35947, 44713, 53479
729	chondrosarcoma associated gene 1	370291	884	359314	9650	18416, 27182, 35948, 44714, 53480
730	chondrosarcoma associated gene 1	452779	885	396520	9651	18417, 27183, 35949, 44715, 53481
731	Chondrosarcoma-associated gene 2/3 protein	599845	886	471227	9652	18418, 27184, 35950, 44716, 53482
732	chorionic gonadotropin, beta polypeptide 2	359342	887	352295	9653	18419, 27185, 35951, 44717, 53483
733	chorionic gonadotropin, beta polypeptide 2	538959	888	443980	9654	18420, 27186, 35952, 44718, 53484
734	chorionic gonadotropin, beta polypeptide 7	356213	889	348545	9655	18421, 27187, 35953, 44719, 53485
735	chorionic gonadotropin, beta polypeptide 7	377280	890	366493	9656	18422, 27188, 35954, 44720, 53486
736	chromobox homolog 3	456948	891	408672	9657	18423, 27189, 35955, 44721, 53487
737	chromodomain helicase DNA binding protein 1-like	579763	892	463454	9658	18424, 27190, 35956, 44722, 53488
738	chromodomain helicase	582612	893	463123	9659	18425, 27191,

	DNA binding protein 1-like					35957, 44723, 53489
739	chromodomain helicase DNA binding protein 1-like	583055	894	464521	9660	18426, 27192, 35958, 44724, 53490
740	chromodomain helicase DNA binding protein 9	219084	895	219084	9661	18427, 27193, 35959, 44725, 53491
741	chromodomain helicase DNA binding protein 9	398510	896	381522	9662	18428, 27194, 35960, 44726, 53492
742	chromodomain helicase DNA binding protein 9	447540	897	396345	9663	18429, 27195, 35961, 44727, 53493
743	chromodomain helicase DNA binding protein 9	450543	898	388729	9664	18430, 27196, 35962, 44728, 53494
744	chromodomain helicase DNA binding protein 9	566029	899	457466	9665	18431, 27197, 35963, 44729, 53495
745	chromosome 1 open reading frame 100	308105	900	311218	9666	18432, 27198, 35964, 44730, 53496
746	chromosome 1 open reading frame 100	366537	901	355495	9667	18433, 27199, 35965, 44731, 53497
747	chromosome 1 open reading frame 105	367727	902	356700	9668	18434, 27200, 35966, 44732, 53498
748	chromosome 1 open reading frame 106	367342	903	356311	9669	18435, 27201, 35967, 44733, 53499
749	chromosome 1 open reading frame 106	413687	904	392105	9670	18436, 27202, 35968, 44734, 53500
750	chromosome 1 open reading frame 106	451872	905	397255	9671	18437, 27203, 35969, 44735, 53501
751	chromosome 1 open reading frame 106	532631	906	431682	9672	18438, 27204, 35970, 44736, 53502
752	chromosome 1 open reading frame 109	358011	907	350704	9673	18439, 27205, 35971, 44737, 53503
753	chromosome 1 open reading frame 110	367910	908	356886	9674	18440, 27206, 35972, 44738, 53504
754	chromosome 1 open reading frame 110	367911	909	356887	9675	18441, 27207, 35973, 44739, 53505

755	chromosome 1 open reading frame 111	367935	910	356912	9676	18442, 27208, 35974, 44740, 53506
756	chromosome 1 open reading frame 114	367805	911	356779	9677	18443, 27209, 35975, 44741, 53507
757	chromosome 1 open reading frame 114	367806	912	356780	9678	18444, 27210, 35976, 44742, 53508
758	chromosome 1 open reading frame 114	456107	913	411000	9679	18445, 27211, 35977, 44743, 53509
759	chromosome 1 open reading frame 114	545005	914	442297	9680	18446, 27212, 35978, 44744, 53510
760	chromosome 1 open reading frame 115	294889	915	294889	9681	18447, 27213, 35979, 44745, 53511
761	chromosome 1 open reading frame 122	373042	916	362133	9682	18448, 27214, 35980, 44746, 53512
762	chromosome 1 open reading frame 122	373043	917	362134	9683	18449, 27215, 35981, 44747, 53513
763	chromosome 1 open reading frame 122	446260	918	389807	9684	18450, 27216, 35982, 44748, 53514
764	chromosome 1 open reading frame 122	468084	919	434520	9685	18451, 27217, 35983, 44749, 53515
765	chromosome 1 open reading frame 123	294360	920	294360	9686	18452, 27218, 35984, 44750, 53516
766	chromosome 1 open reading frame 123	371480	921	360535	9687	18453, 27219, 35985, 44751, 53517
767	chromosome 1 open reading frame 124	8440	922	8440	9688	18454, 27220, 35986, 44752, 53518, 61520, 61578
768	chromosome 1 open reading frame 124	295050	923	295050	9689	18455, 27221, 35987, 44753, 53519
769	chromosome 1 open reading frame 124	366644	924	355604	9690	18456, 27222, 35988, 44754, 53520
770	chromosome 1 open reading frame 124	391858	925	375731	9691	18457, 27223, 35989, 44755, 53521
771	chromosome 1 open reading	545269	926	438214	9692	18458, 27224,

	frame 124					35990, 44756, 53522
772	chromosome 1 open reading frame 127	377004	927	366203	9693	18459, 27225, 35991, 44757, 53523
773	chromosome 1 open reading frame 127	377008	928	366207	9694	18460, 27226, 35992, 44758, 53524
774	chromosome 1 open reading frame 129	367758	929	356732	9695	18461, 27227, 35993, 44759, 53525
775	chromosome 1 open reading frame 129	367759	930	356733	9696	18462, 27228, 35994, 44760, 53526
776	chromosome 1 open reading frame 129	426136	931	403697	9697	18463, 27229, 35995, 44761, 53527
777	chromosome 1 open reading frame 131	318906	932	321341	9698	18464, 27230, 35996, 44762, 53528
778	chromosome 1 open reading frame 131	366648	933	355608	9699	18465, 27231, 35997, 44763, 53529
779	chromosome 1 open reading frame 131	366649	934	355609	9700	18466, 27232, 35998, 44764, 53530
780	chromosome 1 open reading frame 131	366651	935	355611	9701	18467, 27233, 35999, 44765, 53531
781	chromosome 1 open reading frame 131	451322	936	401677	9702	18468, 27234, 36000, 44766, 53532
782	chromosome 1 open reading frame 132	415882	937	390224	9703	18469, 27235, 36001, 44767, 53533
783	chromosome 1 open reading frame 133	437764	938	393830	9704	18470, 27236, 36002, 44768, 53534
784	chromosome 1 open reading frame 135	374298	939	363416	9705	18471, 27237, 36003, 44769, 53535
785	chromosome 1 open reading frame 135	538789	940	443647	9706	18472, 27238, 36004, 44770, 53536
786	chromosome 1 open reading frame 137	369482	941	358494	9707	18473, 27239, 36005, 44771, 53537
787	chromosome 1 open reading frame 138	369035	942	358031	9708	18474, 27240, 36006, 44772, 53538

788	chromosome 1 open reading frame 141	371003	943	360042	9709	18475, 27241, 36007, 44773, 53539
789	chromosome 1 open reading frame 141	371004	944	360043	9710	18476, 27242, 36008, 44774, 53540
790	chromosome 1 open reading frame 141	371005	945	360044	9711	18477, 27243, 36009, 44775, 53541
791	chromosome 1 open reading frame 141	371006	946	360045	9712	18478, 27244, 36010, 44776, 53542
792	chromosome 1 open reading frame 141	371007	947	360046	9713	18479, 27245, 36011, 44777, 53543
793	chromosome 1 open reading frame 141	448166	948	415519	9714	18480, 27246, 36012, 44778, 53544
794	chromosome 1 open reading frame 141	544837	949	444018	9715	18481, 27247, 36013, 44779, 53545
795	chromosome 1 open reading frame 144	375590	950	364740	9716	18482, 27248, 36014, 44780, 53546
796	chromosome 1 open reading frame 144	401088	951	383866	9717	18483, 27249, 36015, 44781, 53547
797	chromosome 1 open reading frame 144	401089	952	383867	9718	18484, 27250, 36016, 44782, 53548
798	chromosome 1 open reading frame 144	434120	953	391840	9719	18485, 27251, 36017, 44783, 53549
799	chromosome 1 open reading frame 146	370373	954	359399	9720	18486, 27252, 36018, 44784, 53550
800	chromosome 1 open reading frame 146	370375	955	359401	9721	18487, 27253, 36019, 44785, 53551
801	chromosome 1 open reading frame 147	367119	956	356086	9722	18488, 27254, 36020, 44786, 53552
802	chromosome 1 open reading frame 148	366713	957	355674	9723	18489, 27255, 36021, 44787, 53553
803	chromosome 1 open reading frame 150	366488	958	355444	9724	18490, 27256, 36022, 44788, 53554
804	chromosome 1 open reading frame 150	366489	959	355445	9725	18491, 27257, 36023, 44789,

						53555
805	chromosome 1 open reading frame 150	366490	960	355446	9726	18492, 27258, 36024, 44790, 53556
806	chromosome 1 open reading frame 150	366491	961	355447	9727	18493, 27259, 36025, 44791, 53557
807	chromosome 1 open reading frame 150	526896	962	436079	9728	18494, 27260, 36026, 44792, 53558
808	chromosome 1 open reading frame 150	536561	963	446460	9729	18495, 27261, 36027, 44793, 53559
809	chromosome 1 open reading frame 158	288048	964	288048	9730	18496, 27262, 36028, 44794, 53560
810	chromosome 1 open reading frame 158	376210	965	365383	9731	18497, 27263, 36029, 44795, 53561
811	chromosome 1 open reading frame 167	433342	966	414909	9732	18498, 27264, 36030, 44796, 53562
812	chromosome 1 open reading frame 167	435090	967	388259	9733	18499, 27265, 36031, 44797, 53563
813	chromosome 1 open reading frame 168	343433	968	345972	9734	18500, 27266, 36032, 44798, 53564
814	chromosome 1 open reading frame 170	433179	969	414022	9735	18501, 27267, 36033, 44799, 53565
815	chromosome 1 open reading frame 172	320567	970	319179	9736	18502, 27268, 36034, 44800, 53566
816	chromosome 1 open reading frame 172	374109	971	363223	9737	18503, 27269, 36035, 44801, 53567
817	chromosome 1 open reading frame 173	326665	972	322609	9738	18504, 27270, 36036, 44802, 53568
818	chromosome 1 open reading frame 173	420661	973	398581	9739	18505, 27271, 36037, 44803, 53569
819	chromosome 1 open reading frame 174	361605	974	355306	9740	18506, 27272, 36038, 44804, 53570
820	chromosome 1 open reading frame 177	358193	975	350924	9741	18507, 27273, 36039, 44805, 53571
821	chromosome 1 open reading	371273	976	360320	9742	18508, 27274,

	frame 177					36040, 44806, 53572
822	chromosome 1 open reading frame 180	327308	977	317943	9743	18509, 27275, 36041, 44807, 53573
823	chromosome 1 open reading frame 180	370624	978	359658	9744	18510, 27276, 36042, 44808, 53574
824	chromosome 1 open reading frame 189	368525	979	357511	9745	18511, 27277, 36043, 44809, 53575
825	chromosome 1 open reading frame 192	367974	980	356951	9746	18512, 27278, 36044, 44810, 53576
826	chromosome 1 open reading frame 194	369948	981	358964	9747	18513, 27279, 36045, 44811, 53577
827	chromosome 1 open reading frame 194	369949	982	358965	9748	18514, 27280, 36046, 44812, 53578
828	chromosome 1 open reading frame 195	376005	983	365173	9749	18515, 27281, 36047, 44813, 53579
829	chromosome 1 open reading frame 195	424792	984	404472	9750	18516, 27282, 36048, 44814, 53580
830	chromosome 1 open reading frame 196	412667	985	412721	9751	18517, 27283, 36049, 44815, 53581
831	chromosome 1 open reading frame 198	366663	986	355623	9752	18518, 27284, 36050, 44816, 53582
832	chromosome 1 open reading frame 198	470540	987	428172	9753	18519, 27285, 36051, 44817, 53583
833	chromosome 1 open reading frame 198	523410	988	430967	9754	18520, 27286, 36052, 44818, 53584
834	chromosome 1 open reading frame 200	377320	989	366537	9755	18521, 27287, 36053, 44819, 53585
835	chromosome 1 open reading frame 201	3583	990	3583	9756	18522, 27288, 36054, 44820, 53586, 61521, 61579
836	chromosome 1 open reading frame 201	337248	991	337461	9757	18523, 27289, 36055, 44821, 53587
837	chromosome 1 open reading frame 201	374404	992	363525	9758	18524, 27290, 36056, 44822,

						53588
838	chromosome 1 open reading frame 201	374409	993	363530	9759	18525, 27291, 36057, 44823, 53589
839	chromosome 1 open reading frame 201	435187	994	392225	9760	18526, 27292, 36058, 44824, 53590
840	chromosome 1 open reading frame 201	437986	995	394930	9761	18527, 27293, 36059, 44825, 53591
841	chromosome 1 open reading frame 201	438866	996	416176	9762	18528, 27294, 36060, 44826, 53592
842	chromosome 1 open reading frame 201	440416	997	408712	9763	18529, 27295, 36061, 44827, 53593
843	chromosome 1 open reading frame 204	368102	998	357082	9764	18530, 27296, 36062, 44828, 53594
844	chromosome 1 open reading frame 21	235307	999	235307	9765	18531, 27297, 36063, 44829, 53595
845	chromosome 1 open reading frame 21	367514	1000	356484	9766	18532, 27298, 36064, 44830, 53596
846	chromosome 1 open reading frame 212	417239	1001	428541	9767	18533, 27299, 36065, 44831, 53597
847	chromosome 1 open reading frame 212	423898	1002	428984	9768	18534, 27300, 36066, 44832, 53598
848	chromosome 1 open reading frame 212	446026	1003	430285	9769	18535, 27301, 36067, 44833, 53599
849	chromosome 1 open reading frame 212	456842	1004	430198	9770	18536, 27302, 36068, 44834, 53600
850	chromosome 1 open reading frame 212	521580	1005	428585	9771	18537, 27303, 36069, 44835, 53601
851	chromosome 1 open reading frame 213	335648	1006	441287	9772	18538, 27304, 36070, 44836, 53602
852	chromosome 1 open reading frame 216	270815	1007	425166	9773	18539, 27305, 36071, 44837, 53603
853	chromosome 1 open reading frame 216	422623	1008	413321	9774	18540, 27306, 36072, 44838, 53604
854	chromosome 1 open reading	319387	1009	319506	9775	18541, 27307,

	frame 220					36073, 44839, 53605
855	chromosome 1 open reading frame 222	270720	1010	270720	9776	18542, 27308, 36074, 44840, 53606
856	chromosome 1 open reading frame 222	434971	1011	408078	9777	18543, 27309, 36075, 44841, 53607
857	chromosome 1 open reading frame 226	420220	1012	398035	9778	18544, 27310, 36076, 44842, 53608
858	chromosome 1 open reading frame 226	426197	1013	413150	9779	18545, 27311, 36077, 44843, 53609
859	chromosome 1 open reading frame 226	458626	1014	437071	9780	18546, 27312, 36078, 44844, 53610
860	chromosome 1 open reading frame 227	332912	1015	419160	9781	18547, 27313, 36079, 44845, 53611
861	chromosome 1 open reading frame 228	458657	1016	420716	9782	18548, 27314, 36080, 44846, 53612
862	chromosome 1 open reading frame 228	535358	1017	440524	9783	18549, 27315, 36081, 44847, 53613
863	chromosome 1 open reading frame 229	408893	1018	386203	9784	18550, 27316, 36082, 44848, 53614
864	chromosome 1 open reading frame 233	422725	1019	389111	9785	18551, 27317, 36083, 44849, 53615
865	chromosome 1 open reading frame 35	272139	1020	272139	9786	18552, 27318, 36084, 44850, 53616
866	chromosome 1 open reading frame 38	328928	1021	329862	9787	18553, 27319, 36085, 44851, 53617
867	chromosome 1 open reading frame 38	373921	1022	363031	9788	18554, 27320, 36086, 44852, 53618
868	chromosome 1 open reading frame 38	373925	1023	363035	9789	18555, 27321, 36087, 44853, 53619
869	chromosome 1 open reading frame 38	373927	1024	363037	9790	18556, 27322, 36088, 44854, 53620
870	chromosome 1 open reading frame 38	427466	1025	392414	9791	18557, 27323, 36089, 44855, 53621

871	chromosome 1 open reading frame 38	442118	1026	413725	9792	18558, 27324, 36090, 44856, 53622
872	chromosome 1 open reading frame 38	456990	1027	398049	9793	18559, 27325, 36091, 44857, 53623
873	chromosome 1 open reading frame 50	372525	1028	361603	9794	18560, 27326, 36092, 44858, 53624
874	chromosome 1 open reading frame 50	438946	1029	415739	9795	18561, 27327, 36093, 44859, 53625
875	chromosome 1 open reading frame 50	536543	1030	438814	9796	18562, 27328, 36094, 44860, 53626
876	chromosome 1 open reading frame 50	421630	1031	398292	9797	18563, 27329, 36095, 44861, 53627
877	chromosome 1 open reading frame 51	290363	1032	290363	9798	18564, 27330, 36096, 44862, 53628
878	chromosome 1 open reading frame 51	369095	1033	358091	9799	18565, 27331, 36097, 44863, 53629
879	chromosome 1 open reading frame 51	584286	1034	461948	9800	18566, 27332, 36098, 44864, 53630
880	chromosome 1 open reading frame 52	344356	1035	345092	9801	18567, 27333, 36099, 44865, 53631
881	chromosome 1 open reading frame 52	471115	1036	419417	9802	18568, 27334, 36100, 44866, 53632
882	chromosome 1 open reading frame 53	367393	1037	356363	9803	18569, 27335, 36101, 44867, 53633
883	chromosome 1 open reading frame 54	580040	1038	463825	9804	18570, 27336, 36102, 44868, 53634
884	chromosome 1 open reading frame 55	272091	1039	272091	9805	18571, 27337, 36103, 44869, 53635
885	chromosome 1 open reading frame 55	366817	1040	355782	9806	18572, 27338, 36104, 44870, 53636
886	chromosome 1 open reading frame 55	366818	1041	355783	9807	18573, 27339, 36105, 44871, 53637
887	chromosome 1 open reading frame 63	243189	1042	243189	9808	18574, 27340, 36106, 44872,

						53638
888	chromosome 1 open reading frame 63	417642	1043	411631	9809	18575, 27341, 36107, 44873, 53639
889	chromosome 1 open reading frame 63	431849	1044	391510	9810	18576, 27342, 36108, 44874, 53640
890	chromosome 1 open reading frame 63	511740	1045	441472	9811	18577, 27343, 36109, 44875, 53641
891	chromosome 1 open reading frame 64	329454	1046	332162	9812	18578, 27344, 36110, 44876, 53642
892	chromosome 1 open reading frame 65	366875	1047	355840	9813	18579, 27345, 36111, 44877, 53643
893	chromosome 1 open reading frame 68	362017	1048	354769	9814	18580, 27346, 36112, 44878, 53644
894	chromosome 1 open reading frame 68	368775	1049	357764	9815	18581, 27347, 36113, 44879, 53645
895	chromosome 1 open reading frame 74	294811	1050	294811	9816	18582, 27348, 36114, 44880, 53646
896	chromosome 1 open reading frame 85	368264	1051	357247	9817	18583, 27349, 36115, 44881, 53647
897	chromosome 1 open reading frame 86	378545	1052	367807	9818	18584, 27350, 36116, 44882, 53648
898	chromosome 1 open reading frame 86	378546	1053	367808	9819	18585, 27351, 36117, 44883, 53649
899	chromosome 1 open reading frame 86	400919	1054	383710	9820	18586, 27352, 36118, 44884, 53650
900	chromosome 1 open reading frame 86	378543	1055	367804	9821	18587, 27353, 36119, 44885, 53651
901	chromosome 1 open reading frame 86	420515	1056	409721	9822	18588, 27354, 36120, 44886, 53652
902	chromosome 1 open reading frame 87	371201	1057	360244	9823	18589, 27355, 36121, 44887, 53653
903	chromosome 1 open reading frame 87	395552	1058	378921	9824	18590, 27356, 36122, 44888, 53654
904	chromosome 1 open reading	450089	1059	389432	9825	18591, 27357,

	frame 87					36123, 44889, 53655
905	chromosome 1 open reading frame 98	367355	1060	356324	9826	18592, 27358, 36124, 44890, 53656
906	chromosome 1 open reading frame 98	367356	1061	356325	9827	18593, 27359, 36125, 44891, 53657
907	chromosome 10 open reading frame 103	440197	1062	394678	9828	18594, 27360, 36126, 44892, 53658
908	chromosome 10 open reading frame 107	330194	1063	328698	9829	18595, 27361, 36127, 44893, 53659
909	chromosome 10 open reading frame 107	389639	1064	374290	9830	18596, 27362, 36128, 44894, 53660
910	chromosome 10 open reading frame 108	381489	1065	370899	9831	18597, 27363, 36129, 44895, 53661
911	chromosome 10 open reading frame 108	441152	1066	414034	9832	18598, 27364, 36130, 44896, 53662
912	chromosome 10 open reading frame 11	354343	1067	346310	9833	18599, 27365, 36131, 44897, 53663
913	chromosome 10 open reading frame 11	372499	1068	361577	9834	18600, 27366, 36132, 44898, 53664
914	chromosome 10 open reading frame 113	377118	1069	366322	9835	18601, 27367, 36133, 44899, 53665
915	chromosome 10 open reading frame 113	529198	1070	434089	9836	18602, 27368, 36134, 44900, 53666
916	chromosome 10 open reading frame 113	534331	1071	433646	9837	18603, 27369, 36135, 44901, 53667
917	chromosome 10 open reading frame 114	377113	1072	366317	9838	18604, 27370, 36136, 44902, 53668
918	chromosome 10 open reading frame 115	376501	1073	365684	9839	18605, 27371, 36137, 44903, 53669
919	chromosome 10 open reading frame 115	399806	1074	382705	9840	18606, 27372, 36138, 44904, 53670
920	chromosome 10 open reading frame 116	372012	1075	361082	9841	18607, 27373, 36139, 44905, 53671

921	chromosome 10 open reading frame 116	372013	1076	361083	9842	18608, 27374, 36140, 44906, 53672
922	chromosome 10 open reading frame 116	416348	1077	394643	9843	18609, 27375, 36141, 44907, 53673
923	chromosome 10 open reading frame 118	369285	1078	358291	9844	18610, 27376, 36142, 44908, 53674
924	chromosome 10 open reading frame 118	369286	1079	358292	9845	18611, 27377, 36143, 44909, 53675
925	chromosome 10 open reading frame 118	369287	1080	358293	9846	18612, 27378, 36144, 44910, 53676
926	chromosome 10 open reading frame 118	428953	1081	415344	9847	18613, 27379, 36145, 44911, 53677
927	chromosome 10 open reading frame 118	430353	1082	411008	9848	18614, 27380, 36146, 44912, 53678
928	chromosome 10 open reading frame 118	543782	1083	441576	9849	18615, 27381, 36147, 44913, 53679
929	chromosome 10 open reading frame 12	286067	1084	286067	9850	18616, 27382, 36148, 44914, 53680
930	chromosome 10 open reading frame 12	539886	1085	441926	9851	18617, 27383, 36149, 44915, 53681
931	chromosome 10 open reading frame 120	329446	1086	331012	9852	18618, 27384, 36150, 44916, 53682
932	chromosome 10 open reading frame 120	432000	1087	410278	9853	18619, 27385, 36151, 44917, 53683
933	chromosome 10 open reading frame 122	368821	1088	357811	9854	18620, 27386, 36152, 44918, 53684
934	chromosome 10 open reading frame 125	278025	1089	278025	9855	18621, 27387, 36153, 44919, 53685
935	chromosome 10 open reading frame 125	368551	1090	357539	9856	18622, 27388, 36154, 44920, 53686
936	chromosome 10 open reading frame 125	368552	1091	357540	9857	18623, 27389, 36155, 44921, 53687
937	chromosome 10 open reading frame 125	447176	1092	413379	9858	18624, 27390, 36156, 44922,

						53688
938	chromosome 10 open reading frame 126	375520	1093	364670	9859	18625, 27391, 36157, 44923, 53689
939	chromosome 10 open reading frame 128	374148	1094	363263	9860	18626, 27392, 36158, 44924, 53690
940	chromosome 10 open reading frame 128	374149	1095	363264	9861	18627, 27393, 36159, 44925, 53691
941	chromosome 10 open reading frame 128	374151	1096	363266	9862	18628, 27394, 36160, 44926, 53692
942	chromosome 10 open reading frame 128	374153	1097	363268	9863	18629, 27395, 36161, 44927, 53693
943	chromosome 10 open reading frame 128	453436	1098	395067	9864	18630, 27396, 36162, 44928, 53694
944	chromosome 10 open reading frame 131	371202	1099	360245	9865	18631, 27397, 36163, 44929, 53695
945	chromosome 10 open reading frame 131	423344	1100	411850	9866	18632, 27398, 36164, 44930, 53696
946	chromosome 10 open reading frame 28	298999	1101	298999	9867	18633, 27399, 36165, 44931, 53697
947	chromosome 10 open reading frame 28	314594	1102	314018	9868	18634, 27400, 36166, 44932, 53698
948	chromosome 10 open reading frame 28	370584	1103	359616	9869	18635, 27401, 36167, 44933, 53699
949	chromosome 10 open reading frame 28	370586	1104	359618	9870	18636, 27402, 36168, 44934, 53700
950	chromosome 10 open reading frame 28	538495	1105	444449	9871	18637, 27403, 36169, 44935, 53701
951	chromosome 10 open reading frame 28	544834	1106	437555	9872	18638, 27404, 36170, 44936, 53702
952	chromosome 10 open reading frame 32	339834	1107	342331	9873	18639, 27405, 36171, 44937, 53703
953	chromosome 10 open reading frame 32	369883	1108	358899	9874	18640, 27406, 36172, 44938, 53704
954	chromosome 10 open	430888	1109	394188	9875	18641, 27407,

	reading frame 40					36173, 44939, 53705
955	chromosome 10 open reading frame 40	444900	1110	391066	9876	18642, 27408, 36174, 44940, 53706
956	chromosome 10 open reading frame 40	521074	1111	430990	9877	18643, 27409, 36175, 44941, 53707
957	chromosome 10 open reading frame 46	340214	1112	342487	9878	18644, 27410, 36176, 44942, 53708
958	chromosome 10 open reading frame 46	369151	1113	358147	9879	18645, 27411, 36177, 44943, 53709
959	chromosome 10 open reading frame 46	369156	1114	358152	9880	18646, 27412, 36178, 44944, 53710
960	chromosome 10 open reading frame 46	544392	1115	443048	9881	18647, 27413, 36179, 44945, 53711
961	chromosome 10 open reading frame 47	277570	1116	277570	9882	18648, 27414, 36180, 44946, 53712
962	chromosome 10 open reading frame 47	379200	1117	368498	9883	18649, 27415, 36181, 44947, 53713
963	chromosome 10 open reading frame 47	379202	1118	368500	9884	18650, 27416, 36182, 44948, 53714
964	chromosome 10 open reading frame 47	379208	1119	368506	9885	18651, 27417, 36183, 44949, 53715
965	chromosome 10 open reading frame 47	444604	1120	407621	9886	18652, 27418, 36184, 44950, 53716
966	chromosome 10 open reading frame 53	374111	1121	363225	9887	18653, 27419, 36185, 44951, 53717
967	chromosome 10 open reading frame 53	374112	1122	363226	9888	18654, 27420, 36186, 44952, 53718
968	chromosome 10 open reading frame 53	374113	1123	363227	9889	18655, 27421, 36187, 44953, 53719
969	chromosome 10 open reading frame 53	535836	1124	437726	9890	18656, 27422, 36188, 44954, 53720
970	chromosome 10 open reading frame 55	409178	1125	386960	9891	18657, 27423, 36189, 44955, 53721

971	chromosome 10 open reading frame 55	412307	1126	409225	9892	18658, 27424, 36190, 44956, 53722
972	chromosome 10 open reading frame 67	323327	1127	321464	9893	18659, 27425, 36191, 44957, 53723
973	chromosome 10 open reading frame 67	376500	1128	365683	9894	18660, 27426, 36192, 44958, 53724
974	chromosome 10 open reading frame 68	302316	1129	303710	9895	18661, 27427, 36193, 44959, 53725
975	chromosome 10 open reading frame 68	375025	1130	364165	9896	18662, 27428, 36194, 44960, 53726
976	chromosome 10 open reading frame 68	375037	1131	364177	9897	18663, 27429, 36195, 44961, 53727
977	chromosome 10 open reading frame 71	323868	1132	318713	9898	18664, 27430, 36196, 44962, 53728
978	chromosome 10 open reading frame 71	374144	1133	363259	9899	18665, 27431, 36197, 44963, 53729
979	chromosome 10 open reading frame 76	431271	1134	394311	9900	18666, 27432, 36198, 44964, 53730
980	chromosome 10 open reading frame 81	354462	1135	346451	9901	18667, 27433, 36199, 44965, 53731
981	chromosome 10 open reading frame 81	361048	1136	354332	9902	18668, 27434, 36200, 44966, 53732
982	chromosome 10 open reading frame 81	369309	1137	358315	9903	18669, 27435, 36201, 44967, 53733
983	chromosome 10 open reading frame 81	369310	1138	358316	9904	18670, 27436, 36202, 44968, 53734
984	chromosome 10 open reading frame 81	369312	1139	358318	9905	18671, 27437, 36203, 44969, 53735
985	chromosome 10 open reading frame 81	448805	1140	390757	9906	18672, 27438, 36204, 44970, 53736
986	chromosome 10 open reading frame 82	369210	1141	358212	9907	18673, 27439, 36205, 44971, 53737
987	chromosome 10 open reading frame 82	388884	1142	373536	9908	18674, 27440, 36206, 44972,

						53738
988	chromosome 10 open reading frame 85	369071	1143	358067	9909	18675, 27441, 36207, 44973, 53739
989	chromosome 10 open reading frame 88	481909	1144	419126	9910	18676, 27442, 36208, 44974, 53740
990	chromosome 10 open reading frame 91	321248	1145	323241	9911	18677, 27443, 36209, 44975, 53741
991	chromosome 10 open reading frame 91	392630	1146	376407	9912	18678, 27444, 36210, 44976, 53742
992	chromosome 10 open reading frame 95	239125	1147	239125	9913	18679, 27445, 36211, 44977, 53743
993	chromosome 10 open reading frame 96	333254	1148	329860	9914	18680, 27446, 36212, 44978, 53744
994	chromosome 10 open reading frame 96	423072	1149	400021	9915	18681, 27447, 36213, 44979, 53745
995	chromosome 11 open reading frame 16	326053	1150	318999	9916	18682, 27448, 36214, 44980, 53746
996	chromosome 11 open reading frame 16	525780	1151	436818	9917	18683, 27449, 36215, 44981, 53747
997	chromosome 11 open reading frame 31	388857	1152	373509	9918	18684, 27450, 36216, 44982, 53748
998	chromosome 11 open reading frame 31	528798	1153	434875	9919	18685, 27451, 36217, 44983, 53749
999	chromosome 11 open reading frame 31	534355	1154	434511	9920	18686, 27452, 36218, 44984, 53750
1000	chromosome 11 open reading frame 35	329451	1155	331167	9921	18687, 27453, 36219, 44985, 53751
1001	chromosome 11 open reading frame 36	420873	1156	436553	9922	18688, 27454, 36220, 44986, 53752
1002	chromosome 11 open reading frame 36	434798	1157	434187	9923	18689, 27455, 36221, 44987, 53753
1003	chromosome 11 open reading frame 36	531711	1158	431161	9924	18690, 27456, 36222, 44988, 53754
1004	chromosome 11 open	541883	1159	444912	9925	18691, 27457,

	reading frame 36					36223, 44989, 53755
1005	chromosome 11 open reading frame 39	536853	1160	441011	9926	18692, 27458, 36224, 44990, 53756
1006	chromosome 11 open reading frame 40	307616	1161	302918	9927	18693, 27459, 36225, 44991, 53757
1007	chromosome 11 open reading frame 42	316375	1162	321021	9928	18694, 27460, 36226, 44992, 53758
1008	chromosome 11 open reading frame 48	354588	1163	346600	9929	18695, 27461, 36227, 44993, 53759
1009	chromosome 11 open reading frame 48	431002	1164	416856	9930	18696, 27462, 36228, 44994, 53760
1010	chromosome 11 open reading frame 48	526490	1165	431471	9931	18697, 27463, 36229, 44995, 53761
1011	chromosome 11 open reading frame 48	532208	1166	436848	9932	18698, 27464, 36230, 44996, 53762
1012	chromosome 11 open reading frame 49	278460	1167	278460	9933	18699, 27465, 36231, 44997, 53763
1013	chromosome 11 open reading frame 49	378615	1168	367878	9934	18700, 27466, 36232, 44998, 53764
1014	chromosome 11 open reading frame 49	395460	1169	378844	9935	18701, 27467, 36233, 44999, 53765
1015	chromosome 11 open reading frame 49	536126	1170	438207	9936	18702, 27468, 36234, 45000, 53766
1016	chromosome 11 open reading frame 49	543718	1171	437689	9937	18703, 27469, 36235, 45001, 53767
1017	chromosome 11 open reading frame 49	378618	1172	367881	9938	18704, 27470, 36236, 45002, 53768
1018	chromosome 11 open reading frame 51	227618	1173	227618	9939	18705, 27471, 36237, 45003, 53769
1019	chromosome 11 open reading frame 51	535234	1174	446412	9940	18706, 27472, 36238, 45004, 53770
1020	chromosome 11 open reading frame 51	535503	1175	443383	9941	18707, 27473, 36239, 45005, 53771

1021	chromosome 11 open reading frame 51	538393	1176	440002	9942	18708, 27474, 36240, 45006, 53772
1022	chromosome 11 open reading frame 51	538919	1177	440983	9943	18709, 27475, 36241, 45007, 53773
1023	chromosome 11 open reading frame 51	539395	1178	440380	9944	18710, 27476, 36242, 45008, 53774
1024	chromosome 11 open reading frame 51	542531	1179	443911	9945	18711, 27477, 36243, 45009, 53775
1025	chromosome 11 open reading frame 51	545333	1180	439362	9946	18712, 27478, 36244, 45010, 53776
1026	chromosome 11 open reading frame 51	545944	1181	446383	9947	18713, 27479, 36245, 45011, 53777
1027	chromosome 11 open reading frame 52	278601	1182	278601	9948	18714, 27480, 36246, 45012, 53778
1028	chromosome 11 open reading frame 52	529342	1183	436268	9949	18715, 27481, 36247, 45013, 53779
1029	chromosome 11 open reading frame 53	280325	1184	280325	9950	18716, 27482, 36248, 45014, 53780
1030	chromosome 11 open reading frame 55	355500	1185	347687	9951	18717, 27483, 36249, 45015, 53781
1031	chromosome 11 open reading frame 57	280352	1186	339076	9952	18718, 27484, 36250, 45016, 53782
1032	chromosome 11 open reading frame 57	393047	1187	376767	9953	18719, 27485, 36251, 45017, 53783
1033	chromosome 11 open reading frame 57	393048	1188	376768	9954	18720, 27486, 36252, 45018, 53784
1034	chromosome 11 open reading frame 57	420986	1189	402208	9955	18721, 27487, 36253, 45019, 53785
1035	chromosome 11 open reading frame 57	525785	1190	435408	9956	18722, 27488, 36254, 45020, 53786
1036	chromosome 11 open reading frame 57	526879	1191	436169	9957	18723, 27489, 36255, 45021, 53787
1037	chromosome 11 open reading frame 57	532163	1192	432188	9958	18724, 27490, 36256, 45022,

						53788
1038	chromosome 11 open reading frame 57	574413	1193	460336	9959	18725, 27491, 36257, 45023, 53789
1039	chromosome 11 open reading frame 58	228136	1194	228136	9960	18726, 27492, 36258, 45024, 53790
1040	chromosome 11 open reading frame 58	422258	1195	406221	9961	18727, 27493, 36259, 45025, 53791
1041	chromosome 11 open reading frame 61	239614	1196	239614	9962	18728, 27494, 36260, 45026, 53792
1042	chromosome 11 open reading frame 61	374979	1197	364118	9963	18729, 27495, 36261, 45027, 53793
1043	chromosome 11 open reading frame 61	526629	1198	435705	9964	18730, 27496, 36262, 45028, 53794
1044	chromosome 11 open reading frame 63	227349	1199	227349	9965	18731, 27497, 36263, 45029, 53795
1045	chromosome 11 open reading frame 63	307257	1200	307695	9966	18732, 27498, 36264, 45030, 53796
1046	chromosome 11 open reading frame 63	531316	1201	431669	9967	18733, 27499, 36265, 45031, 53797
1047	chromosome 11 open reading frame 65	393084	1202	376799	9968	18734, 27500, 36266, 45032, 53798
1048	chromosome 11 open reading frame 65	529391	1203	436400	9969	18735, 27501, 36267, 45033, 53799
1049	chromosome 11 open reading frame 67	393427	1204	377078	9970	18736, 27502, 36268, 45034, 53800
1050	chromosome 11 open reading frame 67	526415	1205	431808	9971	18737, 27503, 36269, 45035, 53801
1051	chromosome 11 open reading frame 68	438576	1206	398350	9972	18738, 27504, 36270, 45036, 53802
1052	chromosome 11 open reading frame 68	449692	1207	409681	9973	18739, 27505, 36271, 45037, 53803
1053	chromosome 11 open reading frame 70	393209	1208	376904	9974	18740, 27506, 36272, 45038, 53804
1054	chromosome 11 open	434758	1209	414390	9975	18741, 27507,

	reading frame 70					36273, 45039, 53805
1055	chromosome 11 open reading frame 70	534360	1210	435482	9976	18742, 27508, 36274, 45040, 53806
1056	chromosome 11 open reading frame 71	325636	1211	325508	9977	18743, 27509, 36275, 45041, 53807
1057	chromosome 11 open reading frame 72	333139	1212	328640	9978	18744, 27510, 36276, 45042, 53808
1058	chromosome 11 open reading frame 72	446232	1213	416700	9979	18745, 27511, 36277, 45043, 53809
1059	chromosome 11 open reading frame 74	334307	1214	334848	9980	18746, 27512, 36278, 45044, 53810
1060	chromosome 11 open reading frame 74	347206	1215	299442	9981	18747, 27513, 36279, 45045, 53811
1061	chromosome 11 open reading frame 74	446510	1216	403937	9982	18748, 27514, 36280, 45046, 53812
1062	chromosome 11 open reading frame 74	527108	1217	435676	9983	18749, 27515, 36281, 45047, 53813
1063	chromosome 11 open reading frame 74	530697	1218	432685	9984	18750, 27516, 36282, 45048, 53814
1064	chromosome 11 open reading frame 74	531554	1219	433407	9985	18751, 27517, 36283, 45049, 53815
1065	chromosome 11 open reading frame 74	532470	1220	431374	9986	18752, 27518, 36284, 45050, 53816
1066	chromosome 11 open reading frame 74	534635	1221	433152	9987	18753, 27519, 36285, 45051, 53817
1067	chromosome 11 open reading frame 80	346672	1222	317408	9988	18754, 27520, 36286, 45052, 53818
1068	chromosome 11 open reading frame 80	360962	1223	354227	9989	18755, 27521, 36287, 45053, 53819
1069	chromosome 11 open reading frame 80	540737	1224	444319	9990	18756, 27522, 36288, 45054, 53820
1070	chromosome 11 open reading frame 84	294244	1225	294244	9991	18757, 27523, 36289, 45055, 53821

1071	chromosome 11 open reading frame 85	301896	1226	301896	9992	18758, 27524, 36290, 45056, 53822
1072	chromosome 11 open reading frame 85	432175	1227	395273	9993	18759, 27525, 36291, 45057, 53823
1073	chromosome 11 open reading frame 85	536065	1228	443649	9994	18760, 27526, 36292, 45058, 53824
1074	chromosome 11 open reading frame 86	308963	1229	311479	9995	18761, 27527, 36293, 45059, 53825
1075	chromosome 11 open reading frame 88	375618	1230	364768	9996	18762, 27528, 36294, 45060, 53826
1076	chromosome 11 open reading frame 88	529167	1231	432911	9997	18763, 27529, 36295, 45061, 53827
1077	chromosome 11 open reading frame 89	391480	1232	375311	9998	18764, 27530, 36296, 45062, 53828
1078	chromosome 11 open reading frame 91	379011	1233	368296	9999	18765, 27531, 36297, 45063, 53829
1079	chromosome 11 open reading frame 91	451594	1234	397954	10000	18766, 27532, 36298, 45064, 53830
1080	chromosome 11 open reading frame 92	355430	1235	347601	10001	18767, 27533, 36299, 45065, 53831
1081	chromosome 11 open reading frame 92	532918	1236	437253	10002	18768, 27534, 36300, 45066, 53832
1082	chromosome 11 open reading frame 92	540738	1237	438980	10003	18769, 27535, 36301, 45067, 53833
1083	chromosome 11 open reading frame 93	398035	1238	381115	10004	18770, 27536, 36302, 45068, 53834
1084	chromosome 11 open reading frame 93	526216	1239	434519	10005	18771, 27537, 36303, 45069, 53835
1085	chromosome 11 open reading frame 93	528846	1240	434938	10006	18772, 27538, 36304, 45070, 53836
1086	chromosome 11 open reading frame 96	339446	1241	340667	10007	18773, 27539, 36305, 45071, 53837
1087	chromosome 11 open reading frame 96	528572	1242	431597	10008	18774, 27540, 36306, 45072,

						53838
1088	chromosome 12 open reading frame 24	377673	1243	366901	10009	18775, 27541, 36307, 45073, 53839
1089	chromosome 12 open reading frame 26	248306	1244	248306	10010	18776, 27542, 36308, 45074, 53840
1090	chromosome 12 open reading frame 28	299350	1245	299350	10011	18777, 27543, 36309, 45075, 53841
1091	chromosome 12 open reading frame 29	356891	1246	349358	10012	18778, 27544, 36310, 45076, 53842
1092	chromosome 12 open reading frame 34	358906	1247	351783	10013	18779, 27545, 36311, 45077, 53843
1093	chromosome 12 open reading frame 34	538780	1248	443292	10014	18780, 27546, 36312, 45078, 53844
1094	chromosome 12 open reading frame 35	312561	1249	310338	10015	18781, 27547, 36313, 45079, 53845
1095	chromosome 12 open reading frame 35	381054	1250	370442	10016	18782, 27548, 36314, 45080, 53846
1096	chromosome 12 open reading frame 35	540924	1251	445152	10017	18783, 27549, 36315, 45081, 53847
1097	chromosome 12 open reading frame 36	318426	1252	443007	10018	18784, 27550, 36316, 45082, 53848
1098	chromosome 12 open reading frame 36	527705	1253	443346	10019	18785, 27551, 36317, 45083, 53849
1099	chromosome 12 open reading frame 4	261250	1254	261250	10020	18786, 27552, 36318, 45084, 53850
1100	chromosome 12 open reading frame 4	545746	1255	439996	10021	18787, 27553, 36319, 45085, 53851
1101	chromosome 12 open reading frame 40	324616	1256	317671	10022	18788, 27554, 36320, 45086, 53852
1102	chromosome 12 open reading frame 40	398716	1257	381701	10023	18789, 27555, 36321, 45087, 53853
1103	chromosome 12 open reading frame 42	315192	1258	324984	10024	18790, 27556, 36322, 45088, 53854
1104	chromosome 12 open	378113	1259	367353	10025	18791, 27557,

	reading frame 42					36323, 45089, 53855
1105	chromosome 12 open reading frame 42	548883	1260	447908	10026	18792, 27558, 36324, 45090, 53856
1106	chromosome 12 open reading frame 42	552578	1261	447795	10027	18793, 27559, 36325, 45091, 53857
1107	chromosome 12 open reading frame 45	552951	1262	447057	10028	18794, 27560, 36326, 45092, 53858
1108	chromosome 12 open reading frame 50	298699	1263	298699	10029	18795, 27561, 36327, 45093, 53859
1109	chromosome 12 open reading frame 50	551163	1264	448855	10030	18796, 27562, 36328, 45094, 53860
1110	chromosome 12 open reading frame 54	314014	1265	316898	10031	18797, 27563, 36329, 45095, 53861
1111	chromosome 12 open reading frame 54	548364	1266	447109	10032	18798, 27564, 36330, 45096, 53862
1112	chromosome 12 open reading frame 56	333722	1267	329698	10033	18799, 27565, 36331, 45097, 53863
1113	chromosome 12 open reading frame 56	433716	1268	391084	10034	18800, 27566, 36332, 45098, 53864
1114	chromosome 12 open reading frame 57	229281	1269	229281	10035	18801, 27567, 36333, 45099, 53865
1115	chromosome 12 open reading frame 60	330828	1270	331691	10036	18802, 27568, 36334, 45100, 53866
1116	chromosome 12 open reading frame 61	408887	1271	386169	10037	18803, 27569, 36335, 45101, 53867
1117	chromosome 12 open reading frame 63	298953	1272	298953	10038	18804, 27570, 36336, 45102, 53868
1118	chromosome 12 open reading frame 63	342887	1273	345466	10039	18805, 27571, 36337, 45103, 53869
1119	chromosome 12 open reading frame 66	398055	1274	381132	10040	18806, 27572, 36338, 45104, 53870
1120	chromosome 12 open reading frame 70	416383	1275	387617	10041	18807, 27573, 36339, 45105, 53871

1121	chromosome 12 open reading frame 70	535986	1276	441688	10042	18808, 27574, 36340, 45106, 53872
1122	chromosome 12 open reading frame 71	398815	1277	381796	10043	18809, 27575, 36341, 45107, 53873
1123	chromosome 12 open reading frame 71	429849	1278	413728	10044	18810, 27576, 36342, 45108, 53874
1124	chromosome 12 open reading frame 74	397833	1279	380933	10045	18811, 27577, 36343, 45109, 53875
1125	chromosome 12 open reading frame 74	544406	1280	446043	10046	18812, 27578, 36344, 45110, 53876
1126	chromosome 12 open reading frame 75	443585	1281	448536	10047	18813, 27579, 36345, 45111, 53877
1127	chromosome 12 open reading frame 76	309050	1282	308368	10048	18814, 27580, 36346, 45112, 53878
1128	chromosome 12 open reading frame 77	549828	1283	447146	10049	18815, 27581, 36347, 45113, 53879
1129	chromosome 13 open reading frame 26	380473	1284	369840	10050	18816, 27582, 36348, 45114, 53880
1130	chromosome 13 open reading frame 27	376019	1285	365187	10051	18817, 27583, 36349, 45115, 53881
1131	chromosome 13 open reading frame 27	376021	1286	365189	10052	18818, 27584, 36350, 45116, 53882
1132	chromosome 13 open reading frame 27	376032	1287	365200	10053	18819, 27585, 36351, 45117, 53883
1133	chromosome 13 open reading frame 30	313851	1288	319336	10054	18820, 27586, 36352, 45118, 53884
1134	chromosome 13 open reading frame 30	537894	1289	445786	10055	18821, 27587, 36353, 45119, 53885
1135	chromosome 13 open reading frame 33	380482	1290	369849	10056	18822, 27588, 36354, 45120, 53886
1136	chromosome 13 open reading frame 35	356049	1291	348337	10057	18823, 27589, 36355, 45121, 53887
1137	chromosome 14 open reading frame 102	354366	1292	346335	10058	18824, 27590, 36356, 45122,

						53888
1138	chromosome 14 open reading frame 102	357904	1293	350579	10059	18825, 27591, 36357, 45123, 53889
1139	chromosome 14 open reading frame 105	216445	1294	216445	10060	18826, 27592, 36358, 45124, 53890
1140	chromosome 14 open reading frame 118	261530	1295	261530	10061	18827, 27593, 36359, 45125, 53891
1141	chromosome 14 open reading frame 118	312858	1296	323775	10062	18828, 27594, 36360, 45126, 53892
1142	chromosome 14 open reading frame 118	336993	1297	337200	10063	18829, 27595, 36361, 45127, 53893
1143	chromosome 14 open reading frame 118	556663	1298	450657	10064	18830, 27596, 36362, 45128, 53894
1144	chromosome 14 open reading frame 118	557263	1299	451587	10065	18831, 27597, 36363, 45129, 53895
1145	chromosome 14 open reading frame 119	319074	1300	322238	10066	18832, 27598, 36364, 45130, 53896
1146	chromosome 14 open reading frame 119	554203	1301	450861	10067	18833, 27599, 36365, 45131, 53897
1147	chromosome 14 open reading frame 142	306954	1302	306320	10068	18834, 27600, 36366, 45132, 53898
1148	chromosome 14 open reading frame 149	247194	1303	247194	10069	18835, 27601, 36367, 45133, 53899
1149	chromosome 14 open reading frame 162	543986	1304	438285	10070	18836, 27602, 36368, 45134, 53900
1150	chromosome 14 open reading frame 164	430154	1305	397830	10071	18837, 27603, 36369, 45135, 53901
1151	chromosome 14 open reading frame 166B	216453	1306	216453	10072	18838, 27604, 36370, 45136, 53902
1152	chromosome 14 open reading frame 166B	393774	1307	377369	10073	18839, 27605, 36371, 45137, 53903
1153	chromosome 14 open reading frame 166B	450042	1308	396260	10074	18840, 27606, 36372, 45138, 53904
1154	chromosome 14 open	418511	1309	453962	10075	18841, 27607,

	reading frame 176					36373, 45139, 53905
1155	chromosome 14 open reading frame 176	556585	1310	451229	10076	18842, 27608, 36374, 45140, 53906
1156	chromosome 14 open reading frame 177	325812	1311	321360	10077	18843, 27609, 36375, 45141, 53907
1157	chromosome 14 open reading frame 177	541516	1312	440687	10078	18844, 27610, 36376, 45142, 53908
1158	chromosome 14 open reading frame 178	355883	1313	348145	10079	18845, 27611, 36377, 45143, 53909
1159	chromosome 14 open reading frame 178	439131	1314	407405	10080	18846, 27612, 36378, 45144, 53910
1160	chromosome 14 open reading frame 178	556047	1315	451531	10081	18847, 27613, 36379, 45145, 53911
1161	chromosome 14 open reading frame 182	399206	1316	382157	10082	18848, 27614, 36380, 45146, 53912
1162	chromosome 14 open reading frame 21	267425	1317	267425	10083	18849, 27615, 36381, 45147, 53913
1163	chromosome 14 open reading frame 21	544934	1318	440168	10084	18850, 27616, 36382, 45148, 53914
1164	chromosome 14 open reading frame 23	399387	1319	382318	10085	18851, 27617, 36383, 45149, 53915
1165	chromosome 14 open reading frame 28	325192	1320	326846	10086	18852, 27618, 36384, 45150, 53916
1166	chromosome 14 open reading frame 38	281581	1321	452964	10087	18853, 27619, 36385, 45151, 53917
1167	chromosome 14 open reading frame 38	537690	1322	453940	10088	18854, 27620, 36386, 45152, 53918
1168	chromosome 14 open reading frame 39	321731	1323	324920	10089	18855, 27621, 36387, 45153, 53919
1169	chromosome 14 open reading frame 39	556799	1324	451441	10090	18856, 27622, 36388, 45154, 53920
1170	chromosome 14 open reading frame 45	394009	1325	377577	10091	18857, 27623, 36389, 45155, 53921

1171	chromosome 14 open reading frame 45	553773	1326	451097	10092	18858, 27624, 36390, 45156, 53922
1172	chromosome 14 open reading frame 57	542853	1327	441438	10093	18859, 27625, 36391, 45157, 53923
1173	chromosome 14 open reading frame 79	547315	1328	450114	10094	18860, 27626, 36392, 45158, 53924
1174	chromosome 14 open reading frame 80	329886	1329	333010	10095	18861, 27627, 36393, 45159, 53925
1175	chromosome 14 open reading frame 80	334656	1330	333959	10096	18862, 27628, 36394, 45160, 53926
1176	chromosome 14 open reading frame 80	354560	1331	346568	10097	18863, 27629, 36395, 45161, 53927
1177	chromosome 14 open reading frame 80	392522	1332	376307	10098	18864, 27630, 36396, 45162, 53928
1178	chromosome 14 open reading frame 80	392523	1333	376308	10099	18865, 27631, 36397, 45163, 53929
1179	chromosome 14 open reading frame 80	392527	1334	376312	10100	18866, 27632, 36398, 45164, 53930
1180	chromosome 14 open reading frame 80	421892	1335	400014	10101	18867, 27633, 36399, 45165, 53931
1181	chromosome 14 open reading frame 80	427614	1336	391365	10102	18868, 27634, 36400, 45166, 53932
1182	chromosome 14 open reading frame 80	443229	1337	398161	10103	18869, 27635, 36401, 45167, 53933
1183	chromosome 14 open reading frame 80	450383	1338	391436	10104	18870, 27636, 36402, 45168, 53934
1184	chromosome 14 open reading frame 80	451719	1339	401319	10105	18871, 27637, 36403, 45169, 53935
1185	chromosome 15 open reading frame 17	357635	1340	350260	10106	18872, 27638, 36404, 45170, 53936
1186	chromosome 15 open reading frame 17	457294	1341	392823	10107	18873, 27639, 36405, 45171, 53937
1187	chromosome 15 open reading frame 26	286732	1342	286732	10108	18874, 27640, 36406, 45172,

						53938
1188	chromosome 15 open reading frame 26	398681	1343	381671	10109	18875, 27641, 36407, 45173, 53939
1189	chromosome 15 open reading frame 32	333334	1344	330267	10110	18876, 27642, 36408, 45174, 53940
1190	chromosome 15 open reading frame 33	299338	1345	299338	10111	18877, 27643, 36409, 45175, 53941
1191	chromosome 15 open reading frame 33	354658	1346	346683	10112	18878, 27644, 36410, 45176, 53942
1192	chromosome 15 open reading frame 33	559905	1347	453379	10113	18879, 27645, 36411, 45177, 53943
1193	chromosome 15 open reading frame 33	561064	1348	453028	10114	18880, 27646, 36412, 45178, 53944
1194	chromosome 15 open reading frame 37	560255	1349	453154	10115	18881, 27647, 36413, 45179, 53945
1195	chromosome 15 open reading frame 38	357484	1350	350075	10116	18882, 27648, 36414, 45180, 53946
1196	chromosome 15 open reading frame 39	360639	1351	353854	10117	18883, 27649, 36415, 45181, 53947
1197	chromosome 15 open reading frame 39	394987	1352	378438	10118	18884, 27650, 36416, 45182, 53948
1198	chromosome 15 open reading frame 39	446981	1353	405727	10119	18885, 27651, 36417, 45183, 53949
1199	chromosome 15 open reading frame 40	304177	1354	307071	10120	18886, 27652, 36418, 45184, 53950
1200	chromosome 15 open reading frame 40	451195	1355	403987	10121	18887, 27653, 36419, 45185, 53951
1201	chromosome 15 open reading frame 40	513601	1356	424666	10122	18888, 27654, 36420, 45186, 53952
1202	chromosome 15 open reading frame 40	538348	1357	441077	10123	18889, 27655, 36421, 45187, 53953
1203	chromosome 15 open reading frame 41	338183	1358	342433	10124	18890, 27656, 36422, 45188, 53954
1204	chromosome 15 open	437989	1359	401362	10125	18891, 27657,

	reading frame 41					36423, 45189, 53955
1205	chromosome 15 open reading frame 41	567389	1360	456736	10126	18892, 27658, 36424, 45190, 53956
1206	chromosome 15 open reading frame 43	340827	1361	340644	10127	18893, 27659, 36425, 45191, 53957
1207	chromosome 15 open reading frame 44	313182	1362	326379	10128	18894, 27660, 36426, 45192, 53958
1208	chromosome 15 open reading frame 44	395644	1363	379006	10129	18895, 27661, 36427, 45193, 53959
1209	chromosome 15 open reading frame 44	420799	1364	408429	10130	18896, 27662, 36428, 45194, 53960
1210	chromosome 15 open reading frame 44	431261	1365	402898	10131	18897, 27663, 36429, 45195, 53961
1211	chromosome 15 open reading frame 44	442903	1366	396314	10132	18898, 27664, 36430, 45196, 53962
1212	chromosome 15 open reading frame 52	397535	1367	380669	10133	18899, 27665, 36431, 45197, 53963
1213	chromosome 15 open reading frame 52	397536	1368	380670	10134	18900, 27666, 36432, 45198, 53964
1214	chromosome 15 open reading frame 52	559313	1369	453969	10135	18901, 27667, 36433, 45199, 53965
1215	chromosome 15 open reading frame 53	318792	1370	325144	10136	18902, 27668, 36434, 45200, 53966
1216	chromosome 15 open reading frame 54	318578	1371	323686	10137	18903, 27669, 36435, 45201, 53967
1217	chromosome 15 open reading frame 54	561223	1372	453476	10138	18904, 27670, 36436, 45202, 53968
1218	chromosome 15 open reading frame 56	319503	1373	315794	10139	18905, 27671, 36437, 45203, 53969
1219	chromosome 15 open reading frame 57	358005	1374	350695	10140	18906, 27672, 36438, 45204, 53970
1220	chromosome 15 open reading frame 57	416810	1375	397515	10141	18907, 27673, 36439, 45205, 53971

1221	chromosome 15 open reading frame 57	558750	1376	452773	10142	18908, 27674, 36440, 45206, 53972
1222	chromosome 15 open reading frame 57	558871	1377	452657	10143	18909, 27675, 36441, 45207, 53973
1223	chromosome 15 open reading frame 57	559103	1378	453899	10144	18910, 27676, 36442, 45208, 53974
1224	chromosome 15 open reading frame 59	379822	1379	369150	10145	18911, 27677, 36443, 45209, 53975
1225	chromosome 15 open reading frame 59	569673	1380	457205	10146	18912, 27678, 36444, 45210, 53976
1226	chromosome 15 open reading frame 60	331090	1381	328423	10147	18913, 27679, 36445, 45211, 53977
1227	chromosome 15 open reading frame 63	406925	1382	384474	10148	18914, 27680, 36446, 45212, 53978
1228	chromosome 15 open reading frame 63	442995	1383	401155	10149	18915, 27681, 36447, 45213, 53979
1229	chromosome 16 open reading frame 11	409413	1384	386499	10150	18916, 27682, 36448, 45214, 53980
1230	chromosome 16 open reading frame 13	301686	1385	445926	10151	18917, 27683, 36449, 45215, 53981
1231	chromosome 16 open reading frame 13	338401	1386	444140	10152	18918, 27684, 36450, 45216, 53982
1232	chromosome 16 open reading frame 13	397664	1387	440475	10153	18919, 27685, 36451, 45217, 53983
1233	chromosome 16 open reading frame 13	397665	1388	444460	10154	18920, 27686, 36452, 45218, 53984
1234	chromosome 16 open reading frame 13	397666	1389	440765	10155	18921, 27687, 36453, 45219, 53985
1235	chromosome 16 open reading frame 42	7390	1390	7390	10156	18922, 27688, 36454, 45220, 53986, 61522, 61580
1236	chromosome 16 open reading frame 45	300006	1391	300006	10157	18923, 27689, 36455, 45221, 53987
1237	chromosome 16 open	452191	1392	408976	10158	18924, 27690,

	reading frame 45					36456, 45222, 53988
1238	chromosome 16 open reading frame 46	299578	1393	299578	10159	18925, 27691, 36457, 45223, 53989
1239	chromosome 16 open reading frame 46	378611	1394	367874	10160	18926, 27692, 36458, 45224, 53990
1240	chromosome 16 open reading frame 46	444657	1395	398751	10161	18927, 27693, 36459, 45225, 53991
1241	chromosome 16 open reading frame 52	542527	1396	454926	10162	18928, 27694, 36460, 45226, 53992
1242	chromosome 16 open reading frame 55	301031	1397	301031	10163	18929, 27695, 36461, 45227, 53993
1243	chromosome 16 open reading frame 55	457689	1398	404547	10164	18930, 27696, 36462, 45228, 53994
1244	chromosome 16 open reading frame 59	361837	1399	355022	10165	18931, 27697, 36463, 45229, 53995
1245	chromosome 16 open reading frame 61	219400	1400	219400	10166	18932, 27698, 36464, 45230, 53996
1246	chromosome 16 open reading frame 7	261625	1401	261625	10167	18933, 27699, 36465, 45231, 53997
1247	chromosome 16 open reading frame 7	389386	1402	374037	10168	18934, 27700, 36466, 45232, 53998
1248	chromosome 16 open reading frame 71	299320	1403	299320	10169	18935, 27701, 36467, 45233, 53999
1249	chromosome 16 open reading frame 71	411541	1404	414394	10170	18936, 27702, 36468, 45234, 54000
1250	chromosome 16 open reading frame 72	327827	1405	331720	10171	18937, 27703, 36469, 45235, 54001
1251	chromosome 16 open reading frame 78	299191	1406	299191	10172	18938, 27704, 36470, 45236, 54002
1252	chromosome 16 open reading frame 79	328540	1407	332389	10173	18939, 27705, 36471, 45237, 54003
1253	chromosome 16 open reading frame 80	262498	1408	262498	10174	18940, 27706, 36472, 45238, 54004

1254	chromosome 16 open reading frame 85	378416	1409	367672	10175	18941, 27707, 36473, 45239, 54005
1255	chromosome 16 open reading frame 86	403458	1410	384117	10176	18942, 27708, 36474, 45240, 54006
1256	chromosome 16 open reading frame 87	285697	1411	285697	10177	18943, 27709, 36475, 45241, 54007
1257	chromosome 16 open reading frame 87	394806	1412	378285	10178	18944, 27710, 36476, 45242, 54008
1258	chromosome 16 open reading frame 90	399645	1413	382553	10179	18945, 27711, 36477, 45243, 54009
1259	chromosome 16 open reading frame 93	543610	1414	437532	10180	18946, 27712, 36478, 45244, 54010
1260	chromosome 16 open reading frame 93	545825	1415	441164	10181	18947, 27713, 36479, 45245, 54011
1261	chromosome 16 open reading frame 95	567970	1416	455079	10182	18948, 27714, 36480, 45246, 54012
1262	chromosome 16 open reading frame 96	444310	1417	415027	10183	18949, 27715, 36481, 45247, 54013
1263	chromosome 17 open reading frame 100	391428	1418	375247	10184	18950, 27716, 36482, 45248, 54014
1264	chromosome 17 open reading frame 102	357754	1419	350392	10185	18951, 27717, 36483, 45249, 54015
1265	chromosome 17 open reading frame 103	399011	1420	454565	10186	18952, 27718, 36484, 45250, 54016
1266	chromosome 17 open reading frame 104	359945	1421	353028	10187	18953, 27719, 36485, 45251, 54017
1267	chromosome 17 open reading frame 104	409122	1422	386452	10188	18954, 27720, 36486, 45252, 54018
1268	chromosome 17 open reading frame 104	409464	1423	386586	10189	18955, 27721, 36487, 45253, 54019
1269	chromosome 17 open reading frame 104	432494	1424	399809	10190	18956, 27722, 36488, 45254, 54020
1270	chromosome 17 open reading frame 104	456912	1425	397957	10191	18957, 27723, 36489, 45255,

						54021
1271	chromosome 17 open reading frame 105	449302	1426	415662	10192	18958, 27724, 36490, 45256, 54022
1272	chromosome 17 open reading frame 107	381365	1427	370770	10193	18959, 27725, 36491, 45257, 54023
1273	chromosome 17 open reading frame 108	379102	1428	368396	10194	18960, 27726, 36492, 45258, 54024
1274	chromosome 17 open reading frame 110	556126	1429	450581	10195	18961, 27727, 36493, 45259, 54025
1275	chromosome 17 open reading frame 39	268719	1430	268719	10196	18962, 27728, 36494, 45260, 54026
1276	chromosome 17 open reading frame 39	376345	1431	365523	10197	18963, 27729, 36495, 45261, 54027
1277	chromosome 17 open reading frame 46	331780	1432	331532	10198	18964, 27730, 36496, 45262, 54028
1278	chromosome 17 open reading frame 46	543122	1433	442724	10199	18965, 27731, 36497, 45263, 54029
1279	chromosome 17 open reading frame 47	321691	1434	354874	10200	18966, 27732, 36498, 45264, 54030
1280	chromosome 17 open reading frame 48	379774	1435	369099	10201	18967, 27733, 36499, 45265, 54031
1281	chromosome 17 open reading frame 50	285023	1436	285023	10202	18968, 27734, 36500, 45266, 54032
1282	chromosome 17 open reading frame 51	391411	1437	384286	10203	18969, 27735, 36501, 45267, 54033
1283	chromosome 17 open reading frame 53	245382	1438	245382	10204	18970, 27736, 36502, 45268, 54034
1284	chromosome 17 open reading frame 53	253405	1439	253405	10205	18971, 27737, 36503, 45269, 54035
1285	chromosome 17 open reading frame 53	319977	1440	313500	10206	18972, 27738, 36504, 45270, 54036
1286	chromosome 17 open reading frame 57	331493	1441	332111	10207	18973, 27739, 36505, 45271, 54037
1287	chromosome 17 open	344176	1442	343917	10208	18974, 27740,

	reading frame 57					36506, 45272, 54038
1288	chromosome 17 open reading frame 57	519772	1443	430802	10209	18975, 27741, 36507, 45273, 54039
1289	chromosome 17 open reading frame 57	523285	1444	427910	10210	18976, 27742, 36508, 45274, 54040
1290	chromosome 17 open reading frame 58	334461	1445	334741	10211	18977, 27743, 36509, 45275, 54041
1291	chromosome 17 open reading frame 58	449250	1446	402020	10212	18978, 27744, 36510, 45276, 54042
1292	chromosome 17 open reading frame 58	536693	1447	443680	10213	18979, 27745, 36511, 45277, 54043
1293	chromosome 17 open reading frame 58	576607	1448	460681	10214	18980, 27746, 36512, 45278, 54044
1294	chromosome 17 open reading frame 63	341217	1449	343115	10215	18981, 27747, 36513, 45279, 54045
1295	chromosome 17 open reading frame 63	452648	1450	413645	10216	18982, 27748, 36514, 45280, 54046
1296	chromosome 17 open reading frame 64	269127	1451	269127	10217	18983, 27749, 36515, 45281, 54047
1297	chromosome 17 open reading frame 65	303061	1452	366342	10218	18984, 27750, 36516, 45282, 54048
1298	chromosome 17 open reading frame 66	311880	1453	309560	10219	18985, 27751, 36517, 45283, 54049
1299	chromosome 17 open reading frame 72	225760	1454	225760	10220	18986, 27752, 36518, 45284, 54050
1300	chromosome 17 open reading frame 72	412177	1455	400986	10221	18987, 27753, 36519, 45285, 54051
1301	chromosome 17 open reading frame 72	425164	1456	396936	10222	18988, 27754, 36520, 45286, 54052
1302	chromosome 17 open reading frame 72	539996	1457	437876	10223	18989, 27755, 36521, 45287, 54053
1303	chromosome 17 open reading frame 72	577953	1458	463279	10224	18990, 27756, 36522, 45288, 54054

1304	chromosome 17 open reading frame 74	333870	1459	328061	10225	18991, 27757, 36523, 45289, 54055
1305	chromosome 17 open reading frame 75	225805	1460	225805	10226	18992, 27758, 36524, 45290, 54056
1306	chromosome 17 open reading frame 75	577809	1461	464275	10227	18993, 27759, 36525, 45291, 54057
1307	chromosome 17 open reading frame 77	328023	1462	329353	10228	18994, 27760, 36526, 45292, 54058
1308	chromosome 17 open reading frame 77	392620	1463	376396	10229	18995, 27761, 36527, 45293, 54059
1309	chromosome 17 open reading frame 77	524389	1464	436223	10230	18996, 27762, 36528, 45294, 54060
1310	chromosome 17 open reading frame 82	335108	1465	335229	10231	18997, 27763, 36529, 45295, 54061
1311	chromosome 17 open reading frame 84	255403	1466	255403	10232	18998, 27764, 36530, 45296, 54062
1312	chromosome 17 open reading frame 85	158149	1467	158149	10233	18999, 27765, 36531, 45297, 54063, 61523, 61581
1313	chromosome 17 open reading frame 85	389005	1468	373657	10234	19000, 27766, 36532, 45298, 54064
1314	chromosome 17 open reading frame 96	325814	1469	317905	10235	19001, 27767, 36533, 45299, 54065
1315	chromosome 17 open reading frame 97	360127	1470	353245	10236	19002, 27768, 36534, 45300, 54066
1316	chromosome 17 open reading frame 98	398575	1471	381580	10237	19003, 27769, 36535, 45301, 54067
1317	chromosome 17 open reading frame 99	340363	1472	343493	10238	19004, 27770, 36536, 45302, 54068
1318	chromosome 17 open reading frame 99	451352	1473	413076	10239	19005, 27771, 36537, 45303, 54069
1319	chromosome 18 open reading frame 21	269194	1474	269194	10240	19006, 27772, 36538, 45304, 54070
1320	chromosome 18 open	333234	1475	329492	10241	19007, 27773,

	reading frame 21					36539, 45305, 54071
1321	chromosome 18 open reading frame 21	592875	1476	465517	10242	19008, 27774, 36540, 45306, 54072
1322	chromosome 18 open reading frame 25	282059	1477	282059	10243	19009, 27775, 36541, 45307, 54073
1323	chromosome 18 open reading frame 25	321319	1478	324294	10244	19010, 27776, 36542, 45308, 54074
1324	chromosome 18 open reading frame 32	318240	1479	323199	10245	19011, 27777, 36543, 45309, 54075
1325	chromosome 18 open reading frame 32	579820	1480	464411	10246	19012, 27778, 36544, 45310, 54076
1326	chromosome 18 open reading frame 34	300227	1481	300227	10247	19013, 27779, 36545, 45311, 54077
1327	chromosome 18 open reading frame 34	383096	1482	372576	10248	19014, 27780, 36546, 45312, 54078
1328	chromosome 18 open reading frame 34	399177	1483	382130	10249	19015, 27781, 36547, 45313, 54079
1329	chromosome 18 open reading frame 34	402325	1484	385234	10250	19016, 27782, 36548, 45314, 54080
1330	chromosome 18 open reading frame 34	403303	1485	385591	10251	19017, 27783, 36549, 45315, 54081
1331	chromosome 18 open reading frame 34	406524	1486	385867	10252	19018, 27784, 36550, 45316, 54082
1332	chromosome 18 open reading frame 42	434239	1487	399075	10253	19019, 27785, 36551, 45317, 54083
1333	chromosome 18 open reading frame 56	323813	1488	316465	10254	19020, 27786, 36552, 45318, 54084
1334	chromosome 18 open reading frame 63	382675	1489	372122	10255	19021, 27787, 36553, 45319, 54085
1335	chromosome 18 open reading frame 8	269221	1490	269221	10256	19022, 27788, 36554, 45320, 54086
1336	chromosome 18 open reading frame 8	540942	1491	439296	10257	19023, 27789, 36555, 45321, 54087

1337	chromosome 18 open reading frame 8	542734	1492	439005	10258	19024, 27790, 36556, 45322, 54088
1338	chromosome 18 open reading frame 8	544799	1493	439363	10259	19025, 27791, 36557, 45323, 54089
1339	chromosome 19 open reading frame 21	215582	1494	215582	10260	19026, 27792, 36558, 45324, 54090
1340	chromosome 19 open reading frame 25	335104	1495	335309	10261	19027, 27793, 36559, 45325, 54091
1341	chromosome 19 open reading frame 25	427685	1496	389254	10262	19028, 27794, 36560, 45326, 54092
1342	chromosome 19 open reading frame 25	436106	1497	397394	10263	19029, 27795, 36561, 45327, 54093
1343	chromosome 19 open reading frame 26	215376	1498	215376	10264	19030, 27796, 36562, 45328, 54094
1344	chromosome 19 open reading frame 35	342063	1499	345102	10265	19031, 27797, 36563, 45329, 54095
1345	chromosome 19 open reading frame 42	487416	1500	417147	10266	19032, 27798, 36564, 45330, 54096
1346	chromosome 19 open reading frame 43	242784	1501	242784	10267	19033, 27799, 36565, 45331, 54097
1347	chromosome 19 open reading frame 45	361664	1502	355241	10268	19034, 27800, 36566, 45332, 54098
1348	chromosome 19 open reading frame 45	419849	1503	416988	10269	19035, 27801, 36567, 45333, 54099
1349	chromosome 19 open reading frame 45	421818	1504	411332	10270	19036, 27802, 36568, 45334, 54100
1350	chromosome 19 open reading frame 47	357884	1505	350556	10271	19037, 27803, 36569, 45335, 54101
1351	chromosome 19 open reading frame 47	392035	1506	375889	10272	19038, 27804, 36570, 45336, 54102
1352	chromosome 19 open reading frame 47	582783	1507	463159	10273	19039, 27805, 36571, 45337, 54103
1353	chromosome 19 open reading frame 48	345523	1508	301419	10274	19040, 27806, 36572, 45338,

						54104
1354	chromosome 19 open reading frame 48	391812	1509	375688	10275	19041, 27807, 36573, 45339, 54105
1355	chromosome 19 open reading frame 51	301249	1510	301249	10276	19042, 27808, 36574, 45340, 54106
1356	chromosome 19 open reading frame 51	391720	1511	375600	10277	19043, 27809, 36575, 45341, 54107
1357	chromosome 19 open reading frame 51	455045	1512	394343	10278	19044, 27810, 36576, 45342, 54108
1358	chromosome 19 open reading frame 52	270502	1513	270502	10279	19045, 27811, 36577, 45343, 54109
1359	chromosome 19 open reading frame 53	221576	1514	221576	10280	19046, 27812, 36578, 45344, 54110
1360	chromosome 19 open reading frame 53	588234	1515	465432	10281	19047, 27813, 36579, 45345, 54111
1361	chromosome 19 open reading frame 54	339153	1516	341122	10282	19048, 27814, 36580, 45346, 54112
1362	chromosome 19 open reading frame 54	378313	1517	367564	10283	19049, 27815, 36581, 45347, 54113
1363	chromosome 19 open reading frame 55	396908	1518	380116	10284	19050, 27816, 36582, 45348, 54114
1364	chromosome 19 open reading frame 55	537459	1519	439886	10285	19051, 27817, 36583, 45349, 54115
1365	chromosome 19 open reading frame 57	346736	1520	254336	10286	19052, 27818, 36584, 45350, 54116
1366	chromosome 19 open reading frame 57	454313	1521	404382	10287	19053, 27819, 36585, 45351, 54117
1367	chromosome 19 open reading frame 60	358607	1522	351422	10288	19054, 27820, 36586, 45352, 54118
1368	chromosome 19 open reading frame 60	450195	1523	398467	10289	19055, 27821, 36587, 45353, 54119
1369	chromosome 19 open reading frame 66	253110	1524	253110	10290	19056, 27822, 36588, 45354, 54120
1370	chromosome 19 open	397881	1525	380978	10291	19057, 27823,

	reading frame 66					36589, 45355, 54121
1371	chromosome 19 open reading frame 68	328759	1526	331363	10292	19058, 27824, 36590, 45356, 54122
1372	chromosome 19 open reading frame 69	378187	1527	367429	10293	19059, 27825, 36591, 45357, 54123
1373	chromosome 19 open reading frame 71	329493	1528	327950	10294	19060, 27826, 36592, 45358, 54124
1374	chromosome 19 open reading frame 73	408991	1529	386230	10295	19061, 27827, 36593, 45359, 54125
1375	chromosome 19 open reading frame 79	456958	1530	392303	10296	19062, 27828, 36594, 45360, 54126
1376	chromosome 2 open reading frame 16	408964	1531	386190	10297	19063, 27829, 36595, 45361, 54127
1377	chromosome 2 open reading frame 27A	355171	1532	347298	10298	19064, 27830, 36596, 45362, 54128
1378	chromosome 2 open reading frame 27B	303798	1533	304065	10299	19065, 27831, 36597, 45363, 54129
1379	chromosome 2 open reading frame 42	264434	1534	264434	10300	19066, 27832, 36598, 45364, 54130
1380	chromosome 2 open reading frame 42	417203	1535	399442	10301	19067, 27833, 36599, 45365, 54131
1381	chromosome 2 open reading frame 42	417865	1536	407799	10302	19068, 27834, 36600, 45366, 54132
1382	chromosome 2 open reading frame 42	419381	1537	389921	10303	19069, 27835, 36601, 45367, 54133
1383	chromosome 2 open reading frame 42	420306	1538	404515	10304	19070, 27836, 36602, 45368, 54134
1384	chromosome 2 open reading frame 42	425268	1539	388437	10305	19071, 27837, 36603, 45369, 54135
1385	chromosome 2 open reading frame 42	428010	1540	394401	10306	19072, 27838, 36604, 45370, 54136
1386	chromosome 2 open reading frame 42	428751	1541	405955	10307	19073, 27839, 36605, 45371, 54137

1387	chromosome 2 open reading frame 42	447804	1542	396751	10308	19074, 27840, 36606, 45372, 54138
1388	chromosome 2 open reading frame 42	457952	1543	391119	10309	19075, 27841, 36607, 45373, 54139
1389	chromosome 2 open reading frame 43	237822	1544	237822	10310	19076, 27842, 36608, 45374, 54140
1390	chromosome 2 open reading frame 43	435420	1545	388635	10311	19077, 27843, 36609, 45375, 54141
1391	chromosome 2 open reading frame 43	440866	1546	400340	10312	19078, 27844, 36610, 45376, 54142
1392	chromosome 2 open reading frame 43	541941	1547	440570	10313	19079, 27845, 36611, 45377, 54143
1393	chromosome 2 open reading frame 44	295148	1548	295148	10314	19080, 27846, 36612, 45378, 54144
1394	chromosome 2 open reading frame 44	443232	1549	413426	10315	19081, 27847, 36613, 45379, 54145
1395	chromosome 2 open reading frame 44	406895	1550	385816	10316	19082, 27848, 36614, 45380, 54146
1396	chromosome 2 open reading frame 48	381786	1551	371205	10317	19083, 27849, 36615, 45381, 54147
1397	chromosome 2 open reading frame 49	258457	1552	258457	10318	19084, 27850, 36616, 45382, 54148
1398	chromosome 2 open reading frame 49	437250	1553	400208	10319	19085, 27851, 36617, 45383, 54149
1399	chromosome 2 open reading frame 50	381585	1554	370997	10320	19086, 27852, 36618, 45384, 54150
1400	chromosome 2 open reading frame 50	405022	1555	384186	10321	19087, 27853, 36619, 45385, 54151
1401	chromosome 2 open reading frame 53	335524	1556	335017	10322	19088, 27854, 36620, 45386, 54152
1402	chromosome 2 open reading frame 54	307486	1557	302779	10323	19089, 27855, 36621, 45387, 54153
1403	chromosome 2 open reading frame 54	388934	1558	373586	10324	19090, 27856, 36622, 45388,

						54154
1404	chromosome 2 open reading frame 54	402775	1559	385338	10325	19091, 27857, 36623, 45389, 54155
1405	chromosome 2 open reading frame 54	414499	1560	390935	10326	19092, 27858, 36624, 45390, 54156
1406	chromosome 2 open reading frame 55	397899	1561	380996	10327	19093, 27859, 36625, 45391, 54157
1407	chromosome 2 open reading frame 57	313965	1562	315557	10328	19094, 27860, 36626, 45392, 54158
1408	chromosome 2 open reading frame 61	294947	1563	294947	10329	19095, 27861, 36627, 45393, 54159
1409	chromosome 2 open reading frame 61	445927	1564	408527	10330	19096, 27862, 36628, 45394, 54160
1410	chromosome 2 open reading frame 62	289388	1565	289388	10331	19097, 27863, 36629, 45395, 54161
1411	chromosome 2 open reading frame 63	401408	1566	384869	10332	19098, 27864, 36630, 45396, 54162
1412	chromosome 2 open reading frame 63	403506	1567	385598	10333	19099, 27865, 36631, 45397, 54163
1413	chromosome 2 open reading frame 63	406437	1568	384810	10334	19100, 27866, 36632, 45398, 54164
1414	chromosome 2 open reading frame 63	407122	1569	385778	10335	19101, 27867, 36633, 45399, 54165
1415	chromosome 2 open reading frame 63	425841	1570	400116	10336	19102, 27868, 36634, 45400, 54166
1416	chromosome 2 open reading frame 63	451916	1571	407575	10337	19103, 27869, 36635, 45401, 54167
1417	chromosome 2 open reading frame 68	306336	1572	304410	10338	19104, 27870, 36636, 45402, 54168
1418	chromosome 2 open reading frame 68	409734	1573	386301	10339	19105, 27871, 36637, 45403, 54169
1419	chromosome 2 open reading frame 70	329615	1574	332875	10340	19106, 27872, 36638, 45404, 54170
1420	chromosome 2 open reading	426997	1575	398725	10341	19107, 27873,

	frame 74					36639, 45405, 54171
1421	chromosome 2 open reading frame 74	432605	1576	402915	10342	19108, 27874, 36640, 45406, 54172
1422	chromosome 2 open reading frame 76	334816	1577	335041	10343	19109, 27875, 36641, 45407, 54173
1423	chromosome 2 open reading frame 76	409466	1578	386302	10344	19110, 27876, 36642, 45408, 54174
1424	chromosome 2 open reading frame 76	409523	1579	386714	10345	19111, 27877, 36643, 45409, 54175
1425	chromosome 2 open reading frame 76	409877	1580	387234	10346	19112, 27878, 36644, 45410, 54176
1426	chromosome 2 open reading frame 77	447353	1581	391504	10347	19113, 27879, 36645, 45411, 54177
1427	chromosome 2 open reading frame 78	342345	1582	340692	10348	19114, 27880, 36646, 45412, 54178
1428	chromosome 2 open reading frame 78	409561	1583	387124	10349	19115, 27881, 36647, 45413, 54179
1429	chromosome 2 open reading frame 80	341287	1584	343171	10350	19116, 27882, 36648, 45414, 54180
1430	chromosome 2 open reading frame 80	449053	1585	397281	10351	19117, 27883, 36649, 45415, 54181
1431	chromosome 2 open reading frame 81	290390	1586	290390	10352	19118, 27884, 36650, 45416, 54182
1432	chromosome 2 open reading frame 82	448993	1587	401100	10353	19119, 27885, 36651, 45417, 54183
1433	chromosome 2 open reading frame 83	264387	1588	264387	10354	19120, 27886, 36652, 45418, 54184
1434	chromosome 2 open reading frame 83	409066	1589	387149	10355	19121, 27887, 36653, 45419, 54185
1435	chromosome 2 open reading frame 84	295150	1590	295150	10356	19122, 27888, 36654, 45420, 54186
1436	chromosome 2 open reading frame 88	340623	1591	345107	10357	19123, 27889, 36655, 45421, 54187

1437	chromosome 2 open reading frame 88	396974	1592	380172	10358	19124, 27890, 36656, 45422, 54188
1438	chromosome 2 open reading frame 88	409545	1593	386976	10359	19125, 27891, 36657, 45423, 54189
1439	chromosome 2 open reading frame 88	409870	1594	386649	10360	19126, 27892, 36658, 45424, 54190
1440	chromosome 2 open reading frame 88	443551	1595	405225	10361	19127, 27893, 36659, 45425, 54191
1441	chromosome 2 open reading frame 88	450357	1596	394370	10362	19128, 27894, 36660, 45426, 54192
1442	chromosome 2 open reading frame 91	378711	1597	367983	10363	19129, 27895, 36661, 45427, 54193
1443	chromosome 20 open reading frame 111	255174	1598	255174	10364	19130, 27896, 36662, 45428, 54194
1444	chromosome 20 open reading frame 111	372970	1599	362061	10365	19131, 27897, 36663, 45429, 54195
1445	chromosome 20 open reading frame 112	201961	1600	201961	10366	19132, 27898, 36664, 45430, 54196
1446	chromosome 20 open reading frame 112	326071	1601	317413	10367	19133, 27899, 36665, 45431, 54197
1447	chromosome 20 open reading frame 112	359676	1602	352704	10368	19134, 27900, 36666, 45432, 54198
1448	chromosome 20 open reading frame 112	375673	1603	364825	10369	19135, 27901, 36667, 45433, 54199
1449	chromosome 20 open reading frame 112	375677	1604	364829	10370	19136, 27902, 36668, 45434, 54200
1450	chromosome 20 open reading frame 112	375678	1605	364830	10371	19137, 27903, 36669, 45435, 54201
1451	chromosome 20 open reading frame 112	397984	1606	381071	10372	19138, 27904, 36670, 45436, 54202
1452	chromosome 20 open reading frame 112	419612	1607	410774	10373	19139, 27905, 36671, 45437, 54203
1453	chromosome 20 open reading frame 132	217333	1608	217333	10374	19140, 27906, 36672, 45438,

						54204
1454	chromosome 20 open reading frame 132	343811	1609	339971	10375	19141, 27907, 36673, 45439, 54205
1455	chromosome 20 open reading frame 132	400440	1610	383290	10376	19142, 27908, 36674, 45440, 54206
1456	chromosome 20 open reading frame 132	400441	1611	383291	10377	19143, 27909, 36675, 45441, 54207
1457	chromosome 20 open reading frame 132	417458	1612	415930	10378	19144, 27910, 36676, 45442, 54208
1458	chromosome 20 open reading frame 132	421643	1613	413544	10379	19145, 27911, 36677, 45443, 54209
1459	chromosome 20 open reading frame 132	422138	1614	400468	10380	19146, 27912, 36678, 45444, 54210
1460	chromosome 20 open reading frame 132	434295	1615	389695	10381	19147, 27913, 36679, 45445, 54211
1461	chromosome 20 open reading frame 132	441008	1616	392144	10382	19148, 27914, 36680, 45446, 54212
1462	chromosome 20 open reading frame 144	375222	1617	364370	10383	19149, 27915, 36681, 45447, 54213
1463	chromosome 20 open reading frame 151	252998	1618	252998	10384	19150, 27916, 36682, 45448, 54214
1464	chromosome 20 open reading frame 152	349339	1619	340954	10385	19151, 27917, 36683, 45449, 54215
1465	chromosome 20 open reading frame 152	373973	1620	363084	10386	19152, 27918, 36684, 45450, 54216
1466	chromosome 20 open reading frame 152	538900	1621	442729	10387	19153, 27919, 36685, 45451, 54217
1467	chromosome 20 open reading frame 160	262659	1622	262659	10388	19154, 27920, 36686, 45452, 54218
1468	chromosome 20 open reading frame 160	300415	1623	300415	10389	19155, 27921, 36687, 45453, 54219
1469	chromosome 20 open reading frame 160	339619	1624	343976	10390	19156, 27922, 36688, 45454, 54220
1470	chromosome 20 open	452892	1625	392448	10391	19157, 27923,

	reading frame 160					36689, 45455, 54221
1471	chromosome 20 open reading frame 166	370523	1626	359554	10392	19158, 27924, 36690, 45456, 54222
1472	chromosome 20 open reading frame 166	370524	1627	359555	10393	19159, 27925, 36691, 45457, 54223
1473	chromosome 20 open reading frame 166	370527	1628	359558	10394	19160, 27926, 36692, 45458, 54224
1474	chromosome 20 open reading frame 173	246199	1629	246199	10395	19161, 27927, 36693, 45459, 54225
1475	chromosome 20 open reading frame 173	444723	1630	403566	10396	19162, 27928, 36694, 45460, 54226
1476	chromosome 20 open reading frame 177	358293	1631	351040	10397	19163, 27929, 36695, 45461, 54227
1477	chromosome 20 open reading frame 177	360816	1632	354056	10398	19164, 27930, 36696, 45462, 54228
1478	chromosome 20 open reading frame 177	421092	1633	414543	10399	19165, 27931, 36697, 45463, 54229
1479	chromosome 20 open reading frame 187	378252	1634	367499	10400	19166, 27932, 36698, 45464, 54230
1480	chromosome 20 open reading frame 187	537362	1635	439615	10401	19167, 27933, 36699, 45465, 54231
1481	chromosome 20 open reading frame 195	370097	1636	359115	10402	19168, 27934, 36700, 45466, 54232
1482	chromosome 20 open reading frame 195	370098	1637	359116	10403	19169, 27935, 36701, 45467, 54233
1483	chromosome 20 open reading frame 196	303142	1638	305875	10404	19170, 27936, 36702, 45468, 54234
1484	chromosome 20 open reading frame 196	378971	1639	368254	10405	19171, 27937, 36703, 45469, 54235
1485	chromosome 20 open reading frame 196	378979	1640	368263	10406	19172, 27938, 36704, 45470, 54236
1486	chromosome 20 open reading frame 196	442185	1641	410534	10407	19173, 27939, 36705, 45471, 54237

1487	chromosome 20 open reading frame 196	445603	1642	399331	10408	19174, 27940, 36706, 45472, 54238
1488	chromosome 20 open reading frame 196	541651	1643	441395	10409	19175, 27941, 36707, 45473, 54239
1489	chromosome 20 open reading frame 197	313426	1644	316457	10410	19176, 27942, 36708, 45474, 54240
1490	chromosome 20 open reading frame 201	308906	1645	310801	10411	19177, 27943, 36709, 45475, 54241
1491	chromosome 20 open reading frame 202	400633	1646	383474	10412	19178, 27944, 36710, 45476, 54242
1492	chromosome 20 open reading frame 26	245957	1647	245957	10413	19179, 27945, 36711, 45477, 54243
1493	chromosome 20 open reading frame 26	339482	1648	345660	10414	19180, 27946, 36712, 45478, 54244
1494	chromosome 20 open reading frame 26	343997	1649	342164	10415	19181, 27947, 36713, 45479, 54245
1495	chromosome 20 open reading frame 26	377293	1650	366508	10416	19182, 27948, 36714, 45480, 54246
1496	chromosome 20 open reading frame 26	377297	1651	366512	10417	19183, 27949, 36715, 45481, 54247
1497	chromosome 20 open reading frame 26	377303	1652	366518	10418	19184, 27950, 36716, 45482, 54248
1498	chromosome 20 open reading frame 26	377306	1653	366521	10419	19185, 27951, 36717, 45483, 54249
1499	chromosome 20 open reading frame 26	377309	1654	366524	10420	19186, 27952, 36718, 45484, 54250
1500	chromosome 20 open reading frame 26	389655	1655	374306	10421	19187, 27953, 36719, 45485, 54251
1501	chromosome 20 open reading frame 26	389656	1656	374307	10422	19188, 27954, 36720, 45486, 54252
1502	chromosome 20 open reading frame 26	451767	1657	414537	10423	19189, 27955, 36721, 45487, 54253
1503	chromosome 20 open reading frame 26	475466	1658	417086	10424	19190, 27956, 36722, 45488,

						54254
1504	chromosome 20 open reading frame 27	217195	1659	217195	10425	19191, 27957, 36723, 45489, 54255
1505	chromosome 20 open reading frame 27	379765	1660	369090	10426	19192, 27958, 36724, 45490, 54256
1506	chromosome 20 open reading frame 27	379772	1661	369097	10427	19193, 27959, 36725, 45491, 54257
1507	chromosome 20 open reading frame 27	399672	1662	382580	10428	19194, 27960, 36726, 45492, 54258
1508	chromosome 20 open reading frame 27	399683	1663	382591	10429	19195, 27961, 36727, 45493, 54259
1509	chromosome 20 open reading frame 29	246041	1664	246041	10430	19196, 27962, 36728, 45494, 54260
1510	chromosome 20 open reading frame 29	379567	1665	368886	10431	19197, 27963, 36729, 45495, 54261
1511	chromosome 20 open reading frame 29	379573	1666	368892	10432	19198, 27964, 36730, 45496, 54262
1512	chromosome 20 open reading frame 29	455742	1667	405487	10433	19199, 27965, 36731, 45497, 54263
1513	chromosome 20 open reading frame 4	320849	1668	313674	10434	19200, 27966, 36732, 45498, 54264
1514	chromosome 20 open reading frame 4	373932	1669	363043	10435	19201, 27967, 36733, 45499, 54265
1515	chromosome 20 open reading frame 43	23939	1670	23939	10436	19202, 27968, 36734, 45500, 54266, 61524, 61582
1516	chromosome 20 open reading frame 43	357348	1671	349906	10437	19203, 27969, 36735, 45501, 54267
1517	chromosome 20 open reading frame 43	435342	1672	407185	10438	19204, 27970, 36736, 45502, 54268
1518	chromosome 20 open reading frame 78	278779	1673	278779	10439	19205, 27971, 36737, 45503, 54269
1519	chromosome 20 open reading frame 79	377428	1674	366645	10440	19206, 27972, 36738, 45504, 54270

1520	chromosome 20 open reading frame 85	371168	1675	360210	10441	19207, 27973, 36739, 45505, 54271
1521	chromosome 20 open reading frame 94	334534	1676	335557	10442	19208, 27974, 36740, 45506, 54272
1522	chromosome 20 open reading frame 96	360321	1677	353470	10443	19209, 27975, 36741, 45507, 54273
1523	chromosome 20 open reading frame 96	382369	1678	371806	10444	19210, 27976, 36742, 45508, 54274
1524	chromosome 20 open reading frame 96	400269	1679	383128	10445	19211, 27977, 36743, 45509, 54275
1525	chromosome 21 open reading frame 119	534991	1680	442411	10446	19212, 27978, 36744, 45510, 54276
1526	chromosome 21 open reading frame 37	440664	1681	388953	10447	19213, 27979, 36745, 45511, 54277
1527	chromosome 21 open reading frame 49	382375	1682	371812	10448	19214, 27980, 36746, 45512, 54278
1528	chromosome 21 open reading frame 49	382378	1683	371815	10449	19215, 27981, 36747, 45513, 54279
1529	chromosome 21 open reading frame 54	440586	1684	406117	10450	19216, 27982, 36748, 45514, 54280
1530	chromosome 21 open reading frame 54	451980	1685	407868	10451	19217, 27983, 36749, 45515, 54281
1531	chromosome 21 open reading frame 58	291691	1686	291691	10452	19218, 27984, 36750, 45516, 54282
1532	chromosome 21 open reading frame 58	397685	1687	380801	10453	19219, 27985, 36751, 45517, 54283
1533	chromosome 21 open reading frame 58	417060	1688	402356	10454	19220, 27986, 36752, 45518, 54284
1534	chromosome 21 open reading frame 62	479548	1689	418653	10455	19221, 27987, 36753, 45519, 54285
1535	chromosome 21 open reading frame 62	487113	1690	418511	10456	19222, 27988, 36754, 45520, 54286
1536	chromosome 21 open reading frame 62	490358	1691	418830	10457	19223, 27989, 36755, 45521,

						54287
1537	chromosome 21 open reading frame 62	536776	1692	444950	10458	19224, 27990, 36756, 45522, 54288
1538	chromosome 21 open reading frame 90	330490	1693	333592	10459	19225, 27991, 36757, 45523, 54289
1539	chromosome 21 open reading frame 91	284881	1694	284881	10460	19226, 27992, 36758, 45524, 54290
1540	chromosome 21 open reading frame 91	400559	1695	383404	10461	19227, 27993, 36759, 45525, 54291
1541	chromosome 21 open reading frame 91	405964	1696	385566	10462	19228, 27994, 36760, 45526, 54292
1542	chromosome 21 open reading frame 91	400558	1697	383403	10463	19229, 27995, 36761, 45527, 54293
1543	chromosome 22 open reading frame 13	407471	1698	386076	10464	19230, 27996, 36762, 45528, 54294
1544	chromosome 22 open reading frame 13	407973	1699	385583	10465	19231, 27997, 36763, 45529, 54295
1545	chromosome 22 open reading frame 15	336186	1700	336688	10466	19232, 27998, 36764, 45530, 54296
1546	chromosome 22 open reading frame 15	382821	1701	372271	10467	19233, 27999, 36765, 45531, 54297
1547	chromosome 22 open reading frame 15	402217	1702	384965	10468	19234, 28000, 36766, 45532, 54298
1548	chromosome 22 open reading frame 23	249079	1703	249079	10469	19235, 28001, 36767, 45533, 54299
1549	chromosome 22 open reading frame 23	403026	1704	384618	10470	19236, 28002, 36768, 45534, 54300
1550	chromosome 22 open reading frame 23	403305	1705	384667	10471	19237, 28003, 36769, 45535, 54301
1551	chromosome 22 open reading frame 23	418863	1706	395077	10472	19238, 28004, 36770, 45536, 54302
1552	chromosome 22 open reading frame 23	422191	1707	407707	10473	19239, 28005, 36771, 45537, 54303
1553	chromosome 22 open	333761	1708	327764	10474	19240, 28006,

	reading frame 26					36772, 45538, 54304
1554	chromosome 22 open reading frame 26	396008	1709	379329	10475	19241, 28007, 36773, 45539, 54305
1555	chromosome 22 open reading frame 29	328554	1710	330596	10476	19242, 28008, 36774, 45540, 54306
1556	chromosome 22 open reading frame 29	405640	1711	384924	10477	19243, 28009, 36775, 45541, 54307
1557	chromosome 22 open reading frame 29	407472	1712	386111	10478	19244, 28010, 36776, 45542, 54308
1558	chromosome 22 open reading frame 31	216071	1713	216071	10479	19245, 28011, 36777, 45543, 54309
1559	chromosome 22 open reading frame 33	381821	1714	371243	10480	19246, 28012, 36778, 45544, 54310
1560	chromosome 22 open reading frame 33	402860	1715	385179	10481	19247, 28013, 36779, 45545, 54311
1561	chromosome 22 open reading frame 33	405091	1716	386118	10482	19248, 28014, 36780, 45546, 54312
1562	chromosome 22 open reading frame 34	400023	1717	382900	10483	19249, 28015, 36781, 45547, 54313
1563	chromosome 22 open reading frame 34	444628	1718	395549	10484	19250, 28016, 36782, 45548, 54314
1564	chromosome 22 open reading frame 39	333059	1719	333064	10485	19251, 28017, 36783, 45549, 54315
1565	chromosome 22 open reading frame 39	399562	1720	382474	10486	19252, 28018, 36784, 45550, 54316
1566	chromosome 22 open reading frame 39	542103	1721	439212	10487	19253, 28019, 36785, 45551, 54317
1567	chromosome 22 open reading frame 42	382097	1722	371529	10488	19254, 28020, 36786, 45552, 54318
1568	chromosome 22 open reading frame 43	317749	1723	316137	10489	19255, 28021, 36787, 45553, 54319
1569	chromosome 22 open reading frame 45	326341	1724	426996	10490	19256, 28022, 36788, 45554, 54320

1570	chromosome 22 open reading frame 45	543438	1725	439933	10491	19257, 28023, 36789, 45555, 54321
1571	chromosome 3 open reading frame 14	232519	1726	232519	10492	19258, 28024, 36790, 45556, 54322
1572	chromosome 3 open reading frame 14	462069	1727	419977	10493	19259, 28025, 36791, 45557, 54323
1573	chromosome 3 open reading frame 14	465142	1728	419937	10494	19260, 28026, 36792, 45558, 54324
1574	chromosome 3 open reading frame 14	494481	1729	418086	10495	19261, 28027, 36793, 45559, 54325
1575	chromosome 3 open reading frame 14	542214	1730	438275	10496	19262, 28028, 36794, 45560, 54326
1576	chromosome 3 open reading frame 19	285042	1731	285042	10497	19263, 28029, 36795, 45561, 54327
1577	chromosome 3 open reading frame 19	383794	1732	373304	10498	19264, 28030, 36796, 45562, 54328
1578	chromosome 3 open reading frame 22	318225	1733	316644	10499	19265, 28031, 36797, 45563, 54329
1579	chromosome 3 open reading frame 24	450660	1734	429608	10500	19266, 28032, 36798, 45564, 54330
1580	chromosome 3 open reading frame 24	524279	1735	429663	10501	19267, 28033, 36799, 45565, 54331
1581	chromosome 3 open reading frame 25	326085	1736	324241	10502	19268, 28034, 36800, 45566, 54332
1582	chromosome 3 open reading frame 25	505956	1737	420854	10503	19269, 28035, 36801, 45567, 54333
1583	chromosome 3 open reading frame 26	421999	1738	410396	10504	19270, 28036, 36802, 45568, 54334
1584	chromosome 3 open reading frame 27	356020	1739	348302	10505	19271, 28037, 36803, 45569, 54335
1585	chromosome 3 open reading frame 30	295622	1740	295622	10506	19272, 28038, 36804, 45570, 54336
1586	chromosome 3 open reading frame 32	317371	1741	324551	10507	19273, 28039, 36805, 45571,

						54337
1587	chromosome 3 open reading frame 32	341795	1742	339150	10508	19274, 28040, 36806, 45572, 54338
1588	chromosome 3 open reading frame 32	415132	1743	410757	10509	19275, 28041, 36807, 45573, 54339
1589	chromosome 3 open reading frame 32	544814	1744	439378	10510	19276, 28042, 36808, 45574, 54340
1590	chromosome 3 open reading frame 36	408895	1745	386219	10511	19277, 28043, 36809, 45575, 54341
1591	chromosome 3 open reading frame 37	383463	1746	372955	10512	19278, 28044, 36810, 45576, 54342
1592	chromosome 3 open reading frame 37	389735	1747	374385	10513	19279, 28045, 36811, 45577, 54343
1593	chromosome 3 open reading frame 37	502878	1748	426215	10514	19280, 28046, 36812, 45578, 54344
1594	chromosome 3 open reading frame 38	318887	1749	322469	10515	19281, 28047, 36813, 45579, 54345
1595	chromosome 3 open reading frame 49	295896	1750	295896	10516	19282, 28048, 36814, 45580, 54346
1596	chromosome 3 open reading frame 55	312275	1751	312323	10517	19283, 28049, 36815, 45581, 54347
1597	chromosome 3 open reading frame 55	426338	1752	387918	10518	19284, 28050, 36816, 45582, 54348
1598	chromosome 3 open reading frame 55	449199	1753	413228	10519	19285, 28051, 36817, 45583, 54349
1599	chromosome 3 open reading frame 56	398112	1754	381182	10520	19286, 28052, 36818, 45584, 54350
1600	chromosome 3 open reading frame 62	343010	1755	341139	10521	19287, 28053, 36819, 45585, 54351
1601	chromosome 3 open reading frame 65	296270	1756	296270	10522	19288, 28054, 36820, 45586, 54352
1602	chromosome 3 open reading frame 67	295966	1757	295966	10523	19289, 28055, 36821, 45587, 54353
1603	chromosome 3 open reading	394474	1758	377984	10524	19290, 28056,

	frame 67					36822, 45588, 54354
1604	chromosome 3 open reading frame 67	482387	1759	417122	10525	19291, 28057, 36823, 45589, 54355
1605	chromosome 3 open reading frame 70	335012	1760	334974	10526	19292, 28058, 36824, 45590, 54356
1606	chromosome 3 open reading frame 72	383165	1761	372651	10527	19293, 28059, 36825, 45591, 54357
1607	chromosome 3 open reading frame 74	541313	1762	437714	10528	19294, 28060, 36826, 45592, 54358
1608	chromosome 3 open reading frame 75	296149	1763	296149	10529	19295, 28061, 36827, 45593, 54359
1609	chromosome 3 open reading frame 75	450051	1764	403082	10530	19296, 28062, 36828, 45594, 54360
1610	chromosome 3 open reading frame 79	446603	1765	389475	10531	19297, 28063, 36829, 45595, 54361
1611	chromosome 3 open reading frame 80	326474	1766	313324	10532	19298, 28064, 36830, 45596, 54362
1612	chromosome 4 open reading frame 17	326581	1767	322582	10533	19299, 28065, 36831, 45597, 54363
1613	chromosome 4 open reading frame 19	284437	1768	284437	10534	19300, 28066, 36832, 45598, 54364
1614	chromosome 4 open reading frame 19	381980	1769	371408	10535	19301, 28067, 36833, 45599, 54365
1615	chromosome 4 open reading frame 22	358105	1770	350818	10536	19302, 28068, 36834, 45600, 54366
1616	chromosome 4 open reading frame 22	508675	1771	425786	10537	19303, 28069, 36835, 45601, 54367
1617	chromosome 4 open reading frame 33	281146	1772	281146	10538	19304, 28070, 36836, 45602, 54368
1618	chromosome 4 open reading frame 33	425929	1773	401090	10539	19305, 28071, 36837, 45603, 54369
1619	chromosome 4 open reading frame 33	508622	1774	427431	10540	19306, 28072, 36838, 45604, 54370

1620	chromosome 4 open reading frame 36	295898	1775	295898	10541	19307, 28073, 36839, 45605, 54371
1621	chromosome 4 open reading frame 36	473559	1776	420949	10542	19308, 28074, 36840, 45606, 54372
1622	chromosome 4 open reading frame 36	504008	1777	422720	10543	19309, 28075, 36841, 45607, 54373
1623	chromosome 4 open reading frame 36	506308	1778	421141	10544	19310, 28076, 36842, 45608, 54374
1624	chromosome 4 open reading frame 37	295268	1779	295268	10545	19311, 28077, 36843, 45609, 54375
1625	chromosome 4 open reading frame 38	506413	1780	421843	10546	19312, 28078, 36844, 45610, 54376
1626	chromosome 4 open reading frame 39	513876	1781	427428	10547	19313, 28079, 36845, 45611, 54377
1627	chromosome 4 open reading frame 42	357591	1782	350204	10548	19314, 28080, 36846, 45612, 54378
1628	chromosome 4 open reading frame 43	358572	1783	351380	10549	19315, 28081, 36847, 45613, 54379
1629	chromosome 4 open reading frame 44	438480	1784	411584	10550	19316, 28082, 36848, 45614, 54380
1630	chromosome 4 open reading frame 45	434826	1785	412215	10551	19317, 28083, 36849, 45615, 54381
1631	chromosome 4 open reading frame 46	379205	1786	368503	10552	19318, 28084, 36850, 45616, 54382
1632	chromosome 4 open reading frame 47	378850	1787	368127	10553	19319, 28085, 36851, 45617, 54383
1633	chromosome 4 open reading frame 47	511138	1788	422279	10554	19320, 28086, 36852, 45618, 54384
1634	chromosome 4 open reading frame 47	511581	1789	423127	10555	19321, 28087, 36853, 45619, 54385
1635	chromosome 4 open reading frame 50	324058	1790	317287	10556	19322, 28088, 36854, 45620, 54386
1636	chromosome 4 open reading frame 50	531445	1791	437121	10557	19323, 28089, 36855, 45621,

						54387
1637	chromosome 4 open reading frame 51	438731	1792	391404	10558	19324, 28090, 36856, 45622, 54388
1638	chromosome 4 open reading frame 51	511965	1793	425306	10559	19325, 28091, 36857, 45623, 54389
1639	chromosome 4 open reading frame 52	412980	1794	441532	10560	19326, 28092, 36858, 45624, 54390
1640	chromosome 4 open reading frame 52	506197	1795	427407	10561	19327, 28093, 36859, 45625, 54391
1641	chromosome 4 open reading frame 6	195455	1796	195455	10562	19328, 28094, 36860, 45626, 54392
1642	chromosome 5 open reading frame 17	507936	1797	426817	10563	19329, 28095, 36861, 45627, 54393
1643	chromosome 5 open reading frame 22	325366	1798	326879	10564	19330, 28096, 36862, 45628, 54394
1644	chromosome 5 open reading frame 22	355907	1799	348171	10565	19331, 28097, 36863, 45629, 54395
1645	chromosome 5 open reading frame 22	543911	1800	444801	10566	19332, 28098, 36864, 45630, 54396
1646	chromosome 5 open reading frame 24	338051	1801	337044	10567	19333, 28099, 36865, 45631, 54397
1647	chromosome 5 open reading frame 24	394976	1802	378427	10568	19334, 28100, 36866, 45632, 54398
1648	chromosome 5 open reading frame 24	435259	1803	395764	10569	19335, 28101, 36867, 45633, 54399
1649	chromosome 5 open reading frame 24	508791	1804	422620	10570	19336, 28102, 36868, 45634, 54400
1650	chromosome 5 open reading frame 25	332772	1805	331311	10571	19337, 28103, 36869, 45635, 54401
1651	chromosome 5 open reading frame 25	341199	1806	342075	10572	19338, 28104, 36870, 45636, 54402
1652	chromosome 5 open reading frame 25	377277	1807	366489	10573	19339, 28105, 36871, 45637, 54403
1653	chromosome 5 open reading	429602	1808	410552	10574	19340, 28106,

	frame 25					36872, 45638, 54404
1654	chromosome 5 open reading frame 25	430704	1809	409287	10575	19341, 28107, 36873, 45639, 54405
1655	chromosome 5 open reading frame 25	443967	1810	406571	10576	19342, 28108, 36874, 45640, 54406
1656	chromosome 5 open reading frame 27	357880	1811	427188	10577	19343, 28109, 36875, 45641, 54407
1657	chromosome 5 open reading frame 27	436592	1812	423049	10578	19344, 28110, 36876, 45642, 54408
1658	chromosome 5 open reading frame 30	319933	1813	326110	10579	19345, 28111, 36877, 45643, 54409
1659	chromosome 5 open reading frame 30	510890	1814	421270	10580	19346, 28112, 36878, 45644, 54410
1660	chromosome 5 open reading frame 30	515669	1815	422836	10581	19347, 28113, 36879, 45645, 54411
1661	chromosome 5 open reading frame 30	575217	1816	458989	10582	19348, 28114, 36880, 45646, 54412
1662	chromosome 5 open reading frame 32	261811	1817	261811	10583	19349, 28115, 36881, 45647, 54413
1663	chromosome 5 open reading frame 34	306862	1818	303490	10584	19350, 28116, 36882, 45648, 54414
1664	chromosome 5 open reading frame 35	285947	1819	285947	10585	19351, 28117, 36883, 45649, 54415
1665	chromosome 5 open reading frame 35	541720	1820	442886	10586	19352, 28118, 36884, 45650, 54416
1666	chromosome 5 open reading frame 39	314890	1821	315915	10587	19353, 28119, 36885, 45651, 54417
1667	chromosome 5 open reading frame 41	296953	1822	296953	10588	19354, 28120, 36886, 45652, 54418
1668	chromosome 5 open reading frame 41	393776	1823	377371	10589	19355, 28121, 36887, 45653, 54419
1669	chromosome 5 open reading frame 41	520420	1824	428290	10590	19356, 28122, 36888, 45654, 54420

1670	chromosome 5 open reading frame 41	522692	1825	431107	10591	19357, 28123, 36889, 45655, 54421
1671	chromosome 5 open reading frame 41	523161	1826	430801	10592	19358, 28124, 36890, 45656, 54422
1672	chromosome 5 open reading frame 41	538538	1827	444756	10593	19359, 28125, 36891, 45657, 54423
1673	chromosome 5 open reading frame 41	540014	1828	440075	10594	19360, 28126, 36892, 45658, 54424
1674	chromosome 5 open reading frame 42	274258	1829	274258	10595	19361, 28127, 36893, 45659, 54425
1675	chromosome 5 open reading frame 42	388739	1830	373391	10596	19362, 28128, 36894, 45660, 54426
1676	chromosome 5 open reading frame 42	425232	1831	389014	10597	19363, 28129, 36895, 45661, 54427
1677	chromosome 5 open reading frame 42	508244	1832	421690	10598	19364, 28130, 36896, 45662, 54428
1678	chromosome 5 open reading frame 44	231526	1833	231526	10599	19365, 28131, 36897, 45663, 54429
1679	chromosome 5 open reading frame 44	399438	1834	382367	10600	19366, 28132, 36898, 45664, 54430
1680	chromosome 5 open reading frame 44	505553	1835	423405	10601	19367, 28133, 36899, 45665, 54431
1681	chromosome 5 open reading frame 44	545191	1836	441066	10602	19368, 28134, 36900, 45666, 54432
1682	chromosome 5 open reading frame 44	438419	1837	409231	10603	19369, 28135, 36901, 45667, 54433
1683	chromosome 5 open reading frame 45	292586	1838	292586	10604	19370, 28136, 36902, 45668, 54434
1684	chromosome 5 open reading frame 45	376931	1839	366130	10605	19371, 28137, 36903, 45669, 54435
1685	chromosome 5 open reading frame 45	403396	1840	384599	10606	19372, 28138, 36904, 45670, 54436
1686	chromosome 5 open reading frame 47	340147	1841	340887	10607	19373, 28139, 36905, 45671,

						54437
1687	chromosome 5 open reading frame 48	357147	1842	349669	10608	19374, 28140, 36906, 45672, 54438
1688	chromosome 5 open reading frame 49	399810	1843	382708	10609	19375, 28141, 36907, 45673, 54439
1689	chromosome 5 open reading frame 50	330910	1844	331214	10610	19376, 28142, 36908, 45674, 54440
1690	chromosome 5 open reading frame 51	381647	1845	371061	10611	19377, 28143, 36909, 45675, 54441
1691	chromosome 5 open reading frame 52	409999	1846	387027	10612	19378, 28144, 36910, 45676, 54442
1692	chromosome 5 open reading frame 54	408953	1847	386184	10613	19379, 28145, 36911, 45677, 54443
1693	chromosome 5 open reading frame 54	523213	1848	428831	10614	19380, 28146, 36912, 45678, 54444
1694	chromosome 5 open reading frame 58	521850	1849	428956	10615	19381, 28147, 36913, 45679, 54445
1695	chromosome 5 open reading frame 58	593851	1850	471984	10616	19382, 28148, 36914, 45680, 54446
1696	chromosome 5 open reading frame 60	448248	1851	404583	10617	19383, 28149, 36915, 45681, 54447
1697	chromosome 5 open reading frame 63	296662	1852	453964	10618	19384, 28150, 36916, 45682, 54448
1698	chromosome 5 open reading frame 63	535381	1853	454153	10619	19385, 28151, 36917, 45683, 54449
1699	chromosome 5 open reading frame 65	434752	1854	416033	10620	19386, 28152, 36918, 45684, 54450
1700	chromosome 6 open reading frame 10	383262	1855	372749	10621	19387, 28153, 36919, 45685, 54451
1701	chromosome 6 open reading frame 10	399749	1856	382654	10622	19388, 28154, 36920, 45686, 54452
1702	chromosome 6 open reading frame 10	413045	1857	410028	10623	19389, 28155, 36921, 45687, 54453
1703	chromosome 6 open reading	422186	1858	400272	10624	19390, 28156,

	frame 10					36922, 45688, 54454
1704	chromosome 6 open reading frame 10	423858	1859	414408	10625	19391, 28157, 36923, 45689, 54455
1705	chromosome 6 open reading frame 10	424621	1860	393107	10626	19392, 28158, 36924, 45690, 54456
1706	chromosome 6 open reading frame 10	425722	1861	390018	10627	19393, 28159, 36925, 45691, 54457
1707	chromosome 6 open reading frame 10	427082	1862	416682	10628	19394, 28160, 36926, 45692, 54458
1708	chromosome 6 open reading frame 10	438312	1863	400675	10629	19395, 28161, 36927, 45693, 54459
1709	chromosome 6 open reading frame 10	449847	1864	406760	10630	19396, 28162, 36928, 45694, 54460
1710	chromosome 6 open reading frame 10	451857	1865	415507	10631	19397, 28163, 36929, 45695, 54461
1711	chromosome 6 open reading frame 10	457429	1866	408514	10632	19398, 28164, 36930, 45696, 54462
1712	chromosome 6 open reading frame 10	552887	1867	450027	10633	19399, 28165, 36931, 45697, 54463
1713	chromosome 6 open reading frame 100	377186	1868	366391	10634	19400, 28166, 36932, 45698, 54464
1714	chromosome 6 open reading frame 100	383656	1869	373152	10635	19401, 28167, 36933, 45699, 54465
1715	chromosome 6 open reading frame 100	421470	1870	410635	10636	19402, 28168, 36934, 45700, 54466
1716	chromosome 6 open reading frame 100	434916	1871	394134	10637	19403, 28169, 36935, 45701, 54467
1717	chromosome 6 open reading frame 100	438403	1872	401725	10638	19404, 28170, 36936, 45702, 54468
1718	chromosome 6 open reading frame 100	438996	1873	396675	10639	19405, 28171, 36937, 45703, 54469
1719	chromosome 6 open reading frame 103	367488	1874	356458	10640	19406, 28172, 36938, 45704, 54470

1720	chromosome 6 open reading frame 103	367493	1875	356463	10641	19407, 28173, 36939, 45705, 54471
1721	chromosome 6 open reading frame 103	397944	1876	381036	10642	19408, 28174, 36940, 45706, 54472
1722	chromosome 6 open reading frame 112	369120	1877	358116	10643	19409, 28175, 36941, 45707, 54473
1723	chromosome 6 open reading frame 112	369122	1878	358118	10644	19410, 28176, 36942, 45708, 54474
1724	chromosome 6 open reading frame 115	367660	1879	356632	10645	19411, 28177, 36943, 45709, 54475
1725	chromosome 6 open reading frame 115	461027	1880	418406	10646	19412, 28178, 36944, 45710, 54476
1726	chromosome 6 open reading frame 118	230301	1881	230301	10647	19413, 28179, 36945, 45711, 54477
1727	chromosome 6 open reading frame 118	543069	1882	439288	10648	19414, 28180, 36946, 45712, 54478
1728	chromosome 6 open reading frame 123	366822	1883	355787	10649	19415, 28181, 36947, 45713, 54479
1729	chromosome 6 open reading frame 123	495520	1884	432981	10650	19416, 28182, 36948, 45714, 54480
1730	chromosome 6 open reading frame 126	360454	1885	353639	10651	19417, 28183, 36949, 45715, 54481
1731	chromosome 6 open reading frame 136	383580	1886	373074	10652	19418, 28184, 36950, 45716, 54482
1732	chromosome 6 open reading frame 136	383581	1887	373075	10653	19419, 28185, 36951, 45717, 54483
1733	chromosome 6 open reading frame 136	411654	1888	415028	10654	19420, 28186, 36952, 45718, 54484
1734	chromosome 6 open reading frame 136	415931	1889	402805	10655	19421, 28187, 36953, 45719, 54485
1735	chromosome 6 open reading frame 136	417076	1890	405594	10656	19422, 28188, 36954, 45720, 54486
1736	chromosome 6 open reading frame 136	417649	1891	395979	10657	19423, 28189, 36955, 45721,

						54487
1737	chromosome 6 open reading frame 136	419321	1892	398769	10658	19424, 28190, 36956, 45722, 54488
1738	chromosome 6 open reading frame 136	422530	1893	390275	10659	19425, 28191, 36957, 45723, 54489
1739	chromosome 6 open reading frame 136	424031	1894	393004	10660	19426, 28192, 36958, 45724, 54490
1740	chromosome 6 open reading frame 136	425581	1895	404588	10661	19427, 28193, 36959, 45725, 54491
1741	chromosome 6 open reading frame 136	430141	1896	396916	10662	19428, 28194, 36960, 45726, 54492
1742	chromosome 6 open reading frame 136	442792	1897	404560	10663	19429, 28195, 36961, 45727, 54493
1743	chromosome 6 open reading frame 136	447330	1898	389259	10664	19430, 28196, 36962, 45728, 54494
1744	chromosome 6 open reading frame 136	447505	1899	415915	10665	19431, 28197, 36963, 45729, 54495
1745	chromosome 6 open reading frame 136	449122	1900	403409	10666	19432, 28198, 36964, 45730, 54496
1746	chromosome 6 open reading frame 136	453871	1901	411113	10667	19433, 28199, 36965, 45731, 54497
1747	chromosome 6 open reading frame 136	455682	1902	391657	10668	19434, 28200, 36966, 45732, 54498
1748	chromosome 6 open reading frame 136	456444	1903	387592	10669	19435, 28201, 36967, 45733, 54499
1749	chromosome 6 open reading frame 136	546452	1904	447695	10670	19436, 28202, 36968, 45734, 54500
1750	chromosome 6 open reading frame 136	547308	1905	449786	10671	19437, 28203, 36969, 45735, 54501
1751	chromosome 6 open reading frame 136	549361	1906	449267	10672	19438, 28204, 36970, 45736, 54502
1752	chromosome 6 open reading frame 136	549800	1907	447446	10673	19439, 28205, 36971, 45737, 54503
1753	chromosome 6 open reading	549861	1908	448284	10674	19440, 28206,

	frame 136					36972, 45738, 54504
1754	chromosome 6 open reading frame 136	552569	1909	447147	10675	19441, 28207, 36973, 45739, 54505
1755	chromosome 6 open reading frame 141	529246	1910	434602	10676	19442, 28208, 36974, 45740, 54506
1756	chromosome 6 open reading frame 146	274673	1911	274673	10677	19443, 28209, 36975, 45741, 54507
1757	chromosome 6 open reading frame 146	538080	1912	445640	10678	19444, 28210, 36976, 45742, 54508
1758	chromosome 6 open reading frame 15	383532	1913	373024	10679	19445, 28211, 36977, 45743, 54509
1759	chromosome 6 open reading frame 15	452899	1914	399436	10680	19446, 28212, 36978, 45744, 54510
1760	chromosome 6 open reading frame 163	369574	1915	358587	10681	19447, 28213, 36979, 45745, 54511
1761	chromosome 6 open reading frame 163	388923	1916	373575	10682	19448, 28214, 36980, 45746, 54512
1762	chromosome 6 open reading frame 164	369570	1917	358583	10683	19449, 28215, 36981, 45747, 54513
1763	chromosome 6 open reading frame 164	369572	1918	358585	10684	19450, 28216, 36982, 45748, 54514
1764	chromosome 6 open reading frame 165	369562	1919	358575	10685	19451, 28217, 36983, 45749, 54515
1765	chromosome 6 open reading frame 165	480123	1920	422494	10686	19452, 28218, 36984, 45750, 54516
1766	chromosome 6 open reading frame 168	389677	1921	374328	10687	19453, 28219, 36985, 45751, 54517
1767	chromosome 6 open reading frame 168	538471	1922	445267	10688	19454, 28220, 36986, 45752, 54518
1768	chromosome 6 open reading frame 195	296847	1923	296847	10689	19455, 28221, 36987, 45753, 54519
1769	chromosome 6 open reading frame 201	333388	1924	330777	10690	19456, 28222, 36988, 45754, 54520

1770	chromosome 6 open reading frame 201	430835	1925	396912	10691	19457, 28223, 36989, 45755, 54521
1771	chromosome 6 open reading frame 201	541127	1926	439073	10692	19458, 28224, 36990, 45756, 54522
1772	chromosome 6 open reading frame 201	380175	1927	420610	10693	19459, 28225, 36991, 45757, 54523
1773	chromosome 6 open reading frame 211	367294	1928	356263	10694	19460, 28226, 36992, 45758, 54524
1774	chromosome 6 open reading frame 211	545879	1929	444121	10695	19461, 28227, 36993, 45759, 54525
1775	chromosome 6 open reading frame 222	437635	1930	418983	10696	19462, 28228, 36994, 45760, 54526
1776	chromosome 6 open reading frame 223	336600	1931	426159	10697	19463, 28229, 36995, 45761, 54527
1777	chromosome 6 open reading frame 223	439969	1932	423262	10698	19464, 28230, 36996, 45762, 54528
1778	chromosome 6 open reading frame 225	368656	1933	357645	10699	19465, 28231, 36997, 45763, 54529
1779	chromosome 6 open reading frame 226	408925	1934	386146	10700	19466, 28232, 36998, 45764, 54530
1780	chromosome 6 open reading frame 228	416247	1935	451866	10701	19467, 28233, 36999, 45765, 54531
1781	chromosome 6 open reading frame 25	411608	1936	392961	10702	19468, 28234, 37000, 45766, 54532
1782	chromosome 6 open reading frame 25	433769	1937	413647	10703	19469, 28235, 37001, 45767, 54533
1783	chromosome 6 open reading frame 25	438769	1938	407683	10704	19470, 28236, 37002, 45768, 54534
1784	chromosome 6 open reading frame 25	441161	1939	407677	10705	19471, 28237, 37003, 45769, 54535
1785	chromosome 6 open reading frame 25	442871	1940	414621	10706	19472, 28238, 37004, 45770, 54536
1786	chromosome 6 open reading frame 47	366431	1941	375392	10707	19473, 28239, 37005, 45771,

						54537
1787	chromosome 6 open reading frame 47	366432	1942	375400	10708	19474, 28240, 37006, 45772, 54538
1788	chromosome 6 open reading frame 47	375911	1943	365076	10709	19475, 28241, 37007, 45773, 54539
1789	chromosome 6 open reading frame 47	413113	1944	395128	10710	19476, 28242, 37008, 45774, 54540
1790	chromosome 6 open reading frame 47	418357	1945	398221	10711	19477, 28243, 37009, 45775, 54541
1791	chromosome 6 open reading frame 47	431256	1946	406870	10712	19478, 28244, 37010, 45776, 54542
1792	chromosome 6 open reading frame 47	442972	1947	407188	10713	19479, 28245, 37011, 45777, 54543
1793	chromosome 6 open reading frame 47	538106	1948	437377	10714	19480, 28246, 37012, 45778, 54544
1794	chromosome 6 open reading frame 48	375633	1949	364784	10715	19481, 28247, 37013, 45779, 54545
1795	chromosome 6 open reading frame 48	375635	1950	364786	10716	19482, 28248, 37014, 45780, 54546
1796	chromosome 6 open reading frame 48	375636	1951	364787	10717	19483, 28249, 37015, 45781, 54547
1797	chromosome 6 open reading frame 48	375638	1952	364789	10718	19484, 28250, 37016, 45782, 54548
1798	chromosome 6 open reading frame 48	375639	1953	364790	10719	19485, 28251, 37017, 45783, 54549
1799	chromosome 6 open reading frame 48	375640	1954	364791	10720	19486, 28252, 37018, 45784, 54550
1800	chromosome 6 open reading frame 48	375641	1955	364792	10721	19487, 28253, 37019, 45785, 54551
1801	chromosome 6 open reading frame 48	375642	1956	364793	10722	19488, 28254, 37020, 45786, 54552
1802	chromosome 6 open reading frame 48	383383	1957	372874	10723	19489, 28255, 37021, 45787, 54553
1803	chromosome 6 open reading	383384	1958	372875	10724	19490, 28256,

	frame 48					37022, 45788, 54554
1804	chromosome 6 open reading frame 48	383385	1959	372876	10725	19491, 28257, 37023, 45789, 54555
1805	chromosome 6 open reading frame 48	395788	1960	379134	10726	19492, 28258, 37024, 45790, 54556
1806	chromosome 6 open reading frame 48	395789	1961	379135	10727	19493, 28259, 37025, 45791, 54557
1807	chromosome 6 open reading frame 48	400034	1962	382909	10728	19494, 28260, 37026, 45792, 54558
1808	chromosome 6 open reading frame 48	400035	1963	382910	10729	19495, 28261, 37027, 45793, 54559
1809	chromosome 6 open reading frame 48	400037	1964	382912	10730	19496, 28262, 37028, 45794, 54560
1810	chromosome 6 open reading frame 48	400038	1965	382913	10731	19497, 28263, 37029, 45795, 54561
1811	chromosome 6 open reading frame 48	400039	1966	382914	10732	19498, 28264, 37030, 45796, 54562
1812	chromosome 6 open reading frame 48	413638	1967	395192	10733	19499, 28265, 37031, 45797, 54563
1813	chromosome 6 open reading frame 48	414434	1968	390420	10734	19500, 28266, 37032, 45798, 54564
1814	chromosome 6 open reading frame 48	414536	1969	387952	10735	19501, 28267, 37033, 45799, 54565
1815	chromosome 6 open reading frame 48	416886	1970	397392	10736	19502, 28268, 37034, 45800, 54566
1816	chromosome 6 open reading frame 48	421039	1971	392591	10737	19503, 28269, 37035, 45801, 54567
1817	chromosome 6 open reading frame 48	421605	1972	405501	10738	19504, 28270, 37036, 45802, 54568
1818	chromosome 6 open reading frame 48	423640	1973	389848	10739	19505, 28271, 37037, 45803, 54569
1819	chromosome 6 open reading frame 48	423916	1974	397287	10740	19506, 28272, 37038, 45804, 54570

1820	chromosome 6 open reading frame 48	424962	1975	415206	10741	19507, 28273, 37039, 45805, 54571
1821	chromosome 6 open reading frame 48	426843	1976	394750	10742	19508, 28274, 37040, 45806, 54572
1822	chromosome 6 open reading frame 48	430690	1977	408280	10743	19509, 28275, 37041, 45807, 54573
1823	chromosome 6 open reading frame 48	433697	1978	397730	10744	19510, 28276, 37042, 45808, 54574
1824	chromosome 6 open reading frame 48	433752	1979	408391	10745	19511, 28277, 37043, 45809, 54575
1825	chromosome 6 open reading frame 48	435938	1980	395285	10746	19512, 28278, 37044, 45810, 54576
1826	chromosome 6 open reading frame 48	436205	1981	406099	10747	19513, 28279, 37045, 45811, 54577
1827	chromosome 6 open reading frame 48	436495	1982	396517	10748	19514, 28280, 37046, 45812, 54578
1828	chromosome 6 open reading frame 48	436558	1983	388964	10749	19515, 28281, 37047, 45813, 54579
1829	chromosome 6 open reading frame 48	439865	1984	397345	10750	19516, 28282, 37048, 45814, 54580
1830	chromosome 6 open reading frame 48	439907	1985	387656	10751	19517, 28283, 37049, 45815, 54581
1831	chromosome 6 open reading frame 48	440361	1986	392656	10752	19518, 28284, 37050, 45816, 54582
1832	chromosome 6 open reading frame 48	443974	1987	401394	10753	19519, 28285, 37051, 45817, 54583
1833	chromosome 6 open reading frame 48	444192	1988	417013	10754	19520, 28286, 37052, 45818, 54584
1834	chromosome 6 open reading frame 48	444331	1989	394438	10755	19521, 28287, 37053, 45819, 54585
1835	chromosome 6 open reading frame 48	444974	1990	402138	10756	19522, 28288, 37054, 45820, 54586
1836	chromosome 6 open reading frame 48	450610	1991	392621	10757	19523, 28289, 37055, 45821,

						54587
1837	chromosome 6 open reading frame 48	456268	1992	388587	10758	19524, 28290, 37056, 45822, 54588
1838	chromosome 6 open reading frame 48	456690	1993	414926	10759	19525, 28291, 37057, 45823, 54589
1839	chromosome 6 open reading frame 48	458514	1994	405706	10760	19526, 28292, 37058, 45824, 54590
1840	chromosome 6 open reading frame 48	534920	1995	444190	10761	19527, 28293, 37059, 45825, 54591
1841	chromosome 6 open reading frame 48	547624	1996	447239	10762	19528, 28294, 37060, 45826, 54592
1842	chromosome 6 open reading frame 48	549426	1997	449901	10763	19529, 28295, 37061, 45827, 54593
1843	chromosome 6 open reading frame 48	550200	1998	446645	10764	19530, 28296, 37062, 45828, 54594
1844	chromosome 6 open reading frame 48	550492	1999	448031	10765	19531, 28297, 37063, 45829, 54595
1845	chromosome 6 open reading frame 48	550685	2000	448996	10766	19532, 28298, 37064, 45830, 54596
1846	chromosome 6 open reading frame 48	551797	2001	449244	10767	19533, 28299, 37065, 45831, 54597
1847	chromosome 6 open reading frame 48	551957	2002	448793	10768	19534, 28300, 37066, 45832, 54598
1848	chromosome 6 open reading frame 48	552514	2003	449921	10769	19535, 28301, 37067, 45833, 54599
1849	chromosome 6 open reading frame 52	259983	2004	259983	10770	19536, 28302, 37068, 45834, 54600
1850	chromosome 6 open reading frame 52	379586	2005	368905	10771	19537, 28303, 37069, 45835, 54601
1851	chromosome 6 open reading frame 62	378102	2006	367342	10772	19538, 28304, 37070, 45836, 54602
1852	chromosome 6 open reading frame 62	378119	2007	367359	10773	19539, 28305, 37071, 45837, 54603
1853	chromosome 6 open reading	540769	2008	446225	10774	19540, 28306,

	frame 62					37072, 45838, 54604
1854	chromosome 6 open reading frame 94	237275	2009	237275	10775	19541, 28307, 37073, 45839, 54605
1855	chromosome 6 open reading frame 94	416313	2010	408502	10776	19542, 28308, 37074, 45840, 54606
1856	chromosome 6 open reading frame 94	454207	2011	400756	10777	19543, 28309, 37075, 45841, 54607
1857	chromosome 6 open reading frame 94	539295	2012	444513	10778	19544, 28310, 37076, 45842, 54608
1858	chromosome 6 open reading frame 97	239374	2013	239374	10779	19545, 28311, 37077, 45843, 54609
1859	chromosome 6 open reading frame 97	367290	2014	356259	10780	19546, 28312, 37078, 45844, 54610
1860	chromosome 6 open reading frame 99	367072	2015	356039	10781	19547, 28313, 37079, 45845, 54611
1861	chromosome 6 open reading frame 99	367073	2016	356040	10782	19548, 28314, 37080, 45846, 54612
1862	chromosome 7 open reading frame 25	350427	2017	343364	10783	19549, 28315, 37081, 45847, 54613
1863	chromosome 7 open reading frame 25	425683	2018	413106	10784	19550, 28316, 37082, 45848, 54614
1864	chromosome 7 open reading frame 25	431882	2019	416290	10785	19551, 28317, 37083, 45849, 54615
1865	chromosome 7 open reading frame 25	432637	2020	416542	10786	19552, 28318, 37084, 45850, 54616
1866	chromosome 7 open reading frame 25	438029	2021	396597	10787	19553, 28319, 37085, 45851, 54617
1867	chromosome 7 open reading frame 25	447342	2022	413029	10788	19554, 28320, 37086, 45852, 54618
1868	chromosome 7 open reading frame 26	344417	2023	340220	10789	19555, 28321, 37087, 45853, 54619
1869	chromosome 7 open reading frame 26	359073	2024	351974	10790	19556, 28322, 37088, 45854, 54620

1870	chromosome 7 open reading frame 29	343855	2025	343242	10791	19557, 28323, 37089, 45855, 54621
1871	chromosome 7 open reading frame 31	283905	2026	283905	10792	19558, 28324, 37090, 45856, 54622
1872	chromosome 7 open reading frame 31	409280	2027	386604	10793	19559, 28325, 37091, 45857, 54623
1873	chromosome 7 open reading frame 31	415598	2028	391212	10794	19560, 28326, 37092, 45858, 54624
1874	chromosome 7 open reading frame 31	443822	2029	388472	10795	19561, 28327, 37093, 45859, 54625
1875	chromosome 7 open reading frame 31	444434	2030	403281	10796	19562, 28328, 37094, 45860, 54626
1876	chromosome 7 open reading frame 33	307003	2031	304071	10797	19563, 28329, 37095, 45861, 54627
1877	chromosome 7 open reading frame 41	324453	2032	324204	10798	19564, 28330, 37096, 45862, 54628
1878	chromosome 7 open reading frame 41	324489	2033	324755	10799	19565, 28331, 37097, 45863, 54629
1879	chromosome 7 open reading frame 41	415604	2034	387585	10800	19566, 28332, 37098, 45864, 54630
1880	chromosome 7 open reading frame 41	455738	2035	389035	10801	19567, 28333, 37099, 45865, 54631
1881	chromosome 7 open reading frame 43	275726	2036	275726	10802	19568, 28334, 37100, 45866, 54632
1882	chromosome 7 open reading frame 43	316937	2037	324741	10803	19569, 28335, 37101, 45867, 54633
1883	chromosome 7 open reading frame 46	344962	2038	342576	10804	19570, 28336, 37102, 45868, 54634
1884	chromosome 7 open reading frame 46	409192	2039	386927	10805	19571, 28337, 37103, 45869, 54635
1885	chromosome 7 open reading frame 46	409994	2040	386631	10806	19572, 28338, 37104, 45870, 54636
1886	chromosome 7 open reading frame 50	357429	2041	350011	10807	19573, 28339, 37105, 45871,

						54637
1887	chromosome 7 open reading frame 50	397098	2042	380286	10808	19574, 28340, 37106, 45872, 54638
1888	chromosome 7 open reading frame 50	397100	2043	380288	10809	19575, 28341, 37107, 45873, 54639
1889	chromosome 7 open reading frame 50	491163	2044	420130	10810	19576, 28342, 37108, 45874, 54640
1890	chromosome 7 open reading frame 57	348904	2045	335500	10811	19577, 28343, 37109, 45875, 54641
1891	chromosome 7 open reading frame 57	539619	2046	442474	10812	19578, 28344, 37110, 45876, 54642
1892	chromosome 7 open reading frame 57	435376	2047	391652	10813	19579, 28345, 37111, 45877, 54643
1893	chromosome 7 open reading frame 59	341942	2048	343118	10814	19580, 28346, 37112, 45878, 54644
1894	chromosome 7 open reading frame 60	297145	2049	297145	10815	19581, 28347, 37113, 45879, 54645
1895	chromosome 7 open reading frame 60	358032	2050	350727	10816	19582, 28348, 37114, 45880, 54646
1896	chromosome 7 open reading frame 61	332375	2051	327732	10817	19583, 28349, 37115, 45881, 54647
1897	chromosome 7 open reading frame 62	297203	2052	297203	10818	19584, 28350, 37116, 45882, 54648
1898	chromosome 7 open reading frame 63	316089	2053	321753	10819	19585, 28351, 37117, 45883, 54649
1899	chromosome 7 open reading frame 63	389297	2054	373948	10820	19586, 28352, 37118, 45884, 54650
1900	chromosome 7 open reading frame 63	449577	2055	391571	10821	19587, 28353, 37119, 45885, 54651
1901	chromosome 7 open reading frame 63	497910	2056	419549	10822	19588, 28354, 37120, 45886, 54652
1902	chromosome 7 open reading frame 65	408988	2057	386198	10823	19589, 28355, 37121, 45887, 54653
1903	chromosome 7 open reading	409974	2058	386749	10824	19590, 28356,

	frame 71					37122, 45888, 54654
1904	chromosome 7 open reading frame 72	297001	2059	297001	10825	19591, 28357, 37123, 45889, 54655
1905	chromosome 7 open reading frame 73	507606	2060	425996	10826	19592, 28358, 37124, 45890, 54656
1906	chromosome 8 open reading frame 12	284481	2061	284481	10827	19593, 28359, 37125, 45891, 54657
1907	chromosome 8 open reading frame 12	533578	2062	431967	10828	19594, 28360, 37126, 45892, 54658
1908	chromosome 8 open reading frame 22	303202	2063	304926	10829	19595, 28361, 37127, 45893, 54659
1909	chromosome 8 open reading frame 22	399653	2064	382561	10830	19596, 28362, 37128, 45894, 54660
1910	chromosome 8 open reading frame 31	395172	2065	378601	10831	19597, 28363, 37129, 45895, 54661
1911	chromosome 8 open reading frame 33	331434	2066	330361	10832	19598, 28364, 37130, 45896, 54662
1912	chromosome 8 open reading frame 34	325233	2067	319532	10833	19599, 28365, 37131, 45897, 54663
1913	chromosome 8 open reading frame 34	337103	2068	337174	10834	19600, 28366, 37132, 45898, 54664
1914	chromosome 8 open reading frame 34	348340	2069	345255	10835	19601, 28367, 37133, 45899, 54665
1915	chromosome 8 open reading frame 34	518698	2070	427820	10836	19602, 28368, 37134, 45900, 54666
1916	chromosome 8 open reading frame 34	523686	2071	429102	10837	19603, 28369, 37135, 45901, 54667
1917	chromosome 8 open reading frame 34	539993	2072	438159	10838	19604, 28370, 37136, 45902, 54668
1918	chromosome 8 open reading frame 37	286688	2073	286688	10839	19605, 28371, 37137, 45903, 54669
1919	chromosome 8 open reading frame 39	391680	2074	375562	10840	19606, 28372, 37138, 45904, 54670

1920	chromosome 8 open reading frame 42	324079	2075	315111	10841	19607, 28373, 37139, 45905, 54671
1921	chromosome 8 open reading frame 42	427263	2076	408126	10842	19608, 28374, 37140, 45906, 54672
1922	chromosome 8 open reading frame 42	523656	2077	430325	10843	19609, 28375, 37141, 45907, 54673
1923	chromosome 8 open reading frame 44	390159	2078	375087	10844	19610, 28376, 37142, 45908, 54674
1924	chromosome 8 open reading frame 44	519561	2079	428002	10845	19611, 28377, 37143, 45909, 54675
1925	chromosome 8 open reading frame 45	313616	2080	317234	10846	19612, 28378, 37144, 45910, 54676
1926	chromosome 8 open reading frame 45	379356	2081	368661	10847	19613, 28379, 37145, 45911, 54677
1927	chromosome 8 open reading frame 45	396592	2082	379837	10848	19614, 28380, 37146, 45912, 54678
1928	chromosome 8 open reading frame 45	422365	2083	413632	10849	19615, 28381, 37147, 45913, 54679
1929	chromosome 8 open reading frame 45	541540	2084	445629	10850	19616, 28382, 37148, 45914, 54680
1930	chromosome 8 open reading frame 46	305454	2085	302260	10851	19617, 28383, 37149, 45915, 54681
1931	chromosome 8 open reading frame 47	318528	2086	315614	10852	19618, 28384, 37150, 45916, 54682
1932	chromosome 8 open reading frame 47	545282	2087	440297	10853	19619, 28385, 37151, 45917, 54683
1933	chromosome 8 open reading frame 48	297324	2088	297324	10854	19620, 28386, 37152, 45918, 54684
1934	chromosome 8 open reading frame 49	525043	2089	436777	10855	19621, 28387, 37153, 45919, 54685
1935	chromosome 8 open reading frame 56	436771	2090	401738	10856	19622, 28388, 37154, 45920, 54686
1936	chromosome 8 open reading frame 56	521246	2091	429525	10857	19623, 28389, 37155, 45921,

						54687
1937	chromosome 8 open reading frame 58	289989	2092	289989	10858	19624, 28390, 37156, 45922, 54688
1938	chromosome 8 open reading frame 58	381191	2093	370587	10859	19625, 28391, 37157, 45923, 54689
1939	chromosome 8 open reading frame 58	409586	2094	386265	10860	19626, 28392, 37158, 45924, 54690
1940	chromosome 8 open reading frame 59	321777	2095	319020	10861	19627, 28393, 37159, 45925, 54691
1941	chromosome 8 open reading frame 59	417663	2096	416245	10862	19628, 28394, 37160, 45926, 54692
1942	chromosome 8 open reading frame 59	421308	2097	404132	10863	19629, 28395, 37161, 45927, 54693
1943	chromosome 8 open reading frame 59	458398	2098	407200	10864	19630, 28396, 37162, 45928, 54694
1944	chromosome 8 open reading frame 59	518091	2099	429521	10865	19631, 28397, 37163, 45929, 54695
1945	chromosome 8 open reading frame 59	523281	2100	428722	10866	19632, 28398, 37164, 45930, 54696
1946	chromosome 8 open reading frame 59	524353	2101	427911	10867	19633, 28399, 37165, 45931, 54697
1947	chromosome 8 open reading frame 59	545322	2102	444092	10868	19634, 28400, 37166, 45932, 54698
1948	chromosome 8 open reading frame 73	398882	2103	381857	10869	19635, 28401, 37167, 45933, 54699
1949	chromosome 8 open reading frame 74	304519	2104	307129	10870	19636, 28402, 37168, 45934, 54700
1950	chromosome 8 open reading frame 76	276704	2105	276704	10871	19637, 28403, 37169, 45935, 54701
1951	chromosome 8 open reading frame 77	527067	2106	433608	10872	19638, 28404, 37170, 45936, 54702
1952	chromosome 8 open reading frame 82	313465	2107	316262	10873	19639, 28405, 37171, 45937, 54703
1953	chromosome 8 open reading	378279	2108	367528	10874	19640, 28406,

	frame 85					37172, 45938, 54704
1954	chromosome 8 open reading frame 86	358138	2109	350856	10875	19641, 28407, 37173, 45939, 54705
1955	chromosome 8 open reading frame 87	521906	2110	428308	10876	19642, 28408, 37174, 45940, 54706
1956	chromosome 9 open reading frame 100	343259	2111	344922	10877	19643, 28409, 37175, 45941, 54707
1957	chromosome 9 open reading frame 100	378387	2112	367638	10878	19644, 28410, 37176, 45942, 54708
1958	chromosome 9 open reading frame 100	378395	2113	367648	10879	19645, 28411, 37177, 45943, 54709
1959	chromosome 9 open reading frame 104	371813	2114	360878	10880	19646, 28412, 37178, 45944, 54710
1960	chromosome 9 open reading frame 107	374801	2115	363934	10881	19647, 28413, 37179, 45945, 54711
1961	chromosome 9 open reading frame 114	361256	2116	354812	10882	19648, 28414, 37180, 45946, 54712
1962	chromosome 9 open reading frame 114	372618	2117	361701	10883	19649, 28415, 37181, 45947, 54713
1963	chromosome 9 open reading frame 116	371789	2118	360854	10884	19650, 28416, 37182, 45948, 54714
1964	chromosome 9 open reading frame 116	371791	2119	360856	10885	19651, 28417, 37183, 45949, 54715
1965	chromosome 9 open reading frame 116	429260	2120	395281	10886	19652, 28418, 37184, 45950, 54716
1966	chromosome 9 open reading frame 117	373293	2121	362391	10887	19653, 28419, 37185, 45951, 54717
1967	chromosome 9 open reading frame 117	373295	2122	362392	10888	19654, 28420, 37186, 45952, 54718
1968	chromosome 9 open reading frame 118	375325	2123	364474	10889	19655, 28421, 37187, 45953, 54719
1969	chromosome 9 open reading frame 128	377984	2124	367222	10890	19656, 28422, 37188, 45954, 54720

1970	chromosome 9 open reading frame 128	423537	2125	415299	10891	19657, 28423, 37189, 45955, 54721
1971	chromosome 9 open reading frame 128	472182	2126	420279	10892	19658, 28424, 37190, 45956, 54722
1972	chromosome 9 open reading frame 129	375419	2127	364568	10893	19659, 28425, 37191, 45957, 54723
1973	chromosome 9 open reading frame 131	312292	2128	308279	10894	19660, 28426, 37192, 45958, 54724
1974	chromosome 9 open reading frame 131	354479	2129	346472	10895	19661, 28427, 37193, 45959, 54725
1975	chromosome 9 open reading frame 131	421362	2130	393683	10896	19662, 28428, 37194, 45960, 54726
1976	chromosome 9 open reading frame 131	435140	2131	392992	10897	19663, 28429, 37195, 45961, 54727
1977	chromosome 9 open reading frame 139	314330	2132	318119	10898	19664, 28430, 37196, 45962, 54728
1978	chromosome 9 open reading frame 141	371629	2133	360692	10899	19665, 28431, 37197, 45963, 54729
1979	chromosome 9 open reading frame 142	371620	2134	360682	10900	19666, 28432, 37198, 45964, 54730
1980	chromosome 9 open reading frame 146	381010	2135	370398	10901	19667, 28433, 37199, 45965, 54731
1981	chromosome 9 open reading frame 147	457681	2136	415527	10902	19668, 28434, 37200, 45966, 54732
1982	chromosome 9 open reading frame 150	319264	2137	321026	10903	19669, 28435, 37201, 45967, 54733
1983	chromosome 9 open reading frame 152	400613	2138	383456	10904	19670, 28436, 37202, 45968, 54734
1984	chromosome 9 open reading frame 153	339137	2139	344865	10905	19671, 28437, 37203, 45969, 54735
1985	chromosome 9 open reading frame 153	376001	2140	365169	10906	19672, 28438, 37204, 45970, 54736
1986	chromosome 9 open reading frame 156	325350	2141	324426	10907	19673, 28439, 37205, 45971,

						54737
1987	chromosome 9 open reading frame 156	375117	2142	364258	10908	19674, 28440, 37206, 45972, 54738
1988	chromosome 9 open reading frame 156	375118	2143	364259	10909	19675, 28441, 37207, 45973, 54739
1989	chromosome 9 open reading frame 156	375119	2144	364260	10910	19676, 28442, 37208, 45974, 54740
1990	chromosome 9 open reading frame 156	455506	2145	408473	10911	19677, 28443, 37209, 45975, 54741
1991	chromosome 9 open reading frame 16	372994	2146	362085	10912	19678, 28444, 37210, 45976, 54742
1992	chromosome 9 open reading frame 163	354376	2147	346345	10913	19679, 28445, 37211, 45977, 54743
1993	chromosome 9 open reading frame 169	359069	2148	351967	10914	19680, 28446, 37212, 45978, 54744
1994	chromosome 9 open reading frame 170	375941	2149	365108	10915	19681, 28447, 37213, 45979, 54745
1995	chromosome 9 open reading frame 171	343036	2150	343290	10916	19682, 28448, 37214, 45980, 54746
1996	chromosome 9 open reading frame 171	393216	2151	376909	10917	19683, 28449, 37215, 45981, 54747
1997	chromosome 9 open reading frame 172	436881	2152	412388	10918	19684, 28450, 37216, 45982, 54748
1998	chromosome 9 open reading frame 173	388931	2153	373583	10919	19685, 28451, 37217, 45983, 54749
1999	chromosome 9 open reading frame 173	412566	2154	391218	10920	19686, 28452, 37218, 45984, 54750
2000	chromosome 9 open reading frame 21	375233	2155	364381	10921	19687, 28453, 37219, 45985, 54751
2001	chromosome 9 open reading frame 21	375234	2156	364382	10922	19688, 28454, 37220, 45986, 54752
2002	chromosome 9 open reading frame 21	411939	2157	412378	10923	19689, 28455, 37221, 45987, 54753
2003	chromosome 9 open reading	446045	2158	398933	10924	19690, 28456,

	frame 21					37222, 45988, 54754
2004	chromosome 9 open reading frame 23	297613	2159	297613	10925	19691, 28457, 37223, 45989, 54755
2005	chromosome 9 open reading frame 23	378959	2160	368242	10926	19692, 28458, 37224, 45990, 54756
2006	chromosome 9 open reading frame 24	379124	2161	368419	10927	19693, 28459, 37225, 45991, 54757
2007	chromosome 9 open reading frame 24	379126	2162	368421	10928	19694, 28460, 37226, 45992, 54758
2008	chromosome 9 open reading frame 24	379127	2163	368422	10929	19695, 28461, 37227, 45993, 54759
2009	chromosome 9 open reading frame 24	379133	2164	368428	10930	19696, 28462, 37228, 45994, 54760
2010	chromosome 9 open reading frame 24	444429	2165	389687	10931	19697, 28463, 37229, 45995, 54761
2011	chromosome 9 open reading frame 25	297620	2166	297620	10932	19698, 28464, 37230, 45996, 54762
2012	chromosome 9 open reading frame 25	379078	2167	368369	10933	19699, 28465, 37231, 45997, 54763
2013	chromosome 9 open reading frame 25	379080	2168	368371	10934	19700, 28466, 37232, 45998, 54764
2014	chromosome 9 open reading frame 25	379081	2169	368372	10935	19701, 28467, 37233, 45999, 54765
2015	chromosome 9 open reading frame 25	379084	2170	368377	10936	19702, 28468, 37234, 46000, 54766
2016	chromosome 9 open reading frame 25	379087	2171	368380	10937	19703, 28469, 37235, 46001, 54767
2017	chromosome 9 open reading frame 25	379089	2172	368382	10938	19704, 28470, 37236, 46002, 54768
2018	chromosome 9 open reading frame 25	422409	2173	409737	10939	19705, 28471, 37237, 46003, 54769
2019	chromosome 9 open reading frame 25	445726	2174	392452	10940	19706, 28472, 37238, 46004, 54770

2020	chromosome 9 open reading frame 29	374302	2175	363420	10941	19707, 28473, 37239, 46005, 54771
2021	chromosome 9 open reading frame 29	374304	2176	363422	10942	19708, 28474, 37240, 46006, 54772
2022	chromosome 9 open reading frame 29	374306	2177	363425	10943	19709, 28475, 37241, 46007, 54773
2023	chromosome 9 open reading frame 29	536054	2178	438393	10944	19710, 28476, 37242, 46008, 54774
2024	chromosome 9 open reading frame 3	297979	2179	297979	10945	19711, 28477, 37243, 46009, 54775
2025	chromosome 9 open reading frame 3	375314	2180	364463	10946	19712, 28478, 37244, 46010, 54776
2026	chromosome 9 open reading frame 3	375315	2181	364464	10947	19713, 28479, 37245, 46011, 54777
2027	chromosome 9 open reading frame 3	375316	2182	364465	10948	19714, 28480, 37246, 46012, 54778
2028	chromosome 9 open reading frame 3	395357	2183	378763	10949	19715, 28481, 37247, 46013, 54779
2029	chromosome 9 open reading frame 3	424143	2184	402171	10950	19716, 28482, 37248, 46014, 54780
2030	chromosome 9 open reading frame 3	425634	2185	411815	10951	19717, 28483, 37249, 46015, 54781
2031	chromosome 9 open reading frame 3	427193	2186	387736	10952	19718, 28484, 37250, 46016, 54782
2032	chromosome 9 open reading frame 3	428313	2187	401854	10953	19719, 28485, 37251, 46017, 54783
2033	chromosome 9 open reading frame 3	433691	2188	399365	10954	19720, 28486, 37252, 46018, 54784
2034	chromosome 9 open reading frame 3	445181	2189	413927	10955	19721, 28487, 37253, 46019, 54785
2035	chromosome 9 open reading frame 3	451893	2190	411451	10956	19722, 28488, 37254, 46020, 54786
2036	chromosome 9 open reading frame 30	374886	2191	364021	10957	19723, 28489, 37255, 46021,

						54787
2037	chromosome 9 open reading frame 30	395067	2192	378506	10958	19724, 28490, 37256, 46022, 54788
2038	chromosome 9 open reading frame 30	398977	2193	415830	10959	19725, 28491, 37257, 46023, 54789
2039	chromosome 9 open reading frame 31	414544	2194	408776	10960	19726, 28492, 37258, 46024, 54790
2040	chromosome 9 open reading frame 35	443737	2195	397294	10961	19727, 28493, 37259, 46025, 54791
2041	chromosome 9 open reading frame 37	371417	2196	360471	10962	19728, 28494, 37260, 46026, 54792
2042	chromosome 9 open reading frame 38	355513	2197	380380	10963	19729, 28495, 37261, 46027, 54793
2043	chromosome 9 open reading frame 41	376830	2198	366026	10964	19730, 28496, 37262, 46028, 54794
2044	chromosome 9 open reading frame 41	376834	2199	366030	10965	19731, 28497, 37263, 46029, 54795
2045	chromosome 9 open reading frame 41	376837	2200	366033	10966	19732, 28498, 37264, 46030, 54796
2046	chromosome 9 open reading frame 41	451153	2201	396353	10967	19733, 28499, 37265, 46031, 54797
2047	chromosome 9 open reading frame 43	288462	2202	288462	10968	19734, 28500, 37266, 46032, 54798
2048	chromosome 9 open reading frame 43	374165	2203	363280	10969	19735, 28501, 37267, 46033, 54799
2049	chromosome 9 open reading frame 5	223608	2204	223608	10970	19736, 28502, 37268, 46034, 54800
2050	chromosome 9 open reading frame 5	374586	2205	363714	10971	19737, 28503, 37269, 46035, 54801
2051	chromosome 9 open reading frame 5	374587	2206	363715	10972	19738, 28504, 37270, 46036, 54802
2052	chromosome 9 open reading frame 50	372478	2207	361556	10973	19739, 28505, 37271, 46037, 54803
2053	chromosome 9 open reading	377689	2208	366918	10974	19740, 28506,

	frame 51					37272, 46038, 54804
2054	chromosome 9 open reading frame 53	441769	2209	414893	10975	19741, 28507, 37273, 46039, 54805
2055	chromosome 9 open reading frame 62	320778	2210	326574	10976	19742, 28508, 37274, 46040, 54806
2056	chromosome 9 open reading frame 64	314700	2211	318375	10977	19743, 28509, 37275, 46041, 54807
2057	chromosome 9 open reading frame 64	376340	2212	365518	10978	19744, 28510, 37276, 46042, 54808
2058	chromosome 9 open reading frame 64	376344	2213	365522	10979	19745, 28511, 37277, 46043, 54809
2059	chromosome 9 open reading frame 66	382387	2214	371824	10980	19746, 28512, 37278, 46044, 54810
2060	chromosome 9 open reading frame 68	381895	2215	371319	10981	19747, 28513, 37279, 46045, 54811
2061	chromosome 9 open reading frame 68	454239	2216	404277	10982	19748, 28514, 37280, 46046, 54812
2062	chromosome 9 open reading frame 69	561457	2217	452750	10983	19749, 28515, 37281, 46047, 54813
2063	chromosome 9 open reading frame 78	372447	2218	361524	10984	19750, 28516, 37282, 46048, 54814
2064	chromosome 9 open reading frame 78	435276	2219	395877	10985	19751, 28517, 37283, 46049, 54815
2065	chromosome 9 open reading frame 82	333916	2220	369431	10986	19752, 28518, 37284, 46050, 54816
2066	chromosome 9 open reading frame 82	535437	2221	444885	10987	19753, 28519, 37285, 46051, 54817
2067	chromosome 9 open reading frame 84	318737	2222	322108	10988	19754, 28520, 37286, 46052, 54818
2068	chromosome 9 open reading frame 84	374283	2223	363401	10989	19755, 28521, 37287, 46053, 54819
2069	chromosome 9 open reading frame 84	374287	2224	363405	10990	19756, 28522, 37288, 46054, 54820

2070	chromosome 9 open reading frame 84	394778	2225	378258	10991	19757, 28523, 37289, 46055, 54821
2071	chromosome 9 open reading frame 84	394779	2226	378259	10992	19758, 28524, 37290, 46056, 54822
2072	chromosome 9 open reading frame 85	334731	2227	334289	10993	19759, 28525, 37291, 46057, 54823
2073	chromosome 9 open reading frame 85	356065	2228	348364	10994	19760, 28526, 37292, 46058, 54824
2074	chromosome 9 open reading frame 85	377031	2229	366230	10995	19761, 28527, 37293, 46059, 54825
2075	chromosome 9 open reading frame 9	350499	2230	298546	10996	19762, 28528, 37294, 46060, 54826
2076	chromosome 9 open reading frame 9	356311	2231	348659	10997	19763, 28529, 37295, 46061, 54827
2077	chromosome 9 open reading frame 9	372136	2232	361209	10998	19764, 28530, 37296, 46062, 54828
2078	chromosome 9 open reading frame 92	357468	2233	350060	10999	19765, 28531, 37297, 46063, 54829
2079	chromosome 9 open reading frame 92	380683	2234	370058	11000	19766, 28532, 37298, 46064, 54830
2080	chromosome 9 open reading frame 92	380685	2235	370060	11001	19767, 28533, 37299, 46065, 54831
2081	chromosome 9 open reading frame 92	433347	2236	412109	11002	19768, 28534, 37300, 46066, 54832
2082	chromosome 9 open reading frame 93	297641	2237	297641	11003	19769, 28535, 37301, 46067, 54833
2083	chromosome 9 open reading frame 93	359391	2238	352352	11004	19770, 28536, 37302, 46068, 54834
2084	chromosome 9 open reading frame 93	380689	2239	370065	11005	19771, 28537, 37303, 46069, 54835
2085	chromosome 9 open reading frame 93	380701	2240	370077	11006	19772, 28538, 37304, 46070, 54836
2086	chromosome 9 open reading frame 93	432954	2241	399526	11007	19773, 28539, 37305, 46071,

						54837
2087	chromosome 9 open reading frame 93	449575	2242	409055	11008	19774, 28540, 37306, 46072, 54838
2088	chromosome 9 open reading frame 93	535968	2243	438838	11009	19775, 28541, 37307, 46073, 54839
2089	chromosome 9 open reading frame 95	361092	2244	354387	11010	19776, 28542, 37308, 46074, 54840
2090	chromosome 9 open reading frame 95	376794	2245	365990	11011	19777, 28543, 37309, 46075, 54841
2091	chromosome 9 open reading frame 95	376808	2246	366004	11012	19778, 28544, 37310, 46076, 54842
2092	chromosome 9 open reading frame 95	376811	2247	366007	11013	19779, 28545, 37311, 46077, 54843
2093	chromosome 9 open reading frame 96	371955	2248	361023	11014	19780, 28546, 37312, 46078, 54844
2094	chromosome 9 open reading frame 96	371957	2249	361025	11015	19781, 28547, 37313, 46079, 54845
2095	chromosome 9 open reading frame 96	426926	2250	398807	11016	19782, 28548, 37314, 46080, 54846
2096	chromosome X open reading frame 21	378962	2251	368245	11017	19783, 28549, 37315, 46081, 54847
2097	chromosome X open reading frame 22	297866	2252	297866	11018	19784, 28550, 37316, 46082, 54848
2098	chromosome X open reading frame 23	340625	2253	342104	11019	19785, 28551, 37317, 46083, 54849
2099	chromosome X open reading frame 23	356980	2254	349470	11020	19786, 28552, 37318, 46084, 54850
2100	chromosome X open reading frame 23	379687	2255	369009	11021	19787, 28553, 37319, 46085, 54851
2101	chromosome X open reading frame 23	539038	2256	443404	11022	19788, 28554, 37320, 46086, 54852
2102	chromosome X open reading frame 24	357412	2257	349989	11023	19789, 28555, 37321, 46087, 54853
2103	chromosome X open	373357	2258	362455	11024	19790, 28556,

	reading frame 26					37322, 46088, 54854
2104	chromosome X open reading frame 26	373358	2259	362456	11025	19791, 28557, 37323, 46089, 54855
2105	chromosome X open reading frame 27	341016	2260	339511	11026	19792, 28558, 37324, 46090, 54856
2106	chromosome X open reading frame 28	420429	2261	397330	11027	19793, 28559, 37325, 46091, 54857
2107	chromosome X open reading frame 28	457435	2262	387744	11028	19794, 28560, 37326, 46092, 54858
2108	chromosome X open reading frame 30	378653	2263	367922	11029	19795, 28561, 37327, 46093, 54859
2109	chromosome X open reading frame 30	378657	2264	367926	11030	19796, 28562, 37328, 46094, 54860
2110	chromosome X open reading frame 30	446478	2265	403069	11031	19797, 28563, 37329, 46095, 54861
2111	chromosome X open reading frame 31	377879	2266	367111	11032	19798, 28564, 37330, 46096, 54862
2112	chromosome X open reading frame 38	327877	2267	330488	11033	19799, 28565, 37331, 46097, 54863
2113	chromosome X open reading frame 38	378418	2268	367674	11034	19800, 28566, 37332, 46098, 54864
2114	chromosome X open reading frame 38	378421	2269	367677	11035	19801, 28567, 37333, 46099, 54865
2115	chromosome X open reading frame 38	378426	2270	367683	11036	19802, 28568, 37334, 46100, 54866
2116	chromosome X open reading frame 38	440784	2271	400019	11037	19803, 28569, 37335, 46101, 54867
2117	chromosome X open reading frame 40A	359293	2272	420882	11038	19804, 28570, 37336, 46102, 54868
2118	chromosome X open reading frame 40A	393985	2273	421745	11039	19805, 28571, 37337, 46103, 54869
2119	chromosome X open reading frame 40A	423421	2274	422512	11040	19806, 28572, 37338, 46104, 54870

2120	chromosome X open reading frame 40A	423540	2275	425520	11041	19807, 28573, 37339, 46105, 54871
2121	chromosome X open reading frame 40A	431132	2276	423447	11042	19808, 28574, 37340, 46106, 54872
2122	chromosome X open reading frame 40A	441248	2277	423099	11043	19809, 28575, 37341, 46107, 54873
2123	chromosome X open reading frame 40A	450602	2278	427540	11044	19810, 28576, 37342, 46108, 54874
2124	chromosome X open reading frame 40A	514208	2279	423708	11045	19811, 28577, 37343, 46109, 54875
2125	chromosome X open reading frame 40A	596374	2280	469025	11046	19812, 28578, 37344, 46110, 54876
2126	chromosome X open reading frame 40A	598640	2281	469172	11047	19813, 28579, 37345, 46111, 54877
2127	chromosome X open reading frame 40B	355203	2282	347339	11048	19814, 28580, 37346, 46112, 54878
2128	chromosome X open reading frame 40B	370404	2283	359432	11049	19815, 28581, 37347, 46113, 54879
2129	chromosome X open reading frame 40B	370406	2284	359434	11050	19816, 28582, 37348, 46114, 54880
2130	chromosome X open reading frame 40B	462691	2285	417546	11051	19817, 28583, 37349, 46115, 54881
2131	chromosome X open reading frame 40B	601122	2286	472654	11052	19818, 28584, 37350, 46116, 54882
2132	chromosome X open reading frame 41	336387	2287	337757	11053	19819, 28585, 37351, 46117, 54883
2133	chromosome X open reading frame 41	372453	2288	361531	11054	19820, 28586, 37352, 46118, 54884
2134	chromosome X open reading frame 41	535523	2289	441930	11055	19821, 28587, 37353, 46119, 54885
2135	chromosome X open reading frame 48	276241	2290	276241	11056	19822, 28588, 37354, 46120, 54886
2136	chromosome X open reading frame 48	344129	2291	343893	11057	19823, 28589, 37355, 46121,

						54887
2137	chromosome X open reading frame 56	320339	2292	320345	11058	19824, 28590, 37356, 46122, 54888
2138	chromosome X open reading frame 56	371594	2293	360652	11059	19825, 28591, 37357, 46123, 54889
2139	chromosome X open reading frame 56	476164	2294	420635	11060	19826, 28592, 37358, 46124, 54890
2140	chromosome X open reading frame 56	486230	2295	420787	11061	19827, 28593, 37359, 46125, 54891
2141	chromosome X open reading frame 56	536133	2296	441786	11062	19828, 28594, 37360, 46126, 54892
2142	chromosome X open reading frame 57	372544	2297	361623	11063	19829, 28595, 37361, 46127, 54893
2143	chromosome X open reading frame 57	372548	2298	361628	11064	19830, 28596, 37362, 46128, 54894
2144	chromosome X open reading frame 57	421550	2299	405866	11065	19831, 28597, 37363, 46129, 54895
2145	chromosome X open reading frame 58	379211	2300	368511	11066	19832, 28598, 37364, 46130, 54896
2146	chromosome X open reading frame 58	435707	2301	407305	11067	19833, 28599, 37365, 46131, 54897
2147	chromosome X open reading frame 64	371125	2302	360166	11068	19834, 28600, 37366, 46132, 54898
2148	chromosome X open reading frame 65	374251	2303	363369	11069	19835, 28601, 37367, 46133, 54899
2149	chromosome X open reading frame 65	438526	2304	411354	11070	19836, 28602, 37368, 46134, 54900
2150	chromosome X open reading frame 67	342995	2305	342680	11071	19837, 28603, 37369, 46135, 54901
2151	chromosome X open reading frame 69	330288	2306	328335	11072	19838, 28604, 37370, 46136, 54902
2152	chromosome Y open reading frame 17	330758	2307	327634	11073	19839, 28605, 37371, 46137, 54903
2153	chromosome Y open	382764	2308	372213	11074	19840, 28606,

	reading frame 17					37372, 46138, 54904
2154	chronic lymphocytic leukemia up-regulated 1 opposite strand	378487	2309	367748	11075	19841, 28607, 37373, 46139, 54905
2155	chronic lymphocytic leukemia up-regulated 1 opposite strand	538965	2310	439051	11076	19842, 28608, 37374, 46140, 54906
2156	CHURC1-FNTB readthrough	447296	2311	406393	11077	19843, 28609, 37375, 46141, 54907
2157	CHURC1-FNTB readthrough	448390	2312	399362	11078	19844, 28610, 37376, 46142, 54908
2158	CHURC1-FNTB readthrough	542227	2313	443140	11079	19845, 28611, 37377, 46143, 54909
2159	CHURC1-FNTB readthrough	549987	2314	447121	11080	19846, 28612, 37378, 46144, 54910
2160	churchill domain containing 1	359118	2315	352026	11081	19847, 28613, 37379, 46145, 54911
2161	churchill domain containing 1	548752	2316	450165	11082	19848, 28614, 37380, 46146, 54912
2162	churchill domain containing 1	549115	2317	448050	11083	19849, 28615, 37381, 46147, 54913
2163	churchill domain containing 1	552002	2318	450144	11084	19850, 28616, 37382, 46148, 54914
2164	chymotrypsin-like elastase family, member 2B	422901	2319	399811	11085	19851, 28617, 37383, 46149, 54915
2165	chymotrypsin-like elastase family, member 3A	290122	2320	290122	11086	19852, 28618, 37384, 46150, 54916
2166	chymotrypsin-like elastase family, member 3A	374661	2321	363793	11087	19853, 28619, 37385, 46151, 54917
2167	chymotrypsin-like elastase family, member 3A	374663	2322	363795	11088	19854, 28620, 37386, 46152, 54918
2168	chymotrypsin-like elastase family, member 3A	400271	2323	383130	11089	19855, 28621, 37387, 46153, 54919
2169	CKLF-CMTM1 readthrough	527729	2324	433998	11090	19856, 28622, 37388, 46154, 54920

2170	CKLF-CMTM1 readthrough	529718	2325	433503	11091	19857, 28623, 37389, 46155, 54921
2171	clathrin heavy chain linker domain containing 1	406076	2326	385512	11092	19858, 28624, 37390, 46156, 54922
2172	claudin 24	541814	2327	438400	11093	19859, 28625, 37391, 46157, 54923
2173	claudin 4	573160	2328	461070	11094	19860, 28626, 37392, 46158, 54924
2174	claudin 4	573932	2329	460384	11095	19861, 28627, 37393, 46159, 54925
2175	cleavage and polyadenylation specific factor 4-like	344935	2330	343900	11096	19862, 28628, 37394, 46160, 54926
2176	cleavage and polyadenylation specific factor 4-like	397671	2331	380788	11097	19863, 28629, 37395, 46161, 54927
2177	cleavage stimulation factor, 3' pre-RNA, subunit 2, 64kDa	413437	2332	415705	11098	19864, 28630, 37396, 46162, 54928
2178	cleavage stimulation factor, 3' pre-RNA, subunit 2, 64kDa	415585	2333	387996	11099	19865, 28631, 37397, 46163, 54929
2179	cms1 ribosomal small subunit homolog (yeast)	489081	2334	419161	11100	19866, 28632, 37398, 46164, 54930
2180	CMT duplicated region transcript 1Uncharacterized protein	312127	2335	385268	11101	19867, 28633, 37399, 46165, 54931
2181	CMT1A duplicated region transcript 1	354433	2336	346416	11102	19868, 28634, 37400, 46166, 54932
2182	CMT1A duplicated region transcript 1 protein	395906	2337	379242	11103	19869, 28635, 37401, 46167, 54933
2183	CMT1A duplicated region transcript 15	420162	2338	402355	11104	19870, 28636, 37402, 46168, 54934
2184	CMT1A duplicated region transcript 15	431716	2339	399575	11105	19871, 28637, 37403, 46169, 54935
2185	CMT1A duplicated region transcript 15-like 2	399044	2340	382000	11106	19872, 28638, 37404, 46170, 54936
2186	CMT1A duplicated region transcript 4	312177	2341	310031	11107	19873, 28639, 37405, 46171,

						54937
2187	CMT1A duplicated region transcript 4	520956	2342	429574	11108	19874, 28640, 37406, 46172, 54938
2188	CMT1A duplicated region transcript 4	524205	2343	452374	11109	19875, 28641, 37407, 46173, 54939
2189	coatomer protein complex, subunit zeta 2	6101	2344	6101	11110	19876, 28642, 37408, 46174, 54940, 61525, 61583
2190	COBL-like 1	194871	2345	194871	11111	19877, 28643, 37409, 46175, 54941
2191	COBL-like 1	342193	2346	341360	11112	19878, 28644, 37410, 46176, 54942
2192	COBL-like 1	375458	2347	364607	11113	19879, 28645, 37411, 46177, 54943
2193	COBL-like 1	392717	2348	376478	11114	19880, 28646, 37412, 46178, 54944
2194	COBL-like 1	409184	2349	387326	11115	19881, 28647, 37413, 46179, 54945
2195	COBL-like 1	414843	2350	387967	11116	19882, 28648, 37414, 46180, 54946
2196	COBL-like 1	448708	2351	406062	11117	19883, 28649, 37415, 46181, 54947
2197	COBW domain containing 5	377392	2352	366609	11118	19884, 28650, 37416, 46182, 54948
2198	COBW domain containing 5	382405	2353	371842	11119	19885, 28651, 37417, 46183, 54949
2199	COBW domain containing 5	377395	2354	366612	11120	19886, 28652, 37418, 46184, 54950
2200	COBW domain containing 6	377439	2355	366658	11121	19887, 28653, 37419, 46185, 54951
2201	COBW domain containing 6	377441	2356	366660	11122	19888, 28654, 37420, 46186, 54952
2202	COBW domain containing 6	377445	2357	366664	11123	19889, 28655, 37421, 46187, 54953

2203	COBW domain containing 6	377449	2358	366668	11124	19890, 28656, 37422, 46188, 54954
2204	COBW domain containing 6	377450	2359	366669	11125	19891, 28657, 37423, 46189, 54955
2205	COBW domain containing 6	377457	2360	366677	11126	19892, 28658, 37424, 46190, 54956
2206	COBW domain containing 6	382399	2361	371836	11127	19893, 28659, 37425, 46191, 54957
2207	COBW domain containing 6	416428	2362	408279	11128	19894, 28660, 37426, 46192, 54958
2208	COBW domain containing 6	536466	2363	445070	11129	19895, 28661, 37427, 46193, 54959
2209	COBW domain containing 7	377391	2364	366608	11130	19896, 28662, 37428, 46194, 54960
2210	COBW domain containing 7	456520	2365	401079	11131	19897, 28663, 37429, 46195, 54961
2211	COBW domain containing 7	457288	2366	402214	11132	19898, 28664, 37430, 46196, 54962
2212	COBW domain containing 7	466582	2367	418355	11133	19899, 28665, 37431, 46197, 54963
2213	coiled-coil and C2 domain containing 1B	284376	2368	284376	11134	19900, 28666, 37432, 46198, 54964
2214	coiled-coil and C2 domain containing 1B	371573	2369	360628	11135	19901, 28667, 37433, 46199, 54965
2215	coiled-coil and C2 domain containing 1B	371575	2370	360631	11136	19902, 28668, 37434, 46200, 54966
2216	coiled-coil and C2 domain containing 1B	371586	2371	360642	11137	19903, 28669, 37435, 46201, 54967
2217	coiled-coil and C2 domain containing 1B	438021	2372	395921	11138	19904, 28670, 37436, 46202, 54968
2218	coiled-coil and C2 domain containing 1B	438831	2373	406300	11139	19905, 28671, 37437, 46203, 54969
2219	coiled-coil and C2 domain containing 1B	450942	2374	402440	11140	19906, 28672, 37438, 46204,

						54970
2220	coiled-coil and C2 domain containing 2B	344386	2375	343747	11141	19907, 28673, 37439, 46205, 54971
2221	coiled-coil and C2 domain containing 2B	371198	2376	360241	11142	19908, 28674, 37440, 46206, 54972
2222	coiled-coil and C2 domain containing 2B	451649	2377	411217	11143	19909, 28675, 37441, 46207, 54973
2223	coiled-coil domain containing 102A	258214	2378	258214	11144	19910, 28676, 37442, 46208, 54974
2224	coiled-coil domain containing 102B	319445	2379	316237	11145	19911, 28677, 37443, 46209, 54975
2225	coiled-coil domain containing 102B	358653	2380	351479	11146	19912, 28678, 37444, 46210, 54976
2226	coiled-coil domain containing 102B	360242	2381	353377	11147	19913, 28679, 37445, 46211, 54977
2227	coiled-coil domain containing 103	357776	2382	350420	11148	19914, 28680, 37446, 46212, 54978
2228	coiled-coil domain containing 103	410006	2383	387252	11149	19915, 28681, 37447, 46213, 54979
2229	coiled-coil domain containing 103	417826	2384	391692	11150	19916, 28682, 37448, 46214, 54980
2230	coiled-coil domain containing 104	339012	2385	342699	11151	19917, 28683, 37449, 46215, 54981
2231	coiled-coil domain containing 104	349456	2386	295117	11152	19918, 28684, 37450, 46216, 54982
2232	coiled-coil domain containing 11	398545	2387	381553	11153	19919, 28685, 37451, 46217, 54983
2233	coiled-coil domain containing 111	314970	2388	313816	11154	19920, 28686, 37452, 46218, 54984
2234	coiled-coil domain containing 112	379611	2389	368931	11155	19921, 28687, 37453, 46219, 54985
2235	coiled-coil domain containing 112	395557	2390	378925	11156	19922, 28688, 37454, 46220, 54986
2236	coiled-coil domain	219299	2391	219299	11157	19923, 28689,

	containing 113					37455, 46221, 54987
2237	coiled-coil domain containing 113	443128	2392	402588	11158	19924, 28690, 37456, 46222, 54988
2238	coiled-coil domain containing 114	315396	2393	318429	11159	19925, 28691, 37457, 46223, 54989
2239	coiled-coil domain containing 116	292779	2394	292779	11160	19926, 28692, 37458, 46224, 54990
2240	coiled-coil domain containing 117	249064	2395	249064	11161	19927, 28693, 37459, 46225, 54991
2241	coiled-coil domain containing 117	421503	2396	387827	11162	19928, 28694, 37460, 46226, 54992
2242	coiled-coil domain containing 117	443309	2397	399363	11163	19929, 28695, 37461, 46227, 54993
2243	coiled-coil domain containing 117	448492	2398	389478	11164	19930, 28696, 37462, 46228, 54994
2244	coiled-coil domain containing 12	292314	2399	292314	11165	19931, 28697, 37463, 46229, 54995
2245	coiled-coil domain containing 12	425441	2400	416263	11166	19932, 28698, 37464, 46230, 54996
2246	coiled-coil domain containing 12	446836	2401	387490	11167	19933, 28699, 37465, 46231, 54997
2247	coiled-coil domain containing 12	546280	2402	441327	11168	19934, 28700, 37466, 46232, 54998
2248	coiled-coil domain containing 120	376396	2403	365577	11169	19935, 28701, 37467, 46233, 54999
2249	coiled-coil domain containing 120	422185	2404	416445	11170	19936, 28702, 37468, 46234, 55000
2250	coiled-coil domain containing 120	536628	2405	443351	11171	19937, 28703, 37469, 46235, 55001
2251	coiled-coil domain containing 121	324364	2406	339087	11172	19938, 28704, 37470, 46236, 55002
2252	coiled-coil domain containing 121	394775	2407	412150	11173	19939, 28705, 37471, 46237, 55003

2253	coiled-coil domain containing 124	445755	2408	408730	11174	19940, 28706, 37472, 46238, 55004
2254	coiled-coil domain containing 124	597436	2409	471455	11175	19941, 28707, 37473, 46239, 55005
2255	coiled-coil domain containing 127	296824	2410	296824	11176	19942, 28708, 37474, 46240, 55006
2256	coiled-coil domain containing 127	441693	2411	411206	11177	19943, 28709, 37475, 46241, 55007
2257	coiled-coil domain containing 129	319386	2412	313062	11178	19944, 28710, 37476, 46242, 55008
2258	coiled-coil domain containing 129	407970	2413	384416	11179	19945, 28711, 37477, 46243, 55009
2259	coiled-coil domain containing 129	409717	2414	387220	11180	19946, 28712, 37478, 46244, 55010
2260	coiled-coil domain containing 129	451887	2415	395835	11181	19947, 28713, 37479, 46245, 55011
2261	coiled-coil domain containing 129	454513	2416	413233	11182	19948, 28714, 37480, 46246, 55012
2262	coiled-coil domain containing 129	456011	2417	390544	11183	19949, 28715, 37481, 46247, 55013
2263	coiled-coil domain containing 129	538406	2418	446218	11184	19950, 28716, 37482, 46248, 55014
2264	coiled-coil domain containing 13	310232	2419	309836	11185	19951, 28717, 37483, 46249, 55015
2265	coiled-coil domain containing 130	221554	2420	221554	11186	19952, 28718, 37484, 46250, 55016
2266	coiled-coil domain containing 130	540216	2421	445580	11187	19953, 28719, 37485, 46251, 55017
2267	coiled-coil domain containing 132	251739	2422	251739	11188	19954, 28720, 37486, 46252, 55018
2268	coiled-coil domain containing 132	305866	2423	307666	11189	19955, 28721, 37487, 46253, 55019
2269	coiled-coil domain containing 132	317751	2424	325582	11190	19956, 28722, 37488, 46254,

						55020
2270	coiled-coil domain containing 132	535481	2425	446089	11191	19957, 28723, 37489, 46255, 55021
2271	coiled-coil domain containing 132	541136	2426	445766	11192	19958, 28724, 37490, 46256, 55022
2272	coiled-coil domain containing 132	544910	2427	443104	11193	19959, 28725, 37491, 46257, 55023
2273	coiled-coil domain containing 138	295124	2428	295124	11194	19960, 28726, 37492, 46258, 55024
2274	coiled-coil domain containing 138	412964	2429	411800	11195	19961, 28727, 37493, 46259, 55025
2275	coiled-coil domain containing 140	295226	2430	295226	11196	19962, 28728, 37494, 46260, 55026
2276	coiled-coil domain containing 140	440903	2431	407652	11197	19963, 28729, 37495, 46261, 55027
2277	coiled-coil domain containing 141	295723	2432	295723	11198	19964, 28730, 37496, 46262, 55028
2278	coiled-coil domain containing 141	343876	2433	344627	11199	19965, 28731, 37497, 46263, 55029
2279	coiled-coil domain containing 141	420890	2434	395995	11200	19966, 28732, 37498, 46264, 55030
2280	coiled-coil domain containing 142	393965	2435	377537	11201	19967, 28733, 37499, 46265, 55031
2281	coiled-coil domain containing 142	290418	2436	290418	11202	19968, 28734, 37500, 46266, 55032
2282	coiled-coil domain containing 144 family, N-terminal like	327925	2437	328054	11203	19969, 28735, 37501, 46267, 55033
2283	coiled-coil domain containing 144A	328495	2438	333750	11204	19970, 28736, 37502, 46268, 55034
2284	coiled-coil domain containing 144A	340621	2439	344740	11205	19971, 28737, 37503, 46269, 55035
2285	coiled-coil domain containing 144A	360495	2440	353685	11206	19972, 28738, 37504, 46270, 55036
2286	coiled-coil domain	360524	2441	353717	11207	19973, 28739,

	containing 144A					37505, 46271, 55037
2287	coiled-coil domain containing 144A	399264	2442	382206	11208	19974, 28740, 37506, 46272, 55038
2288	coiled-coil domain containing 144A	399273	2443	382215	11209	19975, 28741, 37507, 46273, 55039
2289	coiled-coil domain containing 144A	420937	2444	398774	11210	19976, 28742, 37508, 46274, 55040
2290	coiled-coil domain containing 144A	436374	2445	404575	11211	19977, 28743, 37509, 46275, 55041
2291	coiled-coil domain containing 144A	443444	2446	439262	11212	19978, 28744, 37510, 46276, 55042
2292	coiled-coil domain containing 144A	448331	2447	440655	11213	19979, 28745, 37511, 46277, 55043
2293	coiled-coil domain containing 144A	456009	2448	394201	11214	19980, 28746, 37512, 46278, 55044
2294	coiled-coil domain containing 144C	340196	2449	343605	11215	19981, 28747, 37513, 46279, 55045
2295	coiled-coil domain containing 144C	425519	2450	411747	11216	19982, 28748, 37514, 46280, 55046
2296	coiled-coil domain containing 146	285871	2451	285871	11217	19983, 28749, 37515, 46281, 55047
2297	coiled-coil domain containing 146	415750	2452	388649	11218	19984, 28750, 37516, 46282, 55048
2298	coiled-coil domain containing 146	431197	2453	413885	11219	19985, 28751, 37517, 46283, 55049
2299	coiled-coil domain containing 147	312902	2454	323620	11220	19986, 28752, 37518, 46284, 55050
2300	coiled-coil domain containing 147	369703	2455	358717	11221	19987, 28753, 37519, 46285, 55051
2301	coiled-coil domain containing 147	369704	2456	358718	11222	19988, 28754, 37520, 46286, 55052
2302	coiled-coil domain containing 148	283233	2457	283233	11223	19989, 28755, 37521, 46287, 55053

2303	coiled-coil domain containing 148	375617	2458	364767	11224	19990, 28756, 37522, 46288, 55054
2304	coiled-coil domain containing 148	536771	2459	443740	11225	19991, 28757, 37523, 46289, 55055
2305	coiled-coil domain containing 149	382116	2460	371550	11226	19992, 28758, 37524, 46290, 55056
2306	coiled-coil domain containing 149	428116	2461	395668	11227	19993, 28759, 37525, 46291, 55057
2307	coiled-coil domain containing 149	504487	2462	425715	11228	19994, 28760, 37526, 46292, 55058
2308	coiled-coil domain containing 149	389609	2463	374260	11229	19995, 28761, 37527, 46293, 55059
2309	coiled-coil domain containing 150	272831	2464	272831	11230	19996, 28762, 37528, 46294, 55060
2310	coiled-coil domain containing 150	389175	2465	373827	11231	19997, 28763, 37529, 46295, 55061
2311	coiled-coil domain containing 150	409270	2466	387257	11232	19998, 28764, 37530, 46296, 55062
2312	coiled-coil domain containing 150	423093	2467	393634	11233	19999, 28765, 37531, 46297, 55063
2313	coiled-coil domain containing 150	472405	2468	441149	11234	20000, 28766, 37532, 46298, 55064
2314	coiled-coil domain containing 150	536389	2469	437528	11235	20001, 28767, 37533, 46299, 55065
2315	coiled-coil domain containing 151	356392	2470	348757	11236	20002, 28768, 37534, 46300, 55066
2316	coiled-coil domain containing 151	543934	2471	441458	11237	20003, 28769, 37535, 46301, 55067
2317	coiled-coil domain containing 151	545100	2472	442987	11238	20004, 28770, 37536, 46302, 55068
2318	coiled-coil domain containing 152	361970	2473	354888	11239	20005, 28771, 37537, 46303, 55069
2319	coiled-coil domain containing 153	415318	2474	445431	11240	20006, 28772, 37538, 46304,

						55070
2320	coiled-coil domain containing 153	503566	2475	423567	11241	20007, 28773, 37539, 46305, 55071
2321	coiled-coil domain containing 154	389176	2476	373828	11242	20008, 28774, 37540, 46306, 55072
2322	coiled-coil domain containing 154	409671	2477	386744	11243	20009, 28775, 37541, 46307, 55073
2323	coiled-coil domain containing 157	338306	2478	343087	11244	20010, 28776, 37542, 46308, 55074
2324	coiled-coil domain containing 157	405659	2479	385357	11245	20011, 28777, 37543, 46309, 55075
2325	coiled-coil domain containing 158	318586	2480	316815	11246	20012, 28778, 37544, 46310, 55076
2326	coiled-coil domain containing 158	388914	2481	373566	11247	20013, 28779, 37545, 46311, 55077
2327	coiled-coil domain containing 159	427879	2482	390400	11248	20014, 28780, 37546, 46312, 55078
2328	coiled-coil domain containing 159	458408	2483	402239	11249	20015, 28781, 37547, 46313, 55079
2329	coiled-coil domain containing 159	588790	2484	468232	11250	20016, 28782, 37548, 46314, 55080
2330	coiled-coil domain containing 160	370809	2485	359845	11251	20017, 28783, 37549, 46315, 55081
2331	coiled-coil domain containing 160	517294	2486	427951	11252	20018, 28784, 37550, 46316, 55082
2332	coiled-coil domain containing 164	288710	2487	288710	11253	20019, 28785, 37551, 46317, 55083
2333	coiled-coil domain containing 164	439066	2488	395215	11254	20020, 28786, 37552, 46318, 55084
2334	coiled-coil domain containing 165	306285	2489	303670	11255	20021, 28787, 37553, 46319, 55085
2335	coiled-coil domain containing 165	359865	2490	352927	11256	20022, 28788, 37554, 46320, 55086
2336	coiled-coil domain	400050	2491	382924	11257	20023, 28789,

	containing 165					37555, 46321, 55087
2337	coiled-coil domain containing 166	542437	2492	437468	11258	20024, 28790, 37556, 46322, 55088
2338	coiled-coil domain containing 168	322527	2493	320232	11259	20025, 28791, 37557, 46323, 55089
2339	coiled-coil domain containing 169	239859	2494	239859	11260	20026, 28792, 37558, 46324, 55090
2340	coiled-coil domain containing 169	239860	2495	239860	11261	20027, 28793, 37559, 46325, 55091
2341	coiled-coil domain containing 169	379862	2496	369191	11262	20028, 28794, 37560, 46326, 55092
2342	coiled-coil domain containing 169	379864	2497	369193	11263	20029, 28795, 37561, 46327, 55093
2343	coiled-coil domain containing 169	491049	2498	425252	11264	20030, 28796, 37562, 46328, 55094
2344	coiled-coil domain containing 169	510088	2499	427495	11265	20031, 28797, 37563, 46329, 55095
2345	coiled-coil domain containing 169	503173	2500	426174	11266	20032, 28798, 37564, 46330, 55096
2346	coiled-coil domain containing 17	343901	2501	341451	11267	20033, 28799, 37565, 46331, 55097
2347	coiled-coil domain containing 17	445048	2502	411335	11268	20034, 28800, 37566, 46332, 55098
2348	coiled-coil domain containing 17	421127	2503	389415	11269	20035, 28801, 37567, 46333, 55099
2349	coiled-coil domain containing 17	528266	2504	432172	11270	20036, 28802, 37568, 46334, 55100
2350	coiled-coil domain containing 18	334652	2505	334084	11271	20037, 28803, 37569, 46335, 55101
2351	coiled-coil domain containing 18	338949	2506	344380	11272	20038, 28804, 37570, 46336, 55102
2352	coiled-coil domain containing 18	401026	2507	383808	11273	20039, 28805, 37571, 46337, 55103

2353	coiled-coil domain containing 18	557479	2508	451099	11274	20040, 28806, 37572, 46338, 55104
2354	coiled-coil domain containing 23	372521	2509	361599	11275	20041, 28807, 37573, 46339, 55105
2355	coiled-coil domain containing 23	372522	2510	361600	11276	20042, 28808, 37574, 46340, 55106
2356	coiled-coil domain containing 23	537227	2511	442851	11277	20043, 28809, 37575, 46341, 55107
2357	coiled-coil domain containing 24	372318	2512	361392	11278	20044, 28810, 37576, 46342, 55108
2358	coiled-coil domain containing 25	356537	2513	348933	11279	20045, 28811, 37577, 46343, 55109
2359	coiled-coil domain containing 25	539095	2514	437677	11280	20046, 28812, 37578, 46344, 55110
2360	coiled-coil domain containing 27	294600	2515	294600	11281	20047, 28813, 37579, 46345, 55111
2361	coiled-coil domain containing 28A	26464	2516	26464	11282	20048, 28814, 37580, 46346, 55112, 61526, 61584
2362	coiled-coil domain containing 28A	332797	2517	332716	11283	20049, 28815, 37581, 46347, 55113
2363	coiled-coil domain containing 30	340612	2518	340378	11284	20050, 28816, 37582, 46348, 55114
2364	coiled-coil domain containing 30	342022	2519	339280	11285	20051, 28817, 37583, 46349, 55115
2365	coiled-coil domain containing 30	390640	2520	375051	11286	20052, 28818, 37584, 46350, 55116
2366	coiled-coil domain containing 30	428554	2521	397035	11287	20053, 28819, 37585, 46351, 55117
2367	coiled-coil domain containing 30	445157	2522	400685	11288	20054, 28820, 37586, 46352, 55118
2368	coiled-coil domain containing 33	268082	2523	268082	11289	20055, 28821, 37587, 46353, 55119
2369	coiled-coil domain	321288	2524	325012	11290	20056, 28822,

	containing 33					37588, 46354, 55120
2370	coiled-coil domain containing 33	398814	2525	381795	11291	20057, 28823, 37589, 46355, 55121
2371	coiled-coil domain containing 33	558821	2526	452817	11292	20058, 28824, 37590, 46356, 55122
2372	coiled-coil domain containing 36	296449	2527	296449	11293	20059, 28825, 37591, 46357, 55123
2373	coiled-coil domain containing 36	309062	2528	311836	11294	20060, 28826, 37592, 46358, 55124
2374	coiled-coil domain containing 36	366429	2529	403700	11295	20061, 28827, 37593, 46359, 55125
2375	coiled-coil domain containing 36	438782	2530	391788	11296	20062, 28828, 37594, 46360, 55126
2376	coiled-coil domain containing 36	451634	2531	397641	11297	20063, 28829, 37595, 46361, 55127
2377	coiled-coil domain containing 36	452691	2532	407837	11298	20064, 28830, 37596, 46362, 55128
2378	coiled-coil domain containing 37	352312	2533	344749	11299	20065, 28831, 37597, 46363, 55129
2379	coiled-coil domain containing 37	393425	2534	377076	11300	20066, 28832, 37598, 46364, 55130
2380	coiled-coil domain containing 38	344280	2535	345470	11301	20067, 28833, 37599, 46365, 55131
2381	coiled-coil domain containing 41	339839	2536	344655	11302	20068, 28834, 37600, 46366, 55132
2382	coiled-coil domain containing 41	397807	2537	380909	11303	20069, 28835, 37601, 46367, 55133
2383	coiled-coil domain containing 41	397809	2538	380911	11304	20070, 28836, 37602, 46368, 55134
2384	coiled-coil domain containing 41	546527	2539	447449	11305	20071, 28837, 37603, 46369, 55135
2385	coiled-coil domain containing 42	293845	2540	293845	11306	20072, 28838, 37604, 46370, 55136

2386	coiled-coil domain containing 42	539522	2541	444359	11307	20073, 28839, 37605, 46371, 55137
2387	coiled-coil domain containing 42B	335621	2542	333915	11308	20074, 28840, 37606, 46372, 55138
2388	coiled-coil domain containing 43	315286	2543	323782	11309	20075, 28841, 37607, 46373, 55139
2389	coiled-coil domain containing 43	457422	2544	400845	11310	20076, 28842, 37608, 46374, 55140
2390	coiled-coil domain containing 48	436022	2545	414597	11311	20077, 28843, 37609, 46375, 55141
2391	coiled-coil domain containing 54	261058	2546	261058	11312	20078, 28844, 37610, 46376, 55142
2392	coiled-coil domain containing 57	324808	2547	315223	11313	20079, 28845, 37611, 46377, 55143
2393	coiled-coil domain containing 57	389641	2548	374292	11314	20080, 28846, 37612, 46378, 55144
2394	coiled-coil domain containing 57	392347	2549	376158	11315	20081, 28847, 37613, 46379, 55145
2395	coiled-coil domain containing 60	327554	2550	333374	11316	20082, 28848, 37614, 46380, 55146
2396	coiled-coil domain containing 63	308208	2551	312399	11317	20083, 28849, 37615, 46381, 55147
2397	coiled-coil domain containing 64B	389347	2552	373998	11318	20084, 28850, 37616, 46382, 55148
2398	coiled-coil domain containing 66	326595	2553	326050	11319	20085, 28851, 37617, 46383, 55149
2399	coiled-coil domain containing 66	394672	2554	378167	11320	20086, 28852, 37618, 46384, 55150
2400	coiled-coil domain containing 66	436465	2555	404320	11321	20087, 28853, 37619, 46385, 55151
2401	coiled-coil domain containing 66	538560	2556	444919	11322	20088, 28854, 37620, 46386, 55152
2402	coiled-coil domain containing 67	298050	2557	298050	11323	20089, 28855, 37621, 46387,

						55153
2403	coiled-coil domain containing 67	532819	2558	434635	11324	20090, 28856, 37622, 46388, 55154
2404	coiled-coil domain containing 67	534747	2559	432111	11325	20091, 28857, 37623, 46389, 55155
2405	coiled-coil domain containing 68	337363	2560	337209	11326	20092, 28858, 37624, 46390, 55156
2406	coiled-coil domain containing 68	432185	2561	413406	11327	20093, 28859, 37625, 46391, 55157
2407	coiled-coil domain containing 68	591504	2562	466690	11328	20094, 28860, 37626, 46392, 55158
2408	coiled-coil domain containing 69	355417	2563	347586	11329	20095, 28861, 37627, 46393, 55159
2409	coiled-coil domain containing 69	356749	2564	349190	11330	20096, 28862, 37628, 46394, 55160
2410	coiled-coil domain containing 7	277657	2565	277657	11331	20097, 28863, 37629, 46395, 55161
2411	coiled-coil domain containing 7	324147	2566	320733	11332	20098, 28864, 37630, 46396, 55162
2412	coiled-coil domain containing 7	362006	2567	355078	11333	20099, 28865, 37631, 46397, 55163
2413	coiled-coil domain containing 7	435402	2568	401923	11334	20100, 28866, 37632, 46398, 55164
2414	coiled-coil domain containing 7	535327	2569	442531	11335	20101, 28867, 37633, 46399, 55165
2415	coiled-coil domain containing 7	537047	2570	440632	11336	20102, 28868, 37634, 46400, 55166
2416	coiled-coil domain containing 7	539197	2571	441041	11337	20103, 28869, 37635, 46401, 55167
2417	coiled-coil domain containing 7	545067	2572	439930	11338	20104, 28870, 37636, 46402, 55168
2418	coiled-coil domain containing 71	321895	2573	319006	11339	20105, 28871, 37637, 46403, 55169
2419	coiled-coil domain	523505	2574	430897	11340	20106, 28872,

	containing 71-like					37638, 46404, 55170
2420	coiled-coil domain containing 72	438607	2575	397843	11341	20107, 28873, 37639, 46405, 55171
2421	coiled-coil domain containing 74A	295171	2576	295171	11342	20108, 28874, 37640, 46406, 55172
2422	coiled-coil domain containing 74A	467992	2577	444610	11343	20109, 28875, 37641, 46407, 55173
2423	coiled-coil domain containing 74A	409856	2578	387009	11344	20110, 28876, 37642, 46408, 55174
2424	coiled-coil domain containing 74B	310463	2579	308873	11345	20111, 28877, 37643, 46409, 55175
2425	coiled-coil domain containing 74B	392984	2580	376710	11346	20112, 28878, 37644, 46410, 55176
2426	coiled-coil domain containing 74B	409943	2581	386294	11347	20113, 28879, 37645, 46411, 55177
2427	coiled-coil domain containing 74B	457413	2582	399683	11348	20114, 28880, 37646, 46412, 55178
2428	coiled-coil domain containing 75	281932	2583	281932	11349	20115, 28881, 37647, 46413, 55179
2429	coiled-coil domain containing 75	409774	2584	386772	11350	20116, 28882, 37648, 46414, 55180
2430	coiled-coil domain containing 76	370139	2585	359158	11351	20117, 28883, 37649, 46415, 55181
2431	coiled-coil domain containing 76	370141	2586	359160	11352	20118, 28884, 37650, 46416, 55182
2432	coiled-coil domain containing 76	370143	2587	359162	11353	20119, 28885, 37651, 46417, 55183
2433	coiled-coil domain containing 78	293889	2588	293889	11354	20120, 28886, 37652, 46418, 55184
2434	coiled-coil domain containing 78	540512	2589	444907	11355	20121, 28887, 37653, 46419, 55185
2435	coiled-coil domain containing 79	415744	2590	440822	11356	20122, 28888, 37654, 46420, 55186

2436	coiled-coil domain containing 79	432602	2591	446376	11357	20123, 28889, 37655, 46421, 55187
2437	coiled-coil domain containing 79	433154	2592	440536	11358	20124, 28890, 37656, 46422, 55188
2438	coiled-coil domain containing 79	433574	2593	442248	11359	20125, 28891, 37657, 46423, 55189
2439	coiled-coil domain containing 81	278487	2594	278487	11360	20126, 28892, 37658, 46424, 55190
2440	coiled-coil domain containing 81	354755	2595	346800	11361	20127, 28893, 37659, 46425, 55191
2441	coiled-coil domain containing 81	445632	2596	415528	11362	20128, 28894, 37660, 46426, 55192
2442	coiled-coil domain containing 82	278520	2597	278520	11363	20129, 28895, 37661, 46427, 55193
2443	coiled-coil domain containing 82	423339	2598	397156	11364	20130, 28896, 37662, 46428, 55194
2444	coiled-coil domain containing 82	530203	2599	431148	11365	20131, 28897, 37663, 46429, 55195
2445	coiled-coil domain containing 82	538597	2600	442723	11366	20132, 28898, 37664, 46430, 55196
2446	coiled-coil domain containing 82	542662	2601	444010	11367	20133, 28899, 37665, 46431, 55197
2447	coiled-coil domain containing 83	280245	2602	280245	11368	20134, 28900, 37666, 46432, 55198
2448	coiled-coil domain containing 83	342404	2603	344512	11369	20135, 28901, 37667, 46433, 55199
2449	coiled-coil domain containing 83	376067	2604	365235	11370	20136, 28902, 37668, 46434, 55200
2450	coiled-coil domain containing 84	334418	2605	334767	11371	20137, 28903, 37669, 46435, 55201
2451	coiled-coil domain containing 85A	407595	2606	384040	11372	20138, 28904, 37670, 46436, 55202
2452	coiled-coil domain containing 85C	380243	2607	369592	11373	20139, 28905, 37671, 46437,

						55203
2453	coiled-coil domain containing 87	333861	2608	328487	11374	20140, 28906, 37672, 46438, 55204
2454	coiled-coil domain containing 9	221922	2609	221922	11375	20141, 28907, 37673, 46439, 55205
2455	coiled-coil domain containing 9	504556	2610	440868	11376	20142, 28908, 37674, 46440, 55206
2456	coiled-coil domain containing 92	238156	2611	238156	11377	20143, 28909, 37675, 46441, 55207
2457	coiled-coil domain containing 92	539551	2612	442369	11378	20144, 28910, 37676, 46442, 55208
2458	coiled-coil domain containing 92	539761	2613	439441	11379	20145, 28911, 37677, 46443, 55209
2459	coiled-coil domain containing 92	545037	2614	440203	11380	20146, 28912, 37678, 46444, 55210
2460	coiled-coil domain containing 93	376300	2615	365477	11381	20147, 28913, 37679, 46445, 55211
2461	coiled-coil domain containing 94	262962	2616	262962	11382	20148, 28914, 37680, 46446, 55212
2462	coiled-coil domain containing 96	310085	2617	309285	11383	20149, 28915, 37681, 46447, 55213
2463	coiled-coil domain containing 97	269967	2618	269967	11384	20150, 28916, 37682, 46448, 55214
2464	Coiled-coil domain-containing protein 299415	299415	2619	299415	11385	20151, 28917, 37683, 46449, 55215
2465	coiled-coil-helix-coiled-coil-helix domain containing 5	324913	2620	325655	11386	20152, 28918, 37684, 46450, 55216
2466	coiled-coil-helix-coiled-coil-helix domain containing 6	290913	2621	290913	11387	20153, 28919, 37685, 46451, 55217
2467	coiled-coil-helix-coiled-coil-helix domain containing 6	513253	2622	422787	11388	20154, 28920, 37686, 46452, 55218
2468	COMM domain containing 2	473414	2623	419475	11389	20155, 28921, 37687, 46453, 55219
2469	COMM domain containing	376776	2624	365968	11390	20156, 28922,

	3					37688, 46454, 55220
2470	COMM domain containing 3	376787	2625	365983	11391	20157, 28923, 37689, 46455, 55221
2471	COMM domain containing 3	376836	2626	366032	11392	20158, 28924, 37690, 46456, 55222
2472	COMM domain containing 3	444869	2627	408982	11393	20159, 28925, 37691, 46457, 55223
2473	COMM domain containing 3	448361	2628	391237	11394	20160, 28926, 37692, 46458, 55224
2474	COMM domain containing 3	456711	2629	394580	11395	20161, 28927, 37693, 46459, 55225
2475	COMM domain containing 7	278980	2630	278980	11396	20162, 28928, 37694, 46460, 55226
2476	COMM domain containing 7	446419	2631	395339	11397	20163, 28929, 37695, 46461, 55227
2477	COMM domain containing 8	381571	2632	370984	11398	20164, 28930, 37696, 46462, 55228
2478	COMM domain containing 9	263401	2633	263401	11399	20165, 28931, 37697, 46463, 55229
2479	COMM domain containing 9	537683	2634	444855	11400	20166, 28932, 37698, 46464, 55230
2480	COMM domain containing 9	452374	2635	392510	11401	20167, 28933, 37699, 46465, 55231
2481	complement component 1 s subcomponent	594877	2636	471707	11402	20168, 28934, 37700, 46466, 55232
2482	complement component 1 s subcomponent	595575	2637	469947	11403	20169, 28935, 37701, 46467, 55233
2483	complexin 4	299721	2638	299721	11404	20170, 28936, 37702, 46468, 55234
2484	contactin associated protein-like 4	307431	2639	306893	11405	20171, 28937, 37703, 46469, 55235
2485	contactin associated protein-like 4	377504	2640	439733	11406	20172, 28938, 37704, 46470, 55236

2486	contactin associated protein-like 4	478060	2641	418741	11407	20173, 28939, 37705, 46471, 55237
2487	copine family member IX	383831	2642	373342	11408	20174, 28940, 37706, 46472, 55238
2488	copine family member IX	383832	2643	373343	11409	20175, 28941, 37707, 46473, 55239
2489	copine I	317619	2644	326126	11410	20176, 28942, 37708, 46474, 55240
2490	copine I	317677	2645	317257	11411	20177, 28943, 37709, 46475, 55241
2491	copine I	352393	2646	336945	11412	20178, 28944, 37710, 46476, 55242
2492	copine I	397443	2647	380585	11413	20179, 28945, 37711, 46477, 55243
2493	copine I	397445	2648	380587	11414	20180, 28946, 37712, 46478, 55244
2494	copine I	397446	2649	380588	11415	20181, 28947, 37713, 46479, 55245
2495	copine I	414664	2650	404355	11416	20182, 28948, 37714, 46480, 55246
2496	copine I	414711	2651	409955	11417	20183, 28949, 37715, 46481, 55247
2497	copine I	420363	2652	401915	11418	20184, 28950, 37716, 46482, 55248
2498	copine I	434795	2653	409794	11419	20185, 28951, 37717, 46483, 55249
2499	copine I	435747	2654	412806	11420	20186, 28952, 37718, 46484, 55250
2500	copine I	437100	2655	391483	11421	20187, 28953, 37719, 46485, 55251
2501	copine I	439806	2656	387434	11422	20188, 28954, 37720, 46486, 55252
2502	copine I	440240	2657	397638	11423	20189, 28955, 37721, 46487,

						55253
2503	copine II	290776	2658	290776	11424	20190, 28956, 37722, 46488, 55254
2504	copine II	535318	2659	439018	11425	20191, 28957, 37723, 46489, 55255
2505	copine II	537605	2660	445468	11426	20192, 28958, 37724, 46490, 55256
2506	copine IV	429747	2661	411904	11427	20193, 28959, 37725, 46491, 55257
2507	copine IV	502818	2662	421646	11428	20194, 28960, 37726, 46492, 55258
2508	copine IV	505881	2663	425506	11429	20195, 28961, 37727, 46493, 55259
2509	copine IV	512055	2664	421705	11430	20196, 28962, 37728, 46494, 55260
2510	copine IV	512332	2665	424853	11431	20197, 28963, 37729, 46495, 55261
2511	copine VIII	331366	2666	329748	11432	20198, 28964, 37730, 46496, 55262
2512	cordon-bleu homolog (mouse)	265136	2667	265136	11433	20199, 28965, 37731, 46497, 55263
2513	cordon-bleu homolog (mouse)	395540	2668	378910	11434	20200, 28966, 37732, 46498, 55264
2514	cordon-bleu homolog (mouse)	395542	2669	378912	11435	20201, 28967, 37733, 46499, 55265
2515	cordon-bleu homolog (mouse)	431948	2670	413498	11436	20202, 28968, 37734, 46500, 55266
2516	cordon-bleu homolog (mouse)	441453	2671	399500	11437	20203, 28969, 37735, 46501, 55267
2517	cordon-bleu homolog (mouse)	457306	2672	397300	11438	20204, 28970, 37736, 46502, 55268
2518	coronin 7	574025	2673	461702	11439	20205, 28971, 37737, 46503, 55269
2519	cortexin 2	417307	2674	406145	11440	20206, 28972,

						37738, 46504, 55270
2520	cortexin 2	541248	2675	445900	11441	20207, 28973, 37739, 46505, 55271
2521	CPX chromosome region, candidate 1	276127	2676	276127	11442	20208, 28974, 37740, 46506, 55272
2522	CPX chromosome region, candidate 1	373111	2677	362203	11443	20209, 28975, 37741, 46507, 55273
2523	Crm, cramped-like (Drosophila)	262317	2678	262317	11444	20210, 28976, 37742, 46508, 55274
2524	Crm, cramped-like (Drosophila)	293925	2679	293925	11445	20211, 28977, 37743, 46509, 55275
2525	Crm, cramped-like (Drosophila)	397412	2680	380559	11446	20212, 28978, 37744, 46510, 55276
2526	Crm, cramped-like (Drosophila)	436138	2681	413634	11447	20213, 28979, 37745, 46511, 55277
2527	crystallin alpha B	572605	2682	459924	11448	20214, 28980, 37746, 46512, 55278
2528	crystallin alpha B	573313	2683	459140	11449	20215, 28981, 37747, 46513, 55279
2529	crystallin alpha B	574550	2684	461777	11450	20216, 28982, 37748, 46514, 55280
2530	crystallin, gamma N	337323	2685	338613	11451	20217, 28983, 37749, 46515, 55281
2531	CSNK1G2 antisense RNA 1 (non-protein coding)	314315	2686	315669	11452	20218, 28984, 37750, 46516, 55282
2532	CTAGE family, member 5	280083	2687	280083	11453	20219, 28985, 37751, 46517, 55283
2533	CTAGE family, member 5	341502	2688	339286	11454	20220, 28986, 37752, 46518, 55284
2534	CTAGE family, member 5	341749	2689	343897	11455	20221, 28987, 37753, 46519, 55285
2535	CTAGE family, member 5	348007	2690	343912	11456	20222, 28988, 37754, 46520, 55286

2536	CTAGE family, member 5	382245	2691	371680	11457	20223, 28989, 37755, 46521, 55287
2537	CTAGE family, member 5	396158	2692	379462	11458	20224, 28990, 37756, 46522, 55288
2538	CTAGE family, member 5	396165	2693	379468	11459	20225, 28991, 37757, 46523, 55289
2539	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	260327	2694	260327	11460	20226, 28992, 37758, 46524, 55290
2540	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	396780	2695	380000	11461	20227, 28993, 37759, 46525, 55291
2541	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	558373	2696	453051	11462	20228, 28994, 37760, 46526, 55292
2542	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	558791	2697	453612	11463	20229, 28995, 37761, 46527, 55293
2543	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	558966	2698	452837	11464	20230, 28996, 37762, 46528, 55294
2544	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	558968	2699	454154	11465	20231, 28997, 37763, 46529, 55295
2545	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase like 2	559793	2700	454187	11466	20232, 28998, 37764, 46530, 55296
2546	CTD-Protein Coding	319817	2701	318279	11467	20233, 28999, 37765, 46531, 55297
2547	CTD-Protein Coding	398859	2702	381835	11468	20234, 29000, 37766, 46532, 55298
2548	CTD-Protein Coding	544589	2703	442619	11469	20235, 29001, 37767, 46533, 55299
2549	C-type lectin domain family 2, member L	422142	2704	390661	11470	20236, 29002, 37768, 46534, 55300
2550	CUB and zona pellucida-	392790	2705	376540	11471	20237, 29003,

	like domains 1					37769, 46535, 55301
2551	CUB and zona pellucida-like domains 1	545804	2706	441590	11472	20238, 29004, 37770, 46536, 55302
2552	CUE domain containing 1	360238	2707	353373	11473	20239, 29005, 37771, 46537, 55303
2553	CUE domain containing 1	407144	2708	384712	11474	20240, 29006, 37772, 46538, 55304
2554	cutA divalent cation tolerance homolog (E. coli)	374496	2709	363620	11475	20241, 29007, 37773, 46539, 55305
2555	cutA divalent cation tolerance homolog (E. coli)	374500	2710	363624	11476	20242, 29008, 37774, 46540, 55306
2556	cutA divalent cation tolerance homolog (E. coli)	440279	2711	403268	11477	20243, 29009, 37775, 46541, 55307
2557	cutA divalent cation tolerance homolog (E. coli)	440930	2712	400114	11478	20244, 29010, 37776, 46542, 55308
2558	cutA divalent cation tolerance homolog (E. coli)	488034	2713	417544	11479	20245, 29011, 37777, 46543, 55309
2559	cutA divalent cation tolerance homolog (E. coli)	482684	2714	417823	11480	20246, 29012, 37778, 46544, 55310
2560	CWC15 spliceosome-associated protein homolog (S. cerevisiae)	570729	2715	461115	11481	20247, 29013, 37779, 46545, 55311
2561	CWC25 spliceosome-associated protein homolog (S. cerevisiae)	225428	2716	225428	11482	20248, 29014, 37780, 46546, 55312
2562	CWC25 spliceosome-associated protein homolog (S. cerevisiae)	536127	2717	438566	11483	20249, 29015, 37781, 46547, 55313
2563	CWF19-like 1, cell cycle control (S. pombe)	354105	2718	326411	11484	20250, 29016, 37782, 46548, 55314
2564	CWF19-like 1, cell cycle control (S. pombe)	370379	2719	359405	11485	20251, 29017, 37783, 46549, 55315
2565	CWF19-like 1, cell cycle control (S. pombe)	472872	2720	433798	11486	20252, 29018, 37784, 46550, 55316
2566	CWF19-like 2, cell cycle control (S. pombe)	282251	2721	282251	11487	20253, 29019, 37785, 46551, 55317

2567	CWF19-like 2, cell cycle control (S. pombe)	409771	2722	386247	11488	20254, 29020, 37786, 46552, 55318
2568	CWF19-like 2, cell cycle control (S. pombe)	433523	2723	387533	11489	20255, 29021, 37787, 46553, 55319
2569	C-x(9)-C motif containing 4 homolog (S. cerevisiae)	598989	2724	472945	11490	20256, 29022, 37788, 46554, 55320
2570	cyclic nucleotide binding domain containing 1	518476	2725	430073	11491	20257, 29023, 37789, 46555, 55321
2571	cyclin B3	593643	2726	471254	11492	20258, 29024, 37790, 46556, 55322
2572	cyclin B3	594292	2727	472548	11493	20259, 29025, 37791, 46557, 55323
2573	cyclin B3	596541	2728	471997	11494	20260, 29026, 37792, 46558, 55324
2574	cyclin B3	597115	2729	469069	11495	20261, 29027, 37793, 46559, 55325
2575	cyclin B3	598566	2730	471440	11496	20262, 29028, 37794, 46560, 55326
2576	cyclin B3	599832	2731	470722	11497	20263, 29029, 37795, 46561, 55327
2577	cyclin B3	601442	2732	472573	11498	20264, 29030, 37796, 46562, 55328
2578	cyclin B3	602116	2733	468921	11499	20265, 29031, 37797, 46563, 55329
2579	cyclin E2	308108	2734	309181	11500	20266, 29032, 37798, 46564, 55330
2580	cyclin E2	396133	2735	379437	11501	20267, 29033, 37799, 46565, 55331
2581	cyclin E2	520509	2736	429089	11502	20268, 29034, 37800, 46566, 55332
2582	cyclin E2	542725	2737	445726	11503	20269, 29035, 37801, 46567, 55333
2583	cyclin I	237654	2738	237654	11504	20270, 29036, 37802, 46568,

						55334
2584	cyclin I	505609	2739	426467	11505	20271, 29037, 37803, 46569, 55335
2585	cyclin I	513774	2740	426235	11506	20272, 29038, 37804, 46570, 55336
2586	cyclin I	537948	2741	441001	11507	20273, 29039, 37805, 46571, 55337
2587	cyclin I family member 2	378731	2742	368005	11508	20274, 29040, 37806, 46572, 55338
2588	cyclin N-terminal domain containing 1	315066	2743	316647	11509	20275, 29041, 37807, 46573, 55339
2589	cyclin N-terminal domain containing 1	588408	2744	465204	11510	20276, 29042, 37808, 46574, 55340
2590	cyclin N-terminal domain containing 2	430325	2745	396755	11511	20277, 29043, 37809, 46575, 55341
2591	cyclin N-terminal domain containing 2	433940	2746	408707	11512	20278, 29044, 37810, 46576, 55342
2592	cyclin Y-like 1	295414	2747	295414	11513	20279, 29045, 37811, 46577, 55343
2593	cyclin Y-like 1	339882	2748	342344	11514	20280, 29046, 37812, 46578, 55344
2594	cyclin Y-like 1	392209	2749	376045	11515	20281, 29047, 37813, 46579, 55345
2595	cyclin Y-like 2	426433	2750	395902	11516	20282, 29048, 37814, 46580, 55346
2596	cyclin Y-like 2	431603	2751	404907	11517	20283, 29049, 37815, 46581, 55347
2597	cyclin Y-like 3	407030	2752	384923	11518	20284, 29050, 37816, 46582, 55348
2598	cyclin-dependent kinase 15	260967	2753	260967	11519	20285, 29051, 37817, 46583, 55349
2599	cyclin-dependent kinase 15	374598	2754	363726	11520	20286, 29052, 37818, 46584, 55350
2600	cyclin-dependent kinase 15	410091	2755	386901	11521	20287, 29053,

						37819, 46585, 55351
2601	cyclin-dependent kinase 15	434439	2756	412775	11522	20288, 29054, 37820, 46586, 55352
2602	cyclin-dependent kinase 15	450471	2757	406472	11523	20289, 29055, 37821, 46587, 55353
2603	cyclin-dependent kinase 16	276052	2758	276052	11524	20290, 29056, 37822, 46588, 55354
2604	cyclin-dependent kinase 16	357227	2759	349762	11525	20291, 29057, 37823, 46589, 55355
2605	cyclin-dependent kinase 16	457458	2760	405798	11526	20292, 29058, 37824, 46590, 55356
2606	cyclin-dependent kinase 16	518022	2761	429751	11527	20293, 29059, 37825, 46591, 55357
2607	cyclin-dependent kinase 16	518391	2762	429044	11528	20294, 29060, 37826, 46592, 55358
2608	cyclin-dependent kinase 16	519758	2763	429259	11529	20295, 29061, 37827, 46593, 55359
2609	cyclin-dependent kinase 16	520893	2764	428351	11530	20296, 29062, 37828, 46594, 55360
2610	cyclin-dependent kinase 16	522883	2765	431085	11531	20297, 29063, 37829, 46595, 55361
2611	cyclin-dependent kinase 16	540311	2766	445634	11532	20298, 29064, 37830, 46596, 55362
2612	cyclin-dependent kinase 16	540877	2767	438245	11533	20299, 29065, 37831, 46597, 55363
2613	cyclin-dependent kinase 17	261211	2768	261211	11534	20300, 29066, 37832, 46598, 55364
2614	cyclin-dependent kinase 17	543119	2769	444459	11535	20301, 29067, 37833, 46599, 55365
2615	cyclin-dependent kinase 17	551816	2770	450058	11536	20302, 29068, 37834, 46600, 55366
2616	cyclin-dependent kinase 17	552262	2771	448132	11537	20303, 29069, 37835, 46601, 55367

2617	cyclin-dependent kinase 17	552496	2772	447282	11538	20304, 29070, 37836, 46602, 55368
2618	cyclin-dependent kinase 18	360066	2773	353176	11539	20305, 29071, 37837, 46603, 55369
2619	cyclin-dependent kinase 18	419301	2774	391324	11540	20306, 29072, 37838, 46604, 55370
2620	cyclin-dependent kinase 18	429964	2775	399082	11541	20307, 29073, 37839, 46605, 55371
2621	cyclin-dependent kinase 18	437052	2776	406578	11542	20308, 29074, 37840, 46606, 55372
2622	cyclin-dependent kinase 18	506784	2777	423665	11543	20309, 29075, 37841, 46607, 55373
2623	cyclin-dependent kinase 19	323817	2778	317665	11544	20310, 29076, 37842, 46608, 55374
2624	cyclin-dependent kinase 19	368911	2779	357907	11545	20311, 29077, 37843, 46609, 55375
2625	cyclin-dependent kinase 19	392576	2780	376355	11546	20312, 29078, 37844, 46610, 55376
2626	cyclin-dependent kinase 19	413605	2781	410604	11547	20313, 29079, 37845, 46611, 55377
2627	cyclin-dependent kinase 19	457688	2782	415621	11548	20314, 29080, 37846, 46612, 55378
2628	cyclin-dependent kinase 2 associated protein 2	301488	2783	301488	11549	20315, 29081, 37847, 46613, 55379
2629	cyclin-dependent kinase-like 1 (CDC2-related kinase)	395834	2784	379176	11550	20316, 29082, 37848, 46614, 55380
2630	Cyclin-related protein FAM58A	576892	2785	461135	11551	20317, 29083, 37849, 46615, 55381
2631	CYP2B proteinCytochrome P450 2B7 short isoformUncharacterized protein	541697	2786	441190	11552	20318, 29084, 37850, 46616, 55382
2632	cysteine and histidine-rich domain (CHORD) containing 1	320585	2787	319255	11553	20319, 29085, 37851, 46617, 55383
2633	cysteine and histidine-rich	457199	2788	401080	11554	20320, 29086,

	domain (CHORD) containing 1					37852, 46618, 55384
2634	cysteine sulfinic acid decarboxylase	267085	2789	267085	11555	20321, 29087, 37853, 46619, 55385
2635	cysteine sulfinic acid decarboxylase	308926	2790	311209	11556	20322, 29088, 37854, 46620, 55386
2636	cysteine sulfinic acid decarboxylase	379843	2791	369172	11557	20323, 29089, 37855, 46621, 55387
2637	cysteine sulfinic acid decarboxylase	379846	2792	369175	11558	20324, 29090, 37856, 46622, 55388
2638	cysteine sulfinic acid decarboxylase	398047	2793	381125	11559	20325, 29091, 37857, 46623, 55389
2639	cysteine sulfinic acid decarboxylase	444623	2794	415485	11560	20326, 29092, 37858, 46624, 55390
2640	cysteine sulfinic acid decarboxylase	542115	2795	439419	11561	20327, 29093, 37859, 46625, 55391
2641	cysteine sulfinic acid decarboxylase	544139	2796	439936	11562	20328, 29094, 37860, 46626, 55392
2642	cysteine-rich C-terminal 1	368790	2797	357779	11563	20329, 29095, 37861, 46627, 55393
2643	cysteine-rich DPF motif domain containing 1	314567	2798	325301	11564	20330, 29096, 37862, 46628, 55394
2644	cytidine and dCMP deaminase domain containing 1	251108	2799	251108	11565	20331, 29097, 37863, 46629, 55395
2645	cytidine and dCMP deaminase domain containing 1	444959	2800	407226	11566	20332, 29098, 37864, 46630, 55396
2646	cytidine and dCMP deaminase domain containing 1	538056	2801	442779	11567	20333, 29099, 37865, 46631, 55397
2647	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	377989	2802	367228	11568	20334, 29100, 37866, 46632, 55398
2648	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	377993	2803	367232	11569	20335, 29101, 37867, 46633, 55399
2649	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	399346	2804	382283	11570	20336, 29102, 37868, 46634, 55400

2650	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	424282	2805	406449	11571	20337, 29103, 37869, 46635, 55401
2651	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	436589	2806	397893	11572	20338, 29104, 37870, 46636, 55402
2652	cytidine monophospho-N-acetylneuraminic acid hydroxylase, pseudogene	458373	2807	401225	11573	20339, 29105, 37871, 46637, 55403
2653	cytochrome b5 domain containing 1	332439	2808	331479	11574	20340, 29106, 37872, 46638, 55404
2654	cytochrome b5 domain containing 1	541486	2809	444413	11575	20341, 29107, 37873, 46639, 55405
2655	cytochrome b5 reductase-like	287899	2810	287899	11576	20342, 29108, 37874, 46640, 55406
2656	cytochrome b5 reductase-like	401046	2811	383825	11577	20343, 29109, 37875, 46641, 55407
2657	cytochrome b5 reductase-like	419823	2812	409075	11578	20344, 29110, 37876, 46642, 55408
2658	cytochrome b5 reductase-like	497820	2813	431157	11579	20345, 29111, 37877, 46643, 55409
2659	cytochrome b5 reductase-like	534324	2814	434343	11580	20346, 29112, 37878, 46644, 55410
2660	cytochrome b5 reductase-like	537208	2815	443797	11581	20347, 29113, 37879, 46645, 55411
2661	cytochrome b5 reductase-like	542737	2816	438151	11582	20348, 29114, 37880, 46646, 55412
2662	cytochrome c oxidase assembly factor-like precursor	432901	2817	397881	11583	20349, 29115, 37881, 46647, 55413
2663	cytochrome P450, family 2, subfamily A, polypeptide 7 pseudogene 1	301171	2818	301171	11584	20350, 29116, 37882, 46648, 55414
2664	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	354609	2819	442416	11585	20351, 29117, 37883, 46649, 55415
2665	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	381321	2820	446103	11586	20352, 29118, 37884, 46650, 55416
2666	cytochrome P450, family 2, subfamily D, polypeptide 7	428297	2821	439033	11587	20353, 29119, 37885, 46651,

	pseudogene 1					55417
2667	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	436260	2822	443970	11588	20354, 29120, 37886, 46652, 55418
2668	cytochrome P450, family 2, subfamily D, polypeptide 7 pseudogene 1	535769	2823	438874	11589	20355, 29121, 37887, 46653, 55419
2669	cytochrome P450, family 2, subfamily G, polypeptide 1 pseudogene	252909	2824	252909	11590	20356, 29122, 37888, 46654, 55420
2670	cytochrome P450, family 27, subfamily C, polypeptide 1	335247	2825	334128	11591	20357, 29123, 37889, 46655, 55421
2671	cytochrome P450, family 27, subfamily C, polypeptide 1	409327	2826	387198	11592	20358, 29124, 37890, 46656, 55422
2672	cytochrome P450, family 4, subfamily F, polypeptide 31, pseudogene	416266	2827	412278	11593	20359, 29125, 37891, 46657, 55423
2673	cytohesin 1	591455	2828	465665	11594	20360, 29126, 37892, 46658, 55424
2674	cytohesin 4	402997	2829	385997	11595	20361, 29127, 37893, 46659, 55425
2675	cytokine-dependent hematopoietic cell linker	226951	2830	226951	11596	20362, 29128, 37894, 46660, 55426
2676	cytokine-dependent hematopoietic cell linker	429087	2831	414571	11597	20363, 29129, 37895, 46661, 55427
2677	cytokine-dependent hematopoietic cell linker	442825	2832	390744	11598	20364, 29130, 37896, 46662, 55428
2678	cytokine-dependent hematopoietic cell linker	507719	2833	427208	11599	20365, 29131, 37897, 46663, 55429
2679	cytoplasmic polyadenylation element binding protein 1	261723	2834	261723	11600	20366, 29132, 37898, 46664, 55430
2680	cytoplasmic polyadenylation element binding protein 1	398591	2835	381591	11601	20367, 29133, 37899, 46665, 55431
2681	cytoplasmic polyadenylation element binding protein 1	398592	2836	381592	11602	20368, 29134, 37900, 46666, 55432
2682	cytoplasmic polyadenylation element binding protein 1	398593	2837	381593	11603	20369, 29135, 37901, 46667, 55433
2683	cytoplasmic	423133	2838	397526	11604	20370, 29136,

	polyadenylation element binding protein 1					37902, 46668, 55434
2684	cytoplasmic polyadenylation element binding protein 1	450751	2839	414187	11605	20371, 29137, 37903, 46669, 55435
2685	cytoplasmic polyadenylation element binding protein 1	568128	2840	457881	11606	20372, 29138, 37904, 46670, 55436
2686	DALR anticodon binding domain containing 3	395462	2841	378846	11607	20373, 29139, 37905, 46671, 55437
2687	DALR anticodon binding domain containing 3	441576	2842	410623	11608	20374, 29140, 37906, 46672, 55438
2688	DAZ associated protein 2	412716	2843	394699	11609	20375, 29141, 37907, 46673, 55439
2689	DAZ associated protein 2	425012	2844	408251	11610	20376, 29142, 37908, 46674, 55440
2690	DAZ associated protein 2	439799	2845	398804	11611	20377, 29143, 37909, 46675, 55441
2691	DAZ associated protein 2	449723	2846	412812	11612	20378, 29144, 37910, 46676, 55442
2692	DAZ associated protein 2	549555	2847	448051	11613	20379, 29145, 37911, 46677, 55443
2693	DAZ associated protein 2	549732	2848	446554	11614	20380, 29146, 37912, 46678, 55444
2694	DAZ interacting protein 1-like	327532	2849	332148	11615	20381, 29147, 37913, 46679, 55445
2695	DAZ interacting protein 1-like	467030	2850	420600	11616	20382, 29148, 37914, 46680, 55446
2696	DAZ interacting protein 1-like	469243	2851	419486	11617	20383, 29149, 37915, 46681, 55447
2697	DAZ interacting protein 1-like	492010	2852	420051	11618	20384, 29150, 37916, 46682, 55448
2698	DAZ interacting protein 1-like	536706	2853	442417	11619	20385, 29151, 37917, 46683, 55449
2699	DCN1, defective in cullin neddylation 1, domain containing 2 (S. cerevisiae)	375399	2854	364548	11620	20386, 29152, 37918, 46684, 55450

2700	DCN1, defective in cullin neddylation 1, domain containing 2 (S. cerevisiae)	478244	2855	417706	11621	20387, 29153, 37919, 46685, 55451
2701	DCN1, defective in cullin neddylation 1, domain containing 5 (S. cerevisiae)	260247	2856	260247	11622	20388, 29154, 37920, 46686, 55452
2702	DCP1 decapping enzyme homolog A (S. cerevisiae)	294241	2857	453270	11623	20389, 29155, 37921, 46687, 55453
2703	DDB1 and CUL4 associated factor 10	242323	2858	242323	11624	20390, 29156, 37922, 46688, 55454
2704	DDB1 and CUL4 associated factor 10	377724	2859	366953	11625	20391, 29157, 37923, 46689, 55455
2705	DDB1 and CUL4 associated factor 12-like 1	371126	2860	360167	11626	20392, 29158, 37924, 46690, 55456
2706	DDB1 and CUL4 associated factor 12-like 2	360028	2861	353128	11627	20393, 29159, 37925, 46691, 55457
2707	DDB1 and CUL4 associated factor 12-like 2	538699	2862	441489	11628	20394, 29160, 37926, 46692, 55458
2708	DDB1 and CUL4 associated factor 15	254337	2863	254337	11629	20395, 29161, 37927, 46693, 55459
2709	DDB1 and CUL4 associated factor 16	382247	2864	371682	11630	20396, 29162, 37928, 46694, 55460
2710	DDB1 and CUL4 associated factor 16	536863	2865	445736	11631	20397, 29163, 37929, 46695, 55461
2711	DDB1 and CUL4 associated factor 4	358377	2866	351147	11632	20398, 29164, 37930, 46696, 55462
2712	DDB1 and CUL4 associated factor 4	394234	2867	377781	11633	20399, 29165, 37931, 46697, 55463
2713	DDB1 and CUL4 associated factor 4	509153	2868	426178	11634	20400, 29166, 37932, 46698, 55464
2714	DDB1 and CUL4 associated factor 4	555042	2869	452131	11635	20401, 29167, 37933, 46699, 55465
2715	DDB1 and CUL4 associated factor 4-like 1	333141	2870	327796	11636	20402, 29168, 37934, 46700, 55466
2716	DDB1 and CUL4 associated factor 4-like 2	319675	2871	316496	11637	20403, 29169, 37935, 46701,

						55467
2717	DDB1 and CUL4 associated factor 8-like 1	441525	2872	405222	11638	20404, 29170, 37936, 46702, 55468
2718	DDB1 and CUL4 associated factor 8-like 2	451261	2873	462745	11639	20405, 29171, 37937, 46703, 55469
2719	DEAD (Asp-Glu-Ala-Asp) box helicase 6	596625	2874	471023	11640	20406, 29172, 37938, 46704, 55470
2720	DEAD (Asp-Glu-Ala-Asp) box polypeptide 49	247003	2875	247003	11641	20407, 29173, 37939, 46705, 55471
2721	DEAD (Asp-Glu-Ala-Asp) box polypeptide 49	438170	2876	395377	11642	20408, 29174, 37940, 46706, 55472
2722	DEAD (Asp-Glu-Ala-Asp) box polypeptide 55	238146	2877	238146	11643	20409, 29175, 37941, 46707, 55473
2723	DEAD (Asp-Glu-Ala-Asp) box polypeptide 55	538449	2878	439149	11644	20410, 29176, 37942, 46708, 55474
2724	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	331314	2879	330460	11645	20411, 29177, 37943, 46709, 55475
2725	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	367346	2880	356315	11646	20412, 29178, 37944, 46710, 55476
2726	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	367348	2881	356317	11647	20413, 29179, 37945, 46711, 55477
2727	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	436897	2882	391312	11648	20414, 29180, 37946, 46712, 55478
2728	DEAD (Asp-Glu-Ala-Asp) box polypeptide 59	447706	2883	394367	11649	20415, 29181, 37947, 46713, 55479
2729	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	260184	2884	260184	11650	20416, 29182, 37948, 46714, 55480
2730	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	505696	2885	424310	11651	20417, 29183, 37949, 46715, 55481
2731	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	505890	2886	422202	11652	20418, 29184, 37950, 46716, 55482
2732	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	511577	2887	422423	11653	20419, 29185, 37951, 46717, 55483
2733	DEAD (Asp-Glu-Ala-Asp)	512371	2888	427386	11654	20420, 29186,

	box polypeptide 60-like					37952, 46718, 55484
2734	DEAD (Asp-Glu-Ala-Asp) box polypeptide 60-like	514748	2889	424396	11655	20421, 29187, 37953, 46719, 55485
2735	DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 26B	370752	2890	359788	11656	20422, 29188, 37954, 46720, 55486
2736	DEAH (Asp-Glu-Ala-Asp/His) box polypeptide 57	295373	2891	295373	11657	20423, 29189, 37955, 46721, 55487
2737	DEAH (Asp-Glu-Ala-Asp/His) box polypeptide 57	355320	2892	347476	11658	20424, 29190, 37956, 46722, 55488
2738	DEAH (Asp-Glu-Ala-His) box polypeptide 34	257252	2893	257252	11659	20425, 29191, 37957, 46723, 55489
2739	DEAH (Asp-Glu-Ala-His) box polypeptide 34	328771	2894	331907	11660	20426, 29192, 37958, 46724, 55490
2740	DEAH (Asp-Glu-Ala-His) box polypeptide 37	308736	2895	311135	11661	20427, 29193, 37959, 46725, 55491
2741	death domain containing 1	357504	2896	350103	11662	20428, 29194, 37960, 46726, 55492
2742	death domain containing 1	456874	2897	401597	11663	20429, 29195, 37961, 46727, 55493
2743	dedicator of cytokinesis 7	251157	2898	251157	11664	20430, 29196, 37962, 46728, 55494
2744	dedicator of cytokinesis 7	340370	2899	340742	11665	20431, 29197, 37963, 46729, 55495
2745	dedicator of cytokinesis 7	371140	2900	360182	11666	20432, 29198, 37964, 46730, 55496
2746	dedicator of cytokinesis 7	395441	2901	378828	11667	20433, 29199, 37965, 46731, 55497
2747	dedicator of cytokinesis 7	404627	2902	384446	11668	20434, 29200, 37966, 46732, 55498
2748	dedicator of cytokinesis 7	454575	2903	413583	11669	20435, 29201, 37967, 46733, 55499
2749	dedicator of cytokinesis 9	339416	2904	341086	11670	20436, 29202, 37968, 46734, 55500

2750	dedicator of cytokinesis 9	340449	2905	344702	11671	20437, 29203, 37969, 46735, 55501
2751	dedicator of cytokinesis 9	357329	2906	349883	11672	20438, 29204, 37970, 46736, 55502
2752	dedicator of cytokinesis 9	376453	2907	365636	11673	20439, 29205, 37971, 46737, 55503
2753	dedicator of cytokinesis 9	376455	2908	365638	11674	20440, 29206, 37972, 46738, 55504
2754	dedicator of cytokinesis 9	376460	2909	365643	11675	20441, 29207, 37973, 46739, 55505
2755	dedicator of cytokinesis 9	400220	2910	383079	11676	20442, 29208, 37974, 46740, 55506
2756	dedicator of cytokinesis 9	400228	2911	383087	11677	20443, 29209, 37975, 46741, 55507
2757	dedicator of cytokinesis 9	400235	2912	383094	11678	20444, 29210, 37976, 46742, 55508
2758	dedicator of cytokinesis 9	419908	2913	388193	11679	20445, 29211, 37977, 46743, 55509
2759	dedicator of cytokinesis 9	427887	2914	413781	11680	20446, 29212, 37978, 46744, 55510
2760	dedicator of cytokinesis 9	428223	2915	414618	11681	20447, 29213, 37979, 46745, 55511
2761	dedicator of cytokinesis 9	442173	2916	406883	11682	20448, 29214, 37980, 46746, 55512
2762	dedicator of cytokinesis 9	448493	2917	401958	11683	20449, 29215, 37981, 46747, 55513
2763	dedicator of cytokinesis 9	449796	2918	403528	11684	20450, 29216, 37982, 46748, 55514
2764	dedicator of cytokinesis 9	450257	2919	396897	11685	20451, 29217, 37983, 46749, 55515
2765	dedicator of cytokinesis 9	451563	2920	407610	11686	20452, 29218, 37984, 46750, 55516
2766	defects in morphology 1 homolog (S. cerevisiae)	296380	2921	296380	11687	20453, 29219, 37985, 46751,

						55517
2767	defects in morphology 1 homolog (S. cerevisiae)	358527	2922	351328	11688	20454, 29220, 37986, 46752, 55518
2768	defects in morphology 1 homolog (S. cerevisiae)	372703	2923	361788	11689	20455, 29221, 37987, 46753, 55519
2769	defects in morphology 1 homolog (S. cerevisiae)	415550	2924	413565	11690	20456, 29222, 37988, 46754, 55520
2770	defects in morphology 1 homolog (S. cerevisiae)	418186	2925	391240	11691	20457, 29223, 37989, 46755, 55521
2771	defects in morphology 1 homolog (S. cerevisiae)	419161	2926	392115	11692	20458, 29224, 37990, 46756, 55522
2772	defects in morphology 1 homolog (S. cerevisiae)	420209	2927	398437	11693	20459, 29225, 37991, 46757, 55523
2773	defects in morphology 1 homolog (S. cerevisiae)	432259	2928	416857	11694	20460, 29226, 37992, 46758, 55524
2774	defects in morphology 1 homolog (S. cerevisiae)	443729	2929	409715	11695	20461, 29227, 37993, 46759, 55525
2775	defensin, beta 117	391409	2930	375229	11696	20462, 29228, 37994, 46760, 55526
2776	dehydrogenase/reductase (SDR family) member 12	218981	2931	218981	11697	20463, 29229, 37995, 46761, 55527
2777	dehydrogenase/reductase (SDR family) member 12	280056	2932	280056	11698	20464, 29230, 37996, 46762, 55528
2778	dehydrogenase/reductase (SDR family) member 12	444610	2933	411565	11699	20465, 29231, 37997, 46763, 55529
2779	dehydrogenase/reductase (SDR family) member 4 like 2	335125	2934	334801	11700	20466, 29232, 37998, 46764, 55530
2780	dehydrogenase/reductase (SDR family) member 4 like 2	348916	2935	326086	11701	20467, 29233, 37999, 46765, 55531
2781	dehydrogenase/reductase (SDR family) member 4 like 2	382755	2936	372203	11702	20468, 29234, 38000, 46766, 55532
2782	dehydrogenase/reductase (SDR family) member 4 like 2	534993	2937	441095	11703	20469, 29235, 38001, 46767, 55533
2783	dehydrogenase/reductase	543805	2938	441433	11704	20470, 29236,

	(SDR family) member 4 like 2					38002, 46768, 55534
2784	dehydrogenase/reductase (SDR family) member 4 like 2	545240	2939	437883	11705	20471, 29237, 38003, 46769, 55535
2785	dehydrogenase/reductase (SDR family) X-linked	334651	2940	334113	11706	20472, 29238, 38004, 46770, 55536
2786	deleted in lymphocytic leukemia 2-like	340052	2941	340138	11707	20473, 29239, 38005, 46771, 55537
2787	deleted in lymphocytic leukemia 2-like	371086	2942	360127	11708	20474, 29240, 38006, 46772, 55538
2788	deleted in lymphocytic leukemia 7	400393	2943	420976	11709	20475, 29241, 38007, 46773, 55539
2789	deleted in lymphocytic leukemia, 7	335465	2944	439677	11710	20476, 29242, 38008, 46774, 55540
2790	deleted in lymphocytic leukemia, 7	504404	2945	427177	11711	20477, 29243, 38009, 46775, 55541
2791	deleted in primary ciliary dyskinesia homolog (mouse)	370147	2946	359166	11712	20478, 29244, 38010, 46776, 55542
2792	deleted in primary ciliary dyskinesia homolog (mouse)	370148	2947	359167	11713	20479, 29245, 38011, 46777, 55543
2793	deleted in primary ciliary dyskinesia homolog (mouse)	370149	2948	359168	11714	20480, 29246, 38012, 46778, 55544
2794	deleted in primary ciliary dyskinesia homolog (mouse)	370151	2949	359170	11715	20481, 29247, 38013, 46779, 55545
2795	deleted in primary ciliary dyskinesia homolog (mouse)	416979	2950	412584	11716	20482, 29248, 38014, 46780, 55546
2796	deleted in primary ciliary dyskinesia homolog (mouse)	434727	2951	403505	11717	20483, 29249, 38015, 46781, 55547
2797	DENN/MADD domain containing 2A	275884	2952	275884	11718	20484, 29250, 38016, 46782, 55548
2798	DENN/MADD domain containing 2A	477488	2953	418760	11719	20485, 29251, 38017, 46783, 55549
2799	DENN/MADD domain containing 2A	489552	2954	418088	11720	20486, 29252, 38018, 46784, 55550

2800	DENN/MADD domain containing 2A	491728	2955	418844	11721	20487, 29253, 38019, 46785, 55551
2801	DENN/MADD domain containing 2A	492720	2956	419464	11722	20488, 29254, 38020, 46786, 55552
2802	DENN/MADD domain containing 2A	496613	2957	419654	11723	20489, 29255, 38021, 46787, 55553
2803	DENN/MADD domain containing 2A	537639	2958	442245	11724	20490, 29256, 38022, 46788, 55554
2804	DENN/MADD domain containing 2C	369540	2959	358553	11725	20491, 29257, 38023, 46789, 55555
2805	DENN/MADD domain containing 2C	393274	2960	376955	11726	20492, 29258, 38024, 46790, 55556
2806	DENN/MADD domain containing 2C	393276	2961	376957	11727	20493, 29259, 38025, 46791, 55557
2807	DENN/MADD domain containing 2C	393277	2962	376958	11728	20494, 29260, 38026, 46792, 55558
2808	DENN/MADD domain containing 2D	357640	2963	350266	11729	20495, 29261, 38027, 46793, 55559
2809	DENN/MADD domain containing 2D	369752	2964	358767	11730	20496, 29262, 38028, 46794, 55560
2810	DENN/MADD domain containing 3	262585	2965	262585	11731	20497, 29263, 38029, 46795, 55561
2811	DENN/MADD domain containing 3	424248	2966	410594	11732	20498, 29264, 38030, 46796, 55562
2812	DENN/MADD domain containing 4B	361217	2967	354597	11733	20499, 29265, 38031, 46797, 55563
2813	DEP domain containing 4	378250	2968	367497	11734	20500, 29266, 38032, 46798, 55564
2814	DEP domain containing 4	416321	2969	396234	11735	20501, 29267, 38033, 46799, 55565
2815	DEP domain containing 4	422147	2970	407660	11736	20502, 29268, 38034, 46800, 55566
2816	DET1 and DDB1 associated 1	359866	2971	352928	11737	20503, 29269, 38035, 46801,

						55567
2817	developing brain homeobox 1	227256	2972	227256	11738	20504, 29270, 38036, 46802, 55568
2818	developing brain homeobox 1	524983	2973	436881	11739	20505, 29271, 38037, 46803, 55569
2819	Dexi homolog (mouse)	331808	2974	330509	11740	20506, 29272, 38038, 46804, 55570
2820	Diacylglycerol kinase kappa	598251	2975	469442	11741	20507, 29273, 38039, 46805, 55571
2821	diaphanous homolog 3 (Drosophila)	267214	2976	267214	11742	20508, 29274, 38040, 46806, 55572
2822	diaphanous homolog 3 (Drosophila)	400324	2977	383178	11743	20509, 29275, 38041, 46807, 55573
2823	diaphanous homolog 3 (Drosophila)	400327	2978	383181	11744	20510, 29276, 38042, 46808, 55574
2824	diaphanous homolog 3 (Drosophila)	400329	2979	383183	11745	20511, 29277, 38043, 46809, 55575
2825	diaphanous homolog 3 (Drosophila)	400330	2980	383184	11746	20512, 29278, 38044, 46810, 55576
2826	diaphanous homolog 3 (Drosophila)	413168	2981	408935	11747	20513, 29279, 38045, 46811, 55577
2827	diaphanous homolog 3 (Drosophila)	453990	2982	408859	11748	20514, 29280, 38046, 46812, 55578
2828	diaphanous homolog 3 (Drosophila)	267215	2983	267215	11749	20515, 29281, 38047, 46813, 55579
2829	differential display clone 8 isoform 2	322630	2984	312767	11750	20516, 29282, 38048, 46814, 55580
2830	differentially expressed in FDCP 8 homolog (mouse)	268676	2985	268676	11751	20517, 29283, 38049, 46815, 55581
2831	differentially expressed in FDCP 8 homolog (mouse)	418391	2986	412784	11752	20518, 29284, 38050, 46816, 55582
2832	differentially expressed in FDCP 8 homolog (mouse)	563594	2987	458019	11753	20519, 29285, 38051, 46817, 55583
2833	differentially expressed in	570182	2988	456799	11754	20520, 29286,

	FDCP 8 homolog (mouse)					38052, 46818, 55584
2834	dihydrodiol dehydrogenase (dimeric)	221403	2989	221403	11755	20521, 29287, 38053, 46819, 55585
2835	dihydrouridine synthase 1-like (S. cerevisiae)	306796	2990	303515	11756	20522, 29288, 38054, 46820, 55586
2836	dihydrouridine synthase 1-like (S. cerevisiae)	354321	2991	346280	11757	20523, 29289, 38055, 46821, 55587
2837	dihydrouridine synthase 1-like (S. cerevisiae)	538833	2992	445110	11758	20524, 29290, 38056, 46822, 55588
2838	dihydrouridine synthase 1-like (S. cerevisiae)	542088	2993	438718	11759	20525, 29291, 38057, 46823, 55589
2839	dihydrouridine synthase 3-like (S. cerevisiae)	309061	2994	311977	11760	20526, 29292, 38058, 46824, 55590
2840	dihydrouridine synthase 3-like (S. cerevisiae)	320699	2995	315558	11761	20527, 29293, 38059, 46825, 55591
2841	dihydrouridine synthase 4-like (S. cerevisiae)	265720	2996	265720	11762	20528, 29294, 38060, 46826, 55592
2842	dihydrouridine synthase 4-like (S. cerevisiae)	402620	2997	385274	11763	20529, 29295, 38061, 46827, 55593
2843	diphosphoinositol pentakisphosphate kinase 2	576175	2998	458792	11764	20530, 29296, 38062, 46828, 55594
2844	discs large (Drosophila) homolog-associated protein 4	594949	2999	470606	11765	20531, 29297, 38063, 46829, 55595
2845	discs large (Drosophila) homolog-associated protein 4	598628	3000	469167	11766	20532, 29298, 38064, 46830, 55596
2846	discs, large (Drosophila) homolog-associated protein 4	339266	3001	341633	11767	20533, 29299, 38065, 46831, 55597
2847	discs, large (Drosophila) homolog-associated protein 4	340491	3002	345700	11768	20534, 29300, 38066, 46832, 55598
2848	discs, large (Drosophila) homolog-associated protein 4	373907	3003	363014	11769	20535, 29301, 38067, 46833, 55599
2849	discs, large (Drosophila) homolog-associated protein 4	373913	3004	363023	11770	20536, 29302, 38068, 46834, 55600

2850	discs, large (Drosophila) homolog-associated protein 4	401952	3005	384954	11771	20537, 29303, 38069, 46835, 55601
2851	divergent-paired related homeobox	376650	3006	365838	11772	20538, 29304, 38070, 46836, 55602
2852	DIX domain containing 1	577090	3007	461149	11773	20539, 29305, 38071, 46837, 55603
2853	DMRT-like family C1	290273	3008	290273	11774	20540, 29306, 38072, 46838, 55604
2854	DMRT-like family C1	373529	3009	362629	11775	20541, 29307, 38073, 46839, 55605
2855	DMRT-like family C1B	333826	3010	328296	11776	20542, 29308, 38074, 46840, 55606
2856	DMRT-like family C1B	334036	3011	334501	11777	20543, 29309, 38075, 46841, 55607
2857	DMRT-like family C1B	373532	3012	362632	11778	20544, 29310, 38076, 46842, 55608
2858	DMRT-like family C1B	373533	3013	362633	11779	20545, 29311, 38077, 46843, 55609
2859	DMRT-like family C1B	438696	3014	404476	11780	20546, 29312, 38078, 46844, 55610
2860	DMRT-like family C1B	440247	3015	397859	11781	20547, 29313, 38079, 46845, 55611
2861	DMRT-like family C1B	594574	3016	472589	11782	20548, 29314, 38080, 46846, 55612
2862	DNA-damage inducible 1 homolog 1 (S. cerevisiae)	302259	3017	302805	11783	20549, 29315, 38081, 46847, 55613
2863	DNA-damage inducible 1 homolog 2 (S. cerevisiae)	480945	3018	417748	11784	20550, 29316, 38082, 46848, 55614
2864	DnaJ (Hsp40) homolog subfamily C member 28	571432	3019	461665	11785	20551, 29317, 38083, 46849, 55615
2865	DnaJ (Hsp40) homolog subfamily C member 28	572540	3020	461737	11786	20552, 29318, 38084, 46850, 55616
2866	DnaJ (Hsp40) homolog, subfamily A, member 1	330899	3021	369127	11787	20553, 29319, 38085, 46851,

						55617
2867	DnaJ (Hsp40) homolog, subfamily A, member 1	539152	3022	443872	11788	20554, 29320, 38086, 46852, 55618
2868	DnaJ (Hsp40) homolog, subfamily A, member 1	544625	3023	439010	11789	20555, 29321, 38087, 46853, 55619
2869	DnaJ (Hsp40) homolog, subfamily A, member 4	343789	3024	339581	11790	20556, 29322, 38088, 46854, 55620
2870	DnaJ (Hsp40) homolog, subfamily A, member 4	394852	3025	378321	11791	20557, 29323, 38089, 46855, 55621
2871	DnaJ (Hsp40) homolog, subfamily A, member 4	394855	3026	378324	11792	20558, 29324, 38090, 46856, 55622
2872	DnaJ (Hsp40) homolog, subfamily A, member 4	446172	3027	413499	11793	20559, 29325, 38091, 46857, 55623
2873	DnaJ (Hsp40) homolog, subfamily B, member 13	339764	3028	344431	11794	20560, 29326, 38092, 46858, 55624
2874	DnaJ (Hsp40) homolog, subfamily B, member 13	537753	3029	439711	11795	20561, 29327, 38093, 46859, 55625
2875	DnaJ (Hsp40) homolog, subfamily B, member 13	543947	3030	438576	11796	20562, 29328, 38094, 46860, 55626
2876	DnaJ (Hsp40) homolog, subfamily B, member 7	307221	3031	307197	11797	20563, 29329, 38095, 46861, 55627
2877	DnaJ (Hsp40) homolog, subfamily B, member 8	319153	3032	316053	11798	20564, 29330, 38096, 46862, 55628
2878	DnaJ (Hsp40) homolog, subfamily B, member 8	469083	3033	417418	11799	20565, 29331, 38097, 46863, 55629
2879	DnaJ (Hsp40) homolog, subfamily C, member 12	225171	3034	225171	11800	20566, 29332, 38098, 46864, 55630
2880	DnaJ (Hsp40) homolog, subfamily C, member 12	339758	3035	343575	11801	20567, 29333, 38099, 46865, 55631
2881	DnaJ (Hsp40) homolog, subfamily C, member 17	220496	3036	220496	11802	20568, 29334, 38100, 46866, 55632
2882	DnaJ (Hsp40) homolog, subfamily C, member 24	465995	3037	417548	11803	20569, 29335, 38101, 46867, 55633
2883	DnaJ (Hsp40) homolog,	536040	3038	444967	11804	20570, 29336,

	subfamily C, member 24					38102, 46868, 55634
2884	DnaJ (Hsp40) homolog, subfamily C, member 28	314399	3039	320303	11805	20571, 29337, 38103, 46869, 55635
2885	DnaJ (Hsp40) homolog, subfamily C, member 28	381947	3040	371373	11806	20572, 29338, 38104, 46870, 55636
2886	DnaJ (Hsp40) homolog, subfamily C, member 28	402202	3041	385777	11807	20573, 29339, 38105, 46871, 55637
2887	DNAJC25-GNG10 readthrough	374294	3042	363412	11808	20574, 29340, 38106, 46872, 55638
2888	docking protein 6	382713	3043	372160	11809	20575, 29341, 38107, 46873, 55639
2889	double homeobox A	554048	3044	452398	11810	20576, 29342, 38108, 46874, 55640
2890	double zinc ribbon and ankyrin repeat domains 1	262547	3045	262547	11811	20577, 29343, 38109, 46875, 55641
2891	double zinc ribbon and ankyrin repeat domains 1	329494	3046	328866	11812	20578, 29344, 38110, 46876, 55642
2892	double zinc ribbon and ankyrin repeat domains 1	357236	3047	349774	11813	20579, 29345, 38111, 46877, 55643
2893	double zinc ribbon and ankyrin repeat domains 1	358866	3048	351734	11814	20580, 29346, 38112, 46878, 55644
2894	double zinc ribbon and ankyrin repeat domains 1	377630	3049	366857	11815	20581, 29347, 38113, 46879, 55645
2895	double zinc ribbon and ankyrin repeat domains 1	377637	3050	366864	11816	20582, 29348, 38114, 46880, 55646
2896	double zinc ribbon and ankyrin repeat domains 1	414623	3051	408475	11817	20583, 29349, 38115, 46881, 55647
2897	doublecortin domain containing 2B	409358	3052	386870	11818	20584, 29350, 38116, 46882, 55648
2898	doublecortin domain containing 2C	399143	3053	382097	11819	20585, 29351, 38117, 46883, 55649
2899	doublesex- and mab-3-related transcription factor C1	595412	3054	471224	11820	20586, 29352, 38118, 46884, 55650

2900	DPY30 domain containing 1	372202	3055	361276	11821	20587, 29353, 38119, 46885, 55651
2901	DPY30 domain containing 1	372204	3056	361278	11822	20588, 29354, 38120, 46886, 55652
2902	DPY30 domain containing 1	421924	3057	402890	11823	20589, 29355, 38121, 46887, 55653
2903	DPY30 domain containing 1	453477	3058	388160	11824	20590, 29356, 38122, 46888, 55654
2904	DPY30 domain containing 1	454362	3059	414798	11825	20591, 29357, 38123, 46889, 55655
2905	DPY30 domain containing 2	256039	3060	256039	11826	20592, 29358, 38124, 46890, 55656
2906	DPY30 domain containing 2	372197	3061	361271	11827	20593, 29359, 38125, 46891, 55657
2907	DPY30 domain containing 2	372198	3062	361272	11828	20594, 29360, 38126, 46892, 55658
2908	DPY30 domain containing 2	372199	3063	361273	11829	20595, 29361, 38127, 46893, 55659
2909	DPY30 domain containing 2	411538	3064	401333	11830	20596, 29362, 38128, 46894, 55660
2910	DPY30 domain containing 2	444807	3065	410285	11831	20597, 29363, 38129, 46895, 55661
2911	DTW domain containing 1	251250	3066	251250	11832	20598, 29364, 38130, 46896, 55662
2912	DTW domain containing 1	329873	3067	329313	11833	20599, 29365, 38131, 46897, 55663
2913	DTW domain containing 1	403028	3068	385399	11834	20600, 29366, 38132, 46898, 55664
2914	DTW domain containing 1	415425	3069	398958	11835	20601, 29367, 38133, 46899, 55665
2915	DTW domain containing 1	558653	3070	453529	11836	20602, 29368, 38134, 46900, 55666
2916	DTW domain containing 1	559405	3071	452685	11837	20603, 29369, 38135, 46901,

						55667
2917	DTW domain containing 2	510708	3072	425048	11838	20604, 29370, 38136, 46902, 55668
2918	dual specificity phosphatase 27 (putative)	271385	3073	271385	11839	20605, 29371, 38137, 46903, 55669
2919	dual specificity phosphatase 27 (putative)	361200	3074	354483	11840	20606, 29372, 38138, 46904, 55670
2920	dual specificity phosphatase 27 (putative)	443333	3075	404874	11841	20607, 29373, 38139, 46905, 55671
2921	dual specificity phosphatase 28	343217	3076	344235	11842	20608, 29374, 38140, 46906, 55672
2922	dual specificity phosphatase 28	405954	3077	385885	11843	20609, 29375, 38141, 46907, 55673
2923	dual specificity phosphatase 9	595095	3078	472478	11844	20610, 29376, 38142, 46908, 55674
2924	dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 3	581534	3079	462982	11845	20611, 29377, 38143, 46909, 55675
2925	dynein axonemal assembly factor 3	391719	3080	375599	11846	20612, 29378, 38144, 46910, 55676
2926	dynein axonemal assembly factor 3	527223	3081	436975	11847	20613, 29379, 38145, 46911, 55677
2927	dynein axonemal assembly factor 3	528412	3082	433826	11848	20614, 29380, 38146, 46912, 55678
2928	dynein axonemal heavy chain 12	585473	3083	468524	11849	20615, 29381, 38147, 46913, 55679
2929	dynein axonemal heavy chain 17	585328	3084	465516	11850	20616, 29382, 38148, 46914, 55680
2930	dynein, axonemal, heavy chain 17	389840	3085	374490	11851	20617, 29383, 38149, 46915, 55681
2931	dyskeratosis congenita 1 dyskerin	596793	3086	472996	11852	20618, 29384, 38150, 46916, 55682
2932	E3 ubiquitin-protein ligase HUWE1	600670	3087	471959	11853	20619, 29385, 38151, 46917, 55683
2933	E74-like factor 2 (ets	265495	3088	265495	11854	20620, 29386,

	domain transcription factor)					38152, 46918, 55684
2934	E74-like factor 2 (ets domain transcription factor)	358635	3089	351458	11855	20621, 29387, 38153, 46919, 55685
2935	E74-like factor 2 (ets domain transcription factor)	379549	3090	368867	11856	20622, 29388, 38154, 46920, 55686
2936	E74-like factor 2 (ets domain transcription factor)	379550	3091	368868	11857	20623, 29389, 38155, 46921, 55687
2937	E74-like factor 2 (ets domain transcription factor)	394235	3092	377782	11858	20624, 29390, 38156, 46922, 55688
2938	E74-like factor 2 (ets domain transcription factor)	540754	3093	444766	11859	20625, 29391, 38157, 46923, 55689
2939	ecotropic viral integration site 5-like	270530	3094	270530	11860	20626, 29392, 38158, 46924, 55690
2940	ecotropic viral integration site 5-like	538904	3095	445905	11861	20627, 29393, 38159, 46925, 55691
2941	ectopic P-granules autophagy protein 5 homolog (C. elegans)	282041	3096	282041	11862	20628, 29394, 38160, 46926, 55692
2942	ectopic P-granules autophagy protein 5 homolog (C. elegans)	308403	3097	312490	11863	20629, 29395, 38161, 46927, 55693
2943	ectopic P-granules autophagy protein 5 homolog (C. elegans)	540322	3098	442615	11864	20630, 29396, 38162, 46928, 55694
2944	EF-hand calcium binding domain 1	262103	3099	262103	11865	20631, 29397, 38163, 46929, 55695
2945	EF-hand calcium binding domain 1	433756	3100	400873	11866	20632, 29398, 38164, 46930, 55696
2946	EF-hand calcium binding domain 1	450553	3101	414277	11867	20633, 29399, 38165, 46931, 55697
2947	EF-hand calcium binding domain 1	522254	3102	430940	11868	20634, 29400, 38166, 46932, 55698
2948	EF-hand calcium binding domain 1	523092	3103	430765	11869	20635, 29401, 38167, 46933, 55699
2949	EF-hand calcium binding domain 10	480514	3104	418678	11870	20636, 29402, 38168, 46934, 55700

2950	EF-hand calcium binding domain 11	267544	3105	267544	11871	20637, 29403, 38169, 46935, 55701
2951	EF-hand calcium binding domain 11	316738	3106	326267	11872	20638, 29404, 38170, 46936, 55702
2952	EF-hand calcium binding domain 11	555872	3107	452320	11873	20639, 29405, 38171, 46937, 55703
2953	EF-hand calcium binding domain 11	556005	3108	452143	11874	20640, 29406, 38172, 46938, 55704
2954	EF-hand calcium binding domain 13	517484	3109	430048	11875	20641, 29407, 38173, 46939, 55705
2955	EF-hand calcium binding domain 2	366522	3110	355479	11876	20642, 29408, 38174, 46940, 55706
2956	EF-hand calcium binding domain 2	366523	3111	355480	11877	20643, 29409, 38175, 46941, 55707
2957	EF-hand calcium binding domain 2	447569	3112	408661	11878	20644, 29410, 38176, 46942, 55708
2958	EF-hand calcium binding domain 3	305286	3113	302649	11879	20645, 29411, 38177, 46943, 55709
2959	EF-hand calcium binding domain 3	518576	3114	428626	11880	20646, 29412, 38178, 46944, 55710
2960	EF-hand calcium binding domain 3	520404	3115	429124	11881	20647, 29413, 38179, 46945, 55711
2961	EF-hand calcium binding domain 3	450662	3116	403932	11882	20648, 29414, 38180, 46946, 55712
2962	EF-hand calcium binding domain 5	320856	3117	322003	11883	20649, 29415, 38181, 46947, 55713
2963	EF-hand calcium binding domain 5	378738	3118	368012	11884	20650, 29416, 38182, 46948, 55714
2964	EF-hand calcium binding domain 5	394832	3119	378309	11885	20651, 29417, 38183, 46949, 55715
2965	EF-hand calcium binding domain 5	394835	3120	378312	11886	20652, 29418, 38184, 46950, 55716
2966	EF-hand calcium binding domain 5	423598	3121	392831	11887	20653, 29419, 38185, 46951,

						55717
2967	EF-hand calcium binding domain 5	534836	3122	443405	11888	20654, 29420, 38186, 46952, 55718
2968	EF-hand calcium binding domain 5	536908	3123	440619	11889	20655, 29421, 38187, 46953, 55719
2969	EF-hand calcium binding domain 5	541045	3124	445575	11890	20656, 29422, 38188, 46954, 55720
2970	EF-hand calcium binding domain 7	371088	3125	360129	11891	20657, 29423, 38189, 46955, 55721
2971	EF-hand calcium binding domain 9	398186	3126	381247	11892	20658, 29424, 38190, 46956, 55722
2972	EFR3 homolog B (S. cerevisiae)	403714	3127	384081	11893	20659, 29425, 38191, 46957, 55723
2973	EFR3 homolog B (S. cerevisiae)	545169	3128	438906	11894	20660, 29426, 38192, 46958, 55724
2974	EH domain binding protein 1-like 1	309295	3129	312671	11895	20661, 29427, 38193, 46959, 55725
2975	ELMO/CED-12 domain containing 1	265840	3130	265840	11896	20662, 29428, 38194, 46960, 55726
2976	ELMO/CED-12 domain containing 1	443271	3131	412257	11897	20663, 29429, 38195, 46961, 55727
2977	ELMO/CED-12 domain containing 3	315658	3132	318264	11898	20664, 29430, 38196, 46962, 55728
2978	ELMO/CED-12 domain containing 3	393852	3133	377434	11899	20665, 29431, 38197, 46963, 55729
2979	ELMO/CED-12 domain containing 3	409013	3134	387139	11900	20666, 29432, 38198, 46964, 55730
2980	ELMO/CED-12 domain containing 3	409331	3135	386257	11901	20667, 29433, 38199, 46965, 55731
2981	ELMO/CED-12 domain containing 3	409344	3136	386248	11902	20668, 29434, 38200, 46966, 55732
2982	ELMO/CED-12 domain containing 3	409890	3137	386304	11903	20669, 29435, 38201, 46967, 55733
2983	ELMO/CED-12 domain	418268	3138	393443	11904	20670, 29436,

	containing 3					38202, 46968, 55734
2984	ELMO/CED-12 domain containing 3	428955	3139	412692	11905	20671, 29437, 38203, 46969, 55735
2985	elongation factor Tu GTP binding domain containing 1	268206	3140	268206	11906	20672, 29438, 38204, 46970, 55736
2986	elongation factor Tu GTP binding domain containing 1	359445	3141	352418	11907	20673, 29439, 38205, 46971, 55737
2987	elongation factor Tu GTP binding domain containing 1	557844	3142	454186	11908	20674, 29440, 38206, 46972, 55738
2988	elongation factor Tu GTP binding domain containing 1	558974	3143	452990	11909	20675, 29441, 38207, 46973, 55739
2989	Em:AC006547.7 proteinHCG2001938Uncharacterized protein	423736	3144	413821	11910	20676, 29442, 38208, 46974, 55740
2990	emopamil binding protein-like	378270	3145	367519	11911	20677, 29443, 38209, 46975, 55741
2991	emopamil binding protein-like	378282	3146	367531	11912	20678, 29444, 38210, 46976, 55742
2992	endogenous retrovirus group 3, member 1	394323	3147	391594	11913	20679, 29445, 38211, 46977, 55743
2993	endogenous retrovirus group MER34 member 1	440542	3148	460255	11914	20680, 29446, 38212, 46978, 55744
2994	endogenous retrovirus group MER34 member 1	443173	3149	460602	11915	20681, 29447, 38213, 46979, 55745
2995	endogenous retrovirus group V member 2	601417	3150	472919	11916	20682, 29448, 38214, 46980, 55746
2996	endonuclease V	323854	3151	317810	11917	20683, 29449, 38215, 46981, 55747
2997	endonuclease V	518137	3152	429190	11918	20684, 29450, 38216, 46982, 55748
2998	endonuclease V	520367	3153	431036	11919	20685, 29451, 38217, 46983, 55749
2999	enkurin, TRPC channel interacting protein	331161	3154	331044	11920	20686, 29452, 38218, 46984, 55750

3000	enkurin, TRPC channel interacting protein	376363	3155	365541	11921	20687, 29453, 38219, 46985, 55751
3001	enkurin, TRPC channel interacting protein	496261	3156	432930	11922	20688, 29454, 38220, 46986, 55752
3002	enolase 2 (gamma neuronal)	596089	3157	469457	11923	20689, 29455, 38221, 46987, 55753
3003	enolase family member 4	341276	3158	345555	11924	20690, 29456, 38222, 46988, 55754
3004	ENTH domain containing 1	325157	3159	317431	11925	20691, 29457, 38223, 46989, 55755
3005	envoplakin-like	399134	3160	382086	11926	20692, 29458, 38224, 46990, 55756
3006	EP400 N-terminal like	361109	3161	354409	11927	20693, 29459, 38225, 46991, 55757
3007	EP400 N-terminal like	376625	3162	365812	11928	20694, 29460, 38226, 46992, 55758
3008	EP400 N-terminal like	389560	3163	374211	11929	20695, 29461, 38227, 46993, 55759
3009	EP400 N-terminal like	392352	3164	376163	11930	20696, 29462, 38228, 46994, 55760
3010	EP400 N-terminal like	407361	3165	385626	11931	20697, 29463, 38229, 46995, 55761
3011	EP400 N-terminal like	443539	3166	404338	11932	20698, 29464, 38230, 46996, 55762
3012	EP400 N-terminal like	454179	3167	402806	11933	20699, 29465, 38231, 46997, 55763
3013	EP400 N-terminal like	539205	3168	441814	11934	20700, 29466, 38232, 46998, 55764
3014	EPH receptor A6	389672	3169	374323	11935	20701, 29467, 38233, 46999, 55765
3015	EPH receptor A6	442602	3170	403100	11936	20702, 29468, 38234, 47000, 55766
3016	EPH receptor A6	502694	3171	423950	11937	20703, 29469, 38235, 47001,

						55767
3017	EPH receptor A6	542517	3172	439758	11938	20704, 29470, 38236, 47002, 55768
3018	epiplakin 1	525985	3173	436337	11939	20705, 29471, 38237, 47003, 55769
3019	epiplakin 1	568225	3174	456124	11940	20706, 29472, 38238, 47004, 55770
3020	epithelial cell transforming sequence 2 oncogene-like	367682	3175	356655	11941	20707, 29473, 38239, 47005, 55771
3021	epithelial cell transforming sequence 2 oncogene-like	401414	3176	385187	11942	20708, 29474, 38240, 47006, 55772
3022	epithelial cell transforming sequence 2 oncogene-like	423192	3177	387388	11943	20709, 29475, 38241, 47007, 55773
3023	epithelial cell transforming sequence 2 oncogene-like	541398	3178	442307	11944	20710, 29476, 38242, 47008, 55774
3024	ERI1 exoribonuclease family member 2	300005	3179	300005	11945	20711, 29477, 38243, 47009, 55775
3025	ERI1 exoribonuclease family member 2	357967	3180	350651	11946	20712, 29478, 38244, 47010, 55776
3026	ERI1 exoribonuclease family member 2	389345	3181	373996	11947	20713, 29479, 38245, 47011, 55777
3027	ERI1 exoribonuclease family member 3	372253	3182	361327	11948	20714, 29480, 38246, 47012, 55778
3028	ERI1 exoribonuclease family member 3	372257	3183	361331	11949	20715, 29481, 38247, 47013, 55779
3029	ERI1 exoribonuclease family member 3	372259	3184	361333	11950	20716, 29482, 38248, 47014, 55780
3030	ERI1 exoribonuclease family member 3	433471	3185	397358	11951	20717, 29483, 38249, 47015, 55781
3031	ERI1 exoribonuclease family member 3	452396	3186	396764	11952	20718, 29484, 38250, 47016, 55782
3032	ERI1 exoribonuclease family member 3	456170	3187	390710	11953	20719, 29485, 38251, 47017, 55783
3033	ERI1 exoribonuclease	457571	3188	412291	11954	20720, 29486,

	family member 3					38252, 47018, 55784
3034	ERI1 exoribonuclease family member 3	537474	3189	438360	11955	20721, 29487, 38253, 47019, 55785
3035	espin-like	343063	3190	339115	11956	20722, 29488, 38254, 47020, 55786
3036	espin-like	409169	3191	386577	11957	20723, 29489, 38255, 47021, 55787
3037	espin-like	409506	3192	386579	11958	20724, 29490, 38256, 47022, 55788
3038	espin-like	423032	3193	417001	11959	20725, 29491, 38257, 47023, 55789
3039	ethanolaminephosphotransferase 1 (CDP-ethanolamine-specific)	260585	3194	260585	11960	20726, 29492, 38258, 47024, 55790
3040	ethanolaminephosphotransferase 1 (CDP-ethanolamine-specific)	442141	3195	415280	11961	20727, 29493, 38259, 47025, 55791
3041	eukaryotic translation initiation factor 1B	232905	3196	232905	11962	20728, 29494, 38260, 47026, 55792
3042	eukaryotic translation initiation factor 3, subunit C-like	380876	3197	370258	11963	20729, 29495, 38261, 47027, 55793
3043	eukaryotic translation initiation factor 3, subunit C-like	398943	3198	381916	11964	20730, 29496, 38262, 47028, 55794
3044	eukaryotic translation initiation factor 3, subunit C-like	398944	3199	381917	11965	20731, 29497, 38263, 47029, 55795
3045	eukaryotic translation initiation factor 3, subunit C-like	444473	3200	400013	11966	20732, 29498, 38264, 47030, 55796
3046	eukaryotic translation initiation factor 3, subunit C-like	543862	3201	439932	11967	20733, 29499, 38265, 47031, 55797
3047	eukaryotic translation initiation factor 4E family member 1B	318682	3202	323714	11968	20734, 29500, 38266, 47032, 55798
3048	eukaryotic translation initiation factor 4E family member 1B	504597	3203	427633	11969	20735, 29501, 38267, 47033, 55799
3049	eukaryotic translation initiation factor 4E family member 1B	510660	3204	421009	11970	20736, 29502, 38268, 47034, 55800

3050	exocyst complex component 2	230449	3205	230449	11971	20737, 29503, 38269, 47035, 55801
3051	exocyst complex component 2	443083	3206	406400	11972	20738, 29504, 38270, 47036, 55802
3052	exocyst complex component 2	448181	3207	398113	11973	20739, 29505, 38271, 47037, 55803
3053	exocyst complex component 3-like 2	252482	3208	252482	11974	20740, 29506, 38272, 47038, 55804
3054	exocyst complex component 3-like 2	413988	3209	400713	11975	20741, 29507, 38273, 47039, 55805
3055	exocyst complex component 3-like 4	380069	3210	369409	11976	20742, 29508, 38274, 47040, 55806
3056	exonuclease 3'-5' domain containing 1	314992	3211	321029	11977	20743, 29509, 38275, 47041, 55807
3057	exonuclease 3'-5' domain containing 1	458580	3212	415056	11978	20744, 29510, 38276, 47042, 55808
3058	exonuclease 3'-5' domain containing 2	193422	3213	193422	11979	20745, 29511, 38277, 47043, 55809
3059	exonuclease 3'-5' domain containing 2	312994	3214	313140	11980	20746, 29512, 38278, 47044, 55810
3060	exonuclease 3'-5' domain containing 2	409014	3215	386915	11981	20747, 29513, 38279, 47045, 55811
3061	exonuclease 3'-5' domain containing 2	409018	3216	387331	11982	20748, 29514, 38280, 47046, 55812
3062	exonuclease 3'-5' domain containing 2	409242	3217	386839	11983	20749, 29515, 38281, 47047, 55813
3063	exonuclease 3'-5' domain containing 2	409675	3218	386762	11984	20750, 29516, 38282, 47048, 55814
3064	exonuclease 3'-5' domain containing 2	409949	3219	386632	11985	20751, 29517, 38283, 47049, 55815
3065	exonuclease 3'-5' domain containing 2	413191	3220	409089	11986	20752, 29518, 38284, 47050, 55816
3066	exonuclease 3'-5' domain containing 2	449989	3221	392177	11987	20753, 29519, 38285, 47051,

						55817
3067	exonuclease 3'-5' domain containing 3	340951	3222	340474	11988	20754, 29520, 38286, 47052, 55818
3068	exonuclease 3'-5' domain containing 3	342129	3223	343705	11989	20755, 29521, 38287, 47053, 55819
3069	extended synaptotagmin-like protein 2	251527	3224	251527	11990	20756, 29522, 38288, 47054, 55820
3070	extended synaptotagmin-like protein 2	377650	3225	366878	11991	20757, 29523, 38289, 47055, 55821
3071	extended synaptotagmin-like protein 2	421679	3226	402784	11992	20758, 29524, 38290, 47056, 55822
3072	extended synaptotagmin-like protein 2	429474	3227	395865	11993	20759, 29525, 38291, 47057, 55823
3073	extended synaptotagmin-like protein 2	435514	3228	411488	11994	20760, 29526, 38292, 47058, 55824
3074	extracellular leucine-rich repeat and fibronectin type III domain containing 1	424383	3229	456548	11995	20761, 29527, 38293, 47059, 55825
3075	extracellular leucine-rich repeat and fibronectin type III domain containing 1	561626	3230	457193	11996	20762, 29528, 38294, 47060, 55826
3076	FAM18B2-CDRT4 readthrough	522212	3231	429865	11997	20763, 29529, 38295, 47061, 55827
3077	family with sequence similarity 100, member A	283474	3232	283474	11998	20764, 29530, 38296, 47062, 55828
3078	family with sequence similarity 100, member B	327490	3233	331298	11999	20765, 29531, 38297, 47063, 55829
3079	family with sequence similarity 101 member B	566692	3234	454637	12000	20766, 29532, 38298, 47064, 55830
3080	family with sequence similarity 101, member A	324038	3235	315626	12001	20767, 29533, 38299, 47065, 55831
3081	family with sequence similarity 101, member A	338359	3236	345898	12002	20768, 29534, 38300, 47066, 55832
3082	family with sequence similarity 101, member A	389727	3237	374377	12003	20769, 29535, 38301, 47067, 55833
3083	family with sequence	541200	3238	444007	12004	20770, 29536,

	similarity 101, member A					38302, 47068, 55834
3084	family with sequence similarity 101, member A	546355	3239	444080	12005	20771, 29537, 38303, 47069, 55835
3085	family with sequence similarity 101, member B	329099	3240	331915	12006	20772, 29538, 38304, 47070, 55836
3086	family with sequence similarity 102, member B	370035	3241	359052	12007	20773, 29539, 38305, 47071, 55837
3087	family with sequence similarity 102, member B	437902	3242	406213	12008	20774, 29540, 38306, 47072, 55838
3088	family with sequence similarity 103, member A1	304191	3243	307181	12009	20775, 29541, 38307, 47073, 55839
3089	family with sequence similarity 104 member B	472571	3244	420895	12010	20776, 29542, 38308, 47074, 55840
3090	family with sequence similarity 104 member B	477847	3245	421161	12011	20777, 29543, 38309, 47075, 55841
3091	family with sequence similarity 104 member B	489298	3246	423164	12012	20778, 29544, 38310, 47076, 55842
3092	family with sequence similarity 104, member A	403627	3247	384648	12013	20779, 29545, 38311, 47077, 55843
3093	family with sequence similarity 104, member A	405159	3248	384832	12014	20780, 29546, 38312, 47078, 55844
3094	family with sequence similarity 104, member B	332132	3249	333394	12015	20781, 29547, 38313, 47079, 55845
3095	family with sequence similarity 104, member B	358460	3250	364101	12016	20782, 29548, 38314, 47080, 55846
3096	family with sequence similarity 104, member B	425133	3251	397188	12017	20783, 29549, 38315, 47081, 55847
3097	family with sequence similarity 105, member A	274217	3252	274217	12018	20784, 29550, 38316, 47082, 55848
3098	family with sequence similarity 105, member B	284274	3253	284274	12019	20785, 29551, 38317, 47083, 55849
3099	family with sequence similarity 106, member A	392176	3254	437812	12020	20786, 29552, 38318, 47084, 55850

3100	family with sequence similarity 106, member B	379228	3255	368530	12021	20787, 29553, 38319, 47085, 55851
3101	family with sequence similarity 107, member B	181796	3256	181796	12022	20788, 29554, 38320, 47086, 55852
3102	family with sequence similarity 107, member B	378458	3257	367719	12023	20789, 29555, 38321, 47087, 55853
3103	family with sequence similarity 107, member B	378461	3258	367722	12024	20790, 29556, 38322, 47088, 55854
3104	family with sequence similarity 107, member B	378462	3259	367723	12025	20791, 29557, 38323, 47089, 55855
3105	family with sequence similarity 107, member B	378465	3260	367726	12026	20792, 29558, 38324, 47090, 55856
3106	family with sequence similarity 107, member B	378467	3261	367728	12027	20793, 29559, 38325, 47091, 55857
3107	family with sequence similarity 107, member B	378470	3262	367731	12028	20794, 29560, 38326, 47092, 55858
3108	family with sequence similarity 107, member B	442012	3263	397949	12029	20795, 29561, 38327, 47093, 55859
3109	family with sequence similarity 107, member B	452706	3264	413676	12030	20796, 29562, 38328, 47094, 55860
3110	family with sequence similarity 107, member B	468492	3265	420444	12031	20797, 29563, 38329, 47095, 55861
3111	family with sequence similarity 107, member B	468747	3266	418120	12032	20798, 29564, 38330, 47096, 55862
3112	family with sequence similarity 107, member B	472095	3267	419064	12033	20799, 29565, 38331, 47097, 55863
3113	family with sequence similarity 107, member B	475786	3268	417242	12034	20800, 29566, 38332, 47098, 55864
3114	family with sequence similarity 107, member B	478076	3269	417782	12035	20801, 29567, 38333, 47099, 55865
3115	family with sequence similarity 107, member B	479731	3270	419603	12036	20802, 29568, 38334, 47100, 55866
3116	family with sequence similarity 107, member B	482277	3271	417845	12037	20803, 29569, 38335, 47101,

						55867
3117	family with sequence similarity 107, member B	488576	3272	420314	12038	20804, 29570, 38336, 47102, 55868
3118	family with sequence similarity 107, member B	489100	3273	420249	12039	20805, 29571, 38337, 47103, 55869
3119	family with sequence similarity 107, member B	494865	3274	418395	12040	20806, 29572, 38338, 47104, 55870
3120	family with sequence similarity 107, member B	496330	3275	418330	12041	20807, 29573, 38339, 47105, 55871
3121	family with sequence similarity 108, member C1	258884	3276	258884	12042	20808, 29574, 38340, 47106, 55872
3122	family with sequence similarity 108, member C1	558464	3277	452778	12043	20809, 29575, 38341, 47107, 55873
3123	family with sequence similarity 110, member D	374268	3278	363386	12044	20810, 29576, 38342, 47108, 55874
3124	family with sequence similarity 111, member A	361723	3279	355264	12045	20811, 29577, 38343, 47109, 55875
3125	family with sequence similarity 111, member A	420244	3280	406683	12046	20812, 29578, 38344, 47110, 55876
3126	family with sequence similarity 111, member A	527629	3281	436128	12047	20813, 29579, 38345, 47111, 55877
3127	family with sequence similarity 111, member A	528737	3282	434435	12048	20814, 29580, 38346, 47112, 55878
3128	family with sequence similarity 111, member A	531147	3283	431631	12049	20815, 29581, 38347, 47113, 55879
3129	family with sequence similarity 111, member A	531408	3284	432821	12050	20816, 29582, 38348, 47114, 55880
3130	family with sequence similarity 111, member A	533703	3285	433154	12051	20817, 29583, 38349, 47115, 55881
3131	family with sequence similarity 111, member B	343597	3286	341565	12052	20818, 29584, 38350, 47116, 55882
3132	family with sequence similarity 111, member B	411426	3287	393855	12053	20819, 29585, 38351, 47117, 55883
3133	family with sequence	529618	3288	432875	12054	20820, 29586,

	similarity 111, member B					38352, 47118, 55884
3134	family with sequence similarity 111, member B	534403	3289	432143	12055	20821, 29587, 38353, 47119, 55885
3135	family with sequence similarity 113, member A	356872	3290	349334	12056	20822, 29588, 38354, 47120, 55886
3136	family with sequence similarity 113, member A	360652	3291	353868	12057	20823, 29589, 38355, 47121, 55887
3137	family with sequence similarity 113, member A	380531	3292	369903	12058	20824, 29590, 38356, 47122, 55888
3138	family with sequence similarity 113, member A	439542	3293	401711	12059	20825, 29591, 38357, 47123, 55889
3139	family with sequence similarity 113, member A	448755	3294	388935	12060	20826, 29592, 38358, 47124, 55890
3140	family with sequence similarity 113, member B	330951	3295	328560	12061	20827, 29593, 38359, 47125, 55891
3141	family with sequence similarity 113, member B	432328	3296	396040	12062	20828, 29594, 38360, 47126, 55892
3142	family with sequence similarity 113, member B	546455	3297	446688	12063	20829, 29595, 38361, 47127, 55893
3143	family with sequence similarity 113, member B	549500	3298	449680	12064	20830, 29596, 38362, 47128, 55894
3144	family with sequence similarity 113, member B	549630	3299	448000	12065	20831, 29597, 38363, 47129, 55895
3145	family with sequence similarity 113, member B	551777	3300	448926	12066	20832, 29598, 38364, 47130, 55896
3146	family with sequence similarity 114, member A2	351797	3301	341597	12067	20833, 29599, 38365, 47131, 55897
3147	family with sequence similarity 114, member A2	433795	3302	409709	12068	20834, 29600, 38366, 47132, 55898
3148	family with sequence similarity 114, member A2	517605	3303	429919	12069	20835, 29601, 38367, 47133, 55899
3149	family with sequence similarity 114, member A2	518102	3304	428551	12070	20836, 29602, 38368, 47134, 55900

3150	family with sequence similarity 114, member A2	519808	3305	429753	12071	20837, 29603, 38369, 47135, 55901
3151	family with sequence similarity 114, member A2	520667	3306	430384	12072	20838, 29604, 38370, 47136, 55902
3152	family with sequence similarity 114, member A2	522395	3307	430186	12073	20839, 29605, 38371, 47137, 55903
3153	family with sequence similarity 114, member A2	522634	3308	428941	12074	20840, 29606, 38372, 47138, 55904
3154	family with sequence similarity 114, member A2	522858	3309	430489	12075	20841, 29607, 38373, 47139, 55905
3155	family with sequence similarity 114, member A2	523705	3310	428827	12076	20842, 29608, 38374, 47140, 55906
3156	family with sequence similarity 114, member A2	524246	3311	429403	12077	20843, 29609, 38375, 47141, 55907
3157	family with sequence similarity 115, member A	355951	3312	348220	12078	20844, 29610, 38376, 47142, 55908
3158	family with sequence similarity 115, member A	460532	3313	420607	12079	20845, 29611, 38377, 47143, 55909
3159	family with sequence similarity 115, member A	478172	3314	419622	12080	20846, 29612, 38378, 47144, 55910
3160	family with sequence similarity 115, member A	479870	3315	419235	12081	20847, 29613, 38379, 47145, 55911
3161	family with sequence similarity 115, member A	485416	3316	418432	12082	20848, 29614, 38380, 47146, 55912
3162	family with sequence similarity 115, member A	491908	3317	417600	12083	20849, 29615, 38381, 47147, 55913
3163	family with sequence similarity 115, member C	357344	3318	349902	12084	20850, 29616, 38382, 47148, 55914
3164	family with sequence similarity 115, member C	409703	3319	386405	12085	20851, 29617, 38383, 47149, 55915
3165	family with sequence similarity 115, member C	411497	3320	390603	12086	20852, 29618, 38384, 47150, 55916
3166	family with sequence similarity 115, member C	425618	3321	441099	12087	20853, 29619, 38385, 47151,

						55917
3167	family with sequence similarity 115, member C	441159	3322	404265	12088	20854, 29620, 38386, 47152, 55918
3168	family with sequence similarity 115, member C	444908	3323	412724	12089	20855, 29621, 38387, 47153, 55919
3169	family with sequence similarity 116, member A	311128	3324	311401	12090	20856, 29622, 38388, 47154, 55920
3170	family with sequence similarity 116, member B	413817	3325	391524	12091	20857, 29623, 38389, 47155, 55921
3171	family with sequence similarity 117, member A	240364	3326	240364	12092	20858, 29624, 38390, 47156, 55922
3172	family with sequence similarity 117, member B	303116	3327	306299	12093	20859, 29625, 38391, 47157, 55923
3173	family with sequence similarity 117, member B	392238	3328	376071	12094	20860, 29626, 38392, 47158, 55924
3174	family with sequence similarity 118, member B	533050	3329	433343	12095	20861, 29627, 38393, 47159, 55925
3175	family with sequence similarity 120A opposite strand	375409	3330	364558	12096	20862, 29628, 38394, 47160, 55926
3176	family with sequence similarity 120A opposite strand	375412	3331	364561	12097	20863, 29629, 38395, 47161, 55927
3177	family with sequence similarity 122A	377279	3332	366492	12098	20864, 29630, 38396, 47162, 55928
3178	family with sequence similarity 122A	394264	3333	377807	12099	20865, 29631, 38397, 47163, 55929
3179	family with sequence similarity 122B	298090	3334	298090	12100	20866, 29632, 38398, 47164, 55930
3180	family with sequence similarity 122B	343004	3335	339207	12101	20867, 29633, 38399, 47165, 55931
3181	family with sequence similarity 122B	370787	3336	359823	12102	20868, 29634, 38400, 47166, 55932
3182	family with sequence similarity 122B	370790	3337	359826	12103	20869, 29635, 38401, 47167, 55933
3183	family with sequence	394270	3338	377812	12104	20870, 29636,

	similarity 122B					38402, 47168, 55934
3184	family with sequence similarity 122B	486347	3339	419592	12105	20871, 29637, 38403, 47169, 55935
3185	family with sequence similarity 122C	370784	3340	359820	12106	20872, 29638, 38404, 47170, 55936
3186	family with sequence similarity 122C	370785	3341	359821	12107	20873, 29639, 38405, 47171, 55937
3187	family with sequence similarity 122C	414371	3342	402477	12108	20874, 29640, 38406, 47172, 55938
3188	family with sequence similarity 122C	445123	3343	389955	12109	20875, 29641, 38407, 47173, 55939
3189	family with sequence similarity 123A	357816	3344	350469	12110	20876, 29642, 38408, 47174, 55940
3190	family with sequence similarity 123A	381853	3345	371277	12111	20877, 29643, 38409, 47175, 55941
3191	family with sequence similarity 123A	515384	3346	426528	12112	20878, 29644, 38410, 47176, 55942
3192	family with sequence similarity 123C	321420	3347	314914	12113	20879, 29645, 38411, 47177, 55943
3193	family with sequence similarity 123C	423981	3348	392700	12114	20880, 29646, 38412, 47178, 55944
3194	family with sequence similarity 123C	431758	3349	410421	12115	20881, 29647, 38413, 47179, 55945
3195	family with sequence similarity 123C	458606	3350	389242	12116	20882, 29648, 38414, 47180, 55946
3196	family with sequence similarity 124A	280057	3351	280057	12117	20883, 29649, 38415, 47181, 55947
3197	family with sequence similarity 124A	322475	3352	324625	12118	20884, 29650, 38416, 47182, 55948
3198	family with sequence similarity 124B	243806	3353	243806	12119	20885, 29651, 38417, 47183, 55949
3199	family with sequence similarity 124B	389874	3354	374524	12120	20886, 29652, 38418, 47184, 55950

3200	family with sequence similarity 124B	409685	3355	386895	12121	20887, 29653, 38419, 47185, 55951
3201	family with sequence similarity 126, member B	418596	3356	393667	12122	20888, 29654, 38420, 47186, 55952
3202	family with sequence similarity 126, member B	452799	3357	401905	12123	20889, 29655, 38421, 47187, 55953
3203	family with sequence similarity 126, member B	453765	3358	408374	12124	20890, 29656, 38422, 47188, 55954
3204	family with sequence similarity 127, member B	370775	3359	375267	12125	20891, 29657, 38423, 47189, 55955
3205	family with sequence similarity 127, member C	391440	3360	375268	12126	20892, 29658, 38424, 47190, 55956
3206	family with sequence similarity 127, member C	538706	3361	442860	12127	20893, 29659, 38425, 47191, 55957
3207	family with sequence similarity 129, member C	300971	3362	300971	12128	20894, 29660, 38426, 47192, 55958
3208	family with sequence similarity 129, member C	332386	3363	333447	12129	20895, 29661, 38427, 47193, 55959
3209	family with sequence similarity 129, member C	335393	3364	335040	12130	20896, 29662, 38428, 47194, 55960
3210	family with sequence similarity 129, member C	352727	3365	341067	12131	20897, 29663, 38429, 47195, 55961
3211	family with sequence similarity 129, member C	435646	3366	411301	12132	20898, 29664, 38430, 47196, 55962
3212	family with sequence similarity 129, member C	449408	3367	394929	12133	20899, 29665, 38431, 47197, 55963
3213	family with sequence similarity 13, member B	33079	3368	33079	12134	20900, 29666, 38432, 47198, 55964, 61527, 61585
3214	family with sequence similarity 13, member B	420893	3369	388521	12135	20901, 29667, 38433, 47199, 55965
3215	family with sequence similarity 13, member B	425075	3370	394669	12136	20902, 29668, 38434, 47200, 55966
3216	family with sequence	502471	3371	424785	12137	20903, 29669,

	similarity 13, member B					38435, 47201, 55967
3217	family with sequence similarity 13, member B	505961	3372	422673	12138	20904, 29670, 38436, 47202, 55968
3218	family with sequence similarity 13, member B	508403	3373	426863	12139	20905, 29671, 38437, 47203, 55969
3219	family with sequence similarity 13, member B	509596	3374	422311	12140	20906, 29672, 38438, 47204, 55970
3220	family with sequence similarity 13, member B	514310	3375	425326	12141	20907, 29673, 38439, 47205, 55971
3221	family with sequence similarity 13, member C	373867	3376	362974	12142	20908, 29674, 38440, 47206, 55972
3222	family with sequence similarity 13, member C	373868	3377	362975	12143	20909, 29675, 38441, 47207, 55973
3223	family with sequence similarity 13, member C	419214	3378	391993	12144	20910, 29676, 38442, 47208, 55974
3224	family with sequence similarity 13, member C	422313	3379	400241	12145	20911, 29677, 38443, 47209, 55975
3225	family with sequence similarity 13, member C	468840	3380	423896	12146	20912, 29678, 38444, 47210, 55976
3226	family with sequence similarity 13, member C	503444	3381	424797	12147	20913, 29679, 38445, 47211, 55977
3227	family with sequence similarity 13, member C	512919	3382	425820	12148	20914, 29680, 38446, 47212, 55978
3228	family with sequence similarity 131, member B	409222	3383	387147	12149	20915, 29681, 38447, 47213, 55979
3229	family with sequence similarity 131, member B	409346	3384	386984	12150	20916, 29682, 38448, 47214, 55980
3230	family with sequence similarity 131, member B	409408	3385	387017	12151	20917, 29683, 38449, 47215, 55981
3231	family with sequence similarity 131, member B	443739	3386	410603	12152	20918, 29684, 38450, 47216, 55982
3232	family with sequence similarity 131, member B	452076	3387	392002	12153	20919, 29685, 38451, 47217, 55983

3233	family with sequence similarity 131, member C	375662	3388	364814	12154	20920, 29686, 38452, 47218, 55984
3234	family with sequence similarity 133, member A	322139	3389	318974	12155	20921, 29687, 38453, 47219, 55985
3235	family with sequence similarity 133, member A	332647	3390	362169	12156	20922, 29688, 38454, 47220, 55986
3236	family with sequence similarity 133, member A	355813	3391	348067	12157	20923, 29689, 38455, 47221, 55987
3237	family with sequence similarity 133, member A	538690	3392	441389	12158	20924, 29690, 38456, 47222, 55988
3238	family with sequence similarity 133, member B	427372	3393	402843	12159	20925, 29691, 38457, 47223, 55989
3239	family with sequence similarity 133, member B	438306	3394	389783	12160	20926, 29692, 38458, 47224, 55990
3240	family with sequence similarity 133, member B	445716	3395	398401	12161	20927, 29693, 38459, 47225, 55991
3241	family with sequence similarity 133, member B	456502	3396	407458	12162	20928, 29694, 38460, 47226, 55992
3242	family with sequence similarity 138, member A	417324	3397	409362	12163	20929, 29695, 38461, 47227, 55993
3243	family with sequence similarity 138, member C	305248	3398	303458	12164	20930, 29696, 38462, 47228, 55994
3244	family with sequence similarity 138, member C	449442	3399	393278	12165	20931, 29697, 38463, 47229, 55995
3245	family with sequence similarity 138, member F	448235	3400	387981	12166	20932, 29698, 38464, 47230, 55996
3246	family with sequence similarity 149, member A	227065	3401	227065	12167	20933, 29699, 38465, 47231, 55997
3247	family with sequence similarity 149, member A	356371	3402	348732	12168	20934, 29700, 38466, 47232, 55998
3248	family with sequence similarity 149, member A	389354	3403	374005	12169	20935, 29701, 38467, 47233, 55999
3249	family with sequence similarity 149, member A	503432	3404	426835	12170	20936, 29702, 38468, 47234,

						56000
3250	family with sequence similarity 149, member A	510790	3405	421713	12171	20937, 29703, 38469, 47235, 56001
3251	family with sequence similarity 149, member B1	242505	3406	242505	12172	20938, 29704, 38470, 47236, 56002
3252	family with sequence similarity 149, member B1	372955	3407	362046	12173	20939, 29705, 38471, 47237, 56003
3253	family with sequence similarity 149, member B1	429173	3408	391908	12174	20940, 29706, 38472, 47238, 56004
3254	family with sequence similarity 149, member B1	445951	3409	402293	12175	20941, 29707, 38473, 47239, 56005
3255	family with sequence similarity 151, member B	282226	3410	282226	12176	20942, 29708, 38474, 47240, 56006
3256	family with sequence similarity 153, member A	393518	3411	377153	12177	20943, 29709, 38475, 47241, 56007
3257	family with sequence similarity 153, member A	440977	3412	412917	12178	20944, 29710, 38476, 47242, 56008
3258	family with sequence similarity 153, member B	253490	3413	253490	12179	20945, 29711, 38477, 47243, 56009
3259	family with sequence similarity 153, member B	510151	3414	453424	12180	20946, 29712, 38478, 47244, 56010
3260	family with sequence similarity 153, member B	515817	3415	427684	12181	20947, 29713, 38479, 47245, 56011
3261	family with sequence similarity 153, member C	398106	3416	381177	12182	20948, 29714, 38480, 47246, 56012
3262	family with sequence similarity 153, member C	504530	3417	423403	12183	20949, 29715, 38481, 47247, 56013
3263	family with sequence similarity 153, member C	507848	3418	424623	12184	20950, 29716, 38482, 47248, 56014
3264	family with sequence similarity 154, member A	380534	3419	369907	12185	20951, 29717, 38483, 47249, 56015
3265	family with sequence similarity 154, member A	542071	3420	438823	12186	20952, 29718, 38484, 47250, 56016
3266	family with sequence	339465	3421	340445	12187	20953, 29719,

	similarity 154, member B					38485, 47251, 56017
3267	family with sequence similarity 154, member B	427381	3422	403743	12188	20954, 29720, 38486, 47252, 56018
3268	family with sequence similarity 157, member A	431569	3423	396627	12189	20955, 29721, 38487, 47253, 56019
3269	family with sequence similarity 158, member A	216799	3424	216799	12190	20956, 29722, 38488, 47254, 56020
3270	family with sequence similarity 158, member A	419198	3425	403210	12191	20957, 29723, 38489, 47255, 56021
3271	family with sequence similarity 159, member B	389074	3426	373726	12192	20958, 29724, 38490, 47256, 56022
3272	family with sequence similarity 160, member A1	435205	3427	413196	12193	20959, 29725, 38491, 47257, 56023
3273	family with sequence similarity 160, member A1	503146	3428	424175	12194	20960, 29726, 38492, 47258, 56024
3274	family with sequence similarity 160, member A1	505231	3429	421580	12195	20961, 29727, 38493, 47259, 56025
3275	family with sequence similarity 160, member A1	512597	3430	421948	12196	20962, 29728, 38494, 47260, 56026
3276	family with sequence similarity 160, member A1	513086	3431	425333	12197	20963, 29729, 38495, 47261, 56027
3277	family with sequence similarity 160, member A1	513962	3432	426677	12198	20964, 29730, 38496, 47262, 56028
3278	family with sequence similarity 160, member B1	369246	3433	358249	12199	20965, 29731, 38497, 47263, 56029
3279	family with sequence similarity 160, member B1	369248	3434	358251	12200	20966, 29732, 38498, 47264, 56030
3280	family with sequence similarity 160, member B1	369250	3435	358253	12201	20967, 29733, 38499, 47265, 56031
3281	family with sequence similarity 160, member B1	411414	3436	411924	12202	20968, 29734, 38500, 47266, 56032
3282	family with sequence similarity 160, member B2	289921	3437	289921	12203	20969, 29735, 38501, 47267, 56033

3283	family with sequence similarity 160, member B2	356512	3438	348906	12204	20970, 29736, 38502, 47268, 56034
3284	family with sequence similarity 161, member B	286544	3439	286544	12205	20971, 29737, 38503, 47269, 56035
3285	family with sequence similarity 161, member B	534936	3440	445326	12206	20972, 29738, 38504, 47270, 56036
3286	family with sequence similarity 164, member A	263849	3441	263849	12207	20973, 29739, 38505, 47271, 56037
3287	family with sequence similarity 164, member C	439583	3442	390606	12208	20974, 29740, 38506, 47272, 56038
3288	family with sequence similarity 164, member C	524913	3443	435550	12209	20975, 29741, 38507, 47273, 56039
3289	family with sequence similarity 164, member C	525046	3444	435684	12210	20976, 29742, 38508, 47274, 56040
3290	family with sequence similarity 164, member C	526130	3445	437160	12211	20977, 29743, 38509, 47275, 56041
3291	family with sequence similarity 164, member C	534151	3446	434997	12212	20978, 29744, 38510, 47276, 56042
3292	family with sequence similarity 164, member C	554763	3447	451195	12213	20979, 29745, 38511, 47277, 56043
3293	family with sequence similarity 166 member B	399742	3448	382646	12214	20980, 29746, 38512, 47278, 56044
3294	family with sequence similarity 166 member B	447837	3449	412746	12215	20981, 29747, 38513, 47279, 56045
3295	family with sequence similarity 166, member A	344774	3450	344729	12216	20982, 29748, 38514, 47280, 56046
3296	family with sequence similarity 166, member A	388932	3451	373584	12217	20983, 29749, 38515, 47281, 56047
3297	family with sequence similarity 166, member B	537504	3452	446347	12218	20984, 29750, 38516, 47282, 56048
3298	family with sequence similarity 167, member B	373582	3453	362684	12219	20985, 29751, 38517, 47283, 56049
3299	family with sequence similarity 168, member A	64778	3454	64778	12220	20986, 29752, 38518, 47284,

						56050, 61528, 61586
3300	family with sequence similarity 168, member A	356467	3455	348852	12221	20987, 29753, 38519, 47285, 56051
3301	family with sequence similarity 168, member A	450446	3456	390501	12222	20988, 29754, 38520, 47286, 56052
3302	family with sequence similarity 168, member B	354183	3457	346115	12223	20989, 29755, 38521, 47287, 56053
3303	family with sequence similarity 168, member B	389915	3458	374565	12224	20990, 29756, 38522, 47288, 56054
3304	family with sequence similarity 168, member B	409185	3459	387051	12225	20991, 29757, 38523, 47289, 56055
3305	family with sequence similarity 169, member A	380515	3460	369886	12226	20992, 29758, 38524, 47290, 56056
3306	family with sequence similarity 169, member A	389156	3461	373808	12227	20993, 29759, 38525, 47291, 56057
3307	family with sequence similarity 169, member A	506954	3462	421451	12228	20994, 29760, 38526, 47292, 56058
3308	family with sequence similarity 169, member A	513277	3463	423631	12229	20995, 29761, 38527, 47293, 56059
3309	family with sequence similarity 169, member A	514200	3464	423883	12230	20996, 29762, 38528, 47294, 56060
3310	family with sequence similarity 169, member B	332908	3465	332615	12231	20997, 29763, 38529, 47295, 56061
3311	family with sequence similarity 169, member B	558256	3466	453554	12232	20998, 29764, 38530, 47296, 56062
3312	family with sequence similarity 170 member A	335286	3467	334285	12233	20999, 29765, 38531, 47297, 56063
3313	family with sequence similarity 170 member A	379555	3468	368873	12234	21000, 29766, 38532, 47298, 56064
3314	family with sequence similarity 170, member A	296787	3469	296787	12235	21001, 29767, 38533, 47299, 56065
3315	family with sequence similarity 170, member A	515256	3470	422684	12236	21002, 29768, 38534, 47300, 56066

3316	family with sequence similarity 170, member B	311787	3471	308292	12237	21003, 29769, 38535, 47301, 56067
3317	family with sequence similarity 176, member B	270824	3472	270824	12238	21004, 29770, 38536, 47302, 56068
3318	family with sequence similarity 177, member A1	280987	3473	280987	12239	21005, 29771, 38537, 47303, 56069
3319	family with sequence similarity 177, member A1	382406	3474	371843	12240	21006, 29772, 38538, 47304, 56070
3320	family with sequence similarity 177, member A1	396472	3475	379734	12241	21007, 29773, 38539, 47305, 56071
3321	family with sequence similarity 177, member A1	555211	3476	451508	12242	21008, 29774, 38540, 47306, 56072
3322	family with sequence similarity 177, member B	360827	3477	354070	12243	21009, 29775, 38541, 47307, 56073
3323	family with sequence similarity 177, member B	434700	3478	391615	12244	21010, 29776, 38542, 47308, 56074
3324	family with sequence similarity 177, member B	445590	3479	414451	12245	21011, 29777, 38543, 47309, 56075
3325	family with sequence similarity 177, member B	456298	3480	400233	12246	21012, 29778, 38544, 47310, 56076
3326	family with sequence similarity 178, member B	327896	3481	333553	12247	21013, 29779, 38545, 47311, 56077
3327	family with sequence similarity 178, member B	393526	3482	377160	12248	21014, 29780, 38546, 47312, 56078
3328	family with sequence similarity 178, member B	417561	3483	413245	12249	21015, 29781, 38547, 47313, 56079
3329	family with sequence similarity 178, member B	490605	3484	429896	12250	21016, 29782, 38548, 47314, 56080
3330	family with sequence similarity 179, member A	379558	3485	368876	12251	21017, 29783, 38549, 47315, 56081
3331	family with sequence similarity 179, member A	403861	3486	384699	12252	21018, 29784, 38550, 47316, 56082
3332	family with sequence similarity 179, member A	420297	3487	402415	12253	21019, 29785, 38551, 47317,

						56083
3333	family with sequence similarity 179, member B	361577	3488	355045	12254	21020, 29786, 38552, 47318, 56084
3334	family with sequence similarity 179, member B	382233	3489	371668	12255	21021, 29787, 38553, 47319, 56085
3335	family with sequence similarity 179, member B	429476	3490	389572	12256	21022, 29788, 38554, 47320, 56086
3336	family with sequence similarity 181 member A	557000	3491	451445	12257	21023, 29789, 38555, 47321, 56087
3337	family with sequence similarity 181, member A	267594	3492	267594	12258	21024, 29790, 38556, 47322, 56088
3338	family with sequence similarity 181, member A	554404	3493	452393	12259	21025, 29791, 38557, 47323, 56089
3339	family with sequence similarity 181, member A	556222	3494	451678	12260	21026, 29792, 38558, 47324, 56090
3340	family with sequence similarity 181, member A	557719	3495	451802	12261	21027, 29793, 38559, 47325, 56091
3341	family with sequence similarity 181, member B	329203	3496	365295	12262	21028, 29794, 38560, 47326, 56092
3342	family with sequence similarity 182, member A	246000	3497	246000	12263	21029, 29795, 38561, 47327, 56093
3343	family with sequence similarity 182, member A	415411	3498	388057	12264	21030, 29796, 38562, 47328, 56094
3344	family with sequence similarity 182, member B	376404	3499	365586	12265	21031, 29797, 38563, 47329, 56095
3345	family with sequence similarity 183, member A	335282	3500	334415	12266	21032, 29798, 38564, 47330, 56096
3346	family with sequence similarity 184, member A	338891	3501	342604	12267	21033, 29799, 38565, 47331, 56097
3347	family with sequence similarity 184, member A	352896	3502	326608	12268	21034, 29800, 38566, 47332, 56098
3348	family with sequence similarity 184, member B	265018	3503	265018	12269	21035, 29801, 38567, 47333, 56099
3349	family with sequence	409231	3504	387066	12270	21036, 29802,

	similarity 185 member A					38568, 47334, 56100
3350	family with sequence similarity 185, member A	413034	3505	395340	12271	21037, 29803, 38569, 47335, 56101
3351	family with sequence similarity 185, member A	432852	3506	409360	12272	21038, 29804, 38570, 47336, 56102
3352	family with sequence similarity 186, member A	327337	3507	329995	12273	21039, 29805, 38571, 47337, 56103
3353	family with sequence similarity 186, member A	543096	3508	443703	12274	21040, 29806, 38572, 47338, 56104
3354	family with sequence similarity 186, member B	257894	3509	257894	12275	21041, 29807, 38573, 47339, 56105
3355	family with sequence similarity 186, member B	532262	3510	436995	12276	21042, 29808, 38574, 47340, 56106
3356	family with sequence similarity 186, member B	544141	3511	438569	12277	21043, 29809, 38575, 47341, 56107
3357	family with sequence similarity 186, member B	548841	3512	448989	12278	21044, 29810, 38576, 47342, 56108
3358	family with sequence similarity 187, member A	331733	3513	329499	12279	21045, 29811, 38577, 47343, 56109
3359	family with sequence similarity 187, member A	412523	3514	391869	12280	21046, 29812, 38578, 47344, 56110
3360	family with sequence similarity 188, member B	265299	3515	265299	12281	21047, 29813, 38579, 47345, 56111
3361	family with sequence similarity 189 member B	572488	3516	458501	12282	21048, 29814, 38580, 47346, 56112
3362	family with sequence similarity 190, member A	333691	3517	329482	12283	21049, 29815, 38581, 47347, 56113
3363	family with sequence similarity 190, member A	432775	3518	389283	12284	21050, 29816, 38582, 47348, 56114
3364	family with sequence similarity 190, member A	458365	3519	387398	12285	21051, 29817, 38583, 47349, 56115
3365	family with sequence similarity 190, member A	509176	3520	425040	12286	21052, 29818, 38584, 47350, 56116

3366	family with sequence similarity 190, member B	224756	3521	224756	12287	21053, 29819, 38585, 47351, 56117
3367	family with sequence similarity 190, member B	372088	3522	361160	12288	21054, 29820, 38586, 47352, 56118
3368	family with sequence similarity 190, member B	543283	3523	439944	12289	21055, 29821, 38587, 47353, 56119
3369	family with sequence similarity 193 member A	502458	3524	427505	12290	21056, 29822, 38588, 47354, 56120
3370	family with sequence similarity 193 member A	505311	3525	421200	12291	21057, 29823, 38589, 47355, 56121
3371	family with sequence similarity 193 member B	514747	3526	422131	12292	21058, 29824, 38590, 47356, 56122
3372	family with sequence similarity 193, member A	324666	3527	324587	12293	21059, 29825, 38591, 47357, 56123
3373	family with sequence similarity 193, member A	382839	3528	372290	12294	21060, 29826, 38592, 47358, 56124
3374	family with sequence similarity 193, member A	509050	3529	423292	12295	21061, 29827, 38593, 47359, 56125
3375	family with sequence similarity 193, member A	513350	3530	427260	12296	21062, 29828, 38594, 47360, 56126
3376	family with sequence similarity 193, member A	545951	3531	443617	12297	21063, 29829, 38595, 47361, 56127
3377	family with sequence similarity 193, member B	329540	3532	332014	12298	21064, 29830, 38596, 47362, 56128
3378	family with sequence similarity 193, member B	443375	3533	410098	12299	21065, 29831, 38597, 47363, 56129
3379	family with sequence similarity 194, member A	295910	3534	295910	12300	21066, 29832, 38598, 47364, 56130
3380	family with sequence similarity 194, member A	313811	3535	322844	12301	21067, 29833, 38599, 47365, 56131
3381	family with sequence similarity 194, member B	298738	3536	298738	12302	21068, 29834, 38600, 47366, 56132
3382	family with sequence similarity 195, member A	307650	3537	305138	12303	21069, 29835, 38601, 47367,

						56133
3383	family with sequence similarity 195, member A	537787	3538	439763	12304	21070, 29836, 38602, 47368, 56134
3384	family with sequence similarity 195, member B	455127	3539	409009	12305	21071, 29837, 38603, 47369, 56135
3385	family with sequence similarity 195, member B	538396	3540	445543	12306	21072, 29838, 38604, 47370, 56136
3386	family with sequence similarity 196, member A	522781	3541	429763	12307	21073, 29839, 38605, 47371, 56137
3387	family with sequence similarity 196, member B	377365	3542	366582	12308	21074, 29840, 38606, 47372, 56138
3388	family with sequence similarity 199, X-linked	493442	3543	417581	12309	21075, 29841, 38607, 47373, 56139
3389	family with sequence similarity 200 member B	422728	3544	393017	12310	21076, 29842, 38608, 47374, 56140
3390	family with sequence similarity 201, member A	377680	3545	366908	12311	21077, 29843, 38609, 47375, 56141
3391	family with sequence similarity 203, member A	347708	3546	321320	12312	21078, 29844, 38610, 47376, 56142
3392	family with sequence similarity 203, member B	377406	3547	366623	12313	21079, 29845, 38611, 47377, 56143
3393	family with sequence similarity 204, member A	369170	3548	358168	12314	21080, 29846, 38612, 47378, 56144
3394	family with sequence similarity 204, member A	369172	3549	358170	12315	21081, 29847, 38613, 47379, 56145
3395	family with sequence similarity 204, member A	369183	3550	358183	12316	21082, 29848, 38614, 47380, 56146
3396	family with sequence similarity 205, member B	399773	3551	382673	12317	21083, 29849, 38615, 47381, 56147
3397	family with sequence similarity 207, member A	291634	3552	291634	12318	21084, 29850, 38616, 47382, 56148
3398	family with sequence similarity 207, member A	397826	3553	380926	12319	21085, 29851, 38617, 47383, 56149
3399	family with sequence	493960	3554	417509	12320	21086, 29852,

	similarity 208 member A					38618, 47384, 56150
3400	family with sequence similarity 208, member A	355628	3555	347845	12321	21087, 29853, 38619, 47385, 56151
3401	family with sequence similarity 208, member A	431842	3556	399410	12322	21088, 29854, 38620, 47386, 56152
3402	family with sequence similarity 208, member B	328090	3557	328426	12323	21089, 29855, 38621, 47387, 56153
3403	family with sequence similarity 208, member B	442808	3558	394907	12324	21090, 29856, 38622, 47388, 56154
3404	family with sequence similarity 208, member B	496681	3559	434941	12325	21091, 29857, 38623, 47389, 56155
3405	family with sequence similarity 211 member A	409083	3560	386504	12326	21092, 29858, 38624, 47390, 56156
3406	family with sequence similarity 211, member A	470794	3561	419502	12327	21093, 29859, 38625, 47391, 56157
3407	family with sequence similarity 211, member B	318753	3562	320520	12328	21094, 29860, 38626, 47392, 56158
3408	family with sequence similarity 212, member A	333323	3563	329735	12329	21095, 29861, 38627, 47393, 56159
3409	family with sequence similarity 212, member B	357260	3564	349805	12330	21096, 29862, 38628, 47394, 56160
3410	family with sequence similarity 212, member B	444059	3565	408238	12331	21097, 29863, 38629, 47395, 56161
3411	family with sequence similarity 214, member A	261844	3566	261844	12332	21098, 29864, 38630, 47396, 56162
3412	family with sequence similarity 214, member A	399202	3567	382153	12333	21099, 29865, 38631, 47397, 56163
3413	family with sequence similarity 214, member A	534964	3568	444447	12334	21100, 29866, 38632, 47398, 56164
3414	family with sequence similarity 214, member A	546305	3569	443598	12335	21101, 29867, 38633, 47399, 56165
3415	family with sequence similarity 22, member A	381689	3570	371107	12336	21102, 29868, 38634, 47400, 56166

3416	family with sequence similarity 22, member A	381707	3571	371126	12337	21103, 29869, 38635, 47401, 56167
3417	family with sequence similarity 22, member A	416901	3572	391475	12338	21104, 29870, 38636, 47402, 56168
3418	family with sequence similarity 22, member A	432986	3573	437477	12339	21105, 29871, 38637, 47403, 56169
3419	family with sequence similarity 22, member A	451286	3574	390723	12340	21106, 29872, 38638, 47404, 56170
3420	family with sequence similarity 22, member B	342531	3575	344811	12341	21107, 29873, 38639, 47405, 56171
3421	family with sequence similarity 22, member B	372321	3576	361396	12342	21108, 29874, 38640, 47406, 56172
3422	family with sequence similarity 22, member B	429828	3577	394623	12343	21109, 29875, 38641, 47407, 56173
3423	family with sequence similarity 22, member B	448135	3578	391631	12344	21110, 29876, 38642, 47408, 56174
3424	family with sequence similarity 22, member D	330762	3579	328439	12345	21111, 29877, 38643, 47409, 56175
3425	family with sequence similarity 22, member D	381691	3580	371109	12346	21112, 29878, 38644, 47410, 56176
3426	family with sequence similarity 22, member D	381697	3581	371116	12347	21113, 29879, 38645, 47411, 56177
3427	family with sequence similarity 22, member D	412718	3582	396080	12348	21114, 29880, 38646, 47412, 56178
3428	family with sequence similarity 22, member D	451669	3583	390413	12349	21115, 29881, 38647, 47413, 56179
3429	family with sequence similarity 22, member E	429984	3584	407521	12350	21116, 29882, 38648, 47414, 56180
3430	family with sequence similarity 22, member F	253262	3585	253262	12351	21117, 29883, 38649, 47415, 56181
3431	family with sequence similarity 22, member F	335456	3586	335067	12352	21118, 29884, 38650, 47416, 56182
3432	family with sequence similarity 22, member F	341207	3587	343865	12353	21119, 29885, 38651, 47417,

						56183
3433	family with sequence similarity 22, member F	375347	3588	364496	12354	21120, 29886, 38652, 47418, 56184
3434	family with sequence similarity 22, member G	354649	3589	346670	12355	21121, 29887, 38653, 47419, 56185
3435	family with sequence similarity 22, member G	372322	3590	361397	12356	21122, 29888, 38654, 47420, 56186
3436	family with sequence similarity 22, member G	375230	3591	364378	12357	21123, 29889, 38655, 47421, 56187
3437	family with sequence similarity 22, member G	417159	3592	389061	12358	21124, 29890, 38656, 47422, 56188
3438	family with sequence similarity 222 member B	581407	3593	462419	12359	21125, 29891, 38657, 47423, 56189
3439	family with sequence similarity 228 member B	407625	3594	383879	12360	21126, 29892, 38658, 47424, 56190
3440	family with sequence similarity 24, member A	368894	3595	357889	12361	21127, 29893, 38659, 47425, 56191
3441	family with sequence similarity 25, member A	343959	3596	342790	12362	21128, 29894, 38660, 47426, 56192
3442	family with sequence similarity 25, member B	340853	3597	340685	12363	21129, 29895, 38661, 47427, 56193
3443	family with sequence similarity 25, member B	452267	3598	413896	12364	21130, 29896, 38662, 47428, 56194
3444	family with sequence similarity 25, member C	342763	3599	341481	12365	21131, 29897, 38663, 47429, 56195
3445	family with sequence similarity 25, member C	445114	3600	400040	12366	21132, 29898, 38664, 47430, 56196
3446	family with sequence similarity 25, member G	357539	3601	350147	12367	21133, 29899, 38665, 47431, 56197
3447	family with sequence similarity 25, member G	457620	3602	407749	12368	21134, 29900, 38666, 47432, 56198
3448	family with sequence similarity 27, member A	377531	3603	366754	12369	21135, 29901, 38667, 47433, 56199
3449	family with sequence	377484	3604	366704	12370	21136, 29902,

	similarity 27, member B					38668, 47434, 56200
3450	family with sequence similarity 27, member E2	377529	3605	366752	12371	21137, 29903, 38669, 47435, 56201
3451	family with sequence similarity 27-like	426869	3606	388448	12372	21138, 29904, 38670, 47436, 56202
3452	family with sequence similarity 35, member A	298784	3607	298784	12373	21139, 29905, 38671, 47437, 56203
3453	family with sequence similarity 35, member A	298786	3608	298786	12374	21140, 29906, 38672, 47438, 56204
3454	family with sequence similarity 35, member A	342900	3609	339800	12375	21141, 29907, 38673, 47439, 56205
3455	family with sequence similarity 35, member A	358313	3610	351064	12376	21142, 29908, 38674, 47440, 56206
3456	family with sequence similarity 35, member B	301038	3611	301038	12377	21143, 29909, 38675, 47441, 56207
3457	family with sequence similarity 35, member B	539388	3612	438644	12378	21144, 29910, 38676, 47442, 56208
3458	family with sequence similarity 40, member B	249344	3613	249344	12379	21145, 29911, 38677, 47443, 56209
3459	family with sequence similarity 40, member B	435494	3614	392393	12380	21146, 29912, 38678, 47444, 56210
3460	family with sequence similarity 40, member B	450266	3615	394015	12381	21147, 29913, 38679, 47445, 56211
3461	family with sequence similarity 43, member A	329759	3616	371397	12382	21148, 29914, 38680, 47446, 56212
3462	family with sequence similarity 43, member B	332947	3617	331397	12383	21149, 29915, 38681, 47447, 56213
3463	family with sequence similarity 45, member A	361432	3618	354688	12384	21150, 29916, 38682, 47448, 56214
3464	family with sequence similarity 45, member A	535029	3619	444309	12385	21151, 29917, 38683, 47449, 56215
3465	family with sequence similarity 45, member A	544016	3620	443725	12386	21152, 29918, 38684, 47450, 56216

3466	family with sequence similarity 45, member A	546291	3621	442471	12387	21153, 29919, 38685, 47451, 56217
3467	family with sequence similarity 46, member A	369754	3622	358769	12388	21154, 29920, 38686, 47452, 56218
3468	family with sequence similarity 46, member A	369756	3623	358771	12389	21155, 29921, 38687, 47453, 56219
3469	family with sequence similarity 46, member A	412306	3624	401884	12390	21156, 29922, 38688, 47454, 56220
3470	family with sequence similarity 46, member A	423467	3625	404872	12391	21157, 29923, 38689, 47455, 56221
3471	family with sequence similarity 46, member B	289166	3626	289166	12392	21158, 29924, 38690, 47456, 56222
3472	family with sequence similarity 46, member D	308293	3627	308575	12393	21159, 29925, 38691, 47457, 56223
3473	family with sequence similarity 46, member D	538312	3628	443410	12394	21160, 29926, 38692, 47458, 56224
3474	family with sequence similarity 47 member E	510197	3629	422262	12395	21161, 29927, 38693, 47459, 56225
3475	family with sequence similarity 47 member E	515604	3630	422067	12396	21162, 29928, 38694, 47460, 56226
3476	family with sequence similarity 47, member A	346193	3631	345029	12397	21163, 29929, 38695, 47461, 56227
3477	family with sequence similarity 47, member B	329357	3632	328307	12398	21164, 29930, 38696, 47462, 56228
3478	family with sequence similarity 47, member C	358047	3633	367913	12399	21165, 29931, 38697, 47463, 56229
3479	family with sequence similarity 47, member E	339906	3634	340401	12400	21166, 29932, 38698, 47464, 56230
3480	family with sequence similarity 47, member E	424749	3635	409423	12401	21167, 29933, 38699, 47465, 56231
3481	family with sequence similarity 49, member A	355549	3636	347744	12402	21168, 29934, 38700, 47466, 56232
3482	family with sequence similarity 49, member A	381323	3637	370724	12403	21169, 29935, 38701, 47467,

						56233
3483	family with sequence similarity 49, member A	406434	3638	384771	12404	21170, 29936, 38702, 47468, 56234
3484	family with sequence similarity 49, member A	445605	3639	392154	12405	21171, 29937, 38703, 47469, 56235
3485	family with sequence similarity 49, member A	451689	3640	388979	12406	21172, 29938, 38704, 47470, 56236
3486	family with sequence similarity 49, member B	311292	3641	311651	12407	21173, 29939, 38705, 47471, 56237
3487	family with sequence similarity 49, member B	401979	3642	384880	12408	21174, 29940, 38706, 47472, 56238
3488	family with sequence similarity 49, member B	517654	3643	430674	12409	21175, 29941, 38707, 47473, 56239
3489	family with sequence similarity 49, member B	517672	3644	430434	12410	21176, 29942, 38708, 47474, 56240
3490	family with sequence similarity 49, member B	518167	3645	427994	12411	21177, 29943, 38709, 47475, 56241
3491	family with sequence similarity 49, member B	518283	3646	430694	12412	21178, 29944, 38710, 47476, 56242
3492	family with sequence similarity 49, member B	519020	3647	429659	12413	21179, 29945, 38711, 47477, 56243
3493	family with sequence similarity 49, member B	519070	3648	429860	12414	21180, 29946, 38712, 47478, 56244
3494	family with sequence similarity 49, member B	519110	3649	429078	12415	21181, 29947, 38713, 47479, 56245
3495	family with sequence similarity 49, member B	519142	3650	430806	12416	21182, 29948, 38714, 47480, 56246
3496	family with sequence similarity 49, member B	519540	3651	429499	12417	21183, 29949, 38715, 47481, 56247
3497	family with sequence similarity 49, member B	519824	3652	429150	12418	21184, 29950, 38716, 47482, 56248
3498	family with sequence similarity 49, member B	520204	3653	429051	12419	21185, 29951, 38717, 47483, 56249
3499	family with sequence	520254	3654	430127	12420	21186, 29952,

	similarity 49, member B					38718, 47484, 56250
3500	family with sequence similarity 49, member B	522361	3655	430412	12421	21187, 29953, 38719, 47485, 56251
3501	family with sequence similarity 49, member B	522746	3656	428117	12422	21188, 29954, 38720, 47486, 56252
3502	family with sequence similarity 49, member B	523509	3657	429802	12423	21189, 29955, 38721, 47487, 56253
3503	family with sequence similarity 49, member B	523993	3658	429074	12424	21190, 29956, 38722, 47488, 56254
3504	family with sequence similarity 50, member B	380272	3659	369625	12425	21191, 29957, 38723, 47489, 56255
3505	family with sequence similarity 50, member B	380274	3660	369627	12426	21192, 29958, 38724, 47490, 56256
3506	family with sequence similarity 53, member B	337318	3661	338532	12427	21193, 29959, 38725, 47491, 56257
3507	family with sequence similarity 53, member B	392754	3662	376509	12428	21194, 29960, 38726, 47492, 56258
3508	family with sequence similarity 53, member C	239906	3663	239906	12429	21195, 29961, 38727, 47493, 56259
3509	family with sequence similarity 53, member C	434981	3664	403705	12430	21196, 29962, 38728, 47494, 56260
3510	family with sequence similarity 54, member A	420702	3665	395232	12431	21197, 29963, 38729, 47495, 56261
3511	family with sequence similarity 54, member A	451457	3666	407010	12432	21198, 29964, 38730, 47496, 56262
3512	family with sequence similarity 54, member B	374300	3667	363418	12433	21199, 29965, 38731, 47497, 56263
3513	family with sequence similarity 54, member B	374301	3668	363419	12434	21200, 29966, 38732, 47498, 56264
3514	family with sequence similarity 54, member B	374303	3669	363421	12435	21201, 29967, 38733, 47499, 56265
3515	family with sequence similarity 54, member B	374307	3670	363426	12436	21202, 29968, 38734, 47500, 56266

3516	family with sequence similarity 54, member B	424294	3671	390841	12437	21203, 29969, 38735, 47501, 56267
3517	family with sequence similarity 54, member B	466284	3672	434751	12438	21204, 29970, 38736, 47502, 56268
3518	family with sequence similarity 54, member B	474295	3673	435461	12439	21205, 29971, 38737, 47503, 56269
3519	family with sequence similarity 54, member B	525713	3674	434120	12440	21206, 29972, 38738, 47504, 56270
3520	family with sequence similarity 54, member B	526158	3675	431278	12441	21207, 29973, 38739, 47505, 56271
3521	family with sequence similarity 54, member B	529116	3676	434038	12442	21208, 29974, 38740, 47506, 56272
3522	family with sequence similarity 59 member B	407684	3677	384581	12443	21209, 29975, 38741, 47507, 56273
3523	family with sequence similarity 59, member A	269209	3678	269209	12444	21210, 29976, 38742, 47508, 56274
3524	family with sequence similarity 59, member A	399218	3679	382165	12445	21211, 29977, 38743, 47509, 56275
3525	family with sequence similarity 59, member B	401533	3680	384593	12446	21212, 29978, 38744, 47510, 56276
3526	family with sequence similarity 60, member A	337682	3681	337477	12447	21213, 29979, 38745, 47511, 56277
3527	family with sequence similarity 60, member A	395766	3682	379115	12448	21214, 29980, 38746, 47512, 56278
3528	family with sequence similarity 60, member A	398170	3683	441449	12449	21215, 29981, 38747, 47513, 56279
3529	family with sequence similarity 60, member A	454658	3684	393279	12450	21216, 29982, 38748, 47514, 56280
3530	family with sequence similarity 60, member A	539004	3685	443881	12451	21217, 29983, 38749, 47515, 56281
3531	family with sequence similarity 60, member A	543615	3686	437363	12452	21218, 29984, 38750, 47516, 56282
3532	family with sequence similarity 63, member A	312210	3687	310923	12453	21219, 29985, 38751, 47517,

						56283
3533	family with sequence similarity 63, member A	361738	3688	354669	12454	21220, 29986, 38752, 47518, 56284
3534	family with sequence similarity 63, member A	361936	3689	354814	12455	21221, 29987, 38753, 47519, 56285
3535	family with sequence similarity 63, member A	493834	3690	437174	12456	21222, 29988, 38754, 47520, 56286
3536	family with sequence similarity 63, member B	450403	3691	393231	12457	21223, 29989, 38755, 47521, 56287
3537	family with sequence similarity 63, member B	559228	3692	452885	12458	21224, 29990, 38756, 47522, 56288
3538	family with sequence similarity 65, member C	45083	3693	45083	12459	21225, 29991, 38757, 47523, 56289, 61529, 61587
3539	family with sequence similarity 65, member C	327979	3694	332663	12460	21226, 29992, 38758, 47524, 56290
3540	family with sequence similarity 65, member C	535356	3695	439802	12461	21227, 29993, 38759, 47525, 56291
3541	family with sequence similarity 71 member D	311864	3696	431905	12462	21228, 29994, 38760, 47526, 56292
3542	family with sequence similarity 71, member A	294829	3697	294829	12463	21229, 29995, 38761, 47527, 56293
3543	family with sequence similarity 71, member A	545975	3698	442305	12464	21230, 29996, 38762, 47528, 56294
3544	family with sequence similarity 71, member C	324341	3699	315247	12465	21231, 29997, 38763, 47529, 56295
3545	family with sequence similarity 71, member E1	270620	3700	270620	12466	21232, 29998, 38764, 47530, 56296
3546	family with sequence similarity 71, member E1	391816	3701	375692	12467	21233, 29999, 38765, 47531, 56297
3547	family with sequence similarity 71, member E2	424985	3702	398617	12468	21234, 30000, 38766, 47532, 56298
3548	family with sequence similarity 71, member F1	315184	3703	326652	12469	21235, 30001, 38767, 47533, 56299

3549	family with sequence similarity 71, member F2	378704	3704	367976	12470	21236, 30002, 38768, 47534, 56300
3550	family with sequence similarity 71, member F2	434001	3705	401654	12471	21237, 30003, 38769, 47535, 56301
3551	family with sequence similarity 71, member F2	474069	3706	418907	12472	21238, 30004, 38770, 47536, 56302
3552	family with sequence similarity 71, member F2	480462	3707	420140	12473	21239, 30005, 38771, 47537, 56303
3553	family with sequence similarity 72, member A	341209	3708	340661	12474	21240, 30006, 38772, 47538, 56304
3554	family with sequence similarity 72, member A	367128	3709	356096	12475	21241, 30007, 38773, 47539, 56305
3555	family with sequence similarity 72, member A	367129	3710	356097	12476	21242, 30008, 38774, 47540, 56306
3556	family with sequence similarity 72, member B	355228	3711	347368	12477	21243, 30009, 38775, 47541, 56307
3557	family with sequence similarity 72, member B	369390	3712	358397	12478	21244, 30010, 38776, 47542, 56308
3558	family with sequence similarity 72, member B	369392	3713	358399	12479	21245, 30011, 38777, 47543, 56309
3559	family with sequence similarity 72, member B	452190	3714	392882	12480	21246, 30012, 38778, 47544, 56310
3560	family with sequence similarity 72, member C	369175	3715	358174	12481	21247, 30013, 38779, 47545, 56311
3561	family with sequence similarity 72, member D	400889	3716	383682	12482	21248, 30014, 38780, 47546, 56312
3562	family with sequence similarity 75, member B	376458	3717	365641	12483	21249, 30015, 38781, 47547, 56313
3563	family with sequence similarity 76, member A	10299	3718	10299	12484	21250, 30016, 38782, 47548, 56314, 61530, 61588
3564	family with sequence similarity 76, member A	234549	3719	234549	12485	21251, 30017, 38783, 47549, 56315
3565	family with sequence	373949	3720	363060	12486	21252, 30018,

	similarity 76, member A					38784, 47550, 56316
3566	family with sequence similarity 76, member A	373954	3721	363065	12487	21253, 30019, 38785, 47551, 56317
3567	family with sequence similarity 76, member A	419687	3722	395150	12488	21254, 30020, 38786, 47552, 56318
3568	family with sequence similarity 76, member B	358780	3723	351631	12489	21255, 30021, 38787, 47553, 56319
3569	family with sequence similarity 78, member A	372269	3724	361343	12490	21256, 30022, 38788, 47554, 56320
3570	family with sequence similarity 78, member A	372271	3725	361345	12491	21257, 30023, 38789, 47555, 56321
3571	family with sequence similarity 78, member A	464831	3726	419959	12492	21258, 30024, 38790, 47556, 56322
3572	family with sequence similarity 78, member B	338353	3727	339681	12493	21259, 30025, 38791, 47557, 56323
3573	family with sequence similarity 78, member B	354422	3728	346404	12494	21260, 30026, 38792, 47558, 56324
3574	family with sequence similarity 81, member A	288228	3729	288228	12495	21261, 30027, 38793, 47559, 56325
3575	family with sequence similarity 81, member A	557914	3730	452902	12496	21262, 30028, 38794, 47560, 56326
3576	family with sequence similarity 81, member A	558348	3731	453918	12497	21263, 30029, 38795, 47561, 56327
3577	family with sequence similarity 81, member A	559628	3732	453582	12498	21264, 30030, 38796, 47562, 56328
3578	family with sequence similarity 81, member A	560074	3733	453864	12499	21265, 30031, 38797, 47563, 56329
3579	family with sequence similarity 81, member A	560123	3734	453784	12500	21266, 30032, 38798, 47564, 56330
3580	family with sequence similarity 81, member A	560394	3735	452962	12501	21267, 30033, 38799, 47565, 56331
3581	family with sequence similarity 81, member A	561361	3736	453769	12502	21268, 30034, 38800, 47566, 56332

3582	family with sequence similarity 81, member B	283357	3737	283357	12503	21269, 30035, 38801, 47567, 56333
3583	family with sequence similarity 83, member A	276699	3738	276699	12504	21270, 30036, 38802, 47568, 56334
3584	family with sequence similarity 83, member A	318462	3739	323034	12505	21271, 30037, 38803, 47569, 56335
3585	family with sequence similarity 83, member A	518448	3740	428876	12506	21272, 30038, 38804, 47570, 56336
3586	family with sequence similarity 83, member A	522648	3741	427979	12507	21273, 30039, 38805, 47571, 56337
3587	family with sequence similarity 83, member A	536633	3742	445218	12508	21274, 30040, 38806, 47572, 56338
3588	family with sequence similarity 83, member A	546351	3743	440565	12509	21275, 30041, 38807, 47573, 56339
3589	family with sequence similarity 83, member B	306858	3744	304078	12510	21276, 30042, 38808, 47574, 56340
3590	family with sequence similarity 83, member C	374408	3745	363529	12511	21277, 30043, 38809, 47575, 56341
3591	family with sequence similarity 83, member E	263266	3746	263266	12512	21278, 30044, 38810, 47576, 56342
3592	family with sequence similarity 83, member F	333407	3747	330432	12513	21279, 30045, 38811, 47577, 56343
3593	family with sequence similarity 83, member G	345041	3748	343279	12514	21280, 30046, 38812, 47578, 56344
3594	family with sequence similarity 83, member G	388995	3749	373647	12515	21281, 30047, 38813, 47579, 56345
3595	family with sequence similarity 83, member G	399096	3750	382047	12516	21282, 30048, 38814, 47580, 56346
3596	family with sequence similarity 84, member A	295092	3751	295092	12517	21283, 30049, 38815, 47581, 56347
3597	family with sequence similarity 84, member A	331243	3752	330681	12518	21284, 30050, 38816, 47582, 56348
3598	family with sequence similarity 84, member A	359969	3753	353054	12519	21285, 30051, 38817, 47583,

						56349
3599	family with sequence similarity 84, member A	540701	3754	443261	12520	21286, 30052, 38818, 47584, 56350
3600	family with sequence similarity 86, member A	427587	3755	398502	12521	21287, 30053, 38819, 47585, 56351
3601	family with sequence similarity 86, member A	458008	3756	389710	12522	21288, 30054, 38820, 47586, 56352
3602	family with sequence similarity 86, member B1	321602	3757	439686	12523	21289, 30055, 38821, 47587, 56353
3603	family with sequence similarity 86, member B1	340537	3758	342610	12524	21290, 30056, 38822, 47588, 56354
3604	family with sequence similarity 86, member B1	431227	3759	444227	12525	21291, 30057, 38823, 47589, 56355
3605	family with sequence similarity 86, member B1	448228	3760	407067	12526	21292, 30058, 38824, 47590, 56356
3606	family with sequence similarity 86, member B1	534520	3761	431362	12527	21293, 30059, 38825, 47591, 56357
3607	family with sequence similarity 86, member B2	262365	3762	262365	12528	21294, 30060, 38826, 47592, 56358
3608	family with sequence similarity 86, member B2	309608	3763	311330	12529	21295, 30061, 38827, 47593, 56359
3609	family with sequence similarity 86, member B2	351291	3764	283479	12530	21296, 30062, 38828, 47594, 56360
3610	family with sequence similarity 86, member B2	393715	3765	377318	12531	21297, 30063, 38829, 47595, 56361
3611	family with sequence similarity 86, member B2	527331	3766	432491	12532	21298, 30064, 38830, 47596, 56362
3612	family with sequence similarity 86, member B2	532480	3767	436338	12533	21299, 30065, 38831, 47597, 56363
3613	family with sequence similarity 86, member C1	346333	3768	325662	12534	21300, 30066, 38832, 47598, 56364
3614	family with sequence similarity 86, member C1	359244	3769	352182	12535	21301, 30067, 38833, 47599, 56365
3615	family with sequence	426628	3770	391329	12536	21302, 30068,

	similarity 86, member C1					38834, 47600, 56366
3616	family with sequence similarity 89, member A	366654	3771	355614	12537	21303, 30069, 38835, 47601, 56367
3617	family with sequence similarity 89, member B	316409	3772	314829	12538	21304, 30070, 38836, 47602, 56368
3618	family with sequence similarity 89, member B	377088	3773	366292	12539	21305, 30071, 38837, 47603, 56369
3619	family with sequence similarity 89, member B	449319	3774	402439	12540	21306, 30072, 38838, 47604, 56370
3620	family with sequence similarity 89, member B	530349	3775	431459	12541	21307, 30073, 38839, 47605, 56371
3621	family with sequence similarity 91, member A1	334705	3776	335082	12542	21308, 30074, 38840, 47606, 56372
3622	family with sequence similarity 91, member A1	395537	3777	378908	12543	21309, 30075, 38841, 47607, 56373
3623	family with sequence similarity 92, member A1	341186	3778	341363	12544	21310, 30076, 38842, 47608, 56374
3624	family with sequence similarity 92, member A1	436526	3779	397275	12545	21311, 30077, 38843, 47609, 56375
3625	family with sequence similarity 92, member A1	518322	3780	429367	12546	21312, 30078, 38844, 47610, 56376
3626	family with sequence similarity 92, member A1	540007	3781	443529	12547	21313, 30079, 38845, 47611, 56377
3627	family with sequence similarity 96 member A	380290	3782	369644	12548	21314, 30080, 38846, 47612, 56378
3628	family with sequence similarity 96, member A	300030	3783	300030	12549	21315, 30081, 38847, 47613, 56379
3629	family with sequence similarity 96, member A	557835	3784	454079	12550	21316, 30082, 38848, 47614, 56380
3630	family with sequence similarity 98, member A	238823	3785	238823	12551	21317, 30083, 38849, 47615, 56381
3631	family with sequence similarity 98, member A	395190	3786	378617	12552	21318, 30084, 38850, 47616, 56382

3632	family with sequence similarity 98, member A	441530	3787	408716	12553	21319, 30085, 38851, 47617, 56383
3633	family with sequence similarity 98, member B	397609	3788	380734	12554	21320, 30086, 38852, 47618, 56384
3634	family with sequence similarity 98, member B	491535	3789	453166	12555	21321, 30087, 38853, 47619, 56385
3635	fasciculation and elongation protein zeta 2 (zygin II)	305852	3790	305843	12556	21322, 30088, 38854, 47620, 56386
3636	fasciculation and elongation protein zeta 2 (zygin II)	405912	3791	385112	12557	21323, 30089, 38855, 47621, 56387
3637	fasciculation and elongation protein zeta 2 (zygin II)	379245	3792	368547	12558	21324, 30090, 38856, 47622, 56388
3638	fatty acid binding protein 12	360464	3793	353650	12559	21325, 30091, 38857, 47623, 56389
3639	F-box and leucine-rich repeat protein 13	313221	3794	321927	12560	21326, 30092, 38858, 47624, 56390
3640	F-box and leucine-rich repeat protein 13	349747	3795	321552	12561	21327, 30093, 38859, 47625, 56391
3641	F-box and leucine-rich repeat protein 13	379305	3796	368607	12562	21328, 30094, 38860, 47626, 56392
3642	F-box and leucine-rich repeat protein 13	379306	3797	368608	12563	21329, 30095, 38861, 47627, 56393
3643	F-box and leucine-rich repeat protein 13	379308	3798	368610	12564	21330, 30096, 38862, 47628, 56394
3644	F-box and leucine-rich repeat protein 13	393772	3799	377367	12565	21331, 30097, 38863, 47629, 56395
3645	F-box and leucine-rich repeat protein 13	436908	3800	388608	12566	21332, 30098, 38864, 47630, 56396
3646	F-box and leucine-rich repeat protein 13	455112	3801	391550	12567	21333, 30099, 38865, 47631, 56397
3647	F-box and leucine-rich repeat protein 13	456695	3802	409716	12568	21334, 30100, 38866, 47632, 56398
3648	F-box and leucine-rich repeat protein 16	324361	3803	318674	12569	21335, 30101, 38867, 47633,

						56399
3649	F-box and leucine-rich repeat protein 16	397621	3804	380746	12570	21336, 30102, 38868, 47634, 56400
3650	F-box and leucine-rich repeat protein 18	297035	3805	297035	12571	21337, 30103, 38869, 47635, 56401
3651	F-box and leucine-rich repeat protein 18	312577	3806	311990	12572	21338, 30104, 38870, 47636, 56402
3652	F-box and leucine-rich repeat protein 18	382368	3807	371805	12573	21339, 30105, 38871, 47637, 56403
3653	F-box and leucine-rich repeat protein 18	453700	3808	444797	12574	21340, 30106, 38872, 47638, 56404
3654	F-box and leucine-rich repeat protein 22	360587	3809	353794	12575	21341, 30107, 38873, 47639, 56405
3655	F-box and leucine-rich repeat protein 6	331890	3810	330098	12576	21342, 30108, 38874, 47640, 56406
3656	F-box and leucine-rich repeat protein 6	455319	3811	403873	12577	21343, 30109, 38875, 47641, 56407
3657	F-box and leucine-rich repeat protein 8	258200	3812	258200	12578	21344, 30110, 38876, 47642, 56408
3658	F-box and leucine-rich repeat protein 8	519378	3813	430027	12579	21345, 30111, 38877, 47643, 56409
3659	F-box and leucine-rich repeat protein 8	519917	3814	430490	12580	21346, 30112, 38878, 47644, 56410
3660	F-box and leucine-rich repeat protein 8	523893	3815	428379	12581	21347, 30113, 38879, 47645, 56411
3661	F-box and WD repeat domain containing 5	325285	3816	313034	12582	21348, 30114, 38880, 47646, 56412
3662	F-box and WD repeat domain containing 5	428398	3817	404829	12583	21349, 30115, 38881, 47647, 56413
3663	F-box and WD repeat domain containing 5	433269	3818	409102	12584	21350, 30116, 38882, 47648, 56414
3664	F-box and WD repeat domain containing 5	443788	3819	394011	12585	21351, 30117, 38883, 47649, 56415
3665	F-box and WD repeat	380339	3820	369696	12586	21352, 30118,

	domain containing 9					38884, 47650, 56416
3666	F-box and WD repeat domain containing 9	393261	3821	376945	12587	21353, 30119, 38885, 47651, 56417
3667	F-box and WD repeat domain containing 9	544494	3822	442714	12588	21354, 30120, 38886, 47652, 56418
3668	F-box protein 48	377957	3823	367193	12589	21355, 30121, 38887, 47653, 56419
3669	F-box/LRR-repeat protein 22	539570	3824	442112	12590	21356, 30122, 38888, 47654, 56420
3670	Fc fragment of IgG, low affinity IIc, receptor for (CD32) (gene/pseudogene)	543859	3825	444663	12591	21357, 30123, 38889, 47655, 56421
3671	FCH and double SH3 domains 1	435817	3826	399259	12592	21358, 30124, 38890, 47656, 56422
3672	FCH and double SH3 domains 2	311172	3827	308978	12593	21359, 30125, 38891, 47657, 56423
3673	FCH and double SH3 domains 2	409418	3828	386722	12594	21360, 30126, 38892, 47658, 56424
3674	FCH and double SH3 domains 2	409853	3829	386314	12595	21361, 30127, 38893, 47659, 56425
3675	fem-1 homolog c (C. elegans)	274457	3830	274457	12596	21362, 30128, 38894, 47660, 56426
3676	FERM and PDZ domain containing 3	276185	3831	276185	12597	21363, 30129, 38895, 47661, 56427
3677	FERM domain containing 1	283309	3832	283309	12598	21364, 30130, 38896, 47662, 56428
3678	FERM domain containing 1	440994	3833	414115	12599	21365, 30131, 38897, 47663, 56429
3679	FERM domain containing 1	537786	3834	440078	12600	21366, 30132, 38898, 47664, 56430
3680	FERM domain containing 8	317568	3835	319726	12601	21367, 30133, 38899, 47665, 56431
3681	FERM domain containing 8	416776	3836	392111	12602	21368, 30134, 38900, 47666, 56432

3682	FERM domain containing 8	525156	3837	434274	12603	21369, 30135, 38901, 47667, 56433
3683	ferredoxin-fold anticodon binding domain containing 1	260257	3838	260257	12604	21370, 30136, 38902, 47668, 56434
3684	ferredoxin-fold anticodon binding domain containing 1	542429	3839	441304	12605	21371, 30137, 38903, 47669, 56435
3685	FGGY carbohydrate kinase domain containing	303721	3840	305922	12606	21372, 30138, 38904, 47670, 56436
3686	FGGY carbohydrate kinase domain containing	413489	3841	406607	12607	21373, 30139, 38905, 47671, 56437
3687	FGGY carbohydrate kinase domain containing	371212	3842	360256	12608	21374, 30140, 38906, 47672, 56438
3688	FGGY carbohydrate kinase domain containing	371218	3843	360262	12609	21375, 30141, 38907, 47673, 56439
3689	FH2 domain containing 1	260008	3844	260008	12610	21376, 30142, 38908, 47674, 56440
3690	FH2 domain containing 1	511601	3845	427567	12611	21377, 30143, 38909, 47675, 56441
3691	fibronectin type III and SPRY domain containing 2	334574	3846	335651	12612	21378, 30144, 38910, 47676, 56442
3692	fibronectin type III and SPRY domain containing 2	561368	3847	453127	12613	21379, 30145, 38911, 47677, 56443
3693	fibronectin type III domain containing 8	158009	3848	158009	12614	21380, 30146, 38912, 47678, 56444, 61531, 61589
3694	fibrosin	287468	3849	287468	12615	21381, 30147, 38913, 47679, 56445
3695	fibrosin	395073	3850	378511	12616	21382, 30148, 38914, 47680, 56446
3696	fibrosin-like 1	261673	3851	261673	12617	21383, 30149, 38915, 47681, 56447
3697	fibrosin-like 1	434748	3852	396160	12618	21384, 30150, 38916, 47682, 56448
3698	fibrous sheath interacting	350221	3853	280236	12619	21385, 30151,

	protein 1					38917, 47683, 56449
3699	fibrous sheath interacting protein 1	559547	3854	454177	12620	21386, 30152, 38918, 47684, 56450
3700	filamin A alpha	597475	3855	471999	12621	21387, 30153, 38919, 47685, 56451
3701	filamin A interacting protein 1	237172	3856	237172	12622	21388, 30154, 38920, 47686, 56452
3702	filamin A interacting protein 1	370020	3857	359037	12623	21389, 30155, 38921, 47687, 56453
3703	filamin A interacting protein 1	393004	3858	376728	12624	21390, 30156, 38922, 47688, 56454
3704	FK506 binding protein 1C	356170	3859	348493	12625	21391, 30157, 38923, 47689, 56455
3705	FK506 binding protein 1C	370659	3860	359693	12626	21392, 30158, 38924, 47690, 56456
3706	FK506 binding protein 7	350591	3861	335194	12627	21393, 30159, 38925, 47691, 56457
3707	FK506 binding protein 7	424785	3862	413152	12628	21394, 30160, 38926, 47692, 56458
3708	FK506 binding protein 7	434643	3863	415486	12629	21395, 30161, 38927, 47693, 56459
3709	FK506 binding protein like	456854	3864	412439	12630	21396, 30162, 38928, 47694, 56460
3710	FLYWCH family member 2	293981	3865	293981	12631	21397, 30163, 38929, 47695, 56461
3711	FLYWCH family member 2	396958	3866	380159	12632	21398, 30164, 38930, 47696, 56462
3712	folate receptor 3 (gamma)	442948	3867	411161	12633	21399, 30165, 38931, 47697, 56463
3713	folate receptor 3 (gamma)	456237	3868	399235	12634	21400, 30166, 38932, 47698, 56464
3714	forkhead box D1	499003	3869	462795	12635	21401, 30167, 38933, 47699, 56465

3715	forkhead box K1	328914	3870	328720	12636	21402, 30168, 38934, 47700, 56466
3716	forkhead box K1	446823	3871	394442	12637	21403, 30169, 38935, 47701, 56467
3717	forkhead box K1	450194	3872	389711	12638	21404, 30170, 38936, 47702, 56468
3718	forkhead box K1	545598	3873	443575	12639	21405, 30171, 38937, 47703, 56469
3719	forkhead box N1	584474	3874	462876	12640	21406, 30172, 38938, 47704, 56470
3720	forkhead box P3	599169	3875	470432	12641	21407, 30173, 38939, 47705, 56471
3721	forkhead-associated (FHA) phosphopeptide binding domain 1	314740	3876	322979	12642	21408, 30174, 38940, 47706, 56472
3722	forkhead-associated (FHA) phosphopeptide binding domain 1	358897	3877	351770	12643	21409, 30175, 38941, 47707, 56473
3723	forkhead-associated (FHA) phosphopeptide binding domain 1	375999	3878	365167	12644	21410, 30176, 38942, 47708, 56474
3724	forkhead-associated (FHA) phosphopeptide binding domain 1	401090	3879	383868	12645	21411, 30177, 38943, 47709, 56475
3725	forkhead-associated (FHA) phosphopeptide binding domain 1	417793	3880	407615	12646	21412, 30178, 38944, 47710, 56476
3726	formin binding protein 1-like	260506	3881	260506	12647	21413, 30179, 38945, 47711, 56477
3727	formin binding protein 1-like	271234	3882	271234	12648	21414, 30180, 38946, 47712, 56478
3728	formin binding protein 1-like	370253	3883	359275	12649	21415, 30181, 38947, 47713, 56479
3729	formin binding protein 1-like	370256	3884	359278	12650	21416, 30182, 38948, 47714, 56480
3730	formin binding protein 1-like	424449	3885	397451	12651	21417, 30183, 38949, 47715, 56481
3731	formin binding protein 1-like	541733	3886	445735	12652	21418, 30184, 38950, 47716,

						56482
3732	formin binding protein 4	263773	3887	263773	12653	21419, 30185, 38951, 47717, 56483
3733	formin-like 2	288670	3888	288670	12654	21420, 30186, 38952, 47718, 56484
3734	formin-like 2	421344	3889	401393	12655	21421, 30187, 38953, 47719, 56485
3735	formin-like 3	293590	3890	293590	12656	21422, 30188, 38954, 47720, 56486
3736	formin-like 3	335154	3891	335655	12657	21423, 30189, 38955, 47721, 56487
3737	formin-like 3	352151	3892	344311	12658	21424, 30190, 38956, 47722, 56488
3738	formin-like 3	550488	3893	447479	12659	21425, 30191, 38957, 47723, 56489
3739	Fos39347_1Uncharacterized protein	222301	3894	222301	12660	21426, 30192, 38958, 47724, 56490
3740	FPGT-TNNI3K fusion protein isoform a	557284	3895	450895	12661	21427, 30193, 38959, 47725, 56491
3741	FPGT-TNNI3K readthrough	370899	3896	359936	12662	21428, 30194, 38960, 47726, 56492
3742	fragile histidine triad	573237	3897	461165	12663	21429, 30195, 38961, 47727, 56493
3743	fructosamine 3 kinase	300784	3898	300784	12664	21430, 30196, 38962, 47728, 56494
3744	fructosamine 3 kinase	457624	3899	387701	12665	21431, 30197, 38963, 47729, 56495
3745	fructosamine 3 kinase	536165	3900	441399	12666	21432, 30198, 38964, 47730, 56496
3746	FRY-like	264319	3901	264319	12667	21433, 30199, 38965, 47731, 56497
3747	FRY-like	358350	3902	351113	12668	21434, 30200, 38966, 47732, 56498
3748	FRY-like	503238	3903	426064	12669	21435, 30201,

						38967, 47733, 56499
3749	FRY-like	507873	3904	422408	12670	21436, 30202, 38968, 47734, 56500
3750	FRY-like	537810	3905	441114	12671	21437, 30203, 38969, 47735, 56501
3751	FSHD region gene 1 family, member B	278882	3906	278882	12672	21438, 30204, 38970, 47736, 56502
3752	FSHD region gene 1 family, member B	358464	3907	351249	12673	21439, 30205, 38971, 47737, 56503
3753	FSHD region gene 1 family, member B	439954	3908	408863	12674	21440, 30206, 38972, 47738, 56504
3754	FSHD region gene 2	569512	3909	455255	12675	21441, 30207, 38973, 47739, 56505
3755	FSHD region gene 2 family, member C	308062	3910	312299	12676	21442, 30208, 38974, 47740, 56506
3756	FtsJ RNA methyltransferase homolog 1 (E. coli)	594571	3911	471790	12677	21443, 30209, 38975, 47741, 56507
3757	FtsJ RNA methyltransferase homolog 1 (E. coli)	601551	3912	470732	12678	21444, 30210, 38976, 47742, 56508
3758	Full-length cDNA 5-PRIME end of clone CS0CAP004YO05 of Thymus of Homo sapiens (human)	338772	3913	340964	12679	21445, 30211, 38977, 47743, 56509
3759	Full-length cDNA clone CS0DK012YO09 of HeLa cells of Homo sapiens (human)Uncharacterized protein	539688	3914	438796	12680	21446, 30212, 38978, 47744, 56510
3760	fumarylacetoacetate hydrolase domain containing 1	382666	3915	372112	12681	21447, 30213, 38979, 47745, 56511
3761	fumarylacetoacetate hydrolase domain containing 1	382668	3916	372114	12682	21448, 30214, 38980, 47746, 56512
3762	fumarylacetoacetate hydrolase domain containing 1	427358	3917	398053	12683	21449, 30215, 38981, 47747, 56513
3763	fumarylacetoacetate hydrolase domain	233379	3918	233379	12684	21450, 30216, 38982, 47748,

	containing 2A					56514
3764	fumarylacetoacetate hydrolase domain containing 2A	418606	3919	390528	12685	21451, 30217, 38983, 47749, 56515
3765	fumarylacetoacetate hydrolase domain containing 2A	445649	3920	405148	12686	21452, 30218, 38984, 47750, 56516
3766	fumarylacetoacetate hydrolase domain containing 2A	447036	3921	406424	12687	21453, 30219, 38985, 47751, 56517
3767	fumarylacetoacetate hydrolase domain containing 2B	272610	3922	272610	12688	21454, 30220, 38986, 47752, 56518
3768	fumarylacetoacetate hydrolase domain containing 2B	414820	3923	410470	12689	21455, 30221, 38987, 47753, 56519
3769	fumarylacetoacetate hydrolase domain containing 2B	440566	3924	444599	12690	21456, 30222, 38988, 47754, 56520
3770	FUN14 domain containing 1	378045	3925	367284	12691	21457, 30223, 38989, 47755, 56521
3771	FXYD6-FXYD2 readthrough	532984	3926	463024	12692	21458, 30224, 38990, 47756, 56522
3772	FXYD6-FXYD2 readthrough	579800	3927	463494	12693	21459, 30225, 38991, 47757, 56523
3773	FYVE, RhoGEF and PH domain containing 5	543601	3928	445949	12694	21460, 30226, 38992, 47758, 56524
3774	G antigen 12B	361446	3929	354603	12695	21461, 30227, 38993, 47759, 56525
3775	G antigen 12C	600217	3930	469479	12696	21462, 30228, 38994, 47760, 56526
3776	G antigen 12D	600913	3931	472334	12697	21463, 30229, 38995, 47761, 56527
3777	G antigen 12F	601535	3932	471284	12698	21464, 30230, 38996, 47762, 56528
3778	G antigen 12G	601798	3933	473002	12699	21465, 30231, 38997, 47763, 56529
3779	G antigen 12I	415752	3934	391465	12700	21466, 30232, 38998, 47764, 56530
3780	G antigen 4	381700	3935	371119	12701	21467, 30233,

						38999, 47765, 56531
3781	G patch domain containing 2	366934	3936	355901	12702	21468, 30234, 39000, 47766, 56532
3782	G patch domain containing 2	366935	3937	355902	12703	21469, 30235, 39001, 47767, 56533
3783	G patch domain containing 3	361720	3938	354645	12704	21470, 30236, 39002, 47768, 56534
3784	G patch domain containing 3	374122	3939	363236	12705	21471, 30237, 39003, 47769, 56535
3785	G patch domain containing 3	445019	3940	398563	12706	21472, 30238, 39004, 47770, 56536
3786	G patch domain containing 3	450844	3941	399036	12707	21473, 30239, 39005, 47771, 56537
3787	G patch domain containing 3	536641	3942	441534	12708	21474, 30240, 39006, 47772, 56538
3788	G patch domain containing 4	334588	3943	334793	12709	21475, 30241, 39007, 47773, 56539
3789	G patch domain containing 4	368229	3944	357212	12710	21476, 30242, 39008, 47774, 56540
3790	G patch domain containing 4	368232	3945	357215	12711	21477, 30243, 39009, 47775, 56541
3791	G patch domain containing 4	438976	3946	396441	12712	21478, 30244, 39010, 47776, 56542
3792	G protein pathway suppressor 2	575474	3947	468772	12713	21479, 30245, 39011, 47777, 56543
3793	G protein regulated inducer of neurite outgrowth 2	374314	3948	363433	12714	21480, 30246, 39012, 47778, 56544
3794	G protein regulated inducer of neurite outgrowth 2	374317	3949	363436	12715	21481, 30247, 39013, 47779, 56545
3795	G protein regulated inducer of neurite outgrowth 2	572702	3950	458442	12716	21482, 30248, 39014, 47780, 56546
3796	G protein-coupled receptor kinase 4	345167	3951	264764	12717	21483, 30249, 39015, 47781, 56547

3797	G protein-coupled receptor kinase 4	398051	3952	381128	12718	21484, 30250, 39016, 47782, 56548
3798	G protein-coupled receptor kinase 4	442472	3953	392297	12719	21485, 30251, 39017, 47783, 56549
3799	G protein-coupled receptor kinase 4	504933	3954	427445	12720	21486, 30252, 39018, 47784, 56550
3800	galactosidase, beta 1-like 3	389887	3955	374537	12721	21487, 30253, 39019, 47785, 56551
3801	galactosidase, beta 1-like 3	431683	3956	396615	12722	21488, 30254, 39020, 47786, 56552
3802	gametocyte specific factor 1-like	373003	3957	362094	12723	21489, 30255, 39021, 47787, 56553
3803	gametocyte specific factor 1-like	373005	3958	362096	12724	21490, 30256, 39022, 47788, 56554
3804	ganglioside induced differentiation associated protein 2	369442	3959	358450	12725	21491, 30257, 39023, 47789, 56555
3805	ganglioside induced differentiation associated protein 2	369443	3960	358451	12726	21492, 30258, 39024, 47790, 56556
3806	ganglioside-induced differentiation-associated protein 1-like 1	262604	3961	262604	12727	21493, 30259, 39025, 47791, 56557
3807	ganglioside-induced differentiation-associated protein 1-like 1	342560	3962	341782	12728	21494, 30260, 39026, 47792, 56558
3808	ganglioside-induced differentiation-associated protein 1-like 1	372946	3963	362037	12729	21495, 30261, 39027, 47793, 56559
3809	ganglioside-induced differentiation-associated protein 1-like 1	372947	3964	362038	12730	21496, 30262, 39028, 47794, 56560
3810	ganglioside-induced differentiation-associated protein 1-like 1	372952	3965	362043	12731	21497, 30263, 39029, 47795, 56561
3811	ganglioside-induced differentiation-associated protein 1-like 1	438466	3966	392881	12732	21498, 30264, 39030, 47796, 56562
3812	ganglioside-induced differentiation-associated protein 1-like 1	445952	3967	404128	12733	21499, 30265, 39031, 47797, 56563
3813	ganglioside-induced differentiation-associated	447658	3968	391714	12734	21500, 30266, 39032, 47798,

	protein 1-like 1					56564
3814	ganglioside-induced differentiation-associated protein 1-like 1	537864	3969	440498	12735	21501, 30267, 39033, 47799, 56565
3815	ganglioside-induced differentiation-associated protein 1-like 1	545149	3970	443927	12736	21502, 30268, 39034, 47800, 56566
3816	gap junction protein alpha 8 50kDa	578156	3971	462620	12737	21503, 30269, 39035, 47801, 56567
3817	gasdermin D	262580	3972	262580	12738	21504, 30270, 39036, 47802, 56568
3818	gasdermin D	525721	3973	434452	12739	21505, 30271, 39037, 47803, 56569
3819	gasdermin D	526406	3974	433209	12740	21506, 30272, 39038, 47804, 56570
3820	gasdermin D	529854	3975	432351	12741	21507, 30273, 39039, 47805, 56571
3821	gasdermin D	533348	3976	434386	12742	21508, 30274, 39040, 47806, 56572
3822	gasdermin D	533888	3977	437065	12743	21509, 30275, 39041, 47807, 56573
3823	GATA zinc finger domain containing 1	287957	3978	287957	12744	21510, 30276, 39042, 47808, 56574
3824	GATS protein-like 1	361825	3979	354869	12745	21511, 30277, 39043, 47809, 56575
3825	GATS protein-like 2	426327	3980	452571	12746	21512, 30278, 39044, 47810, 56576
3826	GATS protein-like 3	407689	3981	384183	12747	21513, 30279, 39045, 47811, 56577
3827	GATS, stromal antigen 3 opposite strand	436886	3982	389760	12748	21514, 30280, 39046, 47812, 56578
3828	GDP-mannose pyrophosphorylase B	308375	3983	309092	12749	21515, 30281, 39047, 47813, 56579
3829	GDP-mannose pyrophosphorylase B	308388	3984	311130	12750	21516, 30282, 39048, 47814, 56580
3830	GDP-mannose	480687	3985	418565	12751	21517, 30283,

	pyrophosphorylase B					39049, 47815, 56581
3831	gem (nuclear organelle) associated protein 4	437269	3986	392460	12752	21518, 30284, 39050, 47816, 56582
3832	general transcription factor IIH polypeptide 2 44kDa	575673	3987	459636	12753	21519, 30285, 39051, 47817, 56583
3833	general transcription factor IIH polypeptide 2C	577126	3988	460630	12754	21520, 30286, 39052, 47818, 56584
3834	general transcription factor IIIA	439403	3989	393050	12755	21521, 30287, 39053, 47819, 56585
3835	general transcription factor IIIA	381140	3990	370532	12756	21522, 30288, 39054, 47820, 56586
3836	germ cell associated 1	324458	3991	320838	12757	21523, 30289, 39055, 47821, 56587
3837	germ cell associated 1	337630	3992	336816	12758	21524, 30290, 39056, 47822, 56588
3838	germ cell associated 1	351606	3993	336857	12759	21525, 30291, 39057, 47823, 56589
3839	germ cell associated 1	396302	3994	379596	12760	21526, 30292, 39058, 47824, 56590
3840	germ cell associated 1	396310	3995	379604	12761	21527, 30293, 39059, 47825, 56591
3841	germ cell associated 1	405543	3996	384842	12762	21528, 30294, 39060, 47826, 56592
3842	germ cell associated 1	432710	3997	405032	12763	21529, 30295, 39061, 47827, 56593
3843	germ cell associated 1	457134	3998	398384	12764	21530, 30296, 39062, 47828, 56594
3844	germ cell associated 1	537302	3999	441718	12765	21531, 30297, 39063, 47829, 56595
3845	glia maturation factor, beta	354747	4000	346789	12766	21532, 30298, 39064, 47830, 56596
3846	glia maturation factor, beta	358056	4001	350757	12767	21533, 30299, 39065, 47831, 56597

3847	glomulin, FKBP associated protein	370360	4002	359385	12768	21534, 30300, 39066, 47832, 56598
3848	glomulin, FKBP associated protein	534881	4003	440156	12769	21535, 30301, 39067, 47833, 56599
3849	glucosaminyl (N-acetyl) transferase 6	379591	4004	368910	12770	21536, 30302, 39068, 47834, 56600
3850	glucosaminyl (N-acetyl) transferase 6	417671	4005	398277	12771	21537, 30303, 39069, 47835, 56601
3851	glucosidase, beta, acid pseudogene 1	313929	4006	316400	12772	21538, 30304, 39070, 47836, 56602
3852	glucosidase, beta, acid pseudogene 1	368374	4007	357358	12773	21539, 30305, 39071, 47837, 56603
3853	glutamate decarboxylase-like 1	282538	4008	282538	12774	21540, 30306, 39072, 47838, 56604
3854	glutamate receptor ionotropic N-methyl D-aspartate-associated protein 1 (glutamate binding)	569564	4009	456043	12775	21541, 30307, 39073, 47839, 56605
3855	glutamate-rich 1	262109	4010	262109	12776	21542, 30308, 39074, 47840, 56606
3856	glutamate-rich 1	543819	4011	439635	12777	21543, 30309, 39075, 47841, 56607
3857	glutamine and serine rich 1	78652	4012	78652	12778	21544, 30310, 39076, 47842, 56608, 61532, 61590
3858	glutamine and serine rich 1	399302	4013	382241	12779	21545, 30311, 39077, 47843, 56609
3859	glutamine and serine rich 1	528155	4014	436870	12780	21546, 30312, 39078, 47844, 56610
3860	glutamine rich 2	262765	4015	262765	12781	21547, 30313, 39079, 47845, 56611
3861	glutamine rich 2	301613	4016	301613	12782	21548, 30314, 39080, 47846, 56612
3862	glutamine-rich 1	357496	4017	350094	12783	21549, 30315, 39081, 47847, 56613

3863	glutamine-rich 1	395443	4018	378830	12784	21550, 30316, 39082, 47848, 56614
3864	glutamine-rich 1	424300	4019	412890	12785	21551, 30317, 39083, 47849, 56615
3865	glutaredoxin, cysteine rich 2	377976	4020	367214	12786	21552, 30318, 39084, 47850, 56616
3866	glutathione peroxidase 6 (olfactory)	361902	4021	354581	12787	21553, 30319, 39085, 47851, 56617
3867	glutathione peroxidase 6 (olfactory)	399282	4022	382223	12788	21554, 30320, 39086, 47852, 56618
3868	glycerol kinase 5 (putative)	392993	4023	418001	12789	21555, 30321, 39087, 47853, 56619
3869	glycerol kinase 5 (putative)	544571	4024	440860	12790	21556, 30322, 39088, 47854, 56620
3870	glycogenin 2 pseudogene 1	357871	4025	350540	12791	21557, 30323, 39089, 47855, 56621
3871	glycogenin 2 pseudogene 1	382963	4026	372423	12792	21558, 30324, 39090, 47856, 56622
3872	glycogenin 2 pseudogene 1	382965	4027	372425	12793	21559, 30325, 39091, 47857, 56623
3873	glycogenin 2 pseudogene 1	382966	4028	372426	12794	21560, 30326, 39092, 47858, 56624
3874	glycoprotein VI (platelet)	571038	4029	460456	12795	21561, 30327, 39093, 47859, 56625
3875	glycoprotein VI (platelet)	571588	4030	459854	12796	21562, 30328, 39094, 47860, 56626
3876	glycoprotein VI (platelet)	571871	4031	458353	12797	21563, 30329, 39095, 47861, 56627
3877	glycoprotein VI (platelet)	572667	4032	461472	12798	21564, 30330, 39096, 47862, 56628
3878	glycoprotein VI (platelet)	573764	4033	460988	12799	21565, 30331, 39097, 47863, 56629
3879	glycoprotein VI (platelet)	573811	4034	461262	12800	21566, 30332, 39098, 47864,

						56630
3880	glycoprotein VI (platelet)	574603	4035	460778	12801	21567, 30333, 39099, 47865, 56631
3881	glycoprotein VI (platelet)	575740	4036	458526	12802	21568, 30334, 39100, 47866, 56632
3882	glycosyltransferase 8 domain containing 1	266014	4037	266014	12803	21569, 30335, 39101, 47867, 56633
3883	glycosyltransferase 8 domain containing 1	394783	4038	378263	12804	21570, 30336, 39102, 47868, 56634
3884	glycosyltransferase 8 domain containing 1	394786	4039	378266	12805	21571, 30337, 39103, 47869, 56635
3885	glycosyltransferase 8 domain containing 1	407584	4040	385730	12806	21572, 30338, 39104, 47870, 56636
3886	glycosyltransferase 8 domain containing 1	464705	4041	417858	12807	21573, 30339, 39105, 47871, 56637
3887	glycosyltransferase 8 domain containing 1	478968	4042	419612	12808	21574, 30340, 39106, 47872, 56638
3888	glycosyltransferase 8 domain containing 1	479553	4043	417713	12809	21575, 30341, 39107, 47873, 56639
3889	glycosyltransferase 8 domain containing 1	487642	4044	420462	12810	21576, 30342, 39108, 47874, 56640
3890	glycosyltransferase 8 domain containing 1	489119	4045	417551	12811	21577, 30343, 39109, 47875, 56641
3891	glycosyltransferase 8 domain containing 1	491606	4046	418853	12812	21578, 30344, 39110, 47876, 56642
3892	glycosyltransferase 8 domain containing 1	497436	4047	420286	12813	21579, 30345, 39111, 47877, 56643
3893	glycosyltransferase 8 domain containing 1	497953	4048	419094	12814	21580, 30346, 39112, 47878, 56644
3894	glyoxalase domain containing 5	303227	4049	302552	12815	21581, 30347, 39113, 47879, 56645
3895	glyoxalase domain containing 5	445229	4050	409523	12816	21582, 30348, 39114, 47880, 56646
3896	golgin A6 family, member	290438	4051	290438	12817	21583, 30349,

	A					39115, 47881, 56647
3897	golgin A6 family, member B	421285	4052	408132	12818	21584, 30350, 39116, 47882, 56648
3898	golgin A6 family, member C	300576	4053	300576	12819	21585, 30351, 39117, 47883, 56649
3899	golgin A6 family, member D	434739	4054	391085	12820	21586, 30352, 39118, 47884, 56650
3900	golgin A6 family-like 1	316397	4055	320207	12821	21587, 30353, 39119, 47885, 56651
3901	golgin A6 family-like 1	355145	4056	347269	12822	21588, 30354, 39120, 47886, 56652
3902	golgin A6 family-like 10	430944	4057	390083	12823	21589, 30355, 39121, 47887, 56653
3903	golgin A6 family-like 10	439287	4058	388606	12824	21590, 30356, 39122, 47888, 56654
3904	golgin A6 family-like 2	312015	4059	307928	12825	21591, 30357, 39123, 47889, 56655
3905	golgin A6 family-like 2	345070	4060	344626	12826	21592, 30358, 39124, 47890, 56656
3906	golgin A6 family-like 4	422563	4061	389305	12827	21593, 30359, 39125, 47891, 56657
3907	golgin A6 family-like 4	424966	4062	402444	12828	21594, 30360, 39126, 47892, 56658
3908	golgin A6 family-like 6	427390	4063	398615	12829	21595, 30361, 39127, 47893, 56659
3909	golgin A6 family-like 9	300515	4064	300515	12830	21596, 30362, 39128, 47894, 56660
3910	golgin A8 family, member A	359187	4065	352111	12831	21597, 30363, 39129, 47895, 56661
3911	golgin A8 family, member A	360553	4066	353755	12832	21598, 30364, 39130, 47896, 56662
3912	golgin A8 family, member A	432566	4067	402791	12833	21599, 30365, 39131, 47897, 56663

3913	golgin A8 family, member A	543376	4068	438613	12834	21600, 30366, 39132, 47898, 56664
3914	golgin A8 family, member I, pseudogene	450802	4069	399637	12835	21601, 30367, 39133, 47899, 56665
3915	golgin A8 family, member J	341650	4070	345217	12836	21602, 30368, 39134, 47900, 56666
3916	Golgin subfamily A member 6-like protein 9	358583	4071	351392	12837	21603, 30369, 39135, 47901, 56667
3917	Golgin subfamily A member 8-like protein 2	327271	4072	323217	12838	21604, 30370, 39136, 47902, 56668
3918	Golgin subfamily A member 8-like protein 2	544495	4073	440596	12839	21605, 30371, 39137, 47903, 56669
3919	GPN-loop GTPase 2	374131	4074	363246	12840	21606, 30372, 39138, 47904, 56670
3920	GPN-loop GTPase 2	374133	4075	363248	12841	21607, 30373, 39139, 47905, 56671
3921	GPN-loop GTPase 2	374135	4076	363250	12842	21608, 30374, 39140, 47906, 56672
3922	GPN-loop GTPase 2	431781	4077	408257	12843	21609, 30375, 39141, 47907, 56673
3923	GPN-loop GTPase 3	228827	4078	228827	12844	21610, 30376, 39142, 47908, 56674
3924	GPN-loop GTPase 3	537466	4079	443068	12845	21611, 30377, 39143, 47909, 56675
3925	GPN-loop GTPase 3	543199	4080	442770	12846	21612, 30378, 39144, 47910, 56676
3926	GPRIN family member 3	333209	4081	328672	12847	21613, 30379, 39145, 47911, 56677
3927	GRAM domain containing 3	285689	4082	285689	12848	21614, 30380, 39146, 47912, 56678
3928	GRAM domain containing 3	542322	4083	441876	12849	21615, 30381, 39147, 47913, 56679
3929	GRAM domain containing 3	543198	4084	442902	12850	21616, 30382, 39148, 47914,

						56680
3930	GRAM domain containing 3	543367	4085	445954	12851	21617, 30383, 39149, 47915, 56681
3931	GRAM domain containing 3	544396	4086	444049	12852	21618, 30384, 39150, 47916, 56682
3932	GRAM domain containing 3	511134	4087	426088	12853	21619, 30385, 39151, 47917, 56683
3933	GRAM domain containing 3	513040	4088	426120	12854	21620, 30386, 39152, 47918, 56684
3934	GRB2-associated binding protein 3	369575	4089	358588	12855	21621, 30387, 39153, 47919, 56685
3935	GRB2-associated binding protein 3	424127	4090	399588	12856	21622, 30388, 39154, 47920, 56686
3936	GRB2-associated binding protein family, member 4	400588	4091	383431	12857	21623, 30389, 39155, 47921, 56687
3937	GRB2-related adapter protein-like	344415	4092	437409	12858	21624, 30390, 39156, 47922, 56688
3938	GRB2-related adaptor protein	395635	4093	378997	12859	21625, 30391, 39157, 47923, 56689
3939	GRIK1 antisense RNA 2 (non-protein coding)	333765	4094	330087	12860	21626, 30392, 39158, 47924, 56690
3940	growth hormone regulated TBC protein 1	326039	4095	321850	12861	21627, 30393, 39159, 47925, 56691
3941	growth hormone regulated TBC protein 1	375430	4096	364579	12862	21628, 30394, 39160, 47926, 56692
3942	growth hormone regulated TBC protein 1	375431	4097	364580	12863	21629, 30395, 39161, 47927, 56693
3943	Gse1 coiled-coil protein homolog (mouse)	253458	4098	253458	12864	21630, 30396, 39162, 47928, 56694
3944	Gse1 coiled-coil protein homolog (mouse)	405402	4099	384839	12865	21631, 30397, 39163, 47929, 56695
3945	GTPase activating Rap/RanGAP domain-like 3	314904	4100	313970	12866	21632, 30398, 39164, 47930, 56696
3946	GTPase activating	373387	4101	362485	12867	21633, 30399,

	Rap/RanGAP domain-like 3					39165, 47931, 56697
3947	GTPase activating Rap/RanGAP domain-like 3	373399	4102	362497	12868	21634, 30400, 39166, 47932, 56698
3948	GTPase activating Rap/RanGAP domain-like 3	435213	4103	396205	12869	21635, 30401, 39167, 47933, 56699
3949	GTPase activating Rap/RanGAP domain-like 3	439286	4104	400579	12870	21636, 30402, 39168, 47934, 56700
3950	GTPase, IMAP family member 7	313543	4105	315474	12871	21637, 30403, 39169, 47935, 56701
3951	guanine nucleotide binding protein (G protein), gamma 5 pseudogene 2	372054	4106	361124	12872	21638, 30404, 39170, 47936, 56702
3952	gypsy retrotransposon integrase 1	399004	4107	381970	12873	21639, 30405, 39171, 47937, 56703
3953	gypsy retrotransposon integrase 1	508629	4108	427162	12874	21640, 30406, 39172, 47938, 56704
3954	haloacid dehalogenase-like hydrolase domain containing 1	381077	4109	370467	12875	21641, 30407, 39173, 47939, 56705
3955	haloacid dehalogenase-like hydrolase domain containing 1	424830	4110	396452	12876	21642, 30408, 39174, 47940, 56706
3956	haloacid dehalogenase-like hydrolase domain containing 1	540122	4111	441208	12877	21643, 30409, 39175, 47941, 56707
3957	haloacid dehalogenase-like hydrolase domain containing 1	544385	4112	437759	12878	21644, 30410, 39176, 47942, 56708
3958	haloacid dehalogenase-like hydrolase domain containing 1	412827	4113	406260	12879	21645, 30411, 39177, 47943, 56709
3959	haloacid dehalogenase-like hydrolase domain containing 2	300605	4114	300605	12880	21646, 30412, 39178, 47944, 56710
3960	harbinger transposase derived 1	532281	4115	436232	12881	21647, 30413, 39179, 47945, 56711
3961	HCG1774533, isoform CRA_aPRO2268Uncharacterized protein	399333	4116	382270	12882	21648, 30414, 39180, 47946, 56712
3962	HCG1782999PRO0943Uncharacterized protein	332881	4117	332290	12883	21649, 30415, 39181, 47947, 56713

3963	HCG1785179PRO1787Uncharacterized protein	330381	4118	332722	12884	21650, 30416, 39182, 47948, 56714
3964	HCG1786590PRO2533Uncharacterized protein	422482	4119	397622	12885	21651, 30417, 39183, 47949, 56715
3965	HCG1806964, isoform CRA_aUncharacterized proteincDNA FLJ55426cDNA, FLJ79414	445466	4120	416653	12886	21652, 30418, 39184, 47950, 56716
3966	HCG1816754LOH12CR2	381800	4121	371220	12887	21653, 30419, 39185, 47951, 56717
3967	HCG19535Hypothetical gene supported by AK027125Uncharacterized proteincDNA FLJ54628	433511	4122	399632	12888	21654, 30420, 39186, 47952, 56718
3968	HCG1980662Uncharacterized protein	446344	4123	392909	12889	21655, 30421, 39187, 47953, 56719
3969	HCG1981372, isoform CRA_cNovel proteinUncharacterized protein	425492	4124	409862	12890	21656, 30422, 39188, 47954, 56720
3970	HCG1985372Uncharacterized proteincDNA FLJ37541 fis, clone BRCAN2026340	535173	4125	441567	12891	21657, 30423, 39189, 47955, 56721
3971	HCG1987623LOC651900 protein	397549	4126	380682	12892	21658, 30424, 39190, 47956, 56722
3972	HCG1990547Uncharacterized protein	310542	4127	312142	12893	21659, 30425, 39191, 47957, 56723
3973	HCG1992246KBTBD4 protein	450908	4128	403688	12894	21660, 30426, 39192, 47958, 56724
3974	HCG1992346Uncharacterized proteincDNA FLJ90757 fis, clone SKNMC1000014	542745	4129	442580	12895	21661, 30427, 39193, 47959, 56725
3975	HCG1995562Uncharacterized protein	457234	4130	401549	12896	21662, 30428, 39194, 47960, 56726
3976	HCG2000535Uncharacterized proteincDNA FLJ32177 fis, clone PLACE6001294	397094	4131	380282	12897	21663, 30429, 39195, 47961, 56727
3977	HCG2008078MGC45922 proteinUncharacterized protein	326989	4132	315232	12898	21664, 30430, 39196, 47962, 56728
3978	HCG2009141PRO2397Uncharacterized protein	391679	4133	375561	12899	21665, 30431, 39197, 47963,

						56729
3979	HCG2018282Novel protein (FLJ32154)Uncharacterized protein	370520	4134	359551	12900	21666, 30432, 39198, 47964, 56730
3980	HCG2032337PRO1848Uncharacterized protein	391369	4135	375181	12901	21667, 30433, 39199, 47965, 56731
3981	HCG2043693Uncharacterized protein	537552	4136	440123	12902	21668, 30434, 39200, 47966, 56732
3982	HCG2045177Uncharacterized proteincDNA FLJ45743 fis, clone KIDNE2016464	382897	4137	372353	12903	21669, 30435, 39201, 47967, 56733
3983	HCG37415PRO1914Uncharacterized protein	391457	4138	375288	12904	21670, 30436, 39202, 47968, 56734
3984	HD domain containing 3	330334	4139	330721	12905	21671, 30437, 39203, 47969, 56735
3985	HD domain containing 3	394272	4140	377814	12906	21672, 30438, 39204, 47970, 56736
3986	headcase homolog (Drosophila)	367658	4141	356630	12907	21673, 30439, 39205, 47971, 56737
3987	HEAT repeat containing 2	297440	4142	297440	12908	21674, 30440, 39206, 47972, 56738
3988	HEAT repeat containing 2	313147	4143	321451	12909	21675, 30441, 39207, 47973, 56739
3989	HEAT repeat containing 2	537862	4144	443677	12910	21676, 30442, 39208, 47974, 56740
3990	HEAT repeat containing 3	299192	4145	299192	12911	21677, 30443, 39209, 47975, 56741
3991	HEAT repeat containing 4	334988	4146	335447	12912	21678, 30444, 39210, 47976, 56742
3992	HEAT repeat containing 4	553558	4147	450444	12913	21679, 30445, 39211, 47977, 56743
3993	HEAT repeat containing 4	556455	4148	452407	12914	21680, 30446, 39212, 47978, 56744
3994	HEAT repeat containing 4	557603	4149	451367	12915	21681, 30447, 39213, 47979, 56745
3995	HEAT repeat containing 4	560393	4150	453597	12916	21682, 30448,

						39214, 47980, 56746
3996	HEAT repeat containing 5A	389961	4151	374611	12917	21683, 30449, 39215, 47981, 56747
3997	HEAT repeat containing 5A	404677	4152	384646	12918	21684, 30450, 39216, 47982, 56748
3998	HEAT repeat containing 5A	439348	4153	405407	12919	21685, 30451, 39217, 47983, 56749
3999	HEAT repeat containing 5A	439727	4154	408681	12920	21686, 30452, 39218, 47984, 56750
4000	HEAT repeat containing 5A	543095	4155	437968	12921	21687, 30453, 39219, 47985, 56751
4001	HEAT repeat containing 5B	233099	4156	233099	12922	21688, 30454, 39220, 47986, 56752
4002	HEAT repeat containing 5B	354531	4157	346531	12923	21689, 30455, 39221, 47987, 56753
4003	HEAT repeat containing 5B	424416	4158	389819	12924	21690, 30456, 39222, 47988, 56754
4004	HEAT repeat containing 6	184956	4159	184956	12925	21691, 30457, 39223, 47989, 56755
4005	HEAT repeat containing 6	393017	4160	376740	12926	21692, 30458, 39224, 47990, 56756
4006	HEAT repeat containing 7A	326134	4161	321737	12927	21693, 30459, 39225, 47991, 56757
4007	HEAT repeat containing 7A	356585	4162	348993	12928	21694, 30460, 39226, 47992, 56758
4008	HEAT repeat containing 7A	398656	4163	381649	12929	21695, 30461, 39227, 47993, 56759
4009	HEAT repeat containing 7A	420663	4164	398180	12930	21696, 30462, 39228, 47994, 56760
4010	HEAT repeat containing 7A	423230	4165	388174	12931	21697, 30463, 39229, 47995, 56761
4011	HEAT repeat containing 7A	528919	4166	435565	12932	21698, 30464, 39230, 47996, 56762

4012	HEAT repeat containing 7A	544576	4167	437866	12933	21699, 30465, 39231, 47997, 56763
4013	HEAT repeat containing 7A	568089	4168	455272	12934	21700, 30466, 39232, 47998, 56764
4014	HEAT repeat family member 7B2	296803	4169	296803	12935	21701, 30467, 39233, 47999, 56765
4015	HEAT repeat family member 7B2	399564	4170	382476	12936	21702, 30468, 39234, 48000, 56766
4016	heat shock factor binding protein 1-like 1	451882	4171	414236	12937	21703, 30469, 39235, 48001, 56767
4017	Heat shock protein beta-2	573863	4172	459486	12938	21704, 30470, 39236, 48002, 56768
4018	heat shock protein family B (small), member 11	194214	4173	194214	12939	21705, 30471, 39237, 48003, 56769
4019	heat shock protein family B (small), member 11	371376	4174	360427	12940	21706, 30472, 39238, 48004, 56770
4020	heat shock protein family B (small), member 11	371377	4175	360428	12941	21707, 30473, 39239, 48005, 56771
4021	heat shock protein family B (small), member 11	371378	4176	360429	12942	21708, 30474, 39240, 48006, 56772
4022	hect domain and RLD 2 pseudogene 4	433784	4177	402538	12943	21709, 30475, 39241, 48007, 56773
4023	HECT domain containing 1	261312	4178	261312	12944	21710, 30476, 39242, 48008, 56774
4024	HECT domain containing 1	399323	4179	382263	12945	21711, 30477, 39243, 48009, 56775
4025	HECT domain containing 1	399332	4180	382269	12946	21712, 30478, 39244, 48010, 56776
4026	HECT domain containing 1	553700	4181	450697	12947	21713, 30479, 39245, 48011, 56777
4027	HECT domain containing 1	556224	4182	452015	12948	21714, 30480, 39246, 48012, 56778
4028	HECT domain containing 2	298068	4183	298068	12949	21715, 30481, 39247, 48013,

						56779
4029	HECT domain containing 2	371667	4184	360731	12950	21716, 30482, 39248, 48014, 56780
4030	HECT domain containing 2	371668	4185	360732	12951	21717, 30483, 39249, 48015, 56781
4031	HECT domain containing 2	371681	4186	360746	12952	21718, 30484, 39250, 48016, 56782
4032	HECT domain containing 2	446394	4187	401023	12953	21719, 30485, 39251, 48017, 56783
4033	HECT domain containing 2	536715	4188	439687	12954	21720, 30486, 39252, 48018, 56784
4034	helicase, POLQ-like	295488	4189	295488	12955	21721, 30487, 39253, 48019, 56785
4035	hematological and neurological expressed 1	356033	4190	348316	12956	21722, 30488, 39254, 48020, 56786
4036	hematological and neurological expressed 1	392566	4191	440912	12957	21723, 30489, 39255, 48021, 56787
4037	hematological and neurological expressed 1	405458	4192	384619	12958	21724, 30490, 39256, 48022, 56788
4038	hematological and neurological expressed 1	409753	4193	387059	12959	21725, 30491, 39257, 48023, 56789
4039	hematopoietic SH2 domain-containing protein	593154	4194	464833	12960	21726, 30492, 39258, 48024, 56790
4040	hemicentin 2	302481	4195	305590	12961	21727, 30493, 39259, 48025, 56791
4041	Hemicentin-2	277491	4196	277491	12962	21728, 30494, 39260, 48026, 56792
4042	Hepatocellular carcinoma-associated antigen HCA25aUncharacterized protein	444227	4197	416564	12963	21729, 30495, 39261, 48027, 56793
4043	hepatoma derived growth factor-like 1	230012	4198	230012	12964	21730, 30496, 39262, 48028, 56794
4044	hepatoma derived growth factor-like 1	510882	4199	442129	12965	21731, 30497, 39263, 48029, 56795

4045	HERV-H LTR-associating 3	359875	4200	352938	12966	21732, 30498, 39264, 48030, 56796
4046	HERV-H LTR-associating 3	361764	4201	354815	12967	21733, 30499, 39265, 48031, 56797
4047	HERV-H LTR-associating 3	370940	4202	359978	12968	21734, 30500, 39266, 48032, 56798
4048	HERV-H LTR-associating 3	432224	4203	395155	12969	21735, 30501, 39267, 48033, 56799
4049	HERV-H LTR-associating 3	531950	4204	431678	12970	21736, 30502, 39268, 48034, 56800
4050	heterogeneous nuclear ribonucleoprotein H2 (H')	602060	4205	468882	12971	21737, 30503, 39269, 48035, 56801
4051	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	294696	4206	294696	12972	21738, 30504, 39270, 48036, 56802
4052	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	370421	4207	359450	12973	21739, 30505, 39271, 48037, 56803
4053	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	370424	4208	359453	12974	21740, 30506, 39272, 48038, 56804
4054	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	370425	4209	359454	12975	21741, 30507, 39273, 48039, 56805
4055	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	455133	4210	409827	12976	21742, 30508, 39274, 48040, 56806
4056	HFM1, ATP-dependent DNA helicase homolog (S. cerevisiae)	541820	4211	440351	12977	21743, 30509, 39275, 48041, 56807
4057	HIG1 hypoxia inducible domain family, member 1C	398455	4212	381473	12978	21744, 30510, 39276, 48042, 56808
4058	high mobility group box 3	593327	4213	472199	12979	21745, 30511, 39277, 48043, 56809
4059	high mobility group nucleosomal binding domain 2 pseudogene 42	397765	4214	444677	12980	21746, 30512, 39278, 48044, 56810
4060	hippocalcin like 4	372844	4215	361935	12981	21747, 30513, 39279, 48045, 56811
4061	hippocalcin like 4	450300	4216	389363	12982	21748, 30514, 39280, 48046,

						56812
4062	histo-blood group ABO system transferase	319878	4217	439154	12983	21749, 30515, 39281, 48047, 56813
4063	histocompatibility (minor) HB-1	289448	4218	289448	12984	21750, 30516, 39282, 48048, 56814
4064	histone deacetylase 6	595349	4219	470544	12985	21751, 30517, 39283, 48049, 56815
4065	histone H4	578186	4220	462667	12986	21752, 30518, 39284, 48050, 56816
4066	histone H4	579512	4221	462355	12987	21753, 30519, 39285, 48051, 56817
4067	hormonally up-regulated Neu-associated kinase	270112	4222	270112	12988	21754, 30520, 39286, 48052, 56818
4068	HRAS-like suppressor family member 5	539221	4223	443873	12989	21755, 30521, 39287, 48053, 56819
4069	HRAS-like suppressor family member 5	540857	4224	444809	12990	21756, 30522, 39288, 48054, 56820
4070	HRAS-like suppressor family, member 5	301790	4225	301790	12991	21757, 30523, 39289, 48055, 56821
4071	huntingtin interacting protein 1	576304	4226	459517	12992	21758, 30524, 39290, 48056, 56822
4072	hyaluronoglucosaminidase 1	570958	4227	459254	12993	21759, 30525, 39291, 48057, 56823
4073	hyaluronoglucosaminidase 1	572970	4228	461261	12994	21760, 30526, 39292, 48058, 56824
4074	hyaluronoglucosaminidase 2	571614	4229	460851	12995	21761, 30527, 39293, 48059, 56825
4075	hyaluronoglucosaminidase 2	572136	4230	458862	12996	21762, 30528, 39294, 48060, 56826
4076	hyaluronoglucosaminidase 3	572211	4231	458620	12997	21763, 30529, 39295, 48061, 56827
4077	hydroxyacylglutathione hydrolase-like	389701	4232	374351	12998	21764, 30530, 39296, 48062, 56828
4078	hydroxyacylglutathione	389703	4233	374353	12999	21765, 30531,

	hydrolase-like					39297, 48063, 56829
4079	hydroxyacylglutathione hydrolase-like	549114	4234	447170	13000	21766, 30532, 39298, 48064, 56830
4080	Hydroxyacyl-thioester dehydratase type 2, mitochondrial	544156	4235	437652	13001	21767, 30533, 39299, 48065, 56831
4081	hydroxycarboxylic acid receptor 3	528880	4236	436714	13002	21768, 30534, 39300, 48066, 56832
4082	hydroxymethylbilane synthase	571030	4237	461361	13003	21769, 30535, 39301, 48067, 56833
4083	hydroxymethylbilane synthase	575587	4238	460754	13004	21770, 30536, 39302, 48068, 56834
4084	hydroxymethylbilane synthase	575888	4239	461906	13005	21771, 30537, 39303, 48069, 56835
4085	hydroxypyruvate isomerase (putative)	372425	4240	361502	13006	21772, 30538, 39304, 48070, 56836
4086	hydroxypyruvate isomerase (putative)	372426	4241	361503	13007	21773, 30539, 39305, 48071, 56837
4087	hydroxypyruvate isomerase (putative)	372430	4242	361507	13008	21774, 30540, 39306, 48072, 56838
4088	hydroxypyruvate isomerase (putative)	372432	4243	361509	13009	21775, 30541, 39307, 48073, 56839
4089	hydroxypyruvate isomerase (putative)	372434	4244	361511	13010	21776, 30542, 39308, 48074, 56840
4090	IgA-inducing protein homolog (Bos taurus)	333305	4245	327344	13011	21777, 30543, 39309, 48075, 56841
4091	IgLON family member 5	270642	4246	270642	13012	21778, 30544, 39310, 48076, 56842
4092	immediate early response 5-like	372491	4247	361569	13013	21779, 30545, 39311, 48077, 56843
4093	immunity-related GTPase family, cinema	244314	4248	244314	13014	21780, 30546, 39312, 48078, 56844
4094	immunity-related GTPase family, Q	422989	4249	387535	13015	21781, 30547, 39313, 48079, 56845

4095	immunoglobulin superfamily, member 22	513874	4250	421191	13016	21782, 30548, 39314, 48080, 56846
4096	immunoglobulin-like and fibronectin type III domain containing 1	295591	4251	295591	13017	21783, 30549, 39315, 48081, 56847
4097	immunoglobulin-like and fibronectin type III domain containing 1	335211	4252	334714	13018	21784, 30550, 39316, 48082, 56848
4098	immunoglobulin-like and fibronectin type III domain containing 1	451870	4253	398386	13019	21785, 30551, 39317, 48083, 56849
4099	immunoresponsive 1 homolog (mouse)	377462	4254	366682	13020	21786, 30552, 39318, 48084, 56850
4100	immunoresponsive 1 homolog (mouse)	449753	4255	401584	13021	21787, 30553, 39319, 48085, 56851
4101	Impact homolog (mouse)	284202	4256	284202	13022	21788, 30554, 39320, 48086, 56852
4102	Importin subunit alpha-2-like protein	400873	4257	383670	13023	21789, 30555, 39321, 48087, 56853
4103	inactivation escape 1 (non-protein coding)	456273	4258	416095	13024	21790, 30556, 39322, 48088, 56854
4104	inositol polyphosphate-4-phosphatase, type II, 105kDa	262992	4259	262992	13025	21791, 30557, 39323, 48089, 56855
4105	inositol polyphosphate-4-phosphatase, type II, 105kDa	308502	4260	308441	13026	21792, 30558, 39324, 48090, 56856
4106	inositol polyphosphate-4-phosphatase, type II, 105kDa	503927	4261	422052	13027	21793, 30559, 39325, 48091, 56857
4107	inositol polyphosphate-4-phosphatase, type II, 105kDa	506217	4262	424057	13028	21794, 30560, 39326, 48092, 56858
4108	inositol polyphosphate-4-phosphatase, type II, 105kDa	506788	4263	426957	13029	21795, 30561, 39327, 48093, 56859
4109	inositol polyphosphate-4-phosphatase, type II, 105kDa	507861	4264	426897	13030	21796, 30562, 39328, 48094, 56860
4110	inositol polyphosphate-4-phosphatase, type II, 105kDa	508116	4265	423954	13031	21797, 30563, 39329, 48095, 56861
4111	inositol polyphosphate-4-phosphatase, type II,	509777	4266	422793	13032	21798, 30564, 39330, 48096,

	105kDa					56862
4112	inositol polyphosphate-4-phosphatase, type II, 105kDa	510812	4267	427250	13033	21799, 30565, 39331, 48097, 56863
4113	inositol polyphosphate-4-phosphatase, type II, 105kDa	513000	4268	425487	13034	21800, 30566, 39332, 48098, 56864
4114	inositol polyphosphate-4-phosphatase, type II, 105kDa	542702	4269	446046	13035	21801, 30567, 39333, 48099, 56865
4115	inositol polyphosphate-4-phosphatase, type II, 105kDa	543161	4270	445119	13036	21802, 30568, 39334, 48100, 56866
4116	inositol polyphosphate-5-phosphatase F	361976	4271	354519	13037	21803, 30569, 39335, 48101, 56867
4117	inositol polyphosphate-5-phosphatase F	369080	4272	358076	13038	21804, 30570, 39336, 48102, 56868
4118	inositol polyphosphate-5-phosphatase F	369081	4273	358077	13039	21805, 30571, 39337, 48103, 56869
4119	inositol polyphosphate-5-phosphatase F	369083	4274	358079	13040	21806, 30572, 39338, 48104, 56870
4120	insulin-like growth factor 2 antisense (non-protein coding)	381363	4275	370768	13041	21807, 30573, 39339, 48105, 56871
4121	integrator complex subunit 3	576030	4276	460221	13042	21808, 30574, 39340, 48106, 56872
4122	integrin alpha FG-GAP repeat containing 2	228799	4277	228799	13043	21809, 30575, 39341, 48107, 56873
4123	integrin alpha FG-GAP repeat containing 2	419778	4278	401103	13044	21810, 30576, 39342, 48108, 56874
4124	integrin alpha FG-GAP repeat containing 2	542548	4279	437870	13045	21811, 30577, 39343, 48109, 56875
4125	integrin beta 1 binding protein 3	168977	4280	168977	13046	21812, 30578, 39344, 48110, 56876, 61533, 61591
4126	integrin beta 1 binding protein 3	395034	4281	378475	13047	21813, 30579, 39345, 48111, 56877
4127	interferon-induced protein with tetratricopeptide repeats 1B	371809	4282	360874	13048	21814, 30580, 39346, 48112, 56878

4128	interferon-induced protein with tetratricopeptide repeats 5	371795	4283	360860	13049	21815, 30581, 39347, 48113, 56879
4129	interferon-induced protein with tetratricopeptide repeats 5	416601	4284	414042	13050	21816, 30582, 39348, 48114, 56880
4130	interleukin 1 receptor accessory protein-like 2	594988	4285	469497	13051	21817, 30583, 39349, 48115, 56881
4131	interleukin 13 receptor alpha 2	601634	4286	471808	13052	21818, 30584, 39350, 48116, 56882
4132	interleukin 17 receptor E-like	341280	4287	342520	13053	21819, 30585, 39351, 48117, 56883
4133	interleukin 17 receptor E-like	389983	4288	374633	13054	21820, 30586, 39352, 48118, 56884
4134	Interleukin-likeUncharacterized protein	396843	4289	380055	13055	21821, 30587, 39353, 48119, 56885
4135	intermediate filament family orphan 2	304963	4290	305144	13056	21822, 30588, 39354, 48120, 56886
4136	intermediate filament family orphan 2	455833	4291	387941	13057	21823, 30589, 39355, 48121, 56887
4137	intraflagellar transport 140 homolog (Chlamydomonas)	361339	4292	354895	13058	21824, 30590, 39356, 48122, 56888
4138	intraflagellar transport 140 homolog (Chlamydomonas)	397417	4293	380562	13059	21825, 30591, 39357, 48123, 56889
4139	intraflagellar transport 140 homolog (Chlamydomonas)	426508	4294	406012	13060	21826, 30592, 39358, 48124, 56890
4140	intraflagellar transport 140 homolog (Chlamydomonas)	439987	4295	405328	13061	21827, 30593, 39359, 48125, 56891
4141	intraflagellar transport 20 homolog (Chlamydomonas)	575742	4296	458458	13062	21828, 30594, 39360, 48126, 56892
4142	intraflagellar transport 20 homolog (Chlamydomonas)	577872	4297	462871	13063	21829, 30595, 39361, 48127, 56893
4143	intraflagellar transport 20 homolog (Chlamydomonas)	580505	4298	463828	13064	21830, 30596, 39362, 48128, 56894
4144	intraflagellar transport 20 homolog (Chlamydomonas)	580696	4299	463655	13065	21831, 30597, 39363, 48129,

						56895
4145	intraflagellar transport 20 homolog (Chlamydomonas)	581681	4300	462704	13066	21832, 30598, 39364, 48130, 56896
4146	intraflagellar transport 27 homolog (Chlamydomonas)	340630	4301	343593	13067	21833, 30599, 39365, 48131, 56897
4147	intraflagellar transport 27 homolog (Chlamydomonas)	415653	4302	404556	13068	21834, 30600, 39366, 48132, 56898
4148	intraflagellar transport 27 homolog (Chlamydomonas)	417951	4303	392016	13069	21835, 30601, 39367, 48133, 56899
4149	intraflagellar transport 27 homolog (Chlamydomonas)	430701	4304	390016	13070	21836, 30602, 39368, 48134, 56900
4150	intraflagellar transport 27 homolog (Chlamydomonas)	433985	4305	393541	13071	21837, 30603, 39369, 48135, 56901
4151	intraflagellar transport 27 homolog (Chlamydomonas)	440696	4306	399606	13072	21838, 30604, 39370, 48136, 56902
4152	intraflagellar transport 27 homolog (Chlamydomonas)	453009	4307	405394	13073	21839, 30605, 39371, 48137, 56903
4153	intraflagellar transport 52 homolog (Chlamydomonas)	373030	4308	362121	13074	21840, 30606, 39372, 48138, 56904
4154	intraflagellar transport 52 homolog (Chlamydomonas)	373039	4309	362130	13075	21841, 30607, 39373, 48139, 56905
4155	IQ motif containing C	291358	4310	291358	13076	21842, 30608, 39374, 48140, 56906
4156	IQ motif containing C	537469	4311	442291	13077	21843, 30609, 39375, 48141, 56907
4157	IQ motif containing D	299732	4312	299732	13078	21844, 30610, 39376, 48142, 56908
4158	IQ motif containing D	392574	4313	376354	13079	21845, 30611, 39377, 48143, 56909
4159	IQ motif containing D	416617	4314	400669	13080	21846, 30612, 39378, 48144, 56910
4160	IQ motif containing F1	310914	4315	307958	13081	21847, 30613, 39379, 48145, 56911
4161	IQ motif containing F1	535733	4316	443559	13082	21848, 30614,

						39380, 48146, 56912
4162	IQ motif containing F2	333127	4317	329904	13083	21849, 30615, 39381, 48147, 56913
4163	IQ motif containing F3	437810	4318	409373	13084	21850, 30616, 39382, 48148, 56914
4164	IQ motif containing F3	440739	4319	402012	13085	21851, 30617, 39383, 48149, 56915
4165	IQ motif containing F3	446775	4320	401767	13086	21852, 30618, 39384, 48150, 56916
4166	IQ motif containing F3	456080	4321	415609	13087	21853, 30619, 39385, 48151, 56917
4167	IQ motif containing F5	398778	4322	381759	13088	21854, 30620, 39386, 48152, 56918
4168	IQ motif containing F5	446461	4323	394653	13089	21855, 30621, 39387, 48153, 56919
4169	IQ motif containing F6	398780	4324	381760	13090	21856, 30622, 39388, 48154, 56920
4170	IQ motif containing K	308214	4325	309261	13091	21857, 30623, 39389, 48155, 56921
4171	IQ motif containing K	320394	4326	324901	13092	21858, 30624, 39390, 48156, 56922
4172	IQ motif containing K	433597	4327	406013	13093	21859, 30625, 39391, 48157, 56923
4173	IQ motif containing K	541926	4328	439344	13094	21860, 30626, 39392, 48158, 56924
4174	IQ motif containing with AAA domain 1	309507	4329	311951	13095	21861, 30627, 39393, 48159, 56925
4175	IQ motif containing with AAA domain 1	409907	4330	387347	13096	21862, 30628, 39394, 48160, 56926
4176	IQ motif containing with AAA domain 1	412437	4331	387798	13097	21863, 30629, 39395, 48161, 56927
4177	IQ motif containing with AAA domain 1	431676	4332	407213	13098	21864, 30630, 39396, 48162, 56928

4178	IQ motif containing with AAA domain 1	457693	4333	396735	13099	21865, 30631, 39397, 48163, 56929
4179	islet cell autoantigen 1,69kDa-like	358299	4334	351047	13100	21866, 30632, 39398, 48164, 56930
4180	islet cell autoantigen 1,69kDa-like	392237	4335	376070	13101	21867, 30633, 39399, 48165, 56931
4181	islet cell autoantigen 1,69kDa-like	411681	4336	409741	13102	21868, 30634, 39400, 48166, 56932
4182	islet cell autoantigen 1,69kDa-like	412210	4337	387382	13103	21869, 30635, 39401, 48167, 56933
4183	islet cell autoantigen 1,69kDa-like	416760	4338	392609	13104	21870, 30636, 39402, 48168, 56934
4184	islet cell autoantigen 1,69kDa-like	419460	4339	410135	13105	21871, 30637, 39403, 48169, 56935
4185	islet cell autoantigen 1,69kDa-like	421334	4340	414916	13106	21872, 30638, 39404, 48170, 56936
4186	islet cell autoantigen 1,69kDa-like	432273	4341	397827	13107	21873, 30639, 39405, 48171, 56937
4187	islet cell autoantigen 1,69kDa-like	435143	4342	405592	13108	21874, 30640, 39406, 48172, 56938
4188	islet cell autoantigen 1,69kDa-like	441547	4343	404618	13109	21875, 30641, 39407, 48173, 56939
4189	islet cell autoantigen 1,69kDa-like	450143	4344	410747	13110	21876, 30642, 39408, 48174, 56940
4190	islet cell autoantigen 1,69kDa-like	454326	4345	416726	13111	21877, 30643, 39409, 48175, 56941
4191	islet cell autoantigen 1,69kDa-like	457524	4346	404707	13112	21878, 30644, 39410, 48176, 56942
4192	isoamyl acetate-hydrolyzing esterase 1 homolog (S. cerevisiae)	482918	4347	419110	13113	21879, 30645, 39411, 48177, 56943
4193	isoamyl acetate-hydrolyzing esterase 1 homolog (S. cerevisiae)	497473	4348	417580	13114	21880, 30646, 39412, 48178, 56944
4194	isoamyl acetate-hydrolyzing esterase 1 homolog (S.	545602	4349	438534	13115	21881, 30647, 39413, 48179,

	cerevisiae)					56945
4195	isoprenoid synthase domain containing	407010	4350	385478	13116	21882, 30648, 39414, 48180, 56946
4196	ISY1-RAB43 readthrough	418265	4351	411822	13117	21883, 30649, 39415, 48181, 56947
4197	jerky homolog (mouse)	571961	4352	461610	13118	21884, 30650, 39416, 48182, 56948
4198	jerky homolog (mouse)	592696	4353	468566	13119	21885, 30651, 39417, 48183, 56949
4199	JNK1/MAPK8-associated membrane protein	356057	4354	348351	13120	21886, 30652, 39418, 48184, 56950
4200	JNK1/MAPK8-associated membrane protein	261247	4355	261247	13121	21887, 30653, 39419, 48185, 56951
4201	JNK1/MAPK8-associated membrane protein	425728	4356	389699	13122	21888, 30654, 39420, 48186, 56952
4202	Josephin domain containing 1	216039	4357	216039	13123	21889, 30655, 39421, 48187, 56953
4203	Josephin domain containing 1	412832	4358	415189	13124	21890, 30656, 39422, 48188, 56954
4204	Josephin domain containing 1	417712	4359	393131	13125	21891, 30657, 39423, 48189, 56955
4205	Josephin domain containing 1	456626	4360	405182	13126	21892, 30658, 39424, 48190, 56956
4206	Josephin domain containing 2	293431	4361	293431	13127	21893, 30659, 39425, 48191, 56957
4207	Josephin domain containing 2	391815	4362	375691	13128	21894, 30660, 39426, 48192, 56958
4208	Josephin domain containing 2	595669	4363	468860	13129	21895, 30661, 39427, 48193, 56959
4209	Josephin domain containing 2	598418	4364	468956	13130	21896, 30662, 39428, 48194, 56960
4210	jumonji domain containing 4	366758	4365	355720	13131	21897, 30663, 39429, 48195, 56961
4211	jumonji domain containing	438896	4366	387830	13132	21898, 30664,

	4					39430, 48196, 56962
4212	jumonji domain containing 7	397299	4367	380467	13133	21899, 30665, 39431, 48197, 56963
4213	jumonji domain containing 8	293882	4368	293882	13134	21900, 30666, 39432, 48198, 56964
4214	jumonji domain containing 8	412368	4369	399475	13135	21901, 30667, 39433, 48199, 56965
4215	jumonji domain containing 8	454700	4370	394147	13136	21902, 30668, 39434, 48200, 56966
4216	junction plakoglobin	562805	4371	456867	13137	21903, 30669, 39435, 48201, 56967
4217	junction plakoglobin	565780	4372	457186	13138	21904, 30670, 39436, 48202, 56968
4218	junctophilin 4	267407	4373	267407	13139	21905, 30671, 39437, 48203, 56969
4219	karyopherin alpha 2 (RAG cohort 1 importin alpha 1)	571293	4374	460119	13140	21906, 30672, 39438, 48204, 56970
4220	KAT8 regulatory NSL complex subunit 2	357861	4375	350527	13141	21907, 30673, 39439, 48205, 56971
4221	KAT8 regulatory NSL complex subunit 2	420613	4376	415436	13142	21908, 30674, 39440, 48206, 56972
4222	KAT8 regulatory NSL complex subunit 2	548304	4377	446493	13143	21909, 30675, 39441, 48207, 56973
4223	KAT8 regulatory NSL complex subunit 3	354204	4378	346144	13144	21910, 30676, 39442, 48208, 56974
4224	KAT8 regulatory NSL complex subunit 3	431828	4379	396749	13145	21911, 30677, 39443, 48209, 56975
4225	KAT8 regulatory NSL complex subunit 3	435669	4380	407605	13146	21912, 30678, 39444, 48210, 56976
4226	KAT8 regulatory NSL complex subunit 3	441706	4381	400678	13147	21913, 30679, 39445, 48211, 56977
4227	KAT8 regulatory NSL complex subunit 3	447759	4382	394476	13148	21914, 30680, 39446, 48212, 56978

4228	KAT8 regulatory NSL complex subunit 3	452268	4383	397994	13149	21915, 30681, 39447, 48213, 56979
4229	kelch domain containing 10	335420	4384	334140	13150	21916, 30682, 39448, 48214, 56980
4230	kelch domain containing 4	270583	4385	270583	13151	21917, 30683, 39449, 48215, 56981
4231	kelch domain containing 4	316853	4386	326148	13152	21918, 30684, 39450, 48216, 56982
4232	kelch domain containing 4	347925	4387	325717	13153	21919, 30685, 39451, 48217, 56983
4233	kelch domain containing 4	353170	4388	262530	13154	21920, 30686, 39452, 48218, 56984
4234	kelch domain containing 5	381271	4389	370671	13155	21921, 30687, 39453, 48219, 56985
4235	kelch domain containing 7B	395676	4390	379034	13156	21922, 30688, 39454, 48220, 56986
4236	kelch domain containing 8A	367155	4391	356123	13157	21923, 30689, 39455, 48221, 56987
4237	kelch domain containing 8A	367156	4392	356124	13158	21924, 30690, 39456, 48222, 56988
4238	kelch domain containing 8A	537168	4393	443447	13159	21925, 30691, 39457, 48223, 56989
4239	kelch domain containing 8A	539253	4394	442229	13160	21926, 30692, 39458, 48224, 56990
4240	kelch domain containing 9	368011	4395	356990	13161	21927, 30693, 39459, 48225, 56991
4241	kelch domain containing 9	392192	4396	376030	13162	21928, 30694, 39460, 48226, 56992
4242	kelch repeat and BTB (POZ) domain containing 11	320248	4397	321544	13163	21929, 30695, 39461, 48227, 56993
4243	kelch repeat and BTB (POZ) domain containing 12	405109	4398	385957	13164	21930, 30696, 39462, 48228, 56994
4244	kelch repeat and BTB (POZ) domain containing	405256	4399	385879	13165	21931, 30697, 39463, 48229,

	12					56995
4245	kelch repeat and BTB (POZ) domain containing 2	304056	4400	302586	13166	21932, 30698, 39464, 48230, 56996
4246	kelch repeat and BTB (POZ) domain containing 2	423022	4401	407520	13167	21933, 30699, 39465, 48231, 56997
4247	kelch repeat and BTB (POZ) domain containing 2	424468	4402	388236	13168	21934, 30700, 39466, 48232, 56998
4248	kelch repeat and BTB (POZ) domain containing 2	452926	4403	395715	13169	21935, 30701, 39467, 48233, 56999
4249	kelch repeat and BTB (POZ) domain containing 2	453627	4404	407059	13170	21936, 30702, 39468, 48234, 57000
4250	kelch repeat and BTB (POZ) domain containing 2	537125	4405	440299	13171	21937, 30703, 39469, 48235, 57001
4251	kelch repeat and BTB (POZ) domain containing 3	526793	4406	436262	13172	21938, 30704, 39470, 48236, 57002
4252	kelch repeat and BTB (POZ) domain containing 3	531837	4407	432163	13173	21939, 30705, 39471, 48237, 57003
4253	kelch repeat and BTB (POZ) domain containing 4	359900	4408	352971	13174	21940, 30706, 39472, 48238, 57004
4254	kelch repeat and BTB (POZ) domain containing 4	395288	4409	378703	13175	21941, 30707, 39473, 48239, 57005
4255	kelch repeat and BTB (POZ) domain containing 4	430070	4410	415106	13176	21942, 30708, 39474, 48240, 57006
4256	kelch repeat and BTB (POZ) domain containing 5	287777	4411	287777	13177	21943, 30709, 39475, 48241, 57007
4257	kelch repeat and BTB (POZ) domain containing 5	452129	4412	416210	13178	21944, 30710, 39476, 48242, 57008
4258	kelch repeat and BTB (POZ) domain containing 6	379485	4413	368799	13179	21945, 30711, 39477, 48243, 57009
4259	kelch repeat and BTB (POZ) domain containing 6	499385	4414	444326	13180	21946, 30712, 39478, 48244, 57010
4260	kelch repeat and BTB (POZ) domain containing 7	379483	4415	368797	13181	21947, 30713, 39479, 48245, 57011
4261	kelch repeat and BTB	501885	4416	444072	13182	21948, 30714,

	(POZ) domain containing 7					39480, 48246, 57012
4262	kelch repeat and BTB (POZ) domain containing 8	295568	4417	295568	13183	21949, 30715, 39481, 48247, 57013
4263	kelch repeat and BTB (POZ) domain containing 8	417314	4418	401878	13184	21950, 30716, 39482, 48248, 57014
4264	kelch-like 12 (Drosophila)	367258	4419	356227	13185	21951, 30717, 39483, 48249, 57015
4265	kelch-like 12 (Drosophila)	367259	4420	356228	13186	21952, 30718, 39484, 48250, 57016
4266	kelch-like 12 (Drosophila)	367261	4421	356230	13187	21953, 30719, 39485, 48251, 57017
4267	kelch-like 12 (Drosophila)	435533	4422	416886	13188	21954, 30720, 39486, 48252, 57018
4268	kelch-like 15 (Drosophila)	328046	4423	332791	13189	21955, 30721, 39487, 48253, 57019
4269	kelch-like 18 (Drosophila)	232766	4424	232766	13190	21956, 30722, 39488, 48254, 57020
4270	kelch-like 18 (Drosophila)	455924	4425	405585	13191	21957, 30723, 39489, 48255, 57021
4271	kelch-like 22 (Drosophila)	328879	4426	331682	13192	21958, 30724, 39490, 48256, 57022
4272	kelch-like 22 (Drosophila)	440659	4427	405521	13193	21959, 30725, 39491, 48257, 57023
4273	kelch-like 22 (Drosophila)	458248	4428	398616	13194	21960, 30726, 39492, 48258, 57024
4274	kelch-like 23 (Drosophila)	272797	4429	272797	13195	21961, 30727, 39493, 48259, 57025
4275	kelch-like 23 (Drosophila)	392647	4430	376419	13196	21962, 30728, 39494, 48260, 57026
4276	kelch-like 26 (Drosophila)	300976	4431	300976	13197	21963, 30729, 39495, 48261, 57027
4277	kelch-like 26 (Drosophila)	431920	4432	389724	13198	21964, 30730, 39496, 48262, 57028

4278	kelch-like 28 (Drosophila)	396128	4433	379434	13199	21965, 30731, 39497, 48263, 57029
4279	kelch-like 28 (Drosophila)	556239	4434	452591	13200	21966, 30732, 39498, 48264, 57030
4280	kelch-like 28 (Drosophila)	556500	4435	452061	13201	21967, 30733, 39499, 48265, 57031
4281	kelch-like 28 (Drosophila)	557468	4436	450788	13202	21968, 30734, 39500, 48266, 57032
4282	kelch-like 29 (Drosophila)	486442	4437	420659	13203	21969, 30735, 39501, 48267, 57033
4283	kelch-like 30 (Drosophila)	305959	4438	302386	13204	21970, 30736, 39502, 48268, 57034
4284	kelch-like 30 (Drosophila)	409223	4439	386389	13205	21971, 30737, 39503, 48269, 57035
4285	kelch-like 32 (Drosophila)	369254	4440	358258	13206	21972, 30738, 39504, 48270, 57036
4286	kelch-like 32 (Drosophila)	369255	4441	358259	13207	21973, 30739, 39505, 48271, 57037
4287	kelch-like 32 (Drosophila)	369261	4442	358265	13208	21974, 30740, 39506, 48272, 57038
4288	kelch-like 32 (Drosophila)	447886	4443	389310	13209	21975, 30741, 39507, 48273, 57039
4289	kelch-like 32 (Drosophila)	536676	4444	440382	13210	21976, 30742, 39508, 48274, 57040
4290	kelch-like 32 (Drosophila)	539200	4445	441527	13211	21977, 30743, 39509, 48275, 57041
4291	kelch-like 32 (Drosophila)	544166	4446	445453	13212	21978, 30744, 39510, 48276, 57042
4292	kelch-like 33 (Drosophila)	344581	4447	341549	13213	21979, 30745, 39511, 48277, 57043
4293	kelch-like 34 (Drosophila)	379499	4448	368813	13214	21980, 30746, 39512, 48278, 57044
4294	kelch-like 35 (Drosophila)	376292	4449	365469	13215	21981, 30747, 39513, 48279,

						57045
4295	kelch-like 35 (Drosophila)	539798	4450	438526	13216	21982, 30748, 39514, 48280, 57046
4296	kelch-like 36 (Drosophila)	258157	4451	258157	13217	21983, 30749, 39515, 48281, 57047
4297	kelch-like 36 (Drosophila)	325279	4452	317442	13218	21984, 30750, 39516, 48282, 57048
4298	kelch-like 36 (Drosophila)	564996	4453	456743	13219	21985, 30751, 39517, 48283, 57049
4299	kelch-like 38 (Drosophila)	325995	4454	321475	13220	21986, 30752, 39518, 48284, 57050
4300	kelch-like 9 (Drosophila)	359039	4455	351933	13221	21987, 30753, 39519, 48285, 57051
4301	kelch-like 9 (Drosophila)	537938	4456	437733	13222	21988, 30754, 39520, 48286, 57052
4302	keratin 17 pseudogene 1	340966	4457	442538	13223	21989, 30755, 39521, 48287, 57053
4303	keratin 17 pseudogene 1	399211	4458	382160	13224	21990, 30756, 39522, 48288, 57054
4304	keratin associated protein 1-4	576814	4459	458243	13225	21991, 30757, 39523, 48289, 57055
4305	keratin associated protein 2-2	398477	4460	381494	13226	21992, 30758, 39524, 48290, 57056
4306	keratin associated protein 2-2	542910	4461	437407	13227	21993, 30759, 39525, 48291, 57057
4307	keratin associated protein 4-7	391417	4462	375236	13228	21994, 30760, 39526, 48292, 57058
4308	keratin associated protein 5-4	328953	4463	331603	13229	21995, 30761, 39527, 48293, 57059
4309	keratin associated protein 5-4	399682	4464	382590	13230	21996, 30762, 39528, 48294, 57060
4310	keratin associated protein 9-1	318329	4465	325023	13231	21997, 30763, 39529, 48295, 57061
4311	keratin associated protein 9-	377723	4466	366952	13232	21998, 30764,

	1					39530, 48296, 57062
4312	keratin associated protein 9-1	398470	4467	381488	13233	21999, 30765, 39531, 48297, 57063
4313	keratin associated protein 9-6	391355	4468	375150	13234	22000, 30766, 39532, 48298, 57064
4314	keratin associated protein 9-7	391354	4469	375149	13235	22001, 30767, 39533, 48299, 57065
4315	keratin associated protein 9-9	394008	4470	377576	13236	22002, 30768, 39534, 48300, 57066
4316	keratin associated protein 9-9	431129	4471	415438	13237	22003, 30769, 39535, 48301, 57067
4317	KH and NYN domain containing	251343	4472	251343	13238	22004, 30770, 39536, 48302, 57068
4318	KH and NYN domain containing	553935	4473	450799	13239	22005, 30771, 39537, 48303, 57069
4319	KH and NYN domain containing	556510	4474	451004	13240	22006, 30772, 39538, 48304, 57070
4320	KH and NYN domain containing	556842	4475	451106	13241	22007, 30773, 39539, 48305, 57071
4321	KH homology domain containing 1-like	370388	4476	359415	13242	22008, 30774, 39540, 48306, 57072
4322	killer cell immunoglobulin-like receptor 2DL4-like	575775	4477	463717	13243	22009, 30775, 39541, 48307, 57073
4323	killer cell immunoglobulin-like receptor two domains short cytoplasmic tail 2	573129	4478	460718	13244	22010, 30776, 39542, 48308, 57074
4324	killer cell immunoglobulin-like receptor two domains short cytoplasmic tail 2	576413	4479	461341	13245	22011, 30777, 39543, 48309, 57075
4325	killer cell immunoglobulin-like receptor two domains short cytoplasmic tail 5	574219	4480	460839	13246	22012, 30778, 39544, 48310, 57076
4326	Killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 2 (NKAT4)	400827	4481	383628	13247	22013, 30779, 39545, 48311, 57077
4327	Killer cell immunoglobulin-like receptor, three	400829	4482	383630	13248	22014, 30780, 39546, 48312,

	domains, long cytoplasmic tail, 2 (NKAT4)					57078
4328	kinase non-catalytic C-lobe domain (KIND) containing 1	304613	4483	304437	13249	22015, 30781, 39547, 48313, 57079
4329	kinase non-catalytic C-lobe domain (KIND) containing 1	368572	4484	357561	13250	22016, 30782, 39548, 48314, 57080
4330	kinesin family member 16B	450176	4485	396264	13251	22017, 30783, 39549, 48315, 57081
4331	kinesin family member 5C	576072	4486	461857	13252	22018, 30784, 39550, 48316, 57082
4332	kinesin family member C3	597902	4487	469179	13253	22019, 30785, 39551, 48317, 57083
4333	KN motif and ankyrin repeat domains 2	355150	4488	347276	13254	22020, 30786, 39552, 48318, 57084
4334	KN motif and ankyrin repeat domains 2	432929	4489	395650	13255	22021, 30787, 39553, 48319, 57085
4335	KN motif and ankyrin repeat domains 2	586659	4490	465650	13256	22022, 30788, 39554, 48320, 57086
4336	KN motif and ankyrin repeat domains 3	330915	4491	328923	13257	22023, 30789, 39555, 48321, 57087
4337	KN motif and ankyrin repeat domains 3	381056	4492	370444	13258	22024, 30790, 39556, 48322, 57088
4338	KN motif and ankyrin repeat domains 4	317477	4493	321161	13259	22025, 30791, 39557, 48323, 57089
4339	KN motif and ankyrin repeat domains 4	354381	4494	346352	13260	22026, 30792, 39558, 48324, 57090
4340	KN motif and ankyrin repeat domains 4	371150	4495	360192	13261	22027, 30793, 39559, 48325, 57091
4341	KN motif and ankyrin repeat domains 4	371153	4496	360195	13262	22028, 30794, 39560, 48326, 57092
4342	KRAB box domain containing 1	383748	4497	373254	13263	22029, 30795, 39561, 48327, 57093
4343	KRAB box domain containing 1	418176	4498	388094	13264	22030, 30796, 39562, 48328, 57094

4344	KRAB box domain containing 1	426937	4499	413859	13265	22031, 30797, 39563, 48329, 57095
4345	KRAB-A domain containing 1	255992	4500	255992	13266	22032, 30798, 39564, 48330, 57096
4346	KRAB-A domain containing 1	319551	4501	317165	13267	22033, 30799, 39565, 48331, 57097
4347	KRAB-A domain containing 1	497895	4502	417921	13268	22034, 30800, 39566, 48332, 57098
4348	KRAB-A domain containing 2	331336	4503	328017	13269	22035, 30801, 39567, 48333, 57099
4349	KRAB-A domain containing 2	396267	4504	379565	13270	22036, 30802, 39568, 48334, 57100
4350	KRI1 homolog (S. cerevisiae)	312962	4505	320917	13271	22037, 30803, 39569, 48335, 57101
4351	KRI1 homolog (S. cerevisiae)	541101	4506	445847	13272	22038, 30804, 39570, 48336, 57102
4352	KTI12 homolog, chromatin associated (S. cerevisiae)	371614	4507	360676	13273	22039, 30805, 39571, 48337, 57103
4353	KTN1 antisense RNA 1 (non-protein coding)	335142	4508	451586	13274	22040, 30806, 39572, 48338, 57104
4354	KTN1 antisense RNA 1 (non-protein coding)	535211	4509	451911	13275	22041, 30807, 39573, 48339, 57105
4355	KxDL motif containing 1	222307	4510	222307	13276	22042, 30808, 39574, 48340, 57106
4356	KxDL motif containing 1	539106	4511	438903	13277	22043, 30809, 39575, 48341, 57107
4357	KxDL motif containing 1	540691	4512	443549	13278	22044, 30810, 39576, 48342, 57108
4358	L antigen family, member 3	357360	4513	349923	13279	22045, 30811, 39577, 48343, 57109
4359	L1 cell adhesion molecule	594481	4514	469550	13280	22046, 30812, 39578, 48344, 57110
4360	L1 cell adhesion molecule	599241	4515	472713	13281	22047, 30813, 39579, 48345,

						57111
4361	La ribonucleoprotein domain family member 4	522085	4516	429781	13282	22048, 30814, 39580, 48346, 57112
4362	La ribonucleoprotein domain family, member 1B	264584	4517	264584	13283	22049, 30815, 39581, 48347, 57113
4363	La ribonucleoprotein domain family, member 1B	326639	4518	321997	13284	22050, 30816, 39582, 48348, 57114
4364	La ribonucleoprotein domain family, member 1B	354456	4519	346444	13285	22051, 30817, 39583, 48349, 57115
4365	La ribonucleoprotein domain family, member 1B	394288	4520	377829	13286	22052, 30818, 39584, 48350, 57116
4366	La ribonucleoprotein domain family, member 1B	427266	4521	403586	13287	22053, 30819, 39585, 48351, 57117
4367	La ribonucleoprotein domain family, member 1B	432347	4522	390395	13288	22054, 30820, 39586, 48352, 57118
4368	La ribonucleoprotein domain family, member 1B	441387	4523	396521	13289	22055, 30821, 39587, 48353, 57119
4369	La ribonucleoprotein domain family, member 1B	507377	4524	424383	13290	22056, 30822, 39588, 48354, 57120
4370	La ribonucleoprotein domain family, member 4	293618	4525	293618	13291	22057, 30823, 39589, 48355, 57121
4371	La ribonucleoprotein domain family, member 4	347328	4526	340901	13292	22058, 30824, 39590, 48356, 57122
4372	La ribonucleoprotein domain family, member 4	398464	4527	381482	13293	22059, 30825, 39591, 48357, 57123
4373	La ribonucleoprotein domain family, member 4	398473	4528	381490	13294	22060, 30826, 39592, 48358, 57124
4374	La ribonucleoprotein domain family, member 4	429001	4529	415464	13295	22061, 30827, 39593, 48359, 57125
4375	La ribonucleoprotein domain family, member 4	441650	4530	392266	13296	22062, 30828, 39594, 48360, 57126
4376	La ribonucleoprotein domain family, member 4	518444	4531	429077	13297	22063, 30829, 39595, 48361, 57127
4377	La ribonucleoprotein	316157	4532	326128	13298	22064, 30830,

	domain family, member 4B					39596, 48362, 57128
4378	La ribonucleoprotein domain family, member 4B	406525	4533	385229	13299	22065, 30831, 39597, 48363, 57129
4379	La ribonucleoprotein domain family, member 4B	412411	4534	390556	13300	22066, 30832, 39598, 48364, 57130
4380	La ribonucleoprotein domain family, member 4B	440895	4535	403018	13301	22067, 30833, 39599, 48365, 57131
4381	La ribonucleoprotein domain family, member 4B	448368	4536	394545	13302	22068, 30834, 39600, 48366, 57132
4382	laccase (multicopper oxidoreductase) domain containing 1	325686	4537	317619	13303	22069, 30835, 39601, 48367, 57133
4383	laccase (multicopper oxidoreductase) domain containing 1	425906	4538	394179	13304	22070, 30836, 39602, 48368, 57134
4384	laccase (multicopper oxidoreductase) domain containing 1	441843	4539	391747	13305	22071, 30837, 39603, 48369, 57135
4385	laminin alpha 4	584825	4540	462974	13306	22072, 30838, 39604, 48370, 57136
4386	laminin alpha 4	584945	4541	464560	13307	22073, 30839, 39605, 48371, 57137
4387	LanC lantibiotic synthetase component C-like 3 (bacterial)	378619	4542	367882	13308	22074, 30840, 39606, 48372, 57138
4388	LanC lantibiotic synthetase component C-like 3 (bacterial)	378621	4543	367885	13309	22075, 30841, 39607, 48373, 57139
4389	late cornified envelope 6A	431011	4544	411070	13310	22076, 30842, 39608, 48374, 57140
4390	latrophilin 3	573738	4545	459576	13311	22077, 30843, 39609, 48375, 57141
4391	Leber congenital amaurosis 5-like	288350	4546	288350	13312	22078, 30844, 39610, 48376, 57142
4392	Leber congenital amaurosis 5-like	358268	4547	351008	13313	22079, 30845, 39611, 48377, 57143
4393	Leber congenital amaurosis 5-like	380671	4548	370046	13314	22080, 30846, 39612, 48378, 57144

4394	Leber congenital amaurosis 5-like	411566	4549	412691	13315	22081, 30847, 39613, 48379, 57145
4395	Leber congenital amaurosis 5-like	415863	4550	395593	13316	22082, 30848, 39614, 48380, 57146
4396	Leber congenital amaurosis 5-like	418018	4551	404521	13317	22083, 30849, 39615, 48381, 57147
4397	Leber congenital amaurosis 5-like	426783	4552	414784	13318	22084, 30850, 39616, 48382, 57148
4398	Leber congenital amaurosis 5-like	434281	4553	400086	13319	22085, 30851, 39617, 48383, 57149
4399	Leber congenital amaurosis 5-like	438404	4554	405130	13320	22086, 30852, 39618, 48384, 57150
4400	Leber congenital amaurosis 5-like	448288	4555	405598	13321	22087, 30853, 39619, 48385, 57151
4401	Leber congenital amaurosis 5-like	451131	4556	401084	13322	22088, 30854, 39620, 48386, 57152
4402	Leber congenital amaurosis 5-like	456017	4557	407065	13323	22089, 30855, 39621, 48387, 57153
4403	lectin, galactoside-binding, soluble, 16	392051	4558	375904	13324	22090, 30856, 39622, 48388, 57154
4404	lectin, galactoside-binding, soluble, 9B	324290	4559	315564	13325	22091, 30857, 39623, 48389, 57155
4405	lectin, galactoside-binding, soluble, 9B	423676	4560	388841	13326	22092, 30858, 39624, 48390, 57156
4406	lectin, galactoside-binding, soluble, 9C	328114	4561	329932	13327	22093, 30859, 39625, 48391, 57157
4407	lectin, galactoside-binding, soluble, 9C	412421	4562	390286	13328	22094, 30860, 39626, 48392, 57158
4408	lectin, galactoside-binding-like	238875	4563	238875	13329	22095, 30861, 39627, 48393, 57159
4409	leiomodin 2 (cardiac)	332074	4564	405123	13330	22096, 30862, 39628, 48394, 57160
4410	leiomodin 2 (cardiac)	444702	4565	390902	13331	22097, 30863, 39629, 48395,

						57161
4411	leiomodin 2 (cardiac)	458573	4566	411932	13332	22098, 30864, 39630, 48396, 57162
4412	leprecan-like 2	597750	4567	470617	13333	22099, 30865, 39631, 48397, 57163
4413	lethal giant larvae homolog 2 (Drosophila)	545227	4568	439521	13334	22100, 30866, 39632, 48398, 57164
4414	leucine carboxyl methyltransferase 2	305641	4569	307214	13335	22101, 30867, 39633, 48399, 57165
4415	leucine carboxyl methyltransferase 2	544735	4570	442022	13336	22102, 30868, 39634, 48400, 57166
4416	leucine- glutamate- and lysine-rich protein 1 isoform 2	477399	4571	425282	13337	22103, 30869, 39635, 48401, 57167
4417	leucine rich repeat containing 10B	378075	4572	367315	13338	22104, 30870, 39636, 48402, 57168
4418	leucine rich repeat containing 14	292524	4573	292524	13339	22105, 30871, 39637, 48403, 57169
4419	leucine rich repeat containing 14B	328278	4574	327675	13340	22106, 30872, 39638, 48404, 57170
4420	leucine rich repeat containing 16B	334420	4575	334701	13341	22107, 30873, 39639, 48405, 57171
4421	leucine rich repeat containing 16B	342740	4576	340467	13342	22108, 30874, 39640, 48406, 57172
4422	leucine rich repeat containing 20	355790	4577	348043	13343	22109, 30875, 39641, 48407, 57173
4423	leucine rich repeat containing 20	357631	4578	350255	13344	22110, 30876, 39642, 48408, 57174
4424	leucine rich repeat containing 20	358141	4579	350860	13345	22111, 30877, 39643, 48409, 57175
4425	leucine rich repeat containing 20	373224	4580	362321	13346	22112, 30878, 39644, 48410, 57176
4426	leucine rich repeat containing 20	395010	4581	378457	13347	22113, 30879, 39645, 48411, 57177
4427	leucine rich repeat	395011	4582	378458	13348	22114, 30880,

	containing 20					39646, 48412, 57178
4428	leucine rich repeat containing 20	446961	4583	413745	13349	22115, 30881, 39647, 48413, 57179
4429	leucine rich repeat containing 23	7969	4584	7969	13350	22116, 30882, 39648, 48414, 57180, 61534, 61592
4430	leucine rich repeat containing 23	323702	4585	317464	13351	22117, 30883, 39649, 48415, 57181
4431	leucine rich repeat containing 23	415834	4586	408066	13352	22118, 30884, 39650, 48416, 57182
4432	leucine rich repeat containing 23	443597	4587	390932	13353	22119, 30885, 39651, 48417, 57183
4433	leucine rich repeat containing 23	598122	4588	471955	13354	22120, 30886, 39652, 48418, 57184
4434	leucine rich repeat containing 23	599171	4589	469415	13355	22121, 30887, 39653, 48419, 57185
4435	leucine rich repeat containing 27	344079	4590	342641	13356	22122, 30888, 39654, 48420, 57186
4436	leucine rich repeat containing 27	356571	4591	348978	13357	22123, 30889, 39655, 48421, 57187
4437	leucine rich repeat containing 27	368610	4592	357599	13358	22124, 30890, 39656, 48422, 57188
4438	leucine rich repeat containing 27	368612	4593	357601	13359	22125, 30891, 39657, 48423, 57189
4439	leucine rich repeat containing 27	368613	4594	357602	13360	22126, 30892, 39658, 48424, 57190
4440	leucine rich repeat containing 27	368614	4595	357603	13361	22127, 30893, 39659, 48425, 57191
4441	leucine rich repeat containing 27	368615	4596	357604	13362	22128, 30894, 39660, 48426, 57192
4442	leucine rich repeat containing 27	392638	4597	376413	13363	22129, 30895, 39661, 48427, 57193
4443	leucine rich repeat containing 27	432555	4598	407949	13364	22130, 30896, 39662, 48428,

						57194
4444	leucine rich repeat containing 27	450442	4599	393062	13365	22131, 30897, 39663, 48429, 57195
4445	leucine rich repeat containing 28	301981	4600	304923	13366	22132, 30898, 39664, 48430, 57196
4446	leucine rich repeat containing 28	422500	4601	398606	13367	22133, 30899, 39665, 48431, 57197
4447	leucine rich repeat containing 28	442993	4602	404206	13368	22134, 30900, 39666, 48432, 57198
4448	leucine rich repeat containing 28	447360	4603	404520	13369	22135, 30901, 39667, 48433, 57199
4449	leucine rich repeat containing 28	558861	4604	452785	13370	22136, 30902, 39668, 48434, 57200
4450	leucine rich repeat containing 29	341546	4605	344364	13371	22137, 30903, 39669, 48435, 57201
4451	leucine rich repeat containing 29	393992	4606	377561	13372	22138, 30904, 39670, 48436, 57202
4452	leucine rich repeat containing 29	409037	4607	387318	13373	22139, 30905, 39671, 48437, 57203
4453	leucine rich repeat containing 29	409509	4608	386622	13374	22140, 30906, 39672, 48438, 57204
4454	leucine rich repeat containing 29	424285	4609	409459	13375	22141, 30907, 39673, 48439, 57205
4455	leucine rich repeat containing 30	383467	4610	372959	13376	22142, 30908, 39674, 48440, 57206
4456	leucine rich repeat containing 31	264676	4611	264676	13377	22143, 30909, 39675, 48441, 57207
4457	leucine rich repeat containing 31	316428	4612	325978	13378	22144, 30910, 39676, 48442, 57208
4458	leucine rich repeat containing 34	316515	4613	326150	13379	22145, 30911, 39677, 48443, 57209
4459	leucine rich repeat containing 34	446859	4614	414635	13380	22146, 30912, 39678, 48444, 57210
4460	leucine rich repeat	522526	4615	429278	13381	22147, 30913,

	containing 34					39679, 48445, 57211
4461	leucine rich repeat containing 36	290940	4616	290940	13382	22148, 30914, 39680, 48446, 57212
4462	leucine rich repeat containing 36	329956	4617	329943	13383	22149, 30915, 39681, 48447, 57213
4463	leucine rich repeat containing 36	435835	4618	411122	13384	22150, 30916, 39682, 48448, 57214
4464	leucine rich repeat containing 36	541146	4619	445861	13385	22151, 30917, 39683, 48449, 57215
4465	leucine rich repeat containing 36	563189	4620	455103	13386	22152, 30918, 39684, 48450, 57216
4466	leucine rich repeat containing 37 member A2	576629	4621	459551	13387	22153, 30919, 39685, 48451, 57217
4467	leucine rich repeat containing 37, member A2	333412	4622	333071	13388	22154, 30920, 39686, 48452, 57218
4468	leucine rich repeat containing 39	342895	4623	344470	13389	22155, 30921, 39687, 48453, 57219
4469	leucine rich repeat containing 39	370136	4624	359155	13390	22156, 30922, 39688, 48454, 57220
4470	leucine rich repeat containing 39	370137	4625	359156	13391	22157, 30923, 39689, 48455, 57221
4471	leucine rich repeat containing 39	370138	4626	359157	13392	22158, 30924, 39690, 48456, 57222
4472	leucine rich repeat containing 40	370952	4627	359990	13393	22159, 30925, 39691, 48457, 57223
4473	leucine rich repeat containing 41	254454	4628	254454	13394	22160, 30926, 39692, 48458, 57224
4474	leucine rich repeat containing 41	343304	4629	343298	13395	22161, 30927, 39693, 48459, 57225
4475	leucine rich repeat containing 41	371972	4630	361040	13396	22162, 30928, 39694, 48460, 57226
4476	leucine rich repeat containing 42	319223	4631	318185	13397	22163, 30929, 39695, 48461, 57227

4477	leucine rich repeat containing 42	371368	4632	360419	13398	22164, 30930, 39696, 48462, 57228
4478	leucine rich repeat containing 42	371370	4633	360421	13399	22165, 30931, 39697, 48463, 57229
4479	leucine rich repeat containing 42	444987	4634	389368	13400	22166, 30932, 39698, 48464, 57230
4480	leucine rich repeat containing 43	289014	4635	289014	13401	22167, 30933, 39699, 48465, 57231
4481	leucine rich repeat containing 43	339777	4636	344233	13402	22168, 30934, 39700, 48466, 57232
4482	leucine rich repeat containing 43	425921	4637	416628	13403	22169, 30935, 39701, 48467, 57233
4483	leucine rich repeat containing 46	269025	4638	269025	13404	22170, 30936, 39702, 48468, 57234
4484	leucine rich repeat containing 47	378251	4639	367498	13405	22171, 30937, 39703, 48469, 57235
4485	leucine rich repeat containing 53	294635	4640	294635	13406	22172, 30938, 39704, 48470, 57236
4486	leucine rich repeat containing 53	416014	4641	391861	13407	22173, 30939, 39705, 48471, 57237
4487	leucine rich repeat containing 56	270115	4642	270115	13408	22174, 30940, 39706, 48472, 57238
4488	leucine rich repeat containing 57	323443	4643	326817	13409	22175, 30941, 39707, 48473, 57239
4489	leucine rich repeat containing 57	397130	4644	380319	13410	22176, 30942, 39708, 48474, 57240
4490	leucine rich repeat containing 58	295628	4645	295628	13411	22177, 30943, 39709, 48475, 57241
4491	leucine rich repeat containing 61	323078	4646	339047	13412	22178, 30944, 39710, 48476, 57242
4492	leucine rich repeat containing 61	359623	4647	352642	13413	22179, 30945, 39711, 48477, 57243
4493	leucine rich repeat containing 61	493307	4648	420560	13414	22180, 30946, 39712, 48478,

						57244
4494	leucine rich repeat containing 63	446175	4649	408828	13415	22181, 30947, 39713, 48479, 57245
4495	leucine rich repeat containing 69	343709	4650	343221	13416	22182, 30948, 39714, 48480, 57246
4496	leucine rich repeat containing 69	518304	4651	428285	13417	22183, 30949, 39715, 48481, 57247
4497	leucine rich repeat containing 69	448384	4652	400803	13418	22184, 30950, 39716, 48482, 57248
4498	leucine rich repeat containing 71	337428	4653	336661	13419	22185, 30951, 39717, 48483, 57249
4499	leucine rich repeat containing 72	401542	4654	384971	13420	22186, 30952, 39718, 48484, 57250
4500	leucine rich repeat containing 73	372441	4655	361518	13421	22187, 30953, 39719, 48485, 57251
4501	leucine rich repeat protein 1	298288	4656	298288	13422	22188, 30954, 39720, 48486, 57252
4502	leucine rich repeat protein 1	318317	4657	315628	13423	22189, 30955, 39721, 48487, 57253
4503	leucine rich repeat protein 1	361579	4658	354839	13424	22190, 30956, 39722, 48488, 57254
4504	leucine twenty homeobox	396841	4659	380053	13425	22191, 30957, 39723, 48489, 57255
4505	leucine twenty homeobox	556180	4660	451512	13426	22192, 30958, 39724, 48490, 57256
4506	leucine zipper and CTNNBIP1 domain containing	377213	4661	366418	13427	22193, 30959, 39725, 48491, 57257
4507	leucine zipper and CTNNBIP1 domain containing	377223	4662	366430	13428	22194, 30960, 39726, 48492, 57258
4508	leucine zipper and CTNNBIP1 domain containing	400903	4663	383695	13429	22195, 30961, 39727, 48493, 57259
4509	leucine zipper and CTNNBIP1 domain containing	541052	4664	437432	13430	22196, 30962, 39728, 48494, 57260
4510	leucine zipper, down-	341255	4665	340434	13431	22197, 30963,

	regulated in cancer 1-like					39729, 48495, 57261
4511	leucine, glutamate and lysine rich 1	356539	4666	348936	13432	22198, 30964, 39730, 48496, 57262
4512	leucine, glutamate and lysine rich 1	470811	4667	418214	13433	22199, 30965, 39731, 48497, 57263
4513	leucine-rich repeat, immunoglobulin-like and transmembrane domains 2	372113	4668	361185	13434	22200, 30966, 39732, 48498, 57264
4514	leucine-rich repeat, immunoglobulin-like and transmembrane domains 2	538192	4669	438264	13435	22201, 30967, 39733, 48499, 57265
4515	Leucine-rich repeat-containing protein LOC400891	342608	4670	341179	13436	22202, 30968, 39734, 48500, 57266
4516	Leucine-rich repeat-containing protein LOC400891	543388	4671	441009	13437	22203, 30969, 39735, 48501, 57267
4517	leucine-rich repeats and calponin homology (CH) domain containing 2	317135	4672	325091	13438	22204, 30970, 39736, 48502, 57268
4518	leucine-rich repeats and calponin homology (CH) domain containing 2	536655	4673	439862	13439	22205, 30971, 39737, 48503, 57269
4519	leucine-rich repeats and calponin homology (CH) domain containing 2	538422	4674	439366	13440	22206, 30972, 39738, 48504, 57270
4520	leucine-rich repeats and calponin homology (CH) domain containing 2	598874	4675	468963	13441	22207, 30973, 39739, 48505, 57271
4521	leucine-rich repeats and death domain containing 1	343318	4676	339642	13442	22208, 30974, 39740, 48506, 57272
4522	leucine-rich repeats and death domain containing 1	430130	4677	411568	13443	22209, 30975, 39741, 48507, 57273
4523	leucine-rich repeats and death domain containing 1	437357	4678	387628	13444	22210, 30976, 39742, 48508, 57274
4524	leucine-rich repeats and death domain containing 1	454089	4679	392112	13445	22211, 30977, 39743, 48509, 57275
4525	leucine-rich repeats and death domain containing 1	458448	4680	405987	13446	22212, 30978, 39744, 48510, 57276
4526	leucine-rich repeats and guanylate kinase domain containing	285928	4681	285928	13447	22213, 30979, 39745, 48511, 57277

4527	leucine-rich repeats and IQ motif containing 1	378580	4682	367843	13448	22214, 30980, 39746, 48512, 57278
4528	leucine-rich repeats and IQ motif containing 1	393212	4683	376906	13449	22215, 30981, 39747, 48513, 57279
4529	leucine-rich repeats and IQ motif containing 1	393217	4684	376910	13450	22216, 30982, 39748, 48514, 57280
4530	leucine-rich repeats and IQ motif containing 3	354431	4685	346414	13451	22217, 30983, 39749, 48515, 57281
4531	leucine-rich repeats and IQ motif containing 3	388972	4686	373624	13452	22218, 30984, 39750, 48516, 57282
4532	leucine-rich repeats and IQ motif containing 4	340806	4687	342188	13453	22219, 30985, 39751, 48517, 57283
4533	leukemia NUP98 fusion partner 1	383693	4688	373191	13454	22220, 30986, 39752, 48518, 57284
4534	leukocyte immunoglobulin-like receptor subfamily A (with TM domain) member 6	396365	4689	379651	13455	22221, 30987, 39753, 48519, 57285
4535	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	245621	4690	245621	13456	22222, 30988, 39754, 48520, 57286
4536	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	270464	4691	270464	13457	22223, 30989, 39755, 48521, 57287
4537	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	391735	4692	375615	13458	22224, 30990, 39756, 48522, 57288
4538	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	419410	4693	411227	13459	22225, 30991, 39757, 48523, 57289
4539	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	421123	4694	395996	13460	22226, 30992, 39758, 48524, 57290
4540	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 6	440558	4695	390120	13461	22227, 30993, 39759, 48525, 57291
4541	leukocyte receptor cluster	222224	4696	222224	13462	22228, 30994,

	(LRC) member 1					39760, 48526, 57292
4542	leukocyte receptor cluster (LRC) member 8	301196	4697	301196	13463	22229, 30995, 39761, 48527, 57293
4543	leukocyte receptor cluster (LRC) member 8	326764	4698	318374	13464	22230, 30996, 39762, 48528, 57294
4544	leukocyte receptor cluster (LRC) member 8	376514	4699	365697	13465	22231, 30997, 39763, 48529, 57295
4545	leukocyte receptor cluster (LRC) member 8	439657	4700	399507	13466	22232, 30998, 39764, 48530, 57296
4546	leukocyte receptor cluster (LRC) member 8	443957	4701	390010	13467	22233, 30999, 39765, 48531, 57297
4547	leukocyte receptor cluster (LRC) member 8	542665	4702	445094	13468	22234, 31000, 39766, 48532, 57298
4548	leukocyte receptor cluster (LRC) member 9	333834	4703	331647	13469	22235, 31001, 39767, 48533, 57299
4549	LIM and calponin homology domains 1	313860	4704	316891	13470	22236, 31002, 39768, 48534, 57300
4550	LIM and calponin homology domains 1	313875	4705	316974	13471	22237, 31003, 39769, 48535, 57301
4551	LIM and calponin homology domains 1	381753	4706	371172	13472	22238, 31004, 39770, 48536, 57302
4552	LIM and calponin homology domains 1	396595	4707	379840	13473	22239, 31005, 39771, 48537, 57303
4553	LIM and calponin homology domains 1	503057	4708	425631	13474	22240, 31006, 39772, 48538, 57304
4554	LIM and calponin homology domains 1	511496	4709	421242	13475	22241, 31007, 39773, 48539, 57305
4555	LIM and calponin homology domains 1	512820	4710	424437	13476	22242, 31008, 39774, 48540, 57306
4556	LIM and calponin homology domains 1	512946	4711	424645	13477	22243, 31009, 39775, 48541, 57307
4557	LIM and calponin homology domains 1	537405	4712	440255	13478	22244, 31010, 39776, 48542, 57308

4558	LIM and calponin homology domains 1	508501	4713	424825	13479	22245, 31011, 39777, 48543, 57309
4559	LIM domain containing 2	259006	4714	259006	13480	22246, 31012, 39778, 48544, 57310
4560	LIM domain kinase 1	571928	4715	460552	13481	22247, 31013, 39779, 48545, 57311
4561	lin-37 homolog (C. elegans)	301159	4716	301159	13482	22248, 31014, 39780, 48546, 57312
4562	lin-52 homolog (C. elegans)	381098	4717	370488	13483	22249, 31015, 39781, 48547, 57313
4563	lin-52 homolog (C. elegans)	555028	4718	451812	13484	22250, 31016, 39782, 48548, 57314
4564	LINE-1 type transposase domain containing 1	498273	4719	419901	13485	22251, 31017, 39783, 48549, 57315
4565	lines homolog (Drosophila)	314742	4720	318423	13486	22252, 31018, 39784, 48550, 57316
4566	lines homolog (Drosophila)	559577	4721	453642	13487	22253, 31019, 39785, 48551, 57317
4567	lines homolog (Drosophila)	559736	4722	452941	13488	22254, 31020, 39786, 48552, 57318
4568	lines homolog (Drosophila)	560272	4723	453495	13489	22255, 31021, 39787, 48553, 57319
4569	lines homolog (Drosophila)	560934	4724	453692	13490	22256, 31022, 39788, 48554, 57320
4570	lines homolog (Drosophila)	561308	4725	454200	13491	22257, 31023, 39789, 48555, 57321
4571	linker for activation of T cells family member 2	570327	4726	461899	13492	22258, 31024, 39790, 48556, 57322
4572	linker for activation of T cells family member 2	571529	4727	461809	13493	22259, 31025, 39791, 48557, 57323
4573	linker for activation of T cells family member 2	576566	4728	461106	13494	22260, 31026, 39792, 48558, 57324
4574	lipocalin-like 1	408973	4729	386162	13495	22261, 31027, 39793, 48559,

						57325
4575	lipoyl(octanoyl) transferase 2 (putative)	310109	4730	309463	13496	22262, 31028, 39794, 48560, 57326
4576	Lix1 homolog (chicken)	274382	4731	274382	13497	22263, 31029, 39795, 48561, 57327
4577	Lix1 homolog (mouse)-like	369308	4732	358314	13498	22264, 31030, 39796, 48562, 57328
4578	Lix1 homolog (mouse)-like	449167	4733	391413	13499	22265, 31031, 39797, 48563, 57329
4579	LLP homolog, long-term synaptic facilitation (Aplysia)	266604	4734	266604	13500	22266, 31032, 39798, 48564, 57330
4580	LLP homolog, long-term synaptic facilitation (Aplysia)	446587	4735	437372	13501	22267, 31033, 39799, 48565, 57331
4581	LOC339290 proteinUncharacterized protein	458396	4736	394681	13502	22268, 31034, 39800, 48566, 57332
4582	LOC652203 proteinUncharacterized protein	398305	4737	381350	13503	22269, 31035, 39801, 48567, 57333
4583	lon peptidase 2, peroxisomal	416006	4738	415983	13504	22270, 31036, 39802, 48568, 57334
4584	lon peptidase 2, peroxisomal	535754	4739	445426	13505	22271, 31037, 39803, 48569, 57335
4585	lon peptidase 2, peroxisomal	544734	4740	444179	13506	22272, 31038, 39804, 48570, 57336
4586	LON peptidase N-terminal domain and ring finger 1	398246	4741	381298	13507	22273, 31039, 39805, 48571, 57337
4587	LON peptidase N-terminal domain and ring finger 2	393437	4742	377086	13508	22274, 31040, 39806, 48572, 57338
4588	LON peptidase N-terminal domain and ring finger 2	409647	4743	386823	13509	22275, 31041, 39807, 48573, 57339
4589	LON peptidase N-terminal domain and ring finger 3	304778	4744	307732	13510	22276, 31042, 39808, 48574, 57340
4590	LON peptidase N-terminal domain and ring finger 3	365713	4745	360691	13511	22277, 31043, 39809, 48575, 57341
4591	LON peptidase N-terminal	371628	4746	360690	13512	22278, 31044,

	domain and ring finger 3					39810, 48576, 57342
4592	LON peptidase N-terminal domain and ring finger 3	422289	4747	408894	13513	22279, 31045, 39811, 48577, 57343
4593	LON peptidase N-terminal domain and ring finger 3	439603	4748	414519	13514	22280, 31046, 39812, 48578, 57344
4594	long intergenic non-protein coding RNA 273	539813	4749	443070	13515	22281, 31047, 39813, 48579, 57345
4595	long intergenic non-protein coding RNA 346	538077	4750	442216	13516	22282, 31048, 39814, 48580, 57346
4596	long intergenic non-protein coding RNA 470	269201	4751	269201	13517	22283, 31049, 39815, 48581, 57347
4597	long intergenic non-protein coding RNA 470	334697	4752	335226	13518	22284, 31050, 39816, 48582, 57348
4598	long intergenic non-protein coding RNA 470	412816	4753	407778	13519	22285, 31051, 39817, 48583, 57349
4599	long intergenic non-protein coding RNA 482	332012	4754	327588	13520	22286, 31052, 39818, 48584, 57350
4600	loss of heterozygosity, 12, chromosomal region 1	298571	4755	298571	13521	22287, 31053, 39819, 48585, 57351
4601	loss of heterozygosity, 12, chromosomal region 1	314565	4756	321546	13522	22288, 31054, 39820, 48586, 57352
4602	low density lipoprotein receptor class A domain containing 1	420619	4757	411017	13523	22289, 31055, 39821, 48587, 57353
4603	low density lipoprotein receptor class A domain containing 1	545928	4758	445871	13524	22290, 31056, 39822, 48588, 57354
4604	low density lipoprotein receptor-related protein 5-like	402785	4759	384562	13525	22291, 31057, 39823, 48589, 57355
4605	low density lipoprotein receptor-related protein 5-like	402859	4760	384291	13526	22292, 31058, 39824, 48590, 57356
4606	low density lipoprotein receptor-related protein 5-like	444995	4761	407283	13527	22293, 31059, 39825, 48591, 57357
4607	low density lipoprotein receptor-related protein 5-like	468442	4762	437736	13528	22294, 31060, 39826, 48592, 57358

4608	LSM14B, SCD6 homolog B (S. cerevisiae)	253001	4763	253001	13529	22295, 31061, 39827, 48593, 57359
4609	LSM14B, SCD6 homolog B (S. cerevisiae)	279068	4764	279068	13530	22296, 31062, 39828, 48594, 57360
4610	LSM14B, SCD6 homolog B (S. cerevisiae)	279069	4765	279069	13531	22297, 31063, 39829, 48595, 57361
4611	LSM14B, SCD6 homolog B (S. cerevisiae)	361670	4766	355209	13532	22298, 31064, 39830, 48596, 57362
4612	LSM14B, SCD6 homolog B (S. cerevisiae)	370906	4767	359943	13533	22299, 31065, 39831, 48597, 57363
4613	LSM14B, SCD6 homolog B (S. cerevisiae)	370915	4768	359953	13534	22300, 31066, 39832, 48598, 57364
4614	LSM14B, SCD6 homolog B (S. cerevisiae)	400318	4769	383172	13535	22301, 31067, 39833, 48599, 57365
4615	LSM14B, SCD6 homolog B (S. cerevisiae)	444156	4770	391152	13536	22302, 31068, 39834, 48600, 57366
4616	LSM14B, SCD6 homolog B (S. cerevisiae)	479741	4771	435839	13537	22303, 31069, 39835, 48601, 57367
4617	LTV1 homolog (S. cerevisiae)	367576	4772	356548	13538	22304, 31070, 39836, 48602, 57368
4618	LY6/PLAUR domain containing 8	567799	4773	454336	13539	22305, 31071, 39837, 48603, 57369
4619	LY75-CD302 readthrough	504764	4774	423463	13540	22306, 31072, 39838, 48604, 57370
4620	LY75-CD302 readthrough	505052	4775	421035	13541	22307, 31073, 39839, 48605, 57371
4621	lymphocyte antigen 6 complex locus K	572300	4776	458502	13542	22308, 31074, 39840, 48606, 57372
4622	lymphocyte antigen 6 complex, locus G5B	383429	4777	372921	13543	22309, 31075, 39841, 48607, 57373
4623	Lymphocyte antigen 6 complex, locus G5B	443812	4778	416121	13544	22310, 31076, 39842, 48608, 57374
4624	Lymphocyte antigen 6 complex, locus G5B	443952	4779	392194	13545	22311, 31077, 39843, 48609,

						57375
4625	Lymphocyte antigen 6 complex, locus G5B	451335	4780	406867	13546	22312, 31078, 39844, 48610, 57376
4626	lymphocyte antigen 6 complex, locus G5B	456439	4781	395699	13547	22313, 31079, 39845, 48611, 57377
4627	Lymphocyte antigen 6 complex, locus G5B	457089	4782	390345	13548	22314, 31080, 39846, 48612, 57378
4628	lymphocyte antigen 6 complex, locus G5B	462244	4783	418445	13549	22315, 31081, 39847, 48613, 57379
4629	lymphocyte antigen 6 complex, locus G5B	490011	4784	418217	13550	22316, 31082, 39848, 48614, 57380
4630	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	383417	4785	372909	13551	22317, 31083, 39849, 48615, 57381
4631	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	383418	4786	372910	13552	22318, 31084, 39850, 48616, 57382
4632	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	399142	4787	382095	13553	22319, 31085, 39851, 48617, 57383
4633	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	419000	4788	393941	13554	22320, 31086, 39852, 48618, 57384
4634	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized	419767	4789	410718	13555	22321, 31087, 39853, 48619, 57385

	protein					
4635	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	430237	4790	414035	13556	22322, 31088, 39854, 48620, 57386
4636	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	431644	4791	416966	13557	22323, 31089, 39855, 48621, 57387
4637	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	434670	4792	388932	13558	22324, 31090, 39856, 48622, 57388
4638	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	435369	4793	398849	13559	22325, 31091, 39857, 48623, 57389
4639	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	443544	4794	416475	13560	22326, 31092, 39858, 48624, 57390
4640	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	446610	4795	411081	13561	22327, 31093, 39859, 48625, 57391
4641	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	450147	4796	407275	13562	22328, 31094, 39860, 48626, 57392

4642	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	453077	4797	403996	13563	22329, 31095, 39861, 48627, 57393
4643	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	469626	4798	435573	13564	22330, 31096, 39862, 48628, 57394
4644	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	546405	4799	448874	13565	22331, 31097, 39863, 48629, 57395
4645	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	547421	4800	449142	13566	22332, 31098, 39864, 48630, 57396
4646	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	547676	4801	447438	13567	22333, 31099, 39865, 48631, 57397
4647	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	548716	4802	447045	13568	22334, 31100, 39866, 48632, 57398
4648	Lymphocyte antigen 6 complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein	548848	4803	447596	13569	22335, 31101, 39867, 48633, 57399
4649	Lymphocyte antigen 6	550508	4804	448748	13570	22336, 31102,

	complex, locus G6ELymphocyte antigen 6 complex, locus G6E, isoform CRA_aUncharacterized protein					39868, 48634, 57400
4650	lymphocyte antigen 6 complex, locus G6F	383420	4805	372912	13571	22337, 31103, 39869, 48635, 57401
4651	lymphocyte antigen 6 complex, locus G6F	442105	4806	404621	13572	22338, 31104, 39870, 48636, 57402
4652	lymphocyte antigen 6 complex, locus G6F	556331	4807	451243	13573	22339, 31105, 39871, 48637, 57403
4653	LYR motif containing 9	379103	4808	368397	13574	22340, 31106, 39872, 48638, 57404
4654	lysine (K)-specific demethylase 4D	570915	4809	461786	13575	22341, 31107, 39873, 48639, 57405
4655	lysine-rich coiled-coil 1	347055	4810	340083	13576	22342, 31108, 39874, 48640, 57406
4656	LysM, putative peptidoglycan-binding, domain containing 1	368908	4811	357904	13577	22343, 31109, 39875, 48641, 57407
4657	LysM, putative peptidoglycan-binding, domain containing 1	440902	4812	404059	13578	22344, 31110, 39876, 48642, 57408
4658	LysM, putative peptidoglycan-binding, domain containing 2	267838	4813	267838	13579	22345, 31111, 39877, 48643, 57409
4659	LysM, putative peptidoglycan-binding, domain containing 2	454181	4814	410424	13580	22346, 31112, 39878, 48644, 57410
4660	LysM, putative peptidoglycan-binding, domain containing 2	560491	4815	453933	13581	22347, 31113, 39879, 48645, 57411
4661	lysophospholipase II	374501	4816	363625	13582	22348, 31114, 39880, 48646, 57412
4662	lysophospholipase II	374502	4817	363626	13583	22349, 31115, 39881, 48647, 57413
4663	lysophospholipase II	374503	4818	363627	13584	22350, 31116, 39882, 48648, 57414
4664	lysophospholipase II	374505	4819	363629	13585	22351, 31117, 39883, 48649,

						57415
4665	lysophospholipase II	374506	4820	363630	13586	22352, 31118, 39884, 48650, 57416
4666	lysophospholipase II	374514	4821	363638	13587	22353, 31119, 39885, 48651, 57417
4667	lysophospholipase II	400061	4822	382934	13588	22354, 31120, 39886, 48652, 57418
4668	lysophospholipase II	420982	4823	409004	13589	22355, 31121, 39887, 48653, 57419
4669	lysophospholipase II	421070	4824	388003	13590	22356, 31122, 39888, 48654, 57420
4670	Mab-21 domain containing 2	392452	4825	376246	13591	22357, 31123, 39889, 48655, 57421
4671	mab-21-like 3 (C. elegans)	369500	4826	358512	13592	22358, 31124, 39890, 48656, 57422
4672	Macrophage mannose receptor 1	331429	4827	332124	13593	22359, 31125, 39891, 48657, 57423
4673	Macrophage mannose receptor 1	457317	4828	391843	13594	22360, 31126, 39892, 48658, 57424
4674	MAFF interacting protein	400839	4829	383639	13595	22361, 31127, 39893, 48659, 57425
4675	MAGE-like 2	532292	4830	433433	13596	22362, 31128, 39894, 48660, 57426
4676	MAGI family member, X-linked	376338	4831	365516	13597	22363, 31129, 39895, 48661, 57427
4677	MAGI family member, X-linked	376339	4832	365517	13598	22364, 31130, 39896, 48662, 57428
4678	MAGI family member, X-linked	412696	4833	387928	13599	22365, 31131, 39897, 48663, 57429
4679	MAGI family member, X-linked	415364	4834	416219	13600	22366, 31132, 39898, 48664, 57430
4680	MAGI family member, X-linked	425285	4835	411713	13601	22367, 31133, 39899, 48665, 57431
4681	MAGI family member, X-	425661	4836	403515	13602	22368, 31134,

	linked					39900, 48666, 57432
4682	MAGI family member, X-linked	454342	4837	400147	13603	22369, 31135, 39901, 48667, 57433
4683	MAGI family member, X-linked	458388	4838	405887	13604	22370, 31136, 39902, 48668, 57434
4684	magnesium-dependent phosphatase 1	288087	4839	288087	13605	22371, 31137, 39903, 48669, 57435
4685	magnesium-dependent phosphatase 1	396833	4840	380045	13606	22372, 31138, 39904, 48670, 57436
4686	major facilitator superfamily domain containing 2B	338315	4841	342501	13607	22373, 31139, 39905, 48671, 57437
4687	major facilitator superfamily domain containing 2B	406420	4842	385527	13608	22374, 31140, 39906, 48672, 57438
4688	makorin ring finger protein 1	255977	4843	255977	13609	22375, 31141, 39907, 48673, 57439
4689	makorin ring finger protein 1	437223	4844	439823	13610	22376, 31142, 39908, 48674, 57440
4690	makorin ring finger protein 1	539898	4845	439699	13611	22377, 31143, 39909, 48675, 57441
4691	makorin ring finger protein 1	443720	4846	416369	13612	22378, 31144, 39910, 48676, 57442
4692	malate dehydrogenase 1B, NAD (soluble)	374412	4847	363533	13613	22379, 31145, 39911, 48677, 57443
4693	malate dehydrogenase 1B, NAD (soluble)	392214	4848	376049	13614	22380, 31146, 39912, 48678, 57444
4694	malate dehydrogenase 1B, NAD (soluble)	454776	4849	389916	13615	22381, 31147, 39913, 48679, 57445
4695	MAP7 domain containing 2	330274	4850	332677	13616	22382, 31148, 39914, 48680, 57446
4696	MAP7 domain containing 2	379643	4851	368964	13617	22383, 31149, 39915, 48681, 57447
4697	MAP7 domain containing 2	379651	4852	368972	13618	22384, 31150, 39916, 48682, 57448

4698	MAP7 domain containing 2	443379	4853	388239	13619	22385, 31151, 39917, 48683, 57449
4699	MAP7 domain containing 2	452324	4854	413301	13620	22386, 31152, 39918, 48684, 57450
4700	MAP7 domain containing 2	543767	4855	440691	13621	22387, 31153, 39919, 48685, 57451
4701	MAP7 domain containing 2	544957	4856	438664	13622	22388, 31154, 39920, 48686, 57452
4702	MARVEL domain containing 1	285605	4857	441365	13623	22389, 31155, 39921, 48687, 57453
4703	mast cell immunoglobulin-like receptor 1	571603	4858	459467	13624	22390, 31156, 39922, 48688, 57454
4704	matrix metallopeptidase 12 (macrophage elastase)	571244	4859	458585	13625	22391, 31157, 39923, 48689, 57455
4705	mature T-cell proliferation 1	596212	4860	473214	13626	22392, 31158, 39924, 48690, 57456
4706	MCF.2 cell line derived transforming sequence-like 2	328913	4861	328118	13627	22393, 31159, 39925, 48691, 57457
4707	MCF.2 cell line derived transforming sequence-like 2	414362	4862	414131	13628	22394, 31160, 39926, 48692, 57458
4708	MCF.2 cell line derived transforming sequence-like 2	437431	4863	390066	13629	22395, 31161, 39927, 48693, 57459
4709	MCF.2 cell line derived transforming sequence-like 2	447025	4864	388190	13630	22396, 31162, 39928, 48694, 57460
4710	MCF.2 cell line derived transforming sequence-like 2	473233	4865	420070	13631	22397, 31163, 39929, 48695, 57461
4711	MEF2B neighbor	462790	4866	425864	13632	22398, 31164, 39930, 48696, 57462
4712	MEF2B neighbor	477565	4867	424833	13633	22399, 31165, 39931, 48697, 57463
4713	meiosis inhibitor 1	300398	4868	300398	13634	22400, 31166, 39932, 48698, 57464
4714	meiosis inhibitor 1	400107	4869	382978	13635	22401, 31167, 39933, 48699,

						57465
4715	meiosis inhibitor 1	401548	4870	384115	13636	22402, 31168, 39934, 48700, 57466
4716	meiosis inhibitor 1	419798	4871	412666	13637	22403, 31169, 39935, 48701, 57467
4717	meiosis inhibitor 1	540833	4872	444225	13638	22404, 31170, 39936, 48702, 57468
4718	meiosis inhibitor 1	540880	4873	437436	13639	22405, 31171, 39937, 48703, 57469
4719	melanoma antigen family A 11	597305	4874	473110	13640	22406, 31172, 39938, 48704, 57470
4720	melanoma antigen family A 8	596200	4875	469535	13641	22407, 31173, 39939, 48705, 57471
4721	melanoma antigen family A 8	597872	4876	471528	13642	22408, 31174, 39940, 48706, 57472
4722	melanoma antigen family A 8	600776	4877	472386	13643	22409, 31175, 39941, 48707, 57473
4723	melanoma antigen family A, 2B	331220	4878	333487	13644	22410, 31176, 39942, 48708, 57474
4724	melanoma antigen family A, 2B	370293	4879	359316	13645	22411, 31177, 39943, 48709, 57475
4725	melanoma antigen family A, 2B	409560	4880	386463	13646	22412, 31178, 39944, 48710, 57476
4726	melanoma antigen family A, 2B	422085	4881	397216	13647	22413, 31179, 39945, 48711, 57477
4727	melanoma antigen family A, 2B	423993	4882	395386	13648	22414, 31180, 39946, 48712, 57478
4728	melanoma antigen family A, 2B	447530	4883	389223	13649	22415, 31181, 39947, 48713, 57479
4729	melanoma antigen family A, 2B	453150	4884	413384	13650	22416, 31182, 39948, 48714, 57480
4730	melanoma antigen family A, 2B	458057	4885	389999	13651	22417, 31183, 39949, 48715, 57481
4731	melanoma antigen family	325250	4886	314543	13652	22418, 31184,

	B, 18					39950, 48716, 57482
4732	melanoma antigen family D 1	597428	4887	473070	13653	22419, 31185, 39951, 48717, 57483
4733	melanoma antigen family D 1	599927	4888	469692	13654	22420, 31186, 39952, 48718, 57484
4734	melanoma antigen family D 4B	595965	4889	470563	13655	22421, 31187, 39953, 48719, 57485
4735	melanoma antigen family D 4B	600173	4890	472359	13656	22422, 31188, 39954, 48720, 57486
4736	melanoma associated antigen (mutated) 1-like 1	337685	4891	338641	13657	22423, 31189, 39955, 48721, 57487
4737	melanoma associated antigen (mutated) 1-like 1	357175	4892	349699	13658	22424, 31190, 39956, 48722, 57488
4738	melanoma associated antigen (mutated) 1-like 1	372552	4893	361632	13659	22425, 31191, 39957, 48723, 57489
4739	melanoma inhibitory activity	594436	4894	470129	13660	22426, 31192, 39958, 48724, 57490
4740	melanoma-associated antigen D4 isoform 1	599522	4895	472118	13661	22427, 31193, 39959, 48725, 57491
4741	membrane associated guanylate kinase WW and PDZ domain containing 3	307546	4896	304604	13662	22428, 31194, 39960, 48726, 57492
4742	membrane associated guanylate kinase, WW and PDZ domain containing 3	369611	4897	358624	13663	22429, 31195, 39961, 48727, 57493
4743	membrane associated guanylate kinase, WW and PDZ domain containing 3	369615	4898	358628	13664	22430, 31196, 39962, 48728, 57494
4744	membrane associated guanylate kinase, WW and PDZ domain containing 3	546156	4899	446449	13665	22431, 31197, 39963, 48729, 57495
4745	membrane bound O-acyltransferase domain containing 7	572955	4900	461623	13666	22432, 31198, 39964, 48730, 57496
4746	membrane bound O-acyltransferase domain containing 7	576648	4901	459249	13667	22433, 31199, 39965, 48731, 57497
4747	membrane bound O-acyltransferase domain containing 7	593567	4902	470647	13668	22434, 31200, 39966, 48732, 57498

4748	membrane bound O-acyltransferase domain containing 7	595855	4903	472750	13669	22435, 31201, 39967, 48733, 57499
4749	membrane bound O-acyltransferase domain containing 7	596150	4904	472598	13670	22436, 31202, 39968, 48734, 57500
4750	membrane bound O-acyltransferase domain containing 7	596448	4905	472241	13671	22437, 31203, 39969, 48735, 57501
4751	membrane bound O-acyltransferase domain containing 7	596610	4906	471823	13672	22438, 31204, 39970, 48736, 57502
4752	membrane bound O-acyltransferase domain containing 7	597059	4907	471931	13673	22439, 31205, 39971, 48737, 57503
4753	membrane bound O-acyltransferase domain containing 7	597311	4908	473045	13674	22440, 31206, 39972, 48738, 57504
4754	membrane bound O-acyltransferase domain containing 7	598214	4909	471119	13675	22441, 31207, 39973, 48739, 57505
4755	membrane bound O-acyltransferase domain containing 7	600618	4910	470646	13676	22442, 31208, 39974, 48740, 57506
4756	membrane bound O-acyltransferase domain containing 7	601767	4911	469051	13677	22443, 31209, 39975, 48741, 57507
4757	membrane-associated ring finger (C3HC4) 8 E3 ubiquitin protein ligase	574996	4912	459823	13678	22444, 31210, 39976, 48742, 57508
4758	mesoderm development candidate 1	267984	4913	267984	13679	22445, 31211, 39977, 48743, 57509
4759	mesoderm specific transcript homolog (mouse)	578652	4914	462286	13680	22446, 31212, 39978, 48744, 57510
4760	mesoderm specific transcript homolog (mouse)	582292	4915	463571	13681	22447, 31213, 39979, 48745, 57511
4761	mesoderm specific transcript homolog (mouse)	583792	4916	464161	13682	22448, 31214, 39980, 48746, 57512
4762	mesoderm specific transcript homolog (mouse)	585116	4917	463883	13683	22449, 31215, 39981, 48747, 57513
4763	metallo-beta-lactamase domain containing 1	398075	4918	381150	13684	22450, 31216, 39982, 48748, 57514
4764	metallo-beta-lactamase domain containing 1	421390	4919	406055	13685	22451, 31217, 39983, 48749,

						57515
4765	metallo-beta-lactamase domain containing 2	316610	4920	314776	13686	22452, 31218, 39984, 48750, 57516
4766	metallo-beta-lactamase domain containing 2	514906	4921	425600	13687	22453, 31219, 39985, 48751, 57517
4767	metallo-beta-lactamase domain-containing protein 2	546270	4922	441290	13688	22454, 31220, 39986, 48752, 57518
4768	metallo-beta-lactamase domain-containing protein 2	556122	4923	450811	13689	22455, 31221, 39987, 48753, 57519
4769	metallothionein 1C, pseudogene	379816	4924	369144	13690	22456, 31222, 39988, 48754, 57520
4770	metallothionein 1J, pseudogene	444023	4925	412277	13691	22457, 31223, 39989, 48755, 57521
4771	metallothionein 1M	379818	4926	369146	13692	22458, 31224, 39990, 48756, 57522
4772	metastasis suppressor 1-like	254951	4927	254951	13693	22459, 31225, 39991, 48757, 57523
4773	metastasis suppressor 1-like	338779	4928	341171	13694	22460, 31226, 39992, 48758, 57524
4774	methenyltetrahydrofolate synthetase domain containing	322911	4929	326777	13695	22461, 31227, 39993, 48759, 57525
4775	methenyltetrahydrofolate synthetase domain containing	360900	4930	354152	13696	22462, 31228, 39994, 48760, 57526
4776	methenyltetrahydrofolate synthetase domain containing	381214	4931	370612	13697	22463, 31229, 39995, 48761, 57527
4777	methenyltetrahydrofolate synthetase domain containing	543303	4932	444003	13698	22464, 31230, 39996, 48762, 57528
4778	methenyltetrahydrofolate synthetase domain containing	546093	4933	438761	13699	22465, 31231, 39997, 48763, 57529
4779	methionine sulfoxide reductase A	382490	4934	371930	13700	22466, 31232, 39998, 48764, 57530
4780	methionine sulfoxide reductase A	441698	4935	410912	13701	22467, 31233, 39999, 48765, 57531
4781	methionine sulfoxide	528246	4936	436839	13702	22468, 31234,

	reductase A					40000, 48766, 57532
4782	methyl-CpG binding domain protein 3-like 2	381393	4937	370800	13703	22469, 31235, 40001, 48767, 57533
4783	methyl-CpG binding domain protein 3-like 2	412046	4938	411843	13704	22470, 31236, 40002, 48768, 57534
4784	methyl-CpG binding domain protein 3-like 3	333843	4939	333183	13705	22471, 31237, 40003, 48769, 57535
4785	methyl-CpG binding domain protein 3-like 4	381394	4940	370801	13706	22472, 31238, 40004, 48770, 57536
4786	methyl-CpG binding domain protein 3-like 5	329753	4941	331435	13707	22473, 31239, 40005, 48771, 57537
4787	methyl-CpG binding domain protein 3-like 5	450263	4942	392955	13708	22474, 31240, 40006, 48772, 57538
4788	Methyl-CpG-binding domain protein 3-like 2	358469	4943	351254	13709	22475, 31241, 40007, 48773, 57539
4789	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase	216605	4944	216605	13710	22476, 31242, 40008, 48774, 57540
4790	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase	555709	4945	450560	13711	22477, 31243, 40009, 48775, 57541
4791	methyltransferase like 11B	439373	4946	408058	13712	22478, 31244, 40010, 48776, 57542
4792	methyltransferase like 13	341850	4947	341732	13713	22479, 31245, 40011, 48777, 57543
4793	methyltransferase like 13	361735	4948	354920	13714	22480, 31246, 40012, 48778, 57544
4794	methyltransferase like 13	362019	4949	355393	13715	22481, 31247, 40013, 48779, 57545
4795	methyltransferase like 13	367737	4950	356711	13716	22482, 31248,

						40014, 48780, 57546
4796	methyltransferase like 13	458517	4951	401955	13717	22483, 31249, 40015, 48781, 57547
4797	methyltransferase like 15	303459	4952	307251	13718	22484, 31250, 40016, 48782, 57548
4798	methyltransferase like 15	342303	4953	342259	13719	22485, 31251, 40017, 48783, 57549
4799	methyltransferase like 15	379199	4954	368497	13720	22486, 31252, 40018, 48784, 57550
4800	methyltransferase like 15	407364	4955	384369	13721	22487, 31253, 40019, 48785, 57551
4801	methyltransferase like 16	263092	4956	263092	13722	22488, 31254, 40020, 48786, 57552
4802	methyltransferase like 16	399834	4957	382729	13723	22489, 31255, 40021, 48787, 57553
4803	methyltransferase like 16	537138	4958	441105	13724	22490, 31256, 40022, 48788, 57554
4804	methyltransferase like 16	538844	4959	443633	13725	22491, 31257, 40023, 48789, 57555
4805	methyltransferase like 21C	267273	4960	267273	13726	22492, 31258, 40024, 48790, 57556
4806	methyltransferase like 21D	358490	4961	351279	13727	22493, 31259, 40025, 48791, 57557
4807	methyltransferase like 21D	395859	4962	379200	13728	22494, 31260, 40026, 48792, 57558
4808	methyltransferase like 21D	395860	4963	379201	13729	22495, 31261, 40027, 48793, 57559
4809	methyltransferase like 22	163678	4964	163678	13730	22496, 31262, 40028, 48794, 57560, 61535, 61593
4810	methyltransferase like 22	381920	4965	371345	13731	22497, 31263, 40029, 48795, 57561
4811	methyltransferase like 2A	311506	4966	309610	13732	22498, 31264, 40030, 48796,

						57562
4812	methyltransferase like 2A	333483	4967	331401	13733	22499, 31265, 40031, 48797, 57563
4813	methyltransferase like 2B	262432	4968	262432	13734	22500, 31266, 40032, 48798, 57564
4814	methyltransferase like 4	319888	4969	320349	13735	22501, 31267, 40033, 48799, 57565
4815	methyltransferase like 4	574538	4970	458290	13736	22502, 31268, 40034, 48800, 57566
4816	methyltransferase like 6	383790	4971	373300	13737	22503, 31269, 40035, 48801, 57567
4817	methyltransferase like 6	443029	4972	407613	13738	22504, 31270, 40036, 48802, 57568
4818	methyltransferase like 7B	394252	4973	377796	13739	22505, 31271, 40037, 48803, 57569
4819	methyltransferase like 9	358154	4974	350874	13740	22506, 31272, 40038, 48804, 57570
4820	methyltransferase like 9	396014	4975	379335	13741	22507, 31273, 40039, 48805, 57571
4821	methyltransferase like 9	540294	4976	445739	13742	22508, 31274, 40040, 48806, 57572
4822	MGC39584 protein	400767	4977	383578	13743	22509, 31275, 40041, 48807, 57573
4823	MGC9913 proteinUncharacterized protein	299997	4978	299997	13744	22510, 31276, 40042, 48808, 57574
4824	microtubule associated serine/threonine kinase family member 4	261569	4979	261569	13745	22511, 31277, 40043, 48809, 57575
4825	microtubule associated serine/threonine kinase family member 4	380908	4980	370294	13746	22512, 31278, 40044, 48810, 57576
4826	microtubule associated serine/threonine kinase family member 4	403666	4981	384313	13747	22513, 31279, 40045, 48811, 57577
4827	microtubule associated serine/threonine kinase family member 4	404260	4982	385048	13748	22514, 31280, 40046, 48812, 57578
4828	microtubule associated	405643	4983	384099	13749	22515, 31281,

	serine/threonine kinase family member 4					40047, 48813, 57579
4829	microtubule associated serine/threonine kinase family member 4	406374	4984	385088	13750	22516, 31282, 40048, 48814, 57580
4830	microtubule associated serine/threonine kinase family member 4	432399	4985	398073	13751	22517, 31283, 40049, 48815, 57581
4831	microtubule associated serine/threonine kinase family member 4	436277	4986	392478	13752	22518, 31284, 40050, 48816, 57582
4832	microtubule associated serine/threonine kinase family member 4	403625	4987	385727	13753	22519, 31285, 40051, 48817, 57583
4833	microtubule-associated protein tau isoform 8	447599	4988	387667	13754	22520, 31286, 40052, 48818, 57584
4834	microtubule-associated protein tau isoform 8	546644	4989	448412	13755	22521, 31287, 40053, 48819, 57585
4835	microtubule-associated protein tau isoform 8	547239	4990	450128	13756	22522, 31288, 40054, 48820, 57586
4836	microtubule-associated protein tau isoform 8	549053	4991	446927	13757	22523, 31289, 40055, 48821, 57587
4837	microtubule-associated protein tau isoform 8	549598	4992	449194	13758	22524, 31290, 40056, 48822, 57588
4838	microtubule-associated protein tau isoform 8	550493	4993	446811	13759	22525, 31291, 40057, 48823, 57589
4839	microtubule-associated protein tau isoform 8	550769	4994	447709	13760	22526, 31292, 40058, 48824, 57590
4840	microtubule-associated protein tau isoform 8	552530	4995	447810	13761	22527, 31293, 40059, 48825, 57591
4841	microtubule-associated protein tau isoform 8	552974	4996	448114	13762	22528, 31294, 40060, 48826, 57592
4842	microtubule-associated protein tau isoform 8	553101	4997	450356	13763	22529, 31295, 40061, 48827, 57593
4843	migration and invasion inhibitory protein	235332	4998	235332	13764	22530, 31296, 40062, 48828, 57594
4844	migration and invasion inhibitory protein	436478	4999	392417	13765	22531, 31297, 40063, 48829, 57595

4845	minichromosome maintenance complex component 9	243218	5000	243218	13766	22532, 31298, 40064, 48830, 57596
4846	minichromosome maintenance complex component 9	316068	5001	312870	13767	22533, 31299, 40065, 48831, 57597
4847	minichromosome maintenance complex component 9	316316	5002	314505	13768	22534, 31300, 40066, 48832, 57598
4848	minichromosome maintenance complex component 9	425154	5003	394776	13769	22535, 31301, 40067, 48833, 57599
4849	minichromosome maintenance complex component 9	505446	5004	426890	13770	22536, 31302, 40068, 48834, 57600
4850	missing oocyte, meiosis regulator, homolog (Drosophila)	340080	5005	339881	13771	22537, 31303, 40069, 48835, 57601
4851	missing oocyte, meiosis regulator, homolog (Drosophila)	405785	5006	384088	13772	22538, 31304, 40070, 48836, 57602
4852	missing oocyte, meiosis regulator, homolog (Drosophila)	433056	5007	407518	13773	22539, 31305, 40071, 48837, 57603
4853	missing oocyte, meiosis regulator, homolog (Drosophila)	433635	5008	413050	13774	22540, 31306, 40072, 48838, 57604
4854	missing oocyte, meiosis regulator, homolog (Drosophila)	445169	5009	413489	13775	22541, 31307, 40073, 48839, 57605
4855	missing oocyte, meiosis regulator, homolog (Drosophila)	456533	5010	410752	13776	22542, 31308, 40074, 48840, 57606
4856	mitochondrial ribosome recycling factor pseudogene 1	435941	5011	387841	13777	22543, 31309, 40075, 48841, 57607
4857	mitogen-activated protein kinase 1 interacting protein 1-like	395468	5012	378851	13778	22544, 31310, 40076, 48842, 57608
4858	mitogen-activated protein kinase binding protein 1	221214	5013	221214	13779	22545, 31311, 40077, 48843, 57609
4859	mitogen-activated protein kinase binding protein 1	260357	5014	260357	13780	22546, 31312, 40078, 48844, 57610
4860	mitogen-activated protein kinase binding protein 1	456763	5015	393099	13781	22547, 31313, 40079, 48845, 57611
4861	mitogen-activated protein kinase binding protein 1	457542	5016	397570	13782	22548, 31314, 40080, 48846,

						57612
4862	mitogen-activated protein kinase binding protein 1	510535	5017	422132	13783	22549, 31315, 40081, 48847, 57613
4863	mitogen-activated protein kinase binding protein 1	514566	5018	426154	13784	22550, 31316, 40082, 48848, 57614
4864	mitogen-activated protein kinase kinase kinase kinase 3	263881	5019	263881	13785	22551, 31317, 40083, 48849, 57615
4865	mitogen-activated protein kinase kinase kinase kinase 3	341681	5020	345434	13786	22552, 31318, 40084, 48850, 57616
4866	mitogen-activated protein kinase kinase kinase kinase 3	536018	5021	440580	13787	22553, 31319, 40085, 48851, 57617
4867	mitogen-activated protein kinase kinase kinase kinase 3	542094	5022	446291	13788	22554, 31320, 40086, 48852, 57618
4868	Mitogen-activated protein kinase kinase kinase MLK4	366622	5023	355581	13789	22555, 31321, 40087, 48853, 57619
4869	Mitogen-activated protein kinase kinase kinase MLK4	366623	5024	355582	13790	22556, 31322, 40088, 48854, 57620
4870	Mitogen-activated protein kinase kinase kinase MLK4	366624	5025	355583	13791	22557, 31323, 40089, 48855, 57621
4871	mixed lineage kinase domain-like	306247	5026	303118	13792	22558, 31324, 40090, 48856, 57622
4872	mixed lineage kinase domain-like	308807	5027	308351	13793	22559, 31325, 40091, 48857, 57623
4873	MOB kinase activator 1A	396049	5028	379364	13794	22560, 31326, 40092, 48858, 57624
4874	MOB kinase activator 1A	409969	5029	386782	13795	22561, 31327, 40093, 48859, 57625
4875	MOB kinase activator 2	329957	5030	328694	13796	22562, 31328, 40094, 48860, 57626
4876	MOB kinase activator 3A	357066	5031	349575	13797	22563, 31329, 40095, 48861, 57627
4877	MOB kinase activator 3B	262244	5032	262244	13798	22564, 31330, 40096, 48862, 57628
4878	MOB kinase activator 3C	271139	5033	271139	13799	22565, 31331,

						40097, 48863, 57629
4879	MOB kinase activator 3C	319928	5034	315113	13800	22566, 31332, 40098, 48864, 57630
4880	MOB kinase activator 3C	371940	5035	361008	13801	22567, 31333, 40099, 48865, 57631
4881	MON1 homolog A (yeast)	296473	5036	296473	13802	22568, 31334, 40100, 48866, 57632
4882	MON1 homolog A (yeast)	455683	5037	404793	13803	22569, 31335, 40101, 48867, 57633
4883	MON2 homolog (S. cerevisiae)	261188	5038	261188	13804	22570, 31336, 40102, 48868, 57634
4884	MON2 homolog (S. cerevisiae)	280379	5039	280379	13805	22571, 31337, 40103, 48869, 57635
4885	MON2 homolog (S. cerevisiae)	393632	5040	377252	13806	22572, 31338, 40104, 48870, 57636
4886	MON2 homolog (S. cerevisiae)	546600	5041	447407	13807	22573, 31339, 40105, 48871, 57637
4887	MORC family CW-type zinc finger 4	255495	5042	255495	13808	22574, 31340, 40106, 48872, 57638
4888	MORC family CW-type zinc finger 4	355610	5043	347821	13809	22575, 31341, 40107, 48873, 57639
4889	MORC family CW-type zinc finger 4	535534	5044	440359	13810	22576, 31342, 40108, 48874, 57640
4890	Morf4 family associated protein 1-like 1	320848	5045	318154	13811	22577, 31343, 40109, 48875, 57641
4891	MORN repeat containing 1	378525	5046	367786	13812	22578, 31344, 40110, 48876, 57642
4892	MORN repeat containing 1	378529	5047	367790	13813	22579, 31345, 40111, 48877, 57643
4893	MORN repeat containing 1	378531	5048	367792	13814	22580, 31346, 40112, 48878, 57644
4894	MORN repeat containing 1	419785	5049	390690	13815	22581, 31347, 40113, 48879, 57645

4895	MORN repeat containing 1	449373	5050	390261	13816	22582, 31348, 40114, 48880, 57646
4896	MORN repeat containing 2	340556	5051	344551	13817	22583, 31349, 40115, 48881, 57647
4897	MORN repeat containing 2	409665	5052	386874	13818	22584, 31350, 40116, 48882, 57648
4898	MORN repeat containing 2	410014	5053	386563	13819	22585, 31351, 40117, 48883, 57649
4899	MORN repeat containing 3	355329	5054	347486	13820	22586, 31352, 40118, 48884, 57650
4900	MORN repeat containing 4	307450	5055	307636	13821	22587, 31353, 40119, 48885, 57651
4901	MORN repeat containing 4	335628	5056	335498	13822	22588, 31354, 40120, 48886, 57652
4902	MORN repeat containing 4	515674	5057	423222	13823	22589, 31355, 40121, 48887, 57653
4903	MORN repeat containing 5	373764	5058	362869	13824	22590, 31356, 40122, 48888, 57654
4904	MORN repeat containing 5	418632	5059	409949	13825	22591, 31357, 40123, 48889, 57655
4905	MORN repeat containing 5	536616	5060	437483	13826	22592, 31358, 40124, 48890, 57656
4906	MPN domain containing	262966	5061	262966	13827	22593, 31359, 40125, 48891, 57657
4907	MPN domain containing	359935	5062	353015	13828	22594, 31360, 40126, 48892, 57658
4908	MSANTD3-TMEFF1 readthrough	502978	5063	424768	13829	22595, 31361, 40127, 48893, 57659
4909	MSH5-SAPCD1 readthrough (non-protein coding)	491552	5064	419590	13830	22596, 31362, 40128, 48894, 57660
4910	MTERF domain containing 2	391980	5065	375840	13831	22597, 31363, 40129, 48895, 57661
4911	MT-RNR2-like 1	540040	5066	439228	13832	22598, 31364, 40130, 48896,

						57662
4912	MT-RNR2-like 10	545075	5067	442159	13833	22599, 31365, 40131, 48897, 57663
4913	MT-RNR2-like 3	543500	5068	443339	13834	22600, 31366, 40132, 48898, 57664
4914	MT-RNR2-like 4	399974	5069	382856	13835	22601, 31367, 40133, 48899, 57665
4915	MT-RNR2-like 5	512524	5070	437910	13836	22602, 31368, 40134, 48900, 57666
4916	MT-RNR2-like 6	570419	5071	461075	13837	22603, 31369, 40135, 48901, 57667
4917	MT-RNR2-like 7	544824	5072	439985	13838	22604, 31370, 40136, 48902, 57668
4918	MT-RNR2-like 8	536684	5073	439666	13839	22605, 31371, 40137, 48903, 57669
4919	MT-RNR2-like 9 (pseudogene)	544932	5074	445746	13840	22606, 31372, 40138, 48904, 57670
4920	mucin 16, cell surface associated	380951	5075	370338	13841	22607, 31373, 40139, 48905, 57671
4921	mucin 16, cell surface associated	397910	5076	446163	13842	22608, 31374, 40140, 48906, 57672
4922	mucin 16, cell surface associated	441155	5077	408623	13843	22609, 31375, 40141, 48907, 57673
4923	mucin 22	561890	5078	455906	13844	22610, 31376, 40142, 48908, 57674
4924	Mucin-21	430305	5079	414676	13845	22611, 31377, 40143, 48909, 57675
4925	Mucin-21	440457	5080	401817	13846	22612, 31378, 40144, 48910, 57676
4926	Mucin-21	451480	5081	393390	13847	22613, 31379, 40145, 48911, 57677
4927	Mucin-21	547796	5082	447919	13848	22614, 31380, 40146, 48912, 57678
4928	Mucin-21	548519	5083	446869	13849	22615, 31381,

						40147, 48913, 57679
4929	Mucin-21	551445	5084	448909	13850	22616, 31382, 40148, 48914, 57680
4930	mutS homolog 5 (E. coli)	412630	5085	406310	13851	22617, 31383, 40149, 48915, 57681
4931	mutS homolog 5 (E. coli)	412975	5086	409468	13852	22618, 31384, 40150, 48916, 57682
4932	mutS homolog 5 (E. coli)	414810	5087	402188	13853	22619, 31385, 40151, 48917, 57683
4933	mutS homolog 5 (E. coli)	416819	5088	405073	13854	22620, 31386, 40152, 48918, 57684
4934	mutS homolog 5 (E. coli)	420729	5089	415135	13855	22621, 31387, 40153, 48919, 57685
4935	mutS homolog 5 (E. coli)	425344	5090	404249	13856	22622, 31388, 40154, 48920, 57686
4936	mutS homolog 5 (E. coli)	427687	5091	401120	13857	22623, 31389, 40155, 48921, 57687
4937	mutS homolog 5 (E. coli)	427968	5092	401072	13858	22624, 31390, 40156, 48922, 57688
4938	mutS homolog 5 (E. coli)	430216	5093	398538	13859	22625, 31391, 40157, 48923, 57689
4939	mutS homolog 5 (E. coli)	430241	5094	393445	13860	22626, 31392, 40158, 48924, 57690
4940	mutS homolog 5 (E. coli)	442688	5095	387397	13861	22627, 31393, 40159, 48925, 57691
4941	mutS homolog 5 (E. coli)	443906	5096	410698	13862	22628, 31394, 40160, 48926, 57692
4942	mutS homolog 5 (E. coli)	444225	5097	389840	13863	22629, 31395, 40161, 48927, 57693
4943	mutS homolog 5 (E. coli)	445511	5098	415294	13864	22630, 31396, 40162, 48928, 57694
4944	mutS homolog 5 (E. coli)	446724	5099	391330	13865	22631, 31397, 40163, 48929, 57695

4945	mutS homolog 5 (E. coli)	454820	5100	405530	13866	22632, 31398, 40164, 48930, 57696
4946	mutS homolog 5 (E. coli)	456073	5101	399898	13867	22633, 31399, 40165, 48931, 57697
4947	mutS homolog 5 (E. coli)	456436	5102	397187	13868	22634, 31400, 40166, 48932, 57698
4948	mutS homolog 5 (E. coli)	457917	5103	394619	13869	22635, 31401, 40167, 48933, 57699
4949	mutS homolog 5 (E. coli)	458058	5104	413831	13870	22636, 31402, 40168, 48934, 57700
4950	mutS homolog 5 (E. coli)	458424	5105	403809	13871	22637, 31403, 40169, 48935, 57701
4951	mutS homolog 5 (E. coli)	550255	5106	447377	13872	22638, 31404, 40170, 48936, 57702
4952	mutS homolog 5 (E. coli)	554793	5107	451673	13873	22639, 31405, 40171, 48937, 57703
4953	Myb/SANT-like DNA-binding domain containing 3	374885	5108	364020	13874	22640, 31406, 40172, 48938, 57704
4954	myeloid-associated differentiation marker-like 2	330655	5109	327718	13875	22641, 31407, 40173, 48939, 57705
4955	myeloid-associated differentiation marker-like 2	409745	5110	386702	13876	22642, 31408, 40174, 48940, 57706
4956	myeloma overexpressed 2	307266	5111	304147	13877	22643, 31409, 40175, 48941, 57707
4957	myeloma overexpressed 2	403160	5112	383946	13878	22644, 31410, 40176, 48942, 57708
4958	myomesin family, member 3	329601	5113	328415	13879	22645, 31411, 40177, 48943, 57709
4959	myomesin family, member 3	330966	5114	332670	13880	22646, 31412, 40178, 48944, 57710
4960	myomesin family, member 3	338909	5115	342689	13881	22647, 31413, 40179, 48945, 57711
4961	myomesin family, member 3	374434	5116	363557	13882	22648, 31414, 40180, 48946,

						57712
4962	myomesin family, member 3	374442	5117	363565	13883	22649, 31415, 40181, 48947, 57713
4963	myosin binding protein H-like	357155	5118	349678	13884	22650, 31416, 40182, 48948, 57714
4964	myosin XVB pseudogene	293201	5119	293201	13885	22651, 31417, 40183, 48949, 57715
4965	myotubularin related protein 1	594143	5120	472612	13886	22652, 31418, 40184, 48950, 57716
4966	myotubularin related protein 10	314404	5121	313788	13887	22653, 31419, 40185, 48951, 57717
4967	myotubularin related protein 10	340566	5122	340637	13888	22654, 31420, 40186, 48952, 57718
4968	myotubularin related protein 10	425768	5123	412314	13889	22655, 31421, 40187, 48953, 57719
4969	myotubularin related protein 10	435680	5124	402537	13890	22656, 31422, 40188, 48954, 57720
4970	myotubularin related protein 11	361405	5125	354941	13891	22657, 31423, 40189, 48955, 57721
4971	myotubularin related protein 11	369140	5126	358136	13892	22658, 31424, 40190, 48956, 57722
4972	myotubularin related protein 11	405710	5127	384228	13893	22659, 31425, 40191, 48957, 57723
4973	myotubularin related protein 11	406732	5128	383948	13894	22660, 31426, 40192, 48958, 57724
4974	myotubularin related protein 11	439741	5129	391668	13895	22661, 31427, 40193, 48959, 57725
4975	N(alpha)-acetyltransferase 10 NatA catalytic subunit	596061	5130	469041	13896	22662, 31428, 40194, 48960, 57726
4976	N(alpha)-acetyltransferase 10 NatA catalytic subunit	596770	5131	469576	13897	22663, 31429, 40195, 48961, 57727
4977	N(alpha)-acetyltransferase 40, NatD catalytic subunit, homolog (S. cerevisiae)	377793	5132	367024	13898	22664, 31430, 40196, 48962, 57728
4978	N(alpha)-acetyltransferase	456907	5133	407578	13899	22665, 31431,

	40, NatD catalytic subunit, homolog (S. cerevisiae)					40197, 48963, 57729
4979	N-6 adenine-specific DNA methyltransferase 2 (putative)	382754	5134	372202	13900	22666, 31432, 40198, 48964, 57730
4980	N-6 adenine-specific DNA methyltransferase 2 (putative)	382758	5135	372206	13901	22667, 31433, 40199, 48965, 57731
4981	N-acetyltransferase 16 (GCN5-related, putative)	300303	5136	300303	13902	22668, 31434, 40200, 48966, 57732
4982	N-acetyltransferase 16 (GCN5-related, putative)	444446	5137	391769	13903	22669, 31435, 40201, 48967, 57733
4983	N-acetyltransferase 16 (GCN5-related, putative)	455377	5138	395125	13904	22670, 31436, 40202, 48968, 57734
4984	N-acetyltransferase 6 (GCN5-related)	570345	5139	459273	13905	22671, 31437, 40203, 48969, 57735
4985	N-acetyltransferase 6 (GCN5-related)	575928	5140	458407	13906	22672, 31438, 40204, 48970, 57736
4986	N-acetyltransferase 9 (GCN5-related, putative)	357814	5141	350467	13907	22673, 31439, 40205, 48971, 57737
4987	NACHT and WD repeat domain containing 1	339803	5142	340159	13908	22674, 31440, 40206, 48972, 57738
4988	NACHT and WD repeat domain containing 1	379808	5143	369136	13909	22675, 31441, 40207, 48973, 57739
4989	NACHT and WD repeat domain containing 1	420818	5144	391461	13910	22676, 31442, 40208, 48974, 57740
4990	NACHT and WD repeat domain containing 1	523826	5145	428955	13911	22677, 31443, 40209, 48975, 57741
4991	NACHT and WD repeat domain containing 1	524140	5146	428579	13912	22678, 31444, 40210, 48976, 57742
4992	N-acyl phosphatidylethanolamine phospholipase D	341533	5147	340093	13913	22679, 31445, 40211, 48977, 57743
4993	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B	185907	5148	185907	13914	22680, 31446, 40212, 48978, 57744
4994	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B	374006	5149	363118	13915	22681, 31447, 40213, 48979, 57745

4995	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2B	374007	5150	363119	13916	22682, 31448, 40214, 48980, 57746
4996	NAD(P) dependent steroid dehydrogenase-like	597693	5151	468920	13917	22683, 31449, 40215, 48981, 57747
4997	NAD(P) dependent steroid dehydrogenase-like	601774	5152	471515	13918	22684, 31450, 40216, 48982, 57748
4998	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2	393825	5153	377411	13919	22685, 31451, 40217, 48983, 57749
4999	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4-like 2	554503	5154	450664	13920	22686, 31452, 40218, 48984, 57750
5000	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa	379847	5155	369176	13921	22687, 31453, 40219, 48985, 57751
5001	NADP-dependent oxidoreductase domain containing 1	298358	5156	298358	13922	22688, 31454, 40220, 48986, 57752
5002	NADP-dependent oxidoreductase domain containing 1	380835	5157	370215	13923	22689, 31455, 40221, 48987, 57753
5003	NADP-dependent oxidoreductase domain containing 1	555603	5158	450597	13924	22690, 31456, 40222, 48988, 57754
5004	Nanog homeobox pseudogene 1	530989	5159	432545	13925	22691, 31457, 40223, 48989, 57755
5005	natural cytotoxicity triggering receptor 1	570317	5160	459017	13926	22692, 31458, 40224, 48990, 57756
5006	natural cytotoxicity triggering receptor 1	572535	5161	458207	13927	22693, 31459, 40225, 48991, 57757
5007	natural cytotoxicity triggering receptor 1	572865	5162	459679	13928	22694, 31460, 40226, 48992, 57758
5008	natural cytotoxicity triggering receptor 1	573217	5163	461159	13929	22695, 31461, 40227, 48993, 57759
5009	natural cytotoxicity triggering receptor 1	573696	5164	461573	13930	22696, 31462, 40228, 48994, 57760
5010	natural cytotoxicity triggering receptor 1	574562	5165	461704	13931	22697, 31463, 40229, 48995, 57761
5011	natural cytotoxicity triggering receptor 1	576561	5166	460566	13932	22698, 31464, 40230, 48996,

						57762
5012	natural cytotoxicity triggering receptor 1	576773	5167	461161	13933	22699, 31465, 40231, 48997, 57763
5013	NCK-associated protein 5	317721	5168	380603	13934	22700, 31466, 40232, 48998, 57764
5014	NCK-associated protein 5	358991	5169	351882	13935	22701, 31467, 40233, 48999, 57765
5015	NCK-associated protein 5	405974	5170	385692	13936	22702, 31468, 40234, 49000, 57766
5016	NCK-associated protein 5	409213	5171	386952	13937	22703, 31469, 40235, 49001, 57767
5017	NCK-associated protein 5	409261	5172	387128	13938	22704, 31470, 40236, 49002, 57768
5018	NCK-associated protein 5	537661	5173	441491	13939	22705, 31471, 40237, 49003, 57769
5019	NCK-associated protein 5	542834	5174	438467	13940	22706, 31472, 40238, 49004, 57770
5020	NCK-associated protein 5-like	335999	5175	337998	13941	22707, 31473, 40239, 49005, 57771
5021	NCK-associated protein 5-like	354423	5176	346405	13942	22708, 31474, 40240, 49006, 57772
5022	NDRG family member 4	258187	5177	258187	13943	22709, 31475, 40241, 49007, 57773
5023	NDRG family member 4	356752	5178	349193	13944	22710, 31476, 40242, 49008, 57774
5024	NDRG family member 4	394279	5179	377820	13945	22711, 31477, 40243, 49009, 57775
5025	NDRG family member 4	394282	5180	377823	13946	22712, 31478, 40244, 49010, 57776
5026	NDRG family member 4	421602	5181	388125	13947	22713, 31479, 40245, 49011, 57777
5027	NDRG family member 4	566192	5182	454410	13948	22714, 31480, 40246, 49012, 57778
5028	NDRG family member 4	570248	5183	457659	13949	22715, 31481,

						40247, 49013, 57779
5029	NDUFC2-KCTD14 readthrough	530054	5184	432614	13950	22716, 31482, 40248, 49014, 57780
5030	NEDD4 binding protein 2-like 1	380130	5185	369473	13951	22717, 31483, 40249, 49015, 57781
5031	NEDD4 binding protein 2-like 1	530622	5186	435515	13952	22718, 31484, 40250, 49016, 57782
5032	NEDD4 binding protein 2-like 1	380139	5187	369484	13953	22719, 31485, 40251, 49017, 57783
5033	NEDD4 binding protein 2-like 2	267068	5188	267068	13954	22720, 31486, 40252, 49018, 57784
5034	NEDD4 binding protein 2-like 2	357505	5189	350104	13955	22721, 31487, 40253, 49019, 57785
5035	NEDD4 binding protein 2-like 2	399396	5190	382328	13956	22722, 31488, 40254, 49020, 57786
5036	NEDD8-MDP1 readthrough	534348	5191	431482	13957	22723, 31489, 40255, 49021, 57787
5037	neighbor of BRCA1 gene 2 (non-protein coding)	356906	5192	349375	13958	22724, 31490, 40256, 49022, 57788
5038	neural cell adhesion molecule 1	576604	5193	459932	13959	22725, 31491, 40257, 49023, 57789
5039	neural cell adhesion molecule 1	592855	5194	467282	13960	22726, 31492, 40258, 49024, 57790
5040	neural cell adhesion molecule 1	593059	5195	466769	13961	22727, 31493, 40259, 49025, 57791
5041	neuralized homolog 1B (Drosophila)	369800	5196	358815	13962	22728, 31494, 40260, 49026, 57792
5042	neuralized homolog 4 (Drosophila)	315614	5197	319826	13963	22729, 31495, 40261, 49027, 57793
5043	neuralized homolog 4 (Drosophila)	399464	5198	382390	13964	22730, 31496, 40262, 49028, 57794
5044	neuroblastoma breakpoint family member 11	580077	5199	463391	13965	22731, 31497, 40263, 49029, 57795

5045	neuroblastoma breakpoint family, member 24	369226	5200	358228	13966	22732, 31498, 40264, 49030, 57796
5046	neuroblastoma breakpoint family, member 24	369227	5201	358229	13967	22733, 31499, 40265, 49031, 57797
5047	neuroblastoma breakpoint family, member 24	369228	5202	358230	13968	22734, 31500, 40266, 49032, 57798
5048	neuroblastoma breakpoint family, member 24	401006	5203	383791	13969	22735, 31501, 40267, 49033, 57799
5049	neurofascin	295776	5204	295776	13970	22736, 31502, 40268, 49034, 57800
5050	neurofascin	338515	5205	342128	13971	22737, 31503, 40269, 49035, 57801
5051	neurofascin	338586	5206	343509	13972	22738, 31504, 40270, 49036, 57802
5052	neurofascin	339876	5207	344786	13973	22739, 31505, 40271, 49037, 57803
5053	neurofascin	360049	5208	353154	13974	22740, 31506, 40272, 49038, 57804
5054	neurofascin	367169	5209	356137	13975	22741, 31507, 40273, 49039, 57805
5055	neurofascin	367170	5210	356138	13976	22742, 31508, 40274, 49040, 57806
5056	neurofascin	367171	5211	356139	13977	22743, 31509, 40275, 49041, 57807
5057	neurofascin	367172	5212	356140	13978	22744, 31510, 40276, 49042, 57808
5058	neurofascin	401399	5213	385637	13979	22745, 31511, 40277, 49043, 57809
5059	neurofascin	403080	5214	384875	13980	22746, 31512, 40278, 49044, 57810
5060	neurofascin	404907	5215	384061	13981	22747, 31513, 40279, 49045, 57811
5061	neurofascin	430393	5216	415031	13982	22748, 31514, 40280, 49046,

						57812
5062	neurofascin	446412	5217	412161	13983	22749, 31515, 40281, 49047, 57813
5063	neurofascin	505079	5218	427586	13984	22750, 31516, 40282, 49048, 57814
5064	neurofascin	513543	5219	425908	13985	22751, 31517, 40283, 49049, 57815
5065	neurofascin	539706	5220	438614	13986	22752, 31518, 40284, 49050, 57816
5066	neuronal pentraxin receptor	333039	5221	327545	13987	22753, 31519, 40285, 49051, 57817
5067	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 1	300179	5222	300179	13988	22754, 31520, 40286, 49052, 57818
5068	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 1	423930	5223	411861	13989	22755, 31521, 40287, 49053, 57819
5069	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 1	454988	5224	394424	13990	22756, 31522, 40288, 49054, 57820
5070	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 2	272907	5225	272907	13991	22757, 31523, 40289, 49055, 57821
5071	neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor 2	409269	5226	386437	13992	22758, 31524, 40290, 49056, 57822
5072	neuropeptide W	329610	5227	330070	13993	22759, 31525, 40291, 49057, 57823
5073	NF-kappa-B essential modulator isoform a	594239	5228	471166	13994	22760, 31526, 40292, 49058, 57824
5074	NFKB activating protein-like	343684	5229	345716	13995	22761, 31527, 40293, 49059, 57825
5075	NFKB inhibitor interacting Ras-like 2	562265	5230	457014	13996	22762, 31528, 40294, 49060, 57826
5076	NHL repeat containing 2	369301	5231	358307	13997	22763, 31529, 40295, 49061,

						57827
5077	NHL repeat containing 4	424439	5232	410858	13998	22764, 31530, 40296, 49062, 57828
5078	NHL repeat containing 4	540585	5233	442223	13999	22765, 31531, 40297, 49063, 57829
5079	NHS-like 1	343505	5234	344672	14000	22766, 31532, 40298, 49064, 57830
5080	NHS-like 1	427025	5235	394546	14001	22767, 31533, 40299, 49065, 57831
5081	NHS-like 2	373677	5236	362781	14002	22768, 31534, 40300, 49066, 57832
5082	NHS-like 2	535692	5237	444914	14003	22769, 31535, 40301, 49067, 57833
5083	NHS-like 2	540800	5238	444617	14004	22770, 31536, 40302, 49068, 57834
5084	NIMA (never in mitosis gene a)- related kinase 10	341435	5239	343847	14005	22771, 31537, 40303, 49069, 57835
5085	NIMA (never in mitosis gene a)- related kinase 10	357467	5240	350059	14006	22772, 31538, 40304, 49070, 57836
5086	NIMA (never in mitosis gene a)- related kinase 10	383770	5241	373280	14007	22773, 31539, 40305, 49071, 57837
5087	NIMA (never in mitosis gene a)- related kinase 10	383771	5242	373281	14008	22774, 31540, 40306, 49072, 57838
5088	NIMA (never in mitosis gene a)- related kinase 10	396636	5243	379876	14009	22775, 31541, 40307, 49073, 57839
5089	NIMA (never in mitosis gene a)- related kinase 10	429845	5244	395849	14010	22776, 31542, 40308, 49074, 57840
5090	NIMA (never in mitosis gene a)- related kinase 10	435750	5245	395338	14011	22777, 31543, 40309, 49075, 57841
5091	NIMA (never in mitosis gene a)-related kinase 5	355568	5246	347767	14012	22778, 31544, 40310, 49076, 57842
5092	NINP6167Uncharacterized protein	378432	5247	367689	14013	22779, 31545, 40311, 49077, 57843
5093	nipsnap homolog 3B (C.	374762	5248	363894	14014	22780, 31546,

	elegans)					40312, 49078, 57844
5094	nitrogen permease regulator-like 3 (S. cerevisiae)	262313	5249	262313	14015	22781, 31547, 40313, 49079, 57845
5095	nitrogen permease regulator-like 3 (S. cerevisiae)	399951	5250	382832	14016	22782, 31548, 40314, 49080, 57846
5096	nitrogen permease regulator-like 3 (S. cerevisiae)	399953	5251	382834	14017	22783, 31549, 40315, 49081, 57847
5097	nitrogen permease regulator-like 3 (S. cerevisiae)	399957	5252	382838	14018	22784, 31550, 40316, 49082, 57848
5098	NK1 homeobox 2	440536	5253	450924	14019	22785, 31551, 40317, 49083, 57849
5099	NK1 homeobox 2	451024	5254	451945	14020	22786, 31552, 40318, 49084, 57850
5100	NKG2-D type II integral membrane protein	543572	5255	456286	14021	22787, 31553, 40319, 49085, 57851
5101	NLR family pyrin domain containing 2	571222	5256	461575	14022	22788, 31554, 40320, 49086, 57852
5102	NLR family pyrin domain containing 2	571455	5257	461312	14023	22789, 31555, 40321, 49087, 57853
5103	NLR family pyrin domain containing 2	571477	5258	460381	14024	22790, 31556, 40322, 49088, 57854
5104	NLR family pyrin domain containing 2	571803	5259	459395	14025	22791, 31557, 40323, 49089, 57855
5105	NLR family pyrin domain containing 2	572364	5260	460916	14026	22792, 31558, 40324, 49090, 57856
5106	NLR family pyrin domain containing 2	572489	5261	459160	14027	22793, 31559, 40325, 49091, 57857
5107	NLR family pyrin domain containing 2	572578	5262	459694	14028	22794, 31560, 40326, 49092, 57858
5108	NLR family pyrin domain containing 2	572889	5263	461004	14029	22795, 31561, 40327, 49093, 57859
5109	NLR family pyrin domain containing 2	572900	5264	461005	14030	22796, 31562, 40328, 49094, 57860

5110	NLR family pyrin domain containing 2	573459	5265	459970	14031	22797, 31563, 40329, 49095, 57861
5111	NLR family pyrin domain containing 2	574207	5266	458572	14032	22798, 31564, 40330, 49096, 57862
5112	NLR family pyrin domain containing 2	574414	5267	461278	14033	22799, 31565, 40331, 49097, 57863
5113	NLR family pyrin domain containing 2	574461	5268	460772	14034	22800, 31566, 40332, 49098, 57864
5114	NLR family pyrin domain containing 2	574535	5269	459670	14035	22801, 31567, 40333, 49099, 57865
5115	NLR family pyrin domain containing 2	576464	5270	461311	14036	22802, 31568, 40334, 49100, 57866
5116	NLR family pyrin domain containing 2	576515	5271	459053	14037	22803, 31569, 40335, 49101, 57867
5117	NLR family pyrin domain containing 2	576631	5272	458217	14038	22804, 31570, 40336, 49102, 57868
5118	NLR family pyrin domain containing 2	576647	5273	458345	14039	22805, 31571, 40337, 49103, 57869
5119	NLR family pyrin domain containing 2	576909	5274	460773	14040	22806, 31572, 40338, 49104, 57870
5120	NLR family pyrin domain containing 2	576923	5275	459402	14041	22807, 31573, 40339, 49105, 57871
5121	NLR family pyrin domain containing 2	577030	5276	459166	14042	22808, 31574, 40340, 49106, 57872
5122	NLR family pyrin domain containing 7	570389	5277	461532	14043	22809, 31575, 40341, 49107, 57873
5123	NLR family pyrin domain containing 7	571114	5278	461064	14044	22810, 31576, 40342, 49108, 57874
5124	NLR family pyrin domain containing 7	571353	5279	461744	14045	22811, 31577, 40343, 49109, 57875
5125	NLR family pyrin domain containing 7	571397	5280	461321	14046	22812, 31578, 40344, 49110, 57876
5126	NLR family pyrin domain containing 7	571685	5281	459870	14047	22813, 31579, 40345, 49111,

						57877
5127	NLR family pyrin domain containing 7	572166	5282	459861	14048	22814, 31580, 40346, 49112, 57878
5128	NLR family pyrin domain containing 7	573287	5283	460652	14049	22815, 31581, 40347, 49113, 57879
5129	NLR family pyrin domain containing 7	573987	5284	459596	14050	22816, 31582, 40348, 49114, 57880
5130	NLR family pyrin domain containing 7	575015	5285	461257	14051	22817, 31583, 40349, 49115, 57881
5131	NLR family pyrin domain containing 7	575084	5286	458215	14052	22818, 31584, 40350, 49116, 57882
5132	NLR family pyrin domain containing 7	575386	5287	460076	14053	22819, 31585, 40351, 49117, 57883
5133	NLR family pyrin domain containing 7	576007	5288	459959	14054	22820, 31586, 40352, 49118, 57884
5134	NLR family pyrin domain containing 7	576140	5289	458310	14055	22821, 31587, 40353, 49119, 57885
5135	NLR family pyrin domain containing 7	576376	5290	459927	14056	22822, 31588, 40354, 49120, 57886
5136	NLR family pyrin domain containing 7	576609	5291	459548	14057	22823, 31589, 40355, 49121, 57887
5137	NLR family pyrin domain containing 7	576715	5292	458887	14058	22824, 31590, 40356, 49122, 57888
5138	NLR family pyrin domain containing 7	576774	5293	460017	14059	22825, 31591, 40357, 49123, 57889
5139	NLR family pyrin domain containing 7	577047	5294	460480	14060	22826, 31592, 40358, 49124, 57890
5140	NLR family pyrin domain containing 7	588756	5295	467123	14061	22827, 31593, 40359, 49125, 57891
5141	NLR family pyrin domain containing 7	588840	5296	467159	14062	22828, 31594, 40360, 49126, 57892
5142	NLR family pyrin domain containing 7	589382	5297	468657	14063	22829, 31595, 40361, 49127, 57893
5143	NLR family pyrin domain	589500	5298	468589	14064	22830, 31596,

	containing 7					40362, 49128, 57894
5144	NLR family pyrin domain containing 7	591176	5299	465388	14065	22831, 31597, 40363, 49129, 57895
5145	NLR family pyrin domain containing 7	592036	5300	466171	14066	22832, 31598, 40364, 49130, 57896
5146	NLR family pyrin domain containing 7	593150	5301	466209	14067	22833, 31599, 40365, 49131, 57897
5147	NLR family, CARD domain containing 4	342905	5302	339666	14068	22834, 31600, 40366, 49132, 57898
5148	NLR family, CARD domain containing 5	308149	5303	308886	14069	22835, 31601, 40367, 49133, 57899
5149	NLR family, CARD domain containing 5	327982	5304	329394	14070	22836, 31602, 40368, 49134, 57900
5150	NLR family, CARD domain containing 5	436936	5305	389739	14071	22837, 31603, 40369, 49135, 57901
5151	NLR family, CARD domain containing 5	538059	5306	441311	14072	22838, 31604, 40370, 49136, 57902
5152	NLR family, CARD domain containing 5	544641	5307	439464	14073	22839, 31605, 40371, 49137, 57903
5153	NLR family, pyrin domain containing 10	328600	5308	327763	14074	22840, 31606, 40372, 49138, 57904
5154	NLR family, pyrin domain containing 10	526590	5309	436255	14075	22841, 31607, 40373, 49139, 57905
5155	NLR family, pyrin domain containing 11	360133	5310	353251	14076	22842, 31608, 40374, 49140, 57906
5156	NLR family, pyrin domain containing 11	443188	5311	409898	14077	22843, 31609, 40375, 49141, 57907
5157	NLR family, pyrin domain containing 13	342929	5312	343891	14078	22844, 31610, 40376, 49142, 57908
5158	NLR family, pyrin domain containing 14	299481	5313	299481	14079	22845, 31611, 40377, 49143, 57909
5159	NLR family, pyrin domain containing 4	301295	5314	301295	14080	22846, 31612, 40378, 49144, 57910

5160	NLR family, pyrin domain containing 4	346986	5315	344787	14081	22847, 31613, 40379, 49145, 57911
5161	NLR family, pyrin domain containing 7	328092	5316	329568	14082	22848, 31614, 40380, 49146, 57912
5162	NLR family, pyrin domain containing 7	340844	5317	339491	14083	22849, 31615, 40381, 49147, 57913
5163	NLR family, pyrin domain containing 7	399724	5318	399301	14084	22850, 31616, 40382, 49148, 57914
5164	NLR family, pyrin domain containing 7	446217	5319	414273	14085	22851, 31617, 40383, 49149, 57915
5165	NLR family, pyrin domain containing 7	448121	5320	409137	14086	22852, 31618, 40384, 49150, 57916
5166	non-specific cytotoxic cell receptor protein 1 homolog (zebrafish)	339852	5321	342137	14087	22853, 31619, 40385, 49151, 57917
5167	NOP2/Sun domain family member 5	310326	5322	309126	14088	22854, 31620, 40386, 49152, 57918
5168	NOP2/Sun domain family member 5	428206	5323	393081	14089	22855, 31621, 40387, 49153, 57919
5169	NOP2/Sun domain family, member 3	314622	5324	318986	14090	22856, 31622, 40388, 49154, 57920
5170	NOP2/Sun domain family, member 4	474844	5325	419740	14091	22857, 31623, 40389, 49155, 57921
5171	NOP2/Sun domain family, member 4	536062	5326	438912	14092	22858, 31624, 40390, 49156, 57922
5172	NOP2/Sun domain family, member 4	537428	5327	437758	14093	22859, 31625, 40391, 49157, 57923
5173	NOP2/Sun domain family, member 5	252594	5328	252594	14094	22860, 31626, 40392, 49158, 57924
5174	NOP2/Sun domain family, member 5	438747	5329	388464	14095	22861, 31627, 40393, 49159, 57925
5175	NOP2/Sun domain family, member 6	377304	5330	366519	14096	22862, 31628, 40394, 49160, 57926
5176	NOP2/Sun domain family, member 7	381782	5331	371201	14097	22863, 31629, 40395, 49161,

						57927
5177	notch homolog 2 N-terminal-like protein	578207	5332	464060	14098	22864, 31630, 40396, 49162, 57928
5178	NOTCH-regulated ankyrin repeat protein	356628	5333	349041	14099	22865, 31631, 40397, 49163, 57929
5179	Novel protein (FLJ40547)Uncharacterized protein	317652	5334	315214	14100	22866, 31632, 40398, 49164, 57930
5180	Novel protein (KIAA0894)Sorbin and SH3 domain containing 1, isoform CRA_eUncharacterized protein	371228	5335	360272	14101	22867, 31633, 40399, 49165, 57931
5181	Novel protein (KIAA1671)	507732	5336	437831	14102	22868, 31634, 40400, 49166, 57932
5182	Novel protein similar to contactin associated protein-like 3 (CNTNAP3)	414020	5337	391525	14103	22869, 31635, 40401, 49167, 57933
5183	Novel protein similar to contactin associated protein-like 3 (CNTNAP3)	420228	5338	401168	14104	22870, 31636, 40402, 49168, 57934
5184	Novel protein similar to contactin associated protein-like 3 (CNTNAP3)	438517	5339	405700	14105	22871, 31637, 40403, 49169, 57935
5185	Novel proteinSimilar to bA90M5.1 (Novel protein)Uncharacterized protein	380640	5340	370014	14106	22872, 31638, 40404, 49170, 57936
5186	Novel proteinUncharacterized protein	370535	5341	359566	14107	22873, 31639, 40405, 49171, 57937
5187	Novel proteinUncharacterized protein	370707	5342	359741	14108	22874, 31640, 40406, 49172, 57938
5188	Novel proteinUncharacterized protein	379526	5343	368841	14109	22875, 31641, 40407, 49173, 57939
5189	Novel proteinUncharacterized protein	417488	5344	395963	14110	22876, 31642, 40408, 49174, 57940
5190	Novel proteinUncharacterized protein	456982	5345	396371	14111	22877, 31643, 40409, 49175, 57941
5191	NT5C1B-RDH14 readthrough	444297	5346	412639	14112	22878, 31644, 40410, 49176, 57942

5192	NT5C1B-RDH14 readthrough	532967	5347	433415	14113	22879, 31645, 40411, 49177, 57943
5193	NUAK family, SNF1-like kinase, 2	367157	5348	356125	14114	22880, 31646, 40412, 49178, 57944
5194	nuclear cap binding protein subunit 2-like	372379	5349	361454	14115	22881, 31647, 40413, 49179, 57945
5195	nuclear export mediator factor	382135	5350	371570	14116	22882, 31648, 40414, 49180, 57946
5196	nuclear export mediator factor	534912	5351	437931	14117	22883, 31649, 40415, 49181, 57947
5197	nuclear export mediator factor	545773	5352	438309	14118	22884, 31650, 40416, 49182, 57948
5198	nuclear export mediator factor	546046	5353	441016	14119	22885, 31651, 40417, 49183, 57949
5199	nuclear pore complex interacting protein pseudogene 1	358815	5354	440053	14120	22886, 31652, 40418, 49184, 57950
5200	nuclear pore complex interacting protein-like 2	429990	5355	411140	14121	22887, 31653, 40419, 49185, 57951
5201	nuclear pore complex interacting protein-like 3	319334	5356	346048	14122	22888, 31654, 40420, 49186, 57952
5202	nuclear pore complex interacting protein-like 3	447737	5357	442633	14123	22889, 31655, 40421, 49187, 57953
5203	nuclear pore complex interacting protein-like 3	448012	5358	390496	14124	22890, 31656, 40422, 49188, 57954
5204	nuclear pore complex interacting protein-like 3	458643	5359	399107	14125	22891, 31657, 40423, 49189, 57955
5205	nuclear pore complex interacting protein-like 3	542817	5360	444096	14126	22892, 31658, 40424, 49190, 57956
5206	Nuclear pore complex-interacting protein-like 1	327792	5361	331567	14127	22893, 31659, 40425, 49191, 57957
5207	Nuclear pore complex-interacting protein-like 1	422673	5362	410719	14128	22894, 31660, 40426, 49192, 57958
5208	Nuclear pore complex-interacting protein-like 2	355290	5363	347438	14129	22895, 31661, 40427, 49193,

						57959
5209	nuclear protein transcriptional regulator 1-like	329309	5364	455442	14130	22896, 31662, 40428, 49194, 57960
5210	nuclear receptor coactivator 4	581486	5365	462943	14131	22897, 31663, 40429, 49195, 57961
5211	nuclear receptor coactivator 4	583565	5366	463476	14132	22898, 31664, 40430, 49196, 57962
5212	nuclear receptor coactivator 4	585132	5367	464054	14133	22899, 31665, 40431, 49197, 57963
5213	nuclear receptor subfamily 1, group H, member 3	395397	5368	378793	14134	22900, 31666, 40432, 49198, 57964
5214	nuclear receptor subfamily 1, group H, member 3	405853	5369	384745	14135	22901, 31667, 40433, 49199, 57965
5215	nuclear receptor subfamily 1, group H, member 3	407404	5370	385801	14136	22902, 31668, 40434, 49200, 57966
5216	nuclear receptor subfamily 1, group H, member 3	436778	5371	403798	14137	22903, 31669, 40435, 49201, 57967
5217	nuclear receptor subfamily 1, group H, member 3	437276	5372	396132	14138	22904, 31670, 40436, 49202, 57968
5218	nuclear receptor subfamily 1, group H, member 3	441012	5373	387946	14139	22905, 31671, 40437, 49203, 57969
5219	nuclear receptor subfamily 1, group H, member 3	444396	5374	391005	14140	22906, 31672, 40438, 49204, 57970
5220	nuclear receptor subfamily 1, group H, member 3	449369	5375	415591	14141	22907, 31673, 40439, 49205, 57971
5221	nuclear receptor subfamily 1, group H, member 3	457932	5376	413095	14142	22908, 31674, 40440, 49206, 57972
5222	nuclear receptor subfamily 1, group H, member 3	467728	5377	420656	14143	22909, 31675, 40441, 49207, 57973
5223	nuclear RNA export factor 2	600904	5378	469776	14144	22910, 31676, 40442, 49208, 57974
5224	nuclear RNA export factor 2	602195	5379	472530	14145	22911, 31677, 40443, 49209, 57975
5225	nucleoredoxin-like 2	375854	5380	365014	14146	22912, 31678,

						40444, 49210, 57976
5226	nucleoredoxin-like 2	375855	5381	365015	14147	22913, 31679, 40445, 49211, 57977
5227	nucleoside-triphosphatase, cancer-related	366627	5382	355586	14148	22914, 31680, 40446, 49212, 57978
5228	nucleoside-triphosphatase, cancer-related	366628	5383	355587	14149	22915, 31681, 40447, 49213, 57979
5229	nucleosome assembly protein 1-like 6	373518	5384	362617	14150	22916, 31682, 40448, 49214, 57980
5230	nucleotide-binding oligomerization domain containing 2	526417	5385	435451	14151	22917, 31683, 40449, 49215, 57981
5231	nucleotide-binding oligomerization domain containing 2	531674	5386	431681	14152	22918, 31684, 40450, 49216, 57982
5232	NudC domain containing 1	239690	5387	239690	14153	22919, 31685, 40451, 49217, 57983
5233	NudC domain containing 1	427660	5388	410707	14154	22920, 31686, 40452, 49218, 57984
5234	NudC domain containing 2	302764	5389	304854	14155	22921, 31687, 40453, 49219, 57985
5235	NudC domain containing 3	355451	5390	347626	14156	22922, 31688, 40454, 49220, 57986
5236	nudix (nucleoside diphosphate linked moiety X)-type motif 10	598821	5391	469036	14157	22923, 31689, 40455, 49221, 57987
5237	nudix (nucleoside diphosphate linked moiety X)-type motif 15	258662	5392	258662	14158	22924, 31690, 40456, 49222, 57988
5238	nudix (nucleoside diphosphate linked moiety X)-type motif 17	334513	5393	334437	14159	22925, 31691, 40457, 49223, 57989
5239	nudix (nucleoside diphosphate linked moiety X)-type motif 17	444015	5394	392616	14160	22926, 31692, 40458, 49224, 57990
5240	nudix (nucleoside diphosphate linked moiety X)-type motif 18	309188	5395	307852	14161	22927, 31693, 40459, 49225, 57991
5241	nudix (nucleoside diphosphate linked moiety X)-type motif 18	521807	5396	429877	14162	22928, 31694, 40460, 49226, 57992

5242	nudix (nucleoside diphosphate linked moiety X)-type motif 18	522405	5397	430539	14163	22929, 31695, 40461, 49227, 57993
5243	nudix (nucleoside diphosphate linked moiety X)-type motif 19	397061	5398	380251	14164	22930, 31696, 40462, 49228, 57994
5244	nudix (nucleoside diphosphate linked moiety X)-type motif 22	279206	5399	279206	14165	22931, 31697, 40463, 49229, 57995
5245	nudix (nucleoside diphosphate linked moiety X)-type motif 22	441250	5400	407970	14166	22932, 31698, 40464, 49230, 57996
5246	nudix (nucleoside diphosphate linked moiety X)-type motif 22	536237	5401	441717	14167	22933, 31699, 40465, 49231, 57997
5247	nudix (nucleoside diphosphate linked moiety X)-type motif 22	539325	5402	444022	14168	22934, 31700, 40466, 49232, 57998
5248	nudix (nucleoside diphosphate linked moiety X)-type motif 4	337179	5403	338352	14169	22935, 31701, 40467, 49233, 57999
5249	nudix (nucleoside diphosphate linked moiety X)-type motif 4	415493	5404	406612	14170	22936, 31702, 40468, 49234, 58000
5250	nudix (nucleoside diphosphate linked moiety X)-type motif 4	547014	5405	448032	14171	22937, 31703, 40469, 49235, 58001
5251	nudix (nucleoside diphosphate linked moiety X)-type motif 5	378927	5406	368209	14172	22938, 31704, 40470, 49236, 58002
5252	nudix (nucleoside diphosphate linked moiety X)-type motif 5	378937	5407	368219	14173	22939, 31705, 40471, 49237, 58003
5253	nudix (nucleoside diphosphate linked moiety X)-type motif 5	378940	5408	368222	14174	22940, 31706, 40472, 49238, 58004
5254	nudix (nucleoside diphosphate linked moiety X)-type motif 5	444732	5409	407856	14175	22941, 31707, 40473, 49239, 58005
5255	nudix (nucleoside diphosphate linked moiety X)-type motif 5	491614	5410	419628	14176	22942, 31708, 40474, 49240, 58006
5256	nudix (nucleoside diphosphate linked moiety X)-type motif 5	537776	5411	445116	14177	22943, 31709, 40475, 49241, 58007
5257	nudix (nucleoside diphosphate linked moiety X)-type motif 7	268533	5412	268533	14178	22944, 31710, 40476, 49242, 58008
5258	nudix (nucleoside diphosphate linked moiety	437314	5413	387707	14179	22945, 31711, 40477, 49243,

	X)-type motif 7					58009
5259	nudix (nucleoside diphosphate linked moiety X)-type motif 7	564085	5414	457566	14180	22946, 31712, 40478, 49244, 58010
5260	OAF homolog (Drosophila)	328965	5415	332613	14181	22947, 31713, 40479, 49245, 58011
5261	occludin/ELL domain containing 1	215061	5416	215061	14182	22948, 31714, 40480, 49246, 58012
5262	oculomedin	574641	5417	460371	14183	22949, 31715, 40481, 49247, 58013
5263	oleoyl-ACP hydrolase	378217	5418	367462	14184	22950, 31716, 40482, 49248, 58014
5264	oleoyl-ACP hydrolase	378225	5419	367470	14185	22951, 31717, 40483, 49249, 58015
5265	oleoyl-ACP hydrolase	378228	5420	367473	14186	22952, 31718, 40484, 49250, 58016
5266	oleoyl-ACP hydrolase	413672	5421	399449	14187	22953, 31719, 40485, 49251, 58017
5267	oleoyl-ACP hydrolase	428897	5422	399290	14188	22954, 31720, 40486, 49252, 58018
5268	oleoyl-ACP hydrolase	429028	5423	399663	14189	22955, 31721, 40487, 49253, 58019
5269	olfactomedin-like 2A	425732	5424	401075	14190	22956, 31722, 40488, 49254, 58020
5270	olfactory receptor family 13 subfamily A member 1	573291	5425	459002	14191	22957, 31723, 40489, 49255, 58021
5271	olfactory receptor, family 1, subfamily E, member 2	454364	5426	398217	14192	22958, 31724, 40490, 49256, 58022
5272	olfactory receptor, family 11, subfamily A, member 1	411967	5427	409994	14193	22959, 31725, 40491, 49257, 58023
5273	olfactory receptor, family 11, subfamily A, member 1	418560	5428	404787	14194	22960, 31726, 40492, 49258, 58024
5274	olfactory receptor, family 11, subfamily A, member 1	548813	5429	447267	14195	22961, 31727, 40493, 49259, 58025
5275	olfactory receptor, family	377140	5430	366345	14196	22962, 31728,

	12, subfamily D, member 2					40494, 49260, 58026
5276	olfactory receptor, family 12, subfamily D, member 2	414415	5431	414137	14197	22963, 31729, 40495, 49261, 58027
5277	olfactory receptor, family 12, subfamily D, member 2	438569	5432	415065	14198	22964, 31730, 40496, 49262, 58028
5278	olfactory receptor, family 12, subfamily D, member 3	502578	5433	421346	14199	22965, 31731, 40497, 49263, 58029
5279	olfactory receptor, family 12, subfamily D, member 3	508665	5434	424840	14200	22966, 31732, 40498, 49264, 58030
5280	olfactory receptor, family 12, subfamily D, member 3	551240	5435	447118	14201	22967, 31733, 40499, 49265, 58031
5281	olfactory receptor, family 12, subfamily D, member 3	552012	5436	448923	14202	22968, 31734, 40500, 49266, 58032
5282	olfactory receptor, family 14, subfamily I, member 1	342623	5437	339726	14203	22969, 31735, 40501, 49267, 58033
5283	olfactory receptor, family 14, subfamily J, member 1	420495	5438	389802	14204	22970, 31736, 40502, 49268, 58034
5284	olfactory receptor, family 14, subfamily J, member 1	421489	5439	403553	14205	22971, 31737, 40503, 49269, 58035
5285	olfactory receptor, family 14, subfamily J, member 1	435798	5440	400501	14206	22972, 31738, 40504, 49270, 58036
5286	olfactory receptor, family 14, subfamily J, member 1	451272	5441	408647	14207	22973, 31739, 40505, 49271, 58037
5287	olfactory receptor, family 2, subfamily H, member 2	383546	5442	373038	14208	22974, 31740, 40506, 49272, 58038
5288	olfactory receptor, family 2, subfamily H, member 2	439874	5443	403604	14209	22975, 31741, 40507, 49273, 58039
5289	olfactory receptor, family 2, subfamily H, member 2	453513	5444	414688	14210	22976, 31742, 40508, 49274, 58040
5290	olfactory receptor, family 2, subfamily H, member 2	454628	5445	409339	14211	22977, 31743, 40509, 49275, 58041
5291	olfactory receptor, family 2, subfamily J, member 1 (gene/pseudogene)	427659	5446	414527	14212	22978, 31744, 40510, 49276, 58042

5292	olfactory receptor, family 2, subfamily J, member 2	358688	5447	351519	14213	22979, 31745, 40511, 49277, 58043
5293	olfactory receptor, family 2, subfamily J, member 2	377167	5448	366372	14214	22980, 31746, 40512, 49278, 58044
5294	olfactory receptor, family 2, subfamily J, member 2	411588	5449	396524	14215	22981, 31747, 40513, 49279, 58045
5295	olfactory receptor, family 2, subfamily J, member 3	377169	5450	366374	14216	22982, 31748, 40514, 49280, 58046
5296	olfactory receptor, family 2, subfamily T, member 8	319968	5451	326225	14217	22983, 31749, 40515, 49281, 58047
5297	olfactory receptor, family 5, subfamily B, member 21	360374	5452	353537	14218	22984, 31750, 40516, 49282, 58048
5298	olfactory receptor, family 5, subfamily H, member 1	354565	5453	346575	14219	22985, 31751, 40517, 49283, 58049
5299	olfactory receptor, family 5, subfamily H, member 15	356526	5454	373195	14220	22986, 31752, 40518, 49284, 58050
5300	olfactory receptor, family 5, subfamily H, member 15	454529	5455	396659	14221	22987, 31753, 40519, 49285, 58051
5301	olfactory receptor, family 5, subfamily K, member 3	383695	5456	373194	14222	22988, 31754, 40520, 49286, 58052
5302	olfactory receptor, family 5, subfamily V, member 1	230223	5457	230223	14223	22989, 31755, 40521, 49287, 58053
5303	olfactory receptor, family 5, subfamily V, member 1	400698	5458	383534	14224	22990, 31756, 40522, 49288, 58054
5304	olfactory receptor, family 5, subfamily V, member 1	418692	5459	415545	14225	22991, 31757, 40523, 49289, 58055
5305	olfactory receptor, family 5, subfamily V, member 1	421859	5460	412591	14226	22992, 31758, 40524, 49290, 58056
5306	olfactory receptor, family 5, subfamily V, member 1	548546	5461	449041	14227	22993, 31759, 40525, 49291, 58057
5307	olfactory receptor, family 51, subfamily F, member 1	343430	5462	345163	14228	22994, 31760, 40526, 49292, 58058
5308	olfactory receptor, family 51, subfamily F, member 1	380383	5463	369744	14229	22995, 31761, 40527, 49293,

						58059
5309	olfactory receptor, family 51, subfamily M, member 1	328611	5464	333196	14230	22996, 31762, 40528, 49294, 58060
5310	olfactory receptor, family 6, subfamily C, member 6	358433	5465	351211	14231	22997, 31763, 40529, 49295, 58061
5311	olfactory receptor, family 6, subfamily C, member 76	328314	5466	328402	14232	22998, 31764, 40530, 49296, 58062
5312	oligosaccharyltransferase 4 homolog (S. cerevisiae)	456793	5467	457935	14233	22999, 31765, 40531, 49297, 58063
5313	oncomodulin 2	257627	5468	257627	14234	23000, 31766, 40532, 49298, 58064
5314	Oocyte-secreted protein 1 homolog	398992	5469	381960	14235	23001, 31767, 40533, 49299, 58065
5315	opioid growth factor receptor-like 1	370435	5470	359464	14236	23002, 31768, 40534, 49300, 58066
5316	ornithine decarboxylase antizyme 2	326005	5471	463013	14237	23003, 31769, 40535, 49301, 58067
5317	otogelin-like	458043	5472	400895	14238	23004, 31770, 40536, 49302, 58068
5318	otolin 1	327928	5473	330808	14239	23005, 31771, 40537, 49303, 58069
5319	OTU domain containing 5	597676	5474	471884	14240	23006, 31772, 40538, 49304, 58070
5320	OTU domain containing 5	601021	5475	470428	14241	23007, 31773, 40539, 49305, 58071
5321	outer dense fiber of sperm tails 3B	329363	5476	382804	14242	23008, 31774, 40540, 49306, 58072
5322	outer dense fiber of sperm tails 3B	428989	5477	390712	14243	23009, 31775, 40541, 49307, 58073
5323	outer dense fiber of sperm tails 3B	438960	5478	400710	14244	23010, 31776, 40542, 49308, 58074
5324	outer dense fiber of sperm tails 3-like 1	332145	5479	329584	14245	23011, 31777, 40543, 49309, 58075
5325	outer dense fiber of sperm	315489	5480	318029	14246	23012, 31778,

	tails 3-like 2					40544, 49310, 58076
5326	outer dense fiber of sperm tails 3-like 2	382696	5481	372143	14247	23013, 31779, 40545, 49311, 58077
5327	ovochymase 1	318184	5482	326708	14248	23014, 31780, 40546, 49312, 58078
5328	ovochymase 2 (gene/pseudogene)	454689	5483	407158	14249	23015, 31781, 40547, 49313, 58079
5329	ovo-like 3 (Drosophila)	262637	5484	262637	14250	23016, 31782, 40548, 49314, 58080
5330	oxidative stress induced growth inhibitor 1	343939	5485	343376	14251	23017, 31783, 40549, 49315, 58081
5331	oxidative stress induced growth inhibitor 1	361711	5486	355374	14252	23018, 31784, 40550, 49316, 58082
5332	oxidative stress induced growth inhibitor 1	393306	5487	376983	14253	23019, 31785, 40551, 49317, 58083
5333	oxidative stress induced growth inhibitor family member 2	297438	5488	297438	14254	23020, 31786, 40552, 49318, 58084
5334	oxidative stress induced growth inhibitor family member 2	451899	5489	396445	14255	23021, 31787, 40553, 49319, 58085
5335	oxidative-stress responsive 1	311806	5490	311713	14256	23022, 31788, 40554, 49320, 58086
5336	P antigen family member 4 (prostate associated)	595746	5491	472606	14257	23023, 31789, 40555, 49321, 58087
5337	P antigen family, member 2B	374971	5492	364110	14258	23024, 31790, 40556, 49322, 58088
5338	P antigen family, member 2B	453343	5493	406149	14259	23025, 31791, 40557, 49323, 58089
5339	P antigen family, member 5 (prostate associated)	289619	5494	289619	14260	23026, 31792, 40558, 49324, 58090
5340	P antigen family, member 5 (prostate associated)	374952	5495	364090	14261	23027, 31793, 40559, 49325, 58091
5341	P antigen family, member 5 (prostate associated)	374955	5496	364093	14262	23028, 31794, 40560, 49326, 58092

5342	PALM2-AKAP2 readthrough	302798	5497	305861	14263	23029, 31795, 40561, 49327, 58093
5343	PALM2-AKAP2 readthrough	374530	5498	363654	14264	23030, 31796, 40562, 49328, 58094
5344	PALM2-AKAP2 readthrough	413420	5499	397839	14265	23031, 31797, 40563, 49329, 58095
5345	pancreatic lipase-related protein 1	572596	5500	458759	14266	23032, 31798, 40564, 49330, 58096
5346	pancreatic lipase-related protein 2	537242	5501	446346	14267	23033, 31799, 40565, 49331, 58097
5347	pancreatic progenitor cell differentiation and proliferation factor homolog (zebrafish)	370177	5502	359196	14268	23034, 31800, 40566, 49332, 58098
5348	pancreatic progenitor cell differentiation and proliferation factor homolog (zebrafish)	370178	5503	359197	14269	23035, 31801, 40567, 49333, 58099
5349	pancreatic progenitor cell differentiation and proliferation factor homolog (zebrafish)	370179	5504	359198	14270	23036, 31802, 40568, 49334, 58100
5350	PAP associated domain containing 5	357464	5505	350054	14271	23037, 31803, 40569, 49335, 58101
5351	PAP associated domain containing 5	436909	5506	396995	14272	23038, 31804, 40570, 49336, 58102
5352	parahox cluster neighbor	332715	5507	333490	14273	23039, 31805, 40571, 49337, 58103
5353	paralemmin 3	340790	5508	344996	14274	23040, 31806, 40572, 49338, 58104
5354	paraneoplastic antigen like 5	361887	5509	354834	14275	23041, 31807, 40573, 49339, 58105
5355	paraneoplastic antigen like 5	437210	5510	391130	14276	23042, 31808, 40574, 49340, 58106
5356	paraneoplastic antigen like 5	439251	5511	388850	14277	23043, 31809, 40575, 49341, 58107
5357	paraneoplastic antigen like 5	452693	5512	392342	14278	23044, 31810, 40576, 49342,

						58108
5358	paraneoplastic antigen like 5	535214	5513	445775	14279	23045, 31811, 40577, 49343, 58109
5359	paraneoplastic antigen like 6A	453825	5514	405718	14280	23046, 31812, 40578, 49344, 58110
5360	paraneoplastic antigen like 6A	535416	5515	441213	14281	23047, 31813, 40579, 49345, 58111
5361	paraneoplastic antigen like 6B	370261	5516	359283	14282	23048, 31814, 40580, 49346, 58112
5362	paraneoplastic antigen like 6C	421798	5517	391488	14283	23049, 31815, 40581, 49347, 58113
5363	paraneoplastic antigen like 6D	538162	5518	440223	14284	23050, 31816, 40582, 49348, 58114
5364	paraneoplastic Ma antigen family member 5	593850	5519	469706	14285	23051, 31817, 40583, 49349, 58115
5365	paraneoplastic Ma antigen family member 5	597501	5520	469301	14286	23052, 31818, 40584, 49350, 58116
5366	paraneoplastic Ma antigen family member 5	599118	5521	471779	14287	23053, 31819, 40585, 49351, 58117
5367	paraneoplastic Ma antigen family member 5	600760	5522	470399	14288	23054, 31820, 40586, 49352, 58118
5368	paraneoplastic Ma antigen family-like 2	599531	5523	473036	14289	23055, 31821, 40587, 49353, 58119
5369	PARK2 co-regulated-like	295290	5524	295290	14290	23056, 31822, 40588, 49354, 58120
5370	PARK2 co-regulated-like	360916	5525	354171	14291	23057, 31823, 40589, 49355, 58121
5371	PARK2 co-regulated-like	503585	5526	423881	14292	23058, 31824, 40590, 49356, 58122
5372	PARK2 co-regulated-like	504630	5527	420948	14293	23059, 31825, 40591, 49357, 58123
5373	PARK2 co-regulated-like	506745	5528	424391	14294	23060, 31826, 40592, 49358, 58124
5374	PARK2 co-regulated-like	507634	5529	425938	14295	23061, 31827,

						40593, 49359, 58125
5375	PARK2 co-regulated-like	509469	5530	422962	14296	23062, 31828, 40594, 49360, 58126
5376	PARK2 co-regulated-like	513590	5531	422425	14297	23063, 31829, 40595, 49361, 58127
5377	PARK2 co-regulated-like	514485	5532	426643	14298	23064, 31830, 40596, 49362, 58128
5378	PARK2 co-regulated-like	514663	5533	421570	14299	23065, 31831, 40597, 49363, 58129
5379	PARK2 co-regulated-like	538990	5534	438269	14300	23066, 31832, 40598, 49364, 58130
5380	PARK2 co-regulated-like	444671	5535	415832	14301	23067, 31833, 40599, 49365, 58131
5381	patatin-like phospholipase domain containing 4	381042	5536	370430	14302	23068, 31834, 40600, 49366, 58132
5382	patatin-like phospholipase domain containing 4	442940	5537	406698	14303	23069, 31835, 40601, 49367, 58133
5383	patatin-like phospholipase domain containing 4	444736	5538	415245	14304	23070, 31836, 40602, 49368, 58134
5384	patatin-like phospholipase domain containing 4	537427	5539	443157	14305	23071, 31837, 40603, 49369, 58135
5385	PDZ binding kinase	301905	5540	301905	14306	23072, 31838, 40604, 49370, 58136
5386	PDZ domain containing 1	581121	5541	464487	14307	23073, 31839, 40605, 49371, 58137
5387	PDZ domain containing 1	583035	5542	462520	14308	23074, 31840, 40606, 49372, 58138
5388	PDZ domain containing 9	286143	5543	286143	14309	23075, 31841, 40607, 49373, 58139
5389	PDZ domain containing 9	424898	5544	400514	14310	23076, 31842, 40608, 49374, 58140
5390	PDZ domain containing 9	537222	5545	441685	14311	23077, 31843, 40609, 49375, 58141

5391	pentatricopeptide repeat domain 1	292478	5546	292478	14312	23078, 31844, 40610, 49376, 58142
5392	pentatricopeptide repeat domain 1	419981	5547	401600	14313	23079, 31845, 40611, 49377, 58143
5393	pentatricopeptide repeat domain 1	430029	5548	408059	14314	23080, 31846, 40612, 49378, 58144
5394	pentatricopeptide repeat domain 1	430982	5549	390530	14315	23081, 31847, 40613, 49379, 58145
5395	pentatricopeptide repeat domain 1	437572	5550	410697	14316	23082, 31848, 40614, 49380, 58146
5396	pentatricopeptide repeat domain 1	438524	5551	405425	14317	23083, 31849, 40615, 49381, 58147
5397	pentatricopeptide repeat domain 1	555673	5552	450995	14318	23084, 31850, 40616, 49382, 58148
5398	peptidase M20 domain containing 2	275072	5553	275072	14319	23085, 31851, 40617, 49383, 58149
5399	peptidylprolyl isomerase (cyclophilin)-like 6	424445	5554	407731	14320	23086, 31852, 40618, 49384, 58150
5400	peptidylprolyl isomerase (cyclophilin)-like 6	521072	5555	427929	14321	23087, 31853, 40619, 49385, 58151
5401	peptidylprolyl isomerase (cyclophilin)-like 6	440797	5556	392257	14322	23088, 31854, 40620, 49386, 58152
5402	peptidylprolyl isomerase A (cyclophilin A)-like 4D	544708	5557	439444	14323	23089, 31855, 40621, 49387, 58153
5403	peptidylprolyl isomerase A (cyclophilin A)-like 4D	583898	5558	464608	14324	23090, 31856, 40622, 49388, 58154
5404	peptidyl-tRNA hydrolase domain containing 1	328379	5559	330389	14325	23091, 31857, 40623, 49389, 58155
5405	PEST proteolytic signal containing nuclear protein	296024	5560	296024	14326	23092, 31858, 40624, 49390, 58156
5406	PET100 homolog (S. cerevisiae)	594797	5561	470539	14327	23093, 31859, 40625, 49391, 58157
5407	PHD finger protein 14	403050	5562	385795	14328	23094, 31860, 40626, 49392,

						58158
5408	PHD finger protein 14	445996	5563	403907	14329	23095, 31861, 40627, 49393, 58159
5409	PHD finger protein 20-like 1	220847	5564	220847	14330	23096, 31862, 40628, 49394, 58160
5410	PHD finger protein 20-like 1	315808	5565	324519	14331	23097, 31863, 40629, 49395, 58161
5411	PHD finger protein 20-like 1	395382	5566	378780	14332	23098, 31864, 40630, 49396, 58162
5412	PHD finger protein 20-like 1	337920	5567	338269	14333	23099, 31865, 40631, 49397, 58163
5413	PHD finger protein 20-like 1	395386	5568	378784	14334	23100, 31866, 40632, 49398, 58164
5414	PHD finger protein 21B	313237	5569	324403	14335	23101, 31867, 40633, 49399, 58165
5415	PHD finger protein 21B	396103	5570	379410	14336	23102, 31868, 40634, 49400, 58166
5416	PHD finger protein 21B	404079	5571	385105	14337	23103, 31869, 40635, 49401, 58167
5417	PHD finger protein 21B	447824	5572	388619	14338	23104, 31870, 40636, 49402, 58168
5418	phosphatase and actin regulator 1	332995	5573	329880	14339	23105, 31871, 40637, 49403, 58169
5419	phosphatase and actin regulator 1	379329	5574	368633	14340	23106, 31872, 40638, 49404, 58170
5420	phosphatase and actin regulator 1	379335	5575	368639	14341	23107, 31873, 40639, 49405, 58171
5421	phosphatase and actin regulator 1	379345	5576	368650	14342	23108, 31874, 40640, 49406, 58172
5422	phosphatase and actin regulator 1	379348	5577	368653	14343	23109, 31875, 40641, 49407, 58173
5423	phosphatase and actin regulator 1	379350	5578	368655	14344	23110, 31876, 40642, 49408, 58174
5424	phosphatase and actin	406205	5579	384760	14345	23111, 31877,

	regulator 1					40643, 49409, 58175
5425	phosphatase and actin regulator 1	415087	5580	395948	14346	23112, 31878, 40644, 49410, 58176
5426	phosphatase and actin regulator 1	432934	5581	390854	14347	23113, 31879, 40645, 49411, 58177
5427	phosphatase and actin regulator 1	434977	5582	412573	14348	23114, 31880, 40646, 49412, 58178
5428	phosphatase and actin regulator 1	457702	5583	397669	14349	23115, 31881, 40647, 49413, 58179
5429	phosphatase and actin regulator 2	305766	5584	305530	14350	23116, 31882, 40648, 49414, 58180
5430	phosphatase and actin regulator 2	367582	5585	356554	14351	23117, 31883, 40649, 49415, 58181
5431	phosphatase and actin regulator 2	367583	5586	356555	14352	23118, 31884, 40650, 49416, 58182
5432	phosphatase and actin regulator 2	427704	5587	391763	14353	23119, 31885, 40651, 49417, 58183
5433	phosphatase and actin regulator 2	440869	5588	417038	14354	23120, 31886, 40652, 49418, 58184
5434	phosphatase and actin regulator 4	373836	5589	362942	14355	23121, 31887, 40653, 49419, 58185
5435	phosphatase and actin regulator 4	373838	5590	362944	14356	23122, 31888, 40654, 49420, 58186
5436	phosphatase and actin regulator 4	373839	5591	362945	14357	23123, 31889, 40655, 49421, 58187
5437	phosphatase, orphan 1	310544	5592	311925	14358	23124, 31890, 40656, 49422, 58188
5438	phosphatase, orphan 1	413580	5593	406909	14359	23125, 31891, 40657, 49423, 58189
5439	phosphatase, orphan 1	511066	5594	426095	14360	23126, 31892, 40658, 49424, 58190
5440	phosphatase, orphan 1	512250	5595	427397	14361	23127, 31893, 40659, 49425, 58191

5441	phosphatase, orphan 1	514112	5596	427694	14362	23128, 31894, 40660, 49426, 58192
5442	phosphatase, orphan 2	359744	5597	352782	14363	23129, 31895, 40661, 49427, 58193
5443	phosphatase, orphan 2	438710	5598	411844	14364	23130, 31896, 40662, 49428, 58194
5444	phosphatase, orphan 2	438838	5599	393983	14365	23131, 31897, 40663, 49429, 58195
5445	phosphatase, orphan 2	449906	5600	416790	14366	23132, 31898, 40664, 49430, 58196
5446	phosphate cytidylyltransferase 2, ethanolamine	331285	5601	331719	14367	23133, 31899, 40665, 49431, 58197
5447	phosphate cytidylyltransferase 2, ethanolamine	538721	5602	442050	14368	23134, 31900, 40666, 49432, 58198
5448	phosphate cytidylyltransferase 2, ethanolamine	538936	5603	439245	14369	23135, 31901, 40667, 49433, 58199
5449	phosphatidylinositol glycan anchor biosynthesis class W	561548	5604	455647	14370	23136, 31902, 40668, 49434, 58200
5450	phosphatidylinositol transfer protein cytoplasmic 1	580974	5605	463626	14371	23137, 31903, 40669, 49435, 58201
5451	phosphatidylinositol transfer protein, cytoplasmic 1	299954	5606	299954	14372	23138, 31904, 40670, 49436, 58202
5452	phosphatidylinositol transfer protein, cytoplasmic 1	335257	5607	335618	14373	23139, 31905, 40671, 49437, 58203
5453	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	323883	5608	326294	14374	23140, 31906, 40672, 49438, 58204
5454	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	376565	5609	365749	14375	23141, 31907, 40673, 49439, 58205
5455	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	376573	5610	365757	14376	23142, 31908, 40674, 49440, 58206
5456	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	422321	5611	388889	14377	23143, 31909, 40675, 49441, 58207
5457	phosphatidylinositol-5-phosphate 4-kinase, type II,	432610	5612	400230	14378	23144, 31910, 40676, 49442,

	alpha					58208
5458	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	545335	5613	442098	14379	23145, 31911, 40677, 49443, 58209
5459	phosphatidylinositol-specific phospholipase C, X domain containing 1	381657	5614	371073	14380	23146, 31912, 40678, 49444, 58210
5460	phosphatidylinositol-specific phospholipase C, X domain containing 1	381663	5615	371079	14381	23147, 31913, 40679, 49445, 58211
5461	phosphatidylinositol-specific phospholipase C, X domain containing 1	399012	5616	381976	14382	23148, 31914, 40680, 49446, 58212
5462	phosphatidylinositol-specific phospholipase C, X domain containing 1	415337	5617	399510	14383	23149, 31915, 40681, 49447, 58213
5463	phosphatidylinositol-specific phospholipase C, X domain containing 1	429181	5618	400904	14384	23150, 31916, 40682, 49448, 58214
5464	phosphatidylinositol-specific phospholipase C, X domain containing 1	430923	5619	394848	14385	23151, 31917, 40683, 49449, 58215
5465	phosphatidylinositol-specific phospholipase C, X domain containing 1	443019	5620	408558	14386	23152, 31918, 40684, 49450, 58216
5466	phosphatidylinositol-specific phospholipase C, X domain containing 1	445062	5621	412018	14387	23153, 31919, 40685, 49451, 58217
5467	phosphatidylinositol-specific phospholipase C, X domain containing 1	447472	5622	405307	14388	23154, 31920, 40686, 49452, 58218
5468	phosphatidylinositol-specific phospholipase C, X domain containing 1	448477	5623	414181	14389	23155, 31921, 40687, 49453, 58219
5469	phosphatidylinositol-specific phospholipase C, X domain containing 2	393934	5624	377511	14390	23156, 31922, 40688, 49454, 58220
5470	phosphatidylinositol-specific phospholipase C, X domain containing 2	477665	5625	420686	14391	23157, 31923, 40689, 49455, 58221
5471	phosphatidylinositol-specific phospholipase C, X domain containing 3	328457	5626	333751	14392	23158, 31924, 40690, 49456, 58222
5472	phosphatidylinositol-specific phospholipase C, X domain containing 3	377801	5627	367032	14393	23159, 31925, 40691, 49457, 58223
5473	phospholipase A2 inhibitor and LY6/PLAUR domain containing	562255	5628	457623	14394	23160, 31926, 40692, 49458, 58224
5474	phospholipase A2 inhibitor	599207	5629	469886	14395	23161, 31927,

	and LY6/PLAUR domain containing					40693, 49459, 58225
5475	phospholipase A2, group IVE	413860	5630	413897	14396	23162, 31928, 40694, 49460, 58226
5476	phospholipase A2-activating protein	397292	5631	380460	14397	23163, 31929, 40695, 49461, 58227
5477	phospholipase C, delta 3	322765	5632	313731	14398	23164, 31930, 40696, 49462, 58228
5478	phospholipase D family member 5	314833	5633	314748	14399	23165, 31931, 40697, 49463, 58229
5479	phospholipid scramblase family, member 5	443512	5634	390111	14400	23166, 31932, 40698, 49464, 58230
5480	phospholipid scramblase family, member 5	492200	5635	417184	14401	23167, 31933, 40699, 49465, 58231
5481	phosphoribosylglycinamide formyltransferase phosphoribosylglycinamide synthetase phosphoribosylaminoimidazole synthetase	571089	5636	459532	14402	23168, 31934, 40700, 49466, 58232
5482	phosphoribosylglycinamide formyltransferase phosphoribosylglycinamide synthetase phosphoribosylaminoimidazole synthetase	573055	5637	459391	14403	23169, 31935, 40701, 49467, 58233
5483	phosphoribosylglycinamide formyltransferase phosphoribosylglycinamide synthetase phosphoribosylaminoimidazole synthetase	575273	5638	461700	14404	23170, 31936, 40702, 49468, 58234
5484	phytanoyl-CoA 2-hydroxylase interacting protein	454243	5639	415491	14405	23171, 31937, 40703, 49469, 58235
5485	phytanoyl-CoA 2-hydroxylase interacting protein	456132	5640	411446	14406	23172, 31938, 40704, 49470, 58236
5486	phytanoyl-CoA 2-hydroxylase interacting protein	321613	5641	320017	14407	23173, 31939, 40705, 49471, 58237
5487	phytanoyl-CoA dioxygenase domain containing 1	308941	5642	309515	14408	23174, 31940, 40706, 49472, 58238

5488	phytanoyl-CoA dioxygenase domain containing 1	353176	5643	340945	14409	23175, 31941, 40707, 49473, 58239
5489	phytanoyl-CoA dioxygenase domain containing 1	372592	5644	361673	14410	23176, 31942, 40708, 49474, 58240
5490	phytanoyl-CoA dioxygenase domain containing 1	419552	5645	390568	14411	23177, 31943, 40709, 49475, 58241
5491	phytanoyl-CoA dioxygenase domain containing 1	421063	5646	409928	14412	23178, 31944, 40710, 49476, 58242
5492	phytanoyl-CoA dioxygenase domain containing 1	426694	5647	412377	14413	23179, 31945, 40711, 49477, 58243
5493	phytanoyl-CoA dioxygenase domain containing 1	428610	5648	401016	14414	23180, 31946, 40712, 49478, 58244
5494	piggyBac transposable element derived 2	329291	5649	331643	14415	23181, 31947, 40713, 49479, 58245
5495	piggyBac transposable element derived 2	355360	5650	355424	14416	23182, 31948, 40714, 49480, 58246
5496	piggyBac transposable element derived 2	539153	5651	439950	14417	23183, 31949, 40715, 49481, 58247
5497	piggyBac transposable element derived 3	374127	5652	363242	14418	23184, 31950, 40716, 49482, 58248
5498	piggyBac transposable element derived 3	508005	5653	426963	14419	23185, 31951, 40717, 49483, 58249
5499	piggyBac transposable element derived 4	397766	5654	380872	14420	23186, 31952, 40718, 49484, 58250
5500	PIH1 domain containing 2	280350	5655	280350	14421	23187, 31953, 40719, 49485, 58251
5501	PIH1 domain containing 2	431456	5656	388209	14422	23188, 31954, 40720, 49486, 58252
5502	PIH1 domain containing 2	528775	5657	434275	14423	23189, 31955, 40721, 49487, 58253
5503	PIH1 domain containing 2	532211	5658	431841	14424	23190, 31956, 40722, 49488, 58254
5504	PITH (C-terminal proteasome-interacting	246151	5659	246151	14425	23191, 31957, 40723, 49489,

	domain of thioredoxin-like) domain containing 1					58255
5505	PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1	374524	5660	363648	14426	23192, 31958, 40724, 49490, 58256
5506	PITH (C-terminal proteasome-interacting domain of thioredoxin-like) domain containing 1	415372	5661	405957	14427	23193, 31959, 40725, 49491, 58257
5507	pitrilysin metallopeptidase 1	224949	5662	224949	14428	23194, 31960, 40726, 49492, 58258
5508	pitrilysin metallopeptidase 1	380980	5663	370367	14429	23195, 31961, 40727, 49493, 58259
5509	pitrilysin metallopeptidase 1	380989	5664	370377	14430	23196, 31962, 40728, 49494, 58260
5510	pitrilysin metallopeptidase 1	380994	5665	370382	14431	23197, 31963, 40729, 49495, 58261
5511	pitrilysin metallopeptidase 1	424714	5666	402072	14432	23198, 31964, 40730, 49496, 58262
5512	pitrilysin metallopeptidase 1	430362	5667	391526	14433	23199, 31965, 40731, 49497, 58263
5513	pitrilysin metallopeptidase 1	451104	5668	401201	14434	23200, 31966, 40732, 49498, 58264
5514	pitrilysin metallopeptidase 1	451454	5669	413687	14435	23201, 31967, 40733, 49499, 58265
5515	pitrilysin metallopeptidase 1	455371	5670	399307	14436	23202, 31968, 40734, 49500, 58266
5516	PLAC8-like 1	311450	5671	309087	14437	23203, 31969, 40735, 49501, 58267
5517	placenta-specific 8	311507	5672	309509	14438	23204, 31970, 40736, 49502, 58268
5518	placenta-specific 8	411416	5673	412230	14439	23205, 31971, 40737, 49503, 58269
5519	placenta-specific 8	426923	5674	399700	14440	23206, 31972, 40738, 49504, 58270
5520	placenta-specific 8	505406	5675	422526	14441	23207, 31973,

						40739, 49505, 58271
5521	plastin 3	595829	5676	472532	14442	23208, 31974, 40740, 49506, 58272
5522	pleckstrin homology domain containing family A member 5	429027	5677	404296	14443	23209, 31975, 40741, 49507, 58273
5523	pleckstrin homology domain containing family A member 5	540972	5678	439396	14444	23210, 31976, 40742, 49508, 58274
5524	pleckstrin homology domain containing family H (with MyTH4 domain) member 3	591022	5679	468678	14445	23211, 31977, 40743, 49509, 58275
5525	pleckstrin homology domain containing family J member 1	589097	5680	465391	14446	23212, 31978, 40744, 49510, 58276
5526	pleckstrin homology domain containing, family A member 5	299275	5681	299275	14447	23213, 31979, 40745, 49511, 58277
5527	pleckstrin homology domain containing, family A member 5	309364	5682	311239	14448	23214, 31980, 40746, 49512, 58278
5528	pleckstrin homology domain containing, family A member 5	317589	5683	325155	14449	23215, 31981, 40747, 49513, 58279
5529	pleckstrin homology domain containing, family A member 5	355397	5684	347560	14450	23216, 31982, 40748, 49514, 58280
5530	pleckstrin homology domain containing, family A member 5	359180	5685	352104	14451	23217, 31983, 40749, 49515, 58281
5531	pleckstrin homology domain containing, family A member 5	412219	5686	410296	14452	23218, 31984, 40750, 49516, 58282
5532	pleckstrin homology domain containing, family A member 5	424268	5687	400411	14453	23219, 31985, 40751, 49517, 58283
5533	pleckstrin homology domain containing, family A member 5	538714	5688	439673	14454	23220, 31986, 40752, 49518, 58284
5534	pleckstrin homology domain containing, family A member 5	538972	5689	443553	14455	23221, 31987, 40753, 49519, 58285
5535	pleckstrin homology domain containing, family A member 5	539256	5690	440611	14456	23222, 31988, 40754, 49520, 58286
5536	pleckstrin homology domain containing, family	542828	5691	444368	14457	23223, 31989, 40755, 49521,

	A member 5					58287
5537	pleckstrin homology domain containing, family A member 5	543806	5692	439837	14458	23224, 31990, 40756, 49522, 58288
5538	pleckstrin homology domain containing, family A member 6	272203	5693	272203	14459	23225, 31991, 40757, 49523, 58289
5539	pleckstrin homology domain containing, family A member 6	367191	5694	356159	14460	23226, 31992, 40758, 49524, 58290
5540	pleckstrin homology domain containing, family A member 6	414478	5695	402046	14461	23227, 31993, 40759, 49525, 58291
5541	pleckstrin homology domain containing, family A member 6	430806	5696	415746	14462	23228, 31994, 40760, 49526, 58292
5542	pleckstrin homology domain containing, family A member 6	450705	5697	407638	14463	23229, 31995, 40761, 49527, 58293
5543	pleckstrin homology domain containing, family A member 6	454206	5698	412694	14464	23230, 31996, 40762, 49528, 58294
5544	pleckstrin homology domain containing, family A member 6	538441	5699	441155	14465	23231, 31997, 40763, 49529, 58295
5545	pleckstrin homology domain containing, family A member 6	543129	5700	443043	14466	23232, 31998, 40764, 49530, 58296
5546	pleckstrin homology domain containing, family B (evectins) member 2	234115	5701	234115	14467	23233, 31999, 40765, 49531, 58297
5547	pleckstrin homology domain containing, family B (evectins) member 2	303908	5702	306852	14468	23234, 32000, 40766, 49532, 58298
5548	pleckstrin homology domain containing, family B (evectins) member 2	403716	5703	385892	14469	23235, 32001, 40767, 49533, 58299
5549	pleckstrin homology domain containing, family B (evectins) member 2	404460	5704	385609	14470	23236, 32002, 40768, 49534, 58300
5550	pleckstrin homology domain containing, family B (evectins) member 2	409279	5705	386666	14471	23237, 32003, 40769, 49535, 58301
5551	pleckstrin homology domain containing, family B (evectins) member 2	409612	5706	386662	14472	23238, 32004, 40770, 49536, 58302
5552	pleckstrin homology domain containing, family B (evectins) member 2	438882	5707	401193	14473	23239, 32005, 40771, 49537, 58303
5553	pleckstrin homology	439822	5708	389629	14474	23240, 32006,

	domain containing, family B (evectins) member 2					40772, 49538, 58304
5554	pleckstrin homology domain containing, family B (evectins) member 2	538982	5709	444389	14475	23241, 32007, 40773, 49539, 58305
5555	pleckstrin homology domain containing, family D (with coiled-coil domains) member 1	322564	5710	317175	14476	23242, 32008, 40774, 49540, 58306
5556	pleckstrin homology domain containing, family G (with RhoGef domain) member 1	358517	5711	351318	14477	23243, 32009, 40775, 49541, 58307
5557	pleckstrin homology domain containing, family G (with RhoGef domain) member 1	367326	5712	356295	14478	23244, 32010, 40776, 49542, 58308
5558	pleckstrin homology domain containing, family G (with RhoGef domain) member 1	367328	5713	356297	14479	23245, 32011, 40777, 49543, 58309
5559	pleckstrin homology domain containing, family G (with RhoGef domain) member 1	535018	5714	445428	14480	23246, 32012, 40778, 49544, 58310
5560	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	247226	5715	247226	14481	23247, 32013, 40779, 49545, 58311
5561	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	394691	5716	378183	14482	23248, 32014, 40780, 49546, 58312
5562	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	554499	5717	451256	14483	23249, 32015, 40781, 49547, 58313
5563	pleckstrin homology domain containing, family G (with RhoGef domain) member 3	555982	5718	450501	14484	23250, 32016, 40782, 49548, 58314
5564	pleckstrin homology domain containing, family G (with RhoGef domain) member 4B	283426	5719	283426	14485	23251, 32017, 40783, 49549, 58315
5565	pleckstrin homology domain containing, family G (with RhoGef domain) member 7	344636	5720	344961	14486	23252, 32018, 40784, 49550, 58316
5566	pleckstrin homology	329153	5721	330278	14487	23253, 32019,

	domain containing, family H (with MyTH4 domain) member 1					40785, 49551, 58317
5567	pleckstrin homology domain containing, family H (with MyTH4 domain) member 1	417684	5722	397712	14488	23254, 32020, 40786, 49552, 58318
5568	pleckstrin homology domain containing, family H (with MyTH4 domain) member 3	293349	5723	293349	14489	23255, 32021, 40787, 49553, 58319
5569	pleckstrin homology domain containing, family H (with MyTH4 domain) member 3	412503	5724	411885	14490	23256, 32022, 40788, 49554, 58320
5570	pleckstrin homology domain containing, family H (with MyTH4 domain) member 3	456950	5725	394251	14491	23257, 32023, 40789, 49555, 58321
5571	pleckstrin homology domain containing, family J member 1	326631	5726	318075	14492	23258, 32024, 40790, 49556, 58322
5572	pleckstrin homology domain containing, family M (with RUN domain) member 2	375793	5727	364950	14493	23259, 32025, 40791, 49557, 58323
5573	pleckstrin homology domain containing, family M, member 3	389247	5728	373899	14494	23260, 32026, 40792, 49558, 58324
5574	pleckstrin homology domain containing, family M, member 3	427836	5729	417003	14495	23261, 32027, 40793, 49559, 58325
5575	pleckstrin homology domain containing, family M, member 3	447645	5730	395354	14496	23262, 32028, 40794, 49560, 58326
5576	pleckstrin homology domain containing, family N member 1	379407	5731	368717	14497	23263, 32029, 40795, 49561, 58327
5577	pleckstrin homology domain containing, family N member 1	379409	5732	368719	14498	23264, 32030, 40796, 49562, 58328
5578	pleckstrin homology domain containing, family N member 1	379410	5733	368720	14499	23265, 32031, 40797, 49563, 58329
5579	pleckstrin homology domain containing, family O member 2	323544	5734	326706	14500	23266, 32032, 40798, 49564, 58330
5580	pleckstrin homology domain containing, family O member 2	546008	5735	441538	14501	23267, 32033, 40799, 49565, 58331

5581	pleckstrin homology-like domain, family B, member 3	292140	5736	292140	14502	23268, 32034, 40800, 49566, 58332
5582	PMF1-BGLAP protein isoform 1	320139	5737	324909	14503	23269, 32035, 40801, 49567, 58333
5583	PMF1-BGLAP protein isoform 1	368276	5738	357259	14504	23270, 32036, 40802, 49568, 58334
5584	PML-RARA regulated adaptor molecule 1	255612	5739	255612	14505	23271, 32037, 40803, 49569, 58335
5585	PML-RARA regulated adaptor molecule 1	423345	5740	408342	14506	23272, 32038, 40804, 49570, 58336
5586	PML-RARA regulated adaptor molecule 1	536152	5741	444318	14507	23273, 32039, 40805, 49571, 58337
5587	PNMA-like 1	313683	5742	318131	14508	23274, 32040, 40806, 49572, 58338
5588	PNMA-like 1	417103	5743	389114	14509	23275, 32041, 40807, 49573, 58339
5589	PNMA-like 1	438932	5744	410273	14510	23276, 32042, 40808, 49574, 58340
5590	PNMA-like 2	377655	5745	366883	14511	23277, 32043, 40809, 49575, 58341
5591	POC1B-GALNT4 readthrough	413530	5746	389686	14512	23278, 32044, 40810, 49576, 58342
5592	POC1B-GALNT4 readthrough	548729	5747	447852	14513	23279, 32045, 40811, 49577, 58343
5593	pogo transposable element with KRAB domain	537173	5748	442763	14514	23280, 32046, 40812, 49578, 58344
5594	polo-like kinase 5	454744	5749	468376	14515	23281, 32047, 40813, 49579, 58345
5595	poly (ADP-ribose) polymerase family member 6	569795	5750	456348	14516	23282, 32048, 40814, 49580, 58346
5596	poly (ADP-ribose) polymerase family, member 11	228820	5751	228820	14517	23283, 32049, 40815, 49581, 58347
5597	poly (ADP-ribose) polymerase family, member	397096	5752	380284	14518	23284, 32050, 40816, 49582,

	11					58348
5598	poly (ADP-ribose) polymerase family, member 11	427057	5753	397058	14519	23285, 32051, 40817, 49583, 58349
5599	poly (ADP-ribose) polymerase family, member 11	447133	5754	405385	14520	23286, 32052, 40818, 49584, 58350
5600	poly (ADP-ribose) polymerase family, member 11	450737	5755	387481	14521	23287, 32053, 40819, 49585, 58351
5601	poly (ADP-ribose) polymerase family, member 6	260376	5756	260376	14522	23288, 32054, 40820, 49586, 58352
5602	poly (ADP-ribose) polymerase family, member 6	287196	5757	287196	14523	23289, 32055, 40821, 49587, 58353
5603	poly (ADP-ribose) polymerase family, member 6	336471	5758	338599	14524	23290, 32056, 40822, 49588, 58354
5604	poly (ADP-ribose) polymerase family, member 6	413097	5759	388919	14525	23291, 32057, 40823, 49589, 58355
5605	poly (ADP-ribose) polymerase family, member 6	419739	5760	403265	14526	23292, 32058, 40824, 49590, 58356
5606	poly (ADP-ribose) polymerase family, member 6	544520	5761	443723	14527	23293, 32059, 40825, 49591, 58357
5607	poly (ADP-ribose) polymerase family, member 8	281631	5762	281631	14528	23294, 32060, 40826, 49592, 58358
5608	poly (ADP-ribose) polymerase family, member 8	423185	5763	390086	14529	23295, 32061, 40827, 49593, 58359
5609	poly (ADP-ribose) polymerase family, member 8	503665	5764	427138	14530	23296, 32062, 40828, 49594, 58360
5610	poly (ADP-ribose) polymerase family, member 8	503750	5765	440851	14531	23297, 32063, 40829, 49595, 58361
5611	poly (ADP-ribose) polymerase family, member 8	505554	5766	423946	14532	23298, 32064, 40830, 49596, 58362
5612	poly (ADP-ribose) polymerase family, member 8	505697	5767	422217	14533	23299, 32065, 40831, 49597, 58363
5613	poly (ADP-ribose) polymerase family, member 8	514067	5768	424814	14534	23300, 32066, 40832, 49598, 58364
5614	poly (ADP-ribose)	514342	5769	439022	14535	23301, 32067,

	polymerase family, member 8					40833, 49599, 58365
5615	poly(A) binding protein cytoplasmic 1-like 2A	599024	5770	469515	14536	23302, 32068, 40834, 49600, 58366
5616	poly(A) binding protein cytoplasmic 1-like 2B	600221	5771	471628	14537	23303, 32069, 40835, 49601, 58367
5617	poly(A) binding protein cytoplasmic 4-like	421491	5772	463233	14538	23304, 32070, 40836, 49602, 58368
5618	poly(A) binding protein cytoplasmic 4-like	529122	5773	462986	14539	23305, 32071, 40837, 49603, 58369
5619	poly(A) binding protein, cytoplasmic 1-like	217073	5774	217073	14540	23306, 32072, 40838, 49604, 58370, 61536, 61594
5620	poly(A) binding protein, cytoplasmic 1-like	217074	5775	217074	14541	23307, 32073, 40839, 49605, 58371
5621	poly(A) binding protein, cytoplasmic 1-like	217075	5776	217075	14542	23308, 32074, 40840, 49606, 58372
5622	poly(A) binding protein, cytoplasmic 1-like	255136	5777	255136	14543	23309, 32075, 40841, 49607, 58373
5623	poly(A) binding protein, cytoplasmic 1-like	372819	5778	361906	14544	23310, 32076, 40842, 49608, 58374
5624	poly(A) binding protein, cytoplasmic 1-like	372821	5779	361908	14545	23311, 32077, 40843, 49609, 58375
5625	poly(A) binding protein, cytoplasmic 1-like	372822	5780	361909	14546	23312, 32078, 40844, 49610, 58376
5626	poly(A) binding protein, cytoplasmic 1-like	372824	5781	361911	14547	23313, 32079, 40845, 49611, 58377
5627	poly(A) binding protein, cytoplasmic 1-like	372826	5782	361913	14548	23314, 32080, 40846, 49612, 58378
5628	poly(A) binding protein, cytoplasmic 1-like	421240	5783	400662	14549	23315, 32081, 40847, 49613, 58379
5629	poly(A) binding protein, cytoplasmic 1-like	537323	5784	445661	14550	23316, 32082, 40848, 49614, 58380
5630	poly(A) binding protein, cytoplasmic 1-like 2A	373519	5785	362618	14551	23317, 32083, 40849, 49615,

						58381
5631	poly(A) binding protein, cytoplasmic 1-like 2A	453389	5786	393248	14552	23318, 32084, 40850, 49616, 58382
5632	poly(A) binding protein, cytoplasmic 1-like 2B	373521	5787	362621	14553	23319, 32085, 40851, 49617, 58383
5633	poly(A) binding protein, cytoplasmic 1-like 2B	538388	5788	438402	14554	23320, 32086, 40852, 49618, 58384
5634	poly(rC) binding protein 4	294192	5789	294192	14555	23321, 32087, 40853, 49619, 58385
5635	poly(rC) binding protein 4	395013	5790	378460	14556	23322, 32088, 40854, 49620, 58386
5636	poly(rC) binding protein 4	395014	5791	378461	14557	23323, 32089, 40855, 49621, 58387
5637	poly(rC) binding protein 4	428823	5792	395030	14558	23324, 32090, 40856, 49622, 58388
5638	poly(rC) binding protein 4	461544	5793	419672	14559	23325, 32091, 40857, 49623, 58389
5639	poly(rC) binding protein 4	466412	5794	419557	14560	23326, 32092, 40858, 49624, 58390
5640	poly(rC) binding protein 4	468324	5795	419694	14561	23327, 32093, 40859, 49625, 58391
5641	poly(rC) binding protein 4	483411	5796	418997	14562	23328, 32094, 40860, 49626, 58392
5642	poly(rC) binding protein 4	484633	5797	417100	14563	23329, 32095, 40861, 49627, 58393
5643	poly(rC) binding protein 4	489595	5798	420008	14564	23330, 32096, 40862, 49628, 58394
5644	poly(rC) binding protein 4	490063	5799	418312	14565	23331, 32097, 40863, 49629, 58395
5645	poly(rC) binding protein 4	497653	5800	417916	14566	23332, 32098, 40864, 49630, 58396
5646	polyamine modulated factor 1 binding protein 1	237353	5801	237353	14567	23333, 32099, 40865, 49631, 58397
5647	polyamine modulated factor	355636	5802	347854	14568	23334, 32100,

	1 binding protein 1					40866, 49632, 58398
5648	polyamine modulated factor 1 binding protein 1	535461	5803	444953	14569	23335, 32101, 40867, 49633, 58399
5649	polyamine modulated factor 1 binding protein 1	536211	5804	439841	14570	23336, 32102, 40868, 49634, 58400
5650	polyamine modulated factor 1 binding protein 1	537465	5805	443817	14571	23337, 32103, 40869, 49635, 58401
5651	polyamine modulated factor 1 binding protein 1	539172	5806	440941	14572	23338, 32104, 40870, 49636, 58402
5652	polyamine modulated factor 1 binding protein 1	540440	5807	440755	14573	23339, 32105, 40871, 49637, 58403
5653	polyamine oxidase (exo-N4-amino)	278060	5808	278060	14574	23340, 32106, 40872, 49638, 58404
5654	polyamine oxidase (exo-N4-amino)	357296	5809	349847	14575	23341, 32107, 40873, 49639, 58405
5655	polyamine oxidase (exo-N4-amino)	368534	5810	357522	14576	23342, 32108, 40874, 49640, 58406
5656	polyamine oxidase (exo-N4-amino)	368538	5811	357526	14577	23343, 32109, 40875, 49641, 58407
5657	polyamine oxidase (exo-N4-amino)	368539	5812	357527	14578	23344, 32110, 40876, 49642, 58408
5658	polyamine oxidase (exo-N4-amino)	368542	5813	357530	14579	23345, 32111, 40877, 49643, 58409
5659	polyamine oxidase (exo-N4-amino)	368544	5814	357532	14580	23346, 32112, 40878, 49644, 58410
5660	polyamine oxidase (exo-N4-amino)	480071	5815	435514	14581	23347, 32113, 40879, 49645, 58411
5661	polyamine oxidase (exo-N4-amino)	539775	5816	437742	14582	23348, 32114, 40880, 49646, 58412
5662	polycystic kidney disease 1-like 2	337114	5817	337397	14583	23349, 32115, 40881, 49647, 58413
5663	polycystic kidney disease 1-like 2	526632	5818	436389	14584	23350, 32116, 40882, 49648, 58414

5664	polyglutamine binding protein 1	593464	5819	472506	14585	23351, 32117, 40883, 49649, 58415
5665	polyglutamine binding protein 1	594868	5820	469772	14586	23352, 32118, 40884, 49650, 58416
5666	polyglutamine binding protein 1	597699	5821	472009	14587	23353, 32119, 40885, 49651, 58417
5667	polyglutamine binding protein 1	600640	5822	469504	14588	23354, 32120, 40886, 49652, 58418
5668	polymerase (RNA) I polypeptide E, 53kDa	377792	5823	367023	14589	23355, 32121, 40887, 49653, 58419
5669	polymerase (RNA) I polypeptide E, 53kDa	377798	5824	367029	14590	23356, 32122, 40888, 49654, 58420
5670	polymerase (RNA) I polypeptide E, 53kDa	421959	5825	397455	14591	23357, 32123, 40889, 49655, 58421
5671	polymerase (RNA) I polypeptide E, 53kDa	442009	5826	399887	14592	23358, 32124, 40890, 49656, 58422
5672	polymerase (RNA) III (DNA directed) polypeptide G (32kD)-like	369313	5827	358319	14593	23359, 32125, 40891, 49657, 58423
5673	polymerase (RNA) III (DNA directed) polypeptide G (32kD)-like	369314	5828	358320	14594	23360, 32126, 40892, 49658, 58424
5674	poly-U binding splicing factor 60KDa	563311	5829	454452	14595	23361, 32127, 40893, 49659, 58425
5675	poly-U binding splicing factor 60KDa	568960	5830	454822	14596	23362, 32128, 40894, 49660, 58426
5676	poly-U binding splicing factor 60KDa	569567	5831	456170	14597	23363, 32129, 40895, 49661, 58427
5677	POM121 membrane glycoprotein-like 12	408890	5832	386133	14598	23364, 32130, 40896, 49662, 58428
5678	POM121 membrane glycoprotein-like 2	377451	5833	366671	14599	23365, 32131, 40897, 49663, 58429
5679	POM121 membrane glycoprotein-like 2	444565	5834	392726	14600	23366, 32132, 40898, 49664, 58430
5680	POM121 membrane glycoprotein-like 4	412250	5835	443399	14601	23367, 32133, 40899, 49665,

	pseudogene					58431
5681	POM121 membrane glycoprotein-like 7	329949	5836	383394	14602	23368, 32134, 40900, 49666, 58432
5682	POM121 membrane glycoprotein-like 7	419447	5837	410855	14603	23369, 32135, 40901, 49667, 58433
5683	POM121 transmembrane nucleoporin	575107	5838	460606	14604	23370, 32136, 40902, 49668, 58434
5684	porcupine homolog (Drosophila)	595805	5839	471289	14605	23371, 32137, 40903, 49669, 58435
5685	porcupine homolog (Drosophila)	600418	5840	472028	14606	23372, 32138, 40904, 49670, 58436
5686	potassium channel modulatory factor 1	409785	5841	386738	14607	23373, 32139, 40905, 49671, 58437
5687	potassium channel tetramerisation domain containing 15	284006	5842	284006	14608	23374, 32140, 40906, 49672, 58438
5688	potassium channel tetramerisation domain containing 15	413790	5843	406942	14609	23375, 32141, 40907, 49673, 58439
5689	potassium channel tetramerisation domain containing 21	526208	5844	431789	14610	23376, 32142, 40908, 49674, 58440
5690	potassium channel tetramerisation domain containing 21	528776	5845	435025	14611	23377, 32143, 40909, 49675, 58441
5691	potassium channel tetramerisation domain containing 21	529350	5846	431130	14612	23378, 32144, 40910, 49676, 58442
5692	potassium channel tetramerisation domain containing 21	530018	5847	435428	14613	23379, 32145, 40911, 49677, 58443
5693	potassium channel, subfamily U, member 1	399881	5848	382770	14614	23380, 32146, 40912, 49678, 58444
5694	potassium inwardly-rectifying channel subfamily J member 18	563509	5849	456250	14615	23381, 32147, 40913, 49679, 58445
5695	potassium voltage-gated channel subfamily H (eag-related) member 5	394968	5850	378419	14616	23382, 32148, 40914, 49680, 58446
5696	potassium voltage-gated channel subfamily H (eag-related) member 5	420622	5851	395439	14617	23383, 32149, 40915, 49681, 58447
5697	POTE ankyrin domain	327822	5852	329990	14618	23384, 32150,

	family member D					40916, 49682, 58448
5698	POTE ankyrin domain family member E	356920	5853	439189	14619	23385, 32151, 40917, 49683, 58449
5699	POTE ankyrin domain family member E	358087	5854	443049	14620	23386, 32152, 40918, 49684, 58450
5700	POTE ankyrin domain family member M	551509	5855	452296	14621	23387, 32153, 40919, 49685, 58451
5701	POTE ankyrin domain family, member C	358970	5856	351856	14622	23388, 32154, 40920, 49686, 58452
5702	POTE ankyrin domain family, member C	389891	5857	374541	14623	23389, 32155, 40921, 49687, 58453
5703	POTE ankyrin domain family, member G	409832	5858	386971	14624	23390, 32156, 40922, 49688, 58454
5704	POTE ankyrin domain family, member M	344684	5859	340144	14625	23391, 32157, 40923, 49689, 58455
5705	POTE ankyrin domain family, member M	439503	5860	389253	14626	23392, 32158, 40924, 49690, 58456
5706	POU class 5 homeobox 1B	391675	5861	375557	14627	23393, 32159, 40925, 49691, 58457
5707	POU class 5 homeobox 1B	465342	5862	419298	14628	23394, 32160, 40926, 49692, 58458
5708	POU domain class 5 transcription factor 2	510627	5863	464890	14629	23395, 32161, 40927, 49693, 58459
5709	PPAN-P2RY11 readthrough	393796	5864	377385	14630	23396, 32162, 40928, 49694, 58460
5710	PPAN-P2RY11 readthrough	428358	5865	411918	14631	23397, 32163, 40929, 49695, 58461
5711	PPP5 tetratricopeptide repeat domain containing 1	602017	5866	471730	14632	23398, 32164, 40930, 49696, 58462
5712	PPPDE peptidase domain containing 1	263831	5867	263831	14633	23399, 32165, 40931, 49697, 58463
5713	PPPDE peptidase domain containing 1	302550	5868	306528	14634	23400, 32166, 40932, 49698, 58464

5714	PPPDE peptidase domain containing 1	418162	5869	394555	14635	23401, 32167, 40933, 49699, 58465
5715	PR domain containing 10	304538	5870	302669	14636	23402, 32168, 40934, 49700, 58466
5716	PR domain containing 10	358825	5871	351686	14637	23403, 32169, 40935, 49701, 58467
5717	PR domain containing 10	360871	5872	354118	14638	23404, 32170, 40936, 49702, 58468
5718	PR domain containing 10	423662	5873	398431	14639	23405, 32171, 40937, 49703, 58469
5719	PR domain containing 10	526082	5874	432237	14640	23406, 32172, 40938, 49704, 58470
5720	PR domain containing 11	263765	5875	263765	14641	23407, 32173, 40939, 49705, 58471
5721	PR domain containing 11	530656	5876	435976	14642	23408, 32174, 40940, 49706, 58472
5722	PR domain containing 11	424263	5877	394314	14643	23409, 32175, 40941, 49707, 58473
5723	PRAME family member 1	332296	5878	332134	14644	23410, 32176, 40942, 49708, 58474
5724	PRAME family member 1	400814	5879	383616	14645	23411, 32177, 40943, 49709, 58475
5725	PRAME family member 10	235347	5880	235347	14646	23412, 32178, 40944, 49710, 58476
5726	PRAME family member 11	331684	5881	328783	14647	23413, 32179, 40945, 49711, 58477
5727	PRAME family member 11	437584	5882	391839	14648	23414, 32180, 40946, 49712, 58478
5728	PRAME family member 11	535591	5883	439551	14649	23415, 32181, 40947, 49713, 58479
5729	PRAME family member 12	357726	5884	350358	14650	23416, 32182, 40948, 49714, 58480
5730	PRAME family member 13	376132	5885	365302	14651	23417, 32183, 40949, 49715,

						58481
5731	PRAME family member 14	334600	5886	334410	14652	23418, 32184, 40950, 49716, 58482
5732	PRAME family member 14	344998	5887	341333	14653	23419, 32185, 40951, 49717, 58483
5733	PRAME family member 15	330087	5888	330156	14654	23420, 32186, 40952, 49718, 58484
5734	PRAME family member 15	332913	5889	327917	14655	23421, 32187, 40953, 49719, 58485
5735	PRAME family member 16	376121	5890	365289	14656	23422, 32188, 40954, 49720, 58486
5736	PRAME family member 17	376098	5891	365266	14657	23423, 32189, 40955, 49721, 58487
5737	PRAME family member 18	376126	5892	365294	14658	23424, 32190, 40956, 49722, 58488
5738	PRAME family member 19	376101	5893	365269	14659	23425, 32191, 40957, 49723, 58489
5739	PRAME family member 19	540591	5894	446004	14660	23426, 32192, 40958, 49724, 58490
5740	PRAME family member 2	240189	5895	240189	14661	23427, 32193, 40959, 49725, 58491
5741	PRAME family member 20	316412	5896	346275	14662	23428, 32194, 40960, 49726, 58492
5742	PRAME family member 21	327795	5897	333197	14663	23429, 32195, 40961, 49727, 58493
5743	PRAME family member 21	332192	5898	331921	14664	23430, 32196, 40962, 49728, 58494
5744	PRAME family member 22	376187	5899	365358	14665	23431, 32197, 40963, 49729, 58495
5745	PRAME family member 3	353410	5900	334892	14666	23432, 32198, 40964, 49730, 58496
5746	PRAME family member 3	376173	5901	365343	14667	23433, 32199, 40965, 49731, 58497
5747	PRAME family member 4	235349	5902	235349	14668	23434, 32200,

						40966, 49732, 58498
5748	PRAME family member 5	376168	5903	365338	14669	23435, 32201, 40967, 49733, 58499
5749	PRAME family member 6	355096	5904	347211	14670	23436, 32202, 40968, 49734, 58500
5750	PRAME family member 6	376182	5905	365353	14671	23437, 32203, 40969, 49735, 58501
5751	PRAME family member 6	376189	5906	365360	14672	23438, 32204, 40970, 49736, 58502
5752	PRAME family member 6	376192	5907	365363	14673	23439, 32205, 40971, 49737, 58503
5753	PRAME family member 6	414205	5908	393084	14674	23440, 32206, 40972, 49738, 58504
5754	PRAME family member 6	415464	5909	401281	14675	23441, 32207, 40973, 49739, 58505
5755	PRAME family member 7	330881	5910	328915	14676	23442, 32208, 40974, 49740, 58506
5756	PRAME family member 7	361079	5911	354371	14677	23443, 32209, 40975, 49741, 58507
5757	PRAME family member 8	357367	5912	349931	14678	23444, 32210, 40976, 49742, 58508
5758	PRAME family member 9	376152	5913	365322	14679	23445, 32211, 40977, 49743, 58509
5759	prickle homolog 3 (Drosophila)	376310	5914	365487	14680	23446, 32212, 40978, 49744, 58510
5760	prickle homolog 3 (Drosophila)	376317	5915	365494	14681	23447, 32213, 40979, 49745, 58511
5761	prickle homolog 3 (Drosophila)	417014	5916	401337	14682	23448, 32214, 40980, 49746, 58512
5762	prickle homolog 3 (Drosophila)	432913	5917	390620	14683	23449, 32215, 40981, 49747, 58513
5763	prickle homolog 3 (Drosophila)	453382	5918	388599	14684	23450, 32216, 40982, 49748, 58514

5764	prickle homolog 3 (Drosophila)	536904	5919	441385	14685	23451, 32217, 40983, 49749, 58515
5765	prickle homolog 3 (Drosophila)	538114	5920	441743	14686	23452, 32218, 40984, 49750, 58516
5766	prickle homolog 3 (Drosophila)	540849	5921	446051	14687	23453, 32219, 40985, 49751, 58517
5767	Primary ciliary dyskinesia protein 1	295220	5922	295220	14688	23454, 32220, 40986, 49752, 58518
5768	Primary ciliary dyskinesia protein 1	413369	5923	393222	14689	23455, 32221, 40987, 49753, 58519
5769	Primary ciliary dyskinesia protein 1	442513	5924	409912	14690	23456, 32222, 40988, 49754, 58520
5770	Primary ciliary dyskinesia protein 1	443972	5925	413299	14691	23457, 32223, 40989, 49755, 58521
5771	Primary ciliary dyskinesia protein 1	602047	5926	470965	14692	23458, 32224, 40990, 49756, 58522
5772	PRKR interacting protein 1 (IL11 inducible)	569623	5927	457736	14693	23459, 32225, 40991, 49757, 58523
5773	prohibitin 2	596553	5928	472765	14694	23460, 32226, 40992, 49758, 58524
5774	proline and serine rich 1	350125	5929	339123	14695	23461, 32227, 40993, 49759, 58525
5775	proline and serine rich 1	352251	5930	332034	14696	23462, 32228, 40994, 49760, 58526
5776	proline glutamate and leucine rich protein 1	269230	5931	269230	14697	23463, 32229, 40995, 49761, 58527
5777	proline glutamate and leucine rich protein 1	301396	5932	301396	14698	23464, 32230, 40996, 49762, 58528
5778	proline glutamate and leucine rich protein 1	436683	5933	416231	14699	23465, 32231, 40997, 49763, 58529
5779	proline glutamate and leucine rich protein 1	572293	5934	460300	14700	23466, 32232, 40998, 49764, 58530
5780	proline rich 11	262293	5935	262293	14701	23467, 32233, 40999, 49765,

						58531
5781	proline rich 12	246798	5936	246798	14702	23468, 32234, 41000, 49766, 58532
5782	proline rich 12	314734	5937	324524	14703	23469, 32235, 41001, 49767, 58533
5783	proline rich 12	418929	5938	394510	14704	23470, 32236, 41002, 49768, 58534
5784	proline rich 14	287463	5939	287463	14705	23471, 32237, 41003, 49769, 58535
5785	proline rich 14	300835	5940	300835	14706	23472, 32238, 41004, 49770, 58536
5786	proline rich 14	542965	5941	441641	14707	23473, 32239, 41005, 49771, 58537
5787	proline rich 14-like	397493	5942	380630	14708	23474, 32240, 41006, 49772, 58538
5788	proline rich 14-like	434485	5943	388314	14709	23475, 32241, 41007, 49773, 58539
5789	proline rich 14-like	327423	5944	331845	14710	23476, 32242, 41008, 49774, 58540
5790	proline rich 15	319694	5945	317836	14711	23477, 32243, 41009, 49775, 58541
5791	proline rich 15	450427	5946	408158	14712	23478, 32244, 41010, 49776, 58542
5792	proline rich 15-like	300557	5947	300557	14713	23479, 32245, 41011, 49777, 58543
5793	proline rich 16	379551	5948	368869	14714	23480, 32246, 41012, 49778, 58544
5794	proline rich 16	407149	5949	385118	14715	23481, 32247, 41013, 49779, 58545
5795	proline rich 16	446965	5950	405491	14716	23482, 32248, 41014, 49780, 58546
5796	proline rich 16	505123	5951	423446	14717	23483, 32249, 41015, 49781, 58547
5797	proline rich 16	509923	5952	421256	14718	23484, 32250,

						41016, 49782, 58548
5798	proline rich 19	341747	5953	342709	14719	23485, 32251, 41017, 49783, 58549
5799	proline rich 19	499536	5954	445247	14720	23486, 32252, 41018, 49784, 58550
5800	proline rich 20A	377931	5955	367164	14721	23487, 32253, 41019, 49785, 58551
5801	proline rich 20B	377930	5956	367163	14722	23488, 32254, 41020, 49786, 58552
5802	proline rich 20B	544542	5957	439629	14723	23489, 32255, 41021, 49787, 58553
5803	proline rich 20C	435681	5958	412952	14724	23490, 32256, 41022, 49788, 58554
5804	proline rich 20C	544357	5959	438757	14725	23491, 32257, 41023, 49789, 58555
5805	proline rich 20D	430865	5960	396706	14726	23492, 32258, 41024, 49790, 58556
5806	proline rich 20D	452123	5961	392407	14727	23493, 32259, 41025, 49791, 58557
5807	proline rich 20E	434815	5962	404281	14728	23494, 32260, 41026, 49792, 58558
5808	proline rich 20E	445351	5963	405952	14729	23495, 32261, 41027, 49793, 58559
5809	proline rich 21	408934	5964	386166	14730	23496, 32262, 41028, 49794, 58560
5810	proline rich 21	486799	5965	418240	14731	23497, 32263, 41029, 49795, 58561
5811	proline rich 22	419421	5966	407653	14732	23498, 32264, 41030, 49796, 58562
5812	proline rich 23A	383163	5967	372649	14733	23499, 32265, 41031, 49797, 58563
5813	proline rich 23B	329447	5968	328768	14734	23500, 32266, 41032, 49798, 58564

5814	proline rich 23C	413199	5969	396648	14735	23501, 32267, 41033, 49799, 58565
5815	proline rich 23C	502927	5970	438385	14736	23502, 32268, 41034, 49800, 58566
5816	proline rich 24	552360	5971	447679	14737	23503, 32269, 41035, 49801, 58567
5817	proline rich 25	301698	5972	301698	14738	23504, 32270, 41036, 49802, 58568
5818	proline rich 9	368744	5973	357733	14739	23505, 32271, 41037, 49803, 58569
5819	proline rich Gla (G-carboxyglutamic acid) 1	593312	5974	469094	14740	23506, 32272, 41038, 49804, 58570
5820	proline rich Gla (G-carboxyglutamic acid) 1	593805	5975	470278	14741	23507, 32273, 41039, 49805, 58571
5821	proline rich Gla (G-carboxyglutamic acid) 1	597842	5976	472527	14742	23508, 32274, 41040, 49806, 58572
5822	proline rich Gla (G-carboxyglutamic acid) 1	600043	5977	469699	14743	23509, 32275, 41041, 49807, 58573
5823	proline/histidine/glycine-rich 1	448599	5978	410024	14744	23510, 32276, 41042, 49808, 58574
5824	proline/histidine/glycine-rich 1	535816	5979	438992	14745	23511, 32277, 41043, 49809, 58575
5825	proline-rich coiled-coil 2B	320547	5980	326101	14746	23512, 32278, 41044, 49810, 58576
5826	proline-rich coiled-coil 2B	357304	5981	349856	14747	23513, 32279, 41045, 49811, 58577
5827	proline-rich coiled-coil 2B	372249	5982	361323	14748	23514, 32280, 41046, 49812, 58578
5828	proline-rich coiled-coil 2B	405995	5983	384606	14749	23515, 32281, 41047, 49813, 58579
5829	proline-rich coiled-coil 2B	418650	5984	392384	14750	23516, 32282, 41048, 49814, 58580
5830	proline-rich coiled-coil 2B	422467	5985	391063	14751	23517, 32283, 41049, 49815,

						58581
5831	proline-rich coiled-coil 2B	451855	5986	388579	14752	23518, 32284, 41050, 49816, 58582
5832	proline-rich coiled-coil 2B	456307	5987	400608	14753	23519, 32285, 41051, 49817, 58583
5833	proline-rich coiled-coil 2B	458550	5988	398853	14754	23520, 32286, 41052, 49818, 58584
5834	proline-rich coiled-coil 2B	541684	5989	437881	14755	23521, 32287, 41053, 49819, 58585
5835	proline-rich coiled-coil 2C	338920	5990	343629	14756	23522, 32288, 41054, 49820, 58586
5836	proline-rich coiled-coil 2C	392078	5991	375928	14757	23523, 32289, 41055, 49821, 58587
5837	proline-rich coiled-coil 2C	392080	5992	375930	14758	23524, 32290, 41056, 49822, 58588
5838	proline-rich coiled-coil 2C	412837	5993	396375	14759	23525, 32291, 41057, 49823, 58589
5839	proline-rich coiled-coil 2C	426496	5994	410219	14760	23526, 32292, 41058, 49824, 58590
5840	proline-rich coiled-coil 2C	451306	5995	401960	14761	23527, 32293, 41059, 49825, 58591
5841	proline-rich coiled-coil 2C	483654	5996	418004	14762	23528, 32294, 41060, 49826, 58592
5842	proline-rich protein BstNI subfamily 3	381842	5997	371264	14763	23529, 32295, 41061, 49827, 58593
5843	proline-rich protein BstNI subfamily 3	538488	5998	442626	14764	23530, 32296, 41062, 49828, 58594
5844	proline-rich protein HaeIII subfamily 2	572141	5999	458690	14765	23531, 32297, 41063, 49829, 58595
5845	proline-rich protein HaeIII subfamily 2	572835	6000	461080	14766	23532, 32298, 41064, 49830, 58596
5846	proline-rich protein HaeIII subfamily 2	573223	6001	458557	14767	23533, 32299, 41065, 49831, 58597
5847	proline-rich protein HaeIII	575657	6002	461041	14768	23534, 32300,

	subfamily 2					41066, 49832, 58598
5848	prostaglandin E synthase 3 (cytosolic)-like	409446	6003	386902	14769	23535, 32301, 41067, 49833, 58599
5849	prostaglandin E synthase 3 (cytosolic)-like	424284	6004	401675	14770	23536, 32302, 41068, 49834, 58600
5850	prostate and testis expressed 4	457514	6005	411439	14771	23537, 32303, 41069, 49835, 58601
5851	prostate stem cell antigen	571412	6006	460866	14772	23538, 32304, 41070, 49836, 58602
5852	protamine 3	327157	6007	325638	14773	23539, 32305, 41071, 49837, 58603
5853	protease serine 2 (trypsin 2)	570608	6008	459226	14774	23540, 32306, 41072, 49838, 58604
5854	protease serine 46	463091	6009	430307	14775	23541, 32307, 41073, 49839, 58605
5855	protease serine 58	567315	6010	457729	14776	23542, 32308, 41074, 49840, 58606
5856	protease, serine, 45	331814	6011	330940	14777	23543, 32309, 41075, 49841, 58607
5857	protease, serine, 45	442359	6012	401932	14778	23544, 32310, 41076, 49842, 58608
5858	proteasomal ATPase-associated factor 1	310571	6013	311665	14779	23545, 32311, 41077, 49843, 58609
5859	proteasomal ATPase-associated factor 1	376384	6014	365564	14780	23546, 32312, 41078, 49844, 58610
5860	proteasomal ATPase-associated factor 1	504441	6015	439747	14781	23547, 32313, 41079, 49845, 58611
5861	proteasomal ATPase-associated factor 1	536003	6016	438124	14782	23548, 32314, 41080, 49846, 58612
5862	proteasomal ATPase-associated factor 1	543814	6017	438894	14783	23549, 32315, 41081, 49847, 58613
5863	proteasomal ATPase-associated factor 1	544552	6018	441494	14784	23550, 32316, 41082, 49848, 58614

5864	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	415039	6019	407410	14785	23551, 32317, 41083, 49849, 58615
5865	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	540504	6020	444980	14786	23552, 32318, 41084, 49850, 58616
5866	proteasome (prosome, macropain) 26S subunit, non-ATPase, 3	541736	6021	442508	14787	23553, 32319, 41085, 49851, 58617
5867	proteasome (prosome, macropain) assembly chaperone 3	252329	6022	252329	14788	23554, 32320, 41086, 49852, 58618
5868	proteasome (prosome, macropain) assembly chaperone 3	288607	6023	288607	14789	23555, 32321, 41087, 49853, 58619
5869	proteasome (prosome, macropain) assembly chaperone 3	404674	6024	384799	14790	23556, 32322, 41088, 49854, 58620
5870	proteasome (prosome, macropain) assembly chaperone 4	419065	6025	392353	14791	23557, 32323, 41089, 49855, 58621
5871	proteasome (prosome, macropain) assembly chaperone 4	438998	6026	413353	14792	23558, 32324, 41090, 49856, 58622
5872	proteasome (prosome, macropain) assembly chaperone 4	473000	6027	418241	14793	23559, 32325, 41091, 49857, 58623
5873	proteasome (prosome, macropain) subunit, alpha type, 8	343848	6028	345584	14794	23560, 32326, 41092, 49858, 58624
5874	proteasome (prosome, macropain) subunit, alpha type, 8	415576	6029	409284	14795	23561, 32327, 41093, 49859, 58625
5875	proteasome (prosome, macropain) subunit, alpha type, 8	536423	6030	438933	14796	23562, 32328, 41094, 49860, 58626
5876	proteasome (prosome, macropain) subunit, alpha type, 8	538664	6031	440327	14797	23563, 32329, 41095, 49861, 58627
5877	protein associated with topoisomerase II homolog 2 (yeast)	434130	6032	416673	14798	23564, 32330, 41096, 49862, 58628
5878	protein associated with topoisomerase II homolog 2 (yeast)	560775	6033	453915	14799	23565, 32331, 41097, 49863, 58629
5879	Protein Coding	5905	6034	5905	14800	23566, 32332, 41098, 49864, 58630, 61537, 61595
5880	Protein Coding	242109	6035	242109	14801	23567, 32333,

						41099, 49865, 58631
5881	Protein Coding	242315	6036	242315	14802	23568, 32334, 41100, 49866, 58632
5882	Protein Coding	251993	6037	251993	14803	23569, 32335, 41101, 49867, 58633
5883	Protein Coding	253803	6038	253803	14804	23570, 32336, 41102, 49868, 58634
5884	Protein Coding	256858	6039	256858	14805	23571, 32337, 41103, 49869, 58635
5885	Protein Coding	259335	6040	259335	14806	23572, 32338, 41104, 49870, 58636
5886	Protein Coding	261588	6041	261588	14807	23573, 32339, 41105, 49871, 58637
5887	Protein Coding	263468	6042	263468	14808	23574, 32340, 41106, 49872, 58638
5888	Protein Coding	263563	6043	263563	14809	23575, 32341, 41107, 49873, 58639
5889	Protein Coding	265068	6044	265068	14810	23576, 32342, 41108, 49874, 58640
5890	Protein Coding	279024	6045	279024	14811	23577, 32343, 41109, 49875, 58641
5891	Protein Coding	280020	6046	280020	14812	23578, 32344, 41110, 49876, 58642
5892	Protein Coding	290881	6047	290881	14813	23579, 32345, 41111, 49877, 58643
5893	Protein Coding	294521	6048	294521	14814	23580, 32346, 41112, 49878, 58644
5894	Protein Coding	295031	6049	295031	14815	23581, 32347, 41113, 49879, 58645
5895	Protein Coding	295878	6050	295878	14816	23582, 32348, 41114, 49880, 58646
5896	Protein Coding	296121	6051	296121	14817	23583, 32349, 41115, 49881, 58647

5897	Protein Coding	296312	6052	296312	14818	23584, 32350, 41116, 49882, 58648
5898	Protein Coding	296564	6053	296564	14819	23585, 32351, 41117, 49883, 58649
5899	Protein Coding	296775	6054	296775	14820	23586, 32352, 41118, 49884, 58650
5900	Protein Coding	296858	6055	296858	14821	23587, 32353, 41119, 49885, 58651
5901	Protein Coding	297063	6056	297063	14822	23588, 32354, 41120, 49886, 58652
5902	Protein Coding	297423	6057	297423	14823	23589, 32355, 41121, 49887, 58653
5903	Protein Coding	298569	6058	298569	14824	23590, 32356, 41122, 49888, 58654
5904	Protein Coding	299505	6059	299505	14825	23591, 32357, 41123, 49889, 58655
5905	Protein Coding	307659	6060	303928	14826	23592, 32358, 41124, 49890, 58656
5906	Protein Coding	309447	6061	309501	14827	23593, 32359, 41125, 49891, 58657
5907	Protein Coding	309874	6062	311642	14828	23594, 32360, 41126, 49892, 58658
5908	Protein Coding	312019	6063	310465	14829	23595, 32361, 41127, 49893, 58659
5909	Protein Coding	312498	6064	312205	14830	23596, 32362, 41128, 49894, 58660
5910	Protein Coding	313737	6065	324000	14831	23597, 32363, 41129, 49895, 58661
5911	Protein Coding	314073	6066	313933	14832	23598, 32364, 41130, 49896, 58662
5912	Protein Coding	316577	6067	312679	14833	23599, 32365, 41131, 49897, 58663
5913	Protein Coding	316807	6068	324876	14834	23600, 32366, 41132, 49898,

						58664
5914	Protein Coding	317020	6069	319251	14835	23601, 32367, 41133, 49899, 58665
5915	Protein Coding	321830	6070	362959	14836	23602, 32368, 41134, 49900, 58666
5916	Protein Coding	322335	6071	320468	14837	23603, 32369, 41135, 49901, 58667
5917	Protein Coding	322896	6072	315633	14838	23604, 32370, 41136, 49902, 58668
5918	Protein Coding	326958	6073	318340	14839	23605, 32371, 41137, 49903, 58669
5919	Protein Coding	327217	6074	324311	14840	23606, 32372, 41138, 49904, 58670
5920	Protein Coding	328239	6075	404871	14841	23607, 32373, 41139, 49905, 58671
5921	Protein Coding	329378	6076	331385	14842	23608, 32374, 41140, 49906, 58672
5922	Protein Coding	331659	6077	328422	14843	23609, 32375, 41141, 49907, 58673
5923	Protein Coding	333666	6078	327620	14844	23610, 32376, 41142, 49908, 58674
5924	Protein Coding	333957	6079	334229	14845	23611, 32377, 41143, 49909, 58675
5925	Protein Coding	336156	6080	336720	14846	23612, 32378, 41144, 49910, 58676
5926	Protein Coding	337530	6081	336940	14847	23613, 32379, 41145, 49911, 58677
5927	Protein Coding	338005	6082	338013	14848	23614, 32380, 41146, 49912, 58678
5928	Protein Coding	338205	6083	339889	14849	23615, 32381, 41147, 49913, 58679
5929	Protein Coding	338533	6084	344805	14850	23616, 32382, 41148, 49914, 58680
5930	Protein Coding	338857	6085	340488	14851	23617, 32383,

						41149, 49915, 58681
5931	Protein Coding	341011	6086	342423	14852	23618, 32384, 41150, 49916, 58682
5932	Protein Coding	343629	6087	343635	14853	23619, 32385, 41151, 49917, 58683
5933	Protein Coding	343767	6088	345469	14854	23620, 32386, 41152, 49918, 58684
5934	Protein Coding	344649	6089	343456	14855	23621, 32387, 41153, 49919, 58685
5935	Protein Coding	344707	6090	344426	14856	23622, 32388, 41154, 49920, 58686
5936	Protein Coding	346061	6091	328195	14857	23623, 32389, 41155, 49921, 58687
5937	Protein Coding	354689	6092	346720	14858	23624, 32390, 41156, 49922, 58688
5938	Protein Coding	354995	6093	366656	14859	23625, 32391, 41157, 49923, 58689
5939	Protein Coding	356370	6094	348731	14860	23626, 32392, 41158, 49924, 58690
5940	Protein Coding	356559	6095	348964	14861	23627, 32393, 41159, 49925, 58691
5941	Protein Coding	356686	6096	349114	14862	23628, 32394, 41160, 49926, 58692
5942	Protein Coding	356719	6097	349154	14863	23629, 32395, 41161, 49927, 58693
5943	Protein Coding	356822	6098	364391	14864	23630, 32396, 41162, 49928, 58694
5944	Protein Coding	357170	6099	349693	14865	23631, 32397, 41163, 49929, 58695
5945	Protein Coding	357301	6100	349853	14866	23632, 32398, 41164, 49930, 58696
5946	Protein Coding	358431	6101	351207	14867	23633, 32399, 41165, 49931, 58697

5947	Protein Coding	358740	6102	392188	14868	23634, 32400, 41166, 49932, 58698
5948	Protein Coding	358799	6103	351653	14869	23635, 32401, 41167, 49933, 58699
5949	Protein Coding	359871	6104	352933	14870	23636, 32402, 41168, 49934, 58700
5950	Protein Coding	360166	6105	353290	14871	23637, 32403, 41169, 49935, 58701
5951	Protein Coding	361121	6106	355211	14872	23638, 32404, 41170, 49936, 58702
5952	Protein Coding	361786	6107	355319	14873	23639, 32405, 41171, 49937, 58703
5953	Protein Coding	366116	6108	382846	14874	23640, 32406, 41172, 49938, 58704
5954	Protein Coding	366221	6109	407048	14875	23641, 32407, 41173, 49939, 58705
5955	Protein Coding	366261	6110	388733	14876	23642, 32408, 41174, 49940, 58706
5956	Protein Coding	366347	6111	382107	14877	23643, 32409, 41175, 49941, 58707
5957	Protein Coding	366356	6112	444936	14878	23644, 32410, 41176, 49942, 58708
5958	Protein Coding	366377	6113	399523	14879	23645, 32411, 41177, 49943, 58709
5959	Protein Coding	366845	6114	355810	14880	23646, 32412, 41178, 49944, 58710
5960	Protein Coding	367587	6115	356559	14881	23647, 32413, 41179, 49945, 58711
5961	Protein Coding	367588	6116	356560	14882	23648, 32414, 41180, 49946, 58712
5962	Protein Coding	367636	6117	356608	14883	23649, 32415, 41181, 49947, 58713
5963	Protein Coding	368319	6118	357302	14884	23650, 32416, 41182, 49948,

						58714
5964	Protein Coding	368320	6119	357303	14885	23651, 32417, 41183, 49949, 58715
5965	Protein Coding	368321	6120	357304	14886	23652, 32418, 41184, 49950, 58716
5966	Protein Coding	368372	6121	357356	14887	23653, 32419, 41185, 49951, 58717
5967	Protein Coding	370378	6122	359404	14888	23654, 32420, 41186, 49952, 58718
5968	Protein Coding	370733	6123	359768	14889	23655, 32421, 41187, 49953, 58719
5969	Protein Coding	370795	6124	359831	14890	23656, 32422, 41188, 49954, 58720
5970	Protein Coding	371933	6125	361001	14891	23657, 32423, 41189, 49955, 58721
5971	Protein Coding	372963	6126	362054	14892	23658, 32424, 41190, 49956, 58722
5972	Protein Coding	373137	6127	362230	14893	23659, 32425, 41191, 49957, 58723
5973	Protein Coding	373214	6128	362310	14894	23660, 32426, 41192, 49958, 58724
5974	Protein Coding	373398	6129	362496	14895	23661, 32427, 41193, 49959, 58725
5975	Protein Coding	373404	6130	362503	14896	23662, 32428, 41194, 49960, 58726
5976	Protein Coding	373480	6131	362579	14897	23663, 32429, 41195, 49961, 58727
5977	Protein Coding	373524	6132	362624	14898	23664, 32430, 41196, 49962, 58728
5978	Protein Coding	373527	6133	362627	14899	23665, 32431, 41197, 49963, 58729
5979	Protein Coding	374244	6134	363362	14900	23666, 32432, 41198, 49964, 58730
5980	Protein Coding	374378	6135	363499	14901	23667, 32433,

						41199, 49965, 58731
5981	Protein Coding	374383	6136	363504	14902	23668, 32434, 41200, 49966, 58732
5982	Protein Coding	374983	6137	364122	14903	23669, 32435, 41201, 49967, 58733
5983	Protein Coding	375081	6138	364222	14904	23670, 32436, 41202, 49968, 58734
5984	Protein Coding	375625	6139	364776	14905	23671, 32437, 41203, 49969, 58735
5985	Protein Coding	375644	6140	364795	14906	23672, 32438, 41204, 49970, 58736
5986	Protein Coding	375670	6141	364822	14907	23673, 32439, 41205, 49971, 58737
5987	Protein Coding	375671	6142	364823	14908	23674, 32440, 41206, 49972, 58738
5988	Protein Coding	375684	6143	364836	14909	23675, 32441, 41207, 49973, 58739
5989	Protein Coding	376271	6144	365447	14910	23676, 32442, 41208, 49974, 58740
5990	Protein Coding	377548	6145	366771	14911	23677, 32443, 41209, 49975, 58741
5991	Protein Coding	378007	6146	367246	14912	23678, 32444, 41210, 49976, 58742
5992	Protein Coding	378108	6147	367348	14913	23679, 32445, 41211, 49977, 58743
5993	Protein Coding	378305	6148	367555	14914	23680, 32446, 41212, 49978, 58744
5994	Protein Coding	378340	6149	367591	14915	23681, 32447, 41213, 49979, 58745
5995	Protein Coding	378417	6150	367673	14916	23682, 32448, 41214, 49980, 58746
5996	Protein Coding	378781	6151	368057	14917	23683, 32449, 41215, 49981, 58747

5997	Protein Coding	378784	6152	368061	14918	23684, 32450, 41216, 49982, 58748
5998	Protein Coding	378787	6153	368064	14919	23685, 32451, 41217, 49983, 58749
5999	Protein Coding	378797	6154	368074	14920	23686, 32452, 41218, 49984, 58750
6000	Protein Coding	378904	6155	368184	14921	23687, 32453, 41219, 49985, 58751
6001	Protein Coding	379151	6156	368447	14922	23688, 32454, 41220, 49986, 58752
6002	Protein Coding	379963	6157	369297	14923	23689, 32455, 41221, 49987, 58753
6003	Protein Coding	380145	6158	369490	14924	23690, 32456, 41222, 49988, 58754
6004	Protein Coding	381977	6159	371404	14925	23691, 32457, 41223, 49989, 58755
6005	Protein Coding	382225	6160	371660	14926	23692, 32458, 41224, 49990, 58756
6006	Protein Coding	382326	6161	371763	14927	23693, 32459, 41225, 49991, 58757
6007	Protein Coding	383055	6162	372528	14928	23694, 32460, 41226, 49992, 58758
6008	Protein Coding	383686	6163	373184	14929	23695, 32461, 41227, 49993, 58759
6009	Protein Coding	389003	6164	373655	14930	23696, 32462, 41228, 49994, 58760, 61538, 61596
6010	Protein Coding	389851	6165	374501	14931	23697, 32463, 41229, 49995, 58761
6011	Protein Coding	389908	6166	374558	14932	23698, 32464, 41230, 49996, 58762
6012	Protein Coding	391437	6167	375259	14933	23699, 32465, 41231, 49997, 58763
6013	Protein Coding	391612	6168	375470	14934	23700, 32466,

						41232, 49998, 58764
6014	Protein Coding	391654	6169	375533	14935	23701, 32467, 41233, 49999, 58765
6015	Protein Coding	391681	6170	375563	14936	23702, 32468, 41234, 50000, 58766
6016	Protein Coding	391684	6171	375566	14937	23703, 32469, 41235, 50001, 58767
6017	Protein Coding	393725	6172	377326	14938	23704, 32470, 41236, 50002, 58768
6018	Protein Coding	394167	6173	377722	14939	23705, 32471, 41237, 50003, 58769
6019	Protein Coding	394168	6174	377723	14940	23706, 32472, 41238, 50004, 58770
6020	Protein Coding	395215	6175	378641	14941	23707, 32473, 41239, 50005, 58771
6021	Protein Coding	396985	6176	380182	14942	23708, 32474, 41240, 50006, 58772
6022	Protein Coding	397365	6177	380522	14943	23709, 32475, 41241, 50007, 58773
6023	Protein Coding	397571	6178	380701	14944	23710, 32476, 41242, 50008, 58774
6024	Protein Coding	397584	6179	398731	14945	23711, 32477, 41243, 50009, 58775
6025	Protein Coding	397897	6180	380994	14946	23712, 32478, 41244, 50010, 58776
6026	Protein Coding	398049	6181	381127	14947	23713, 32479, 41245, 50011, 58777
6027	Protein Coding	398067	6182	381142	14948	23714, 32480, 41246, 50012, 58778
6028	Protein Coding	398113	6183	381183	14949	23715, 32481, 41247, 50013, 58779
6029	Protein Coding	398130	6184	381198	14950	23716, 32482, 41248, 50014, 58780

6030	Protein Coding	398177	6185	381239	14951	23717, 32483, 41249, 50015, 58781
6031	Protein Coding	398275	6186	381324	14952	23718, 32484, 41250, 50016, 58782
6032	Protein Coding	398554	6187	381562	14953	23719, 32485, 41251, 50017, 58783
6033	Protein Coding	398617	6188	381618	14954	23720, 32486, 41252, 50018, 58784
6034	Protein Coding	398669	6189	381661	14955	23721, 32487, 41253, 50019, 58785
6035	Protein Coding	398706	6190	381693	14956	23722, 32488, 41254, 50020, 58786
6036	Protein Coding	399077	6191	382027	14957	23723, 32489, 41255, 50021, 58787
6037	Protein Coding	399246	6192	382190	14958	23724, 32490, 41256, 50022, 58788
6038	Protein Coding	399413	6193	382345	14959	23725, 32491, 41257, 50023, 58789
6039	Protein Coding	399484	6194	407971	14960	23726, 32492, 41258, 50024, 58790
6040	Protein Coding	399868	6195	382758	14961	23727, 32493, 41259, 50025, 58791
6041	Protein Coding	399933	6196	382815	14962	23728, 32494, 41260, 50026, 58792
6042	Protein Coding	399967	6197	382849	14963	23729, 32495, 41261, 50027, 58793
6043	Protein Coding	399979	6198	382861	14964	23730, 32496, 41262, 50028, 58794
6044	Protein Coding	400102	6199	382973	14965	23731, 32497, 41263, 50029, 58795
6045	Protein Coding	400144	6200	444229	14966	23732, 32498, 41264, 50030, 58796
6046	Protein Coding	400312	6201	383166	14967	23733, 32499, 41265, 50031,

						58797
6047	Protein Coding	400553	6202	383399	14968	23734, 32500, 41266, 50032, 58798
6048	Protein Coding	400710	6203	383546	14969	23735, 32501, 41267, 50033, 58799
6049	Protein Coding	401073	6204	383851	14970	23736, 32502, 41268, 50034, 58800
6050	Protein Coding	401395	6205	385377	14971	23737, 32503, 41269, 50035, 58801
6051	Protein Coding	401847	6206	400386	14972	23738, 32504, 41270, 50036, 58802
6052	Protein Coding	401851	6207	384640	14973	23739, 32505, 41271, 50037, 58803
6053	Protein Coding	402291	6208	385579	14974	23740, 32506, 41272, 50038, 58804
6054	Protein Coding	402510	6209	384670	14975	23741, 32507, 41273, 50039, 58805
6055	Protein Coding	406486	6210	385152	14976	23742, 32508, 41274, 50040, 58806
6056	Protein Coding	409154	6211	386957	14977	23743, 32509, 41275, 50041, 58807
6057	Protein Coding	411881	6212	446125	14978	23744, 32510, 41276, 50042, 58808
6058	Protein Coding	412198	6213	415612	14979	23745, 32511, 41277, 50043, 58809
6059	Protein Coding	412510	6214	388274	14980	23746, 32512, 41278, 50044, 58810
6060	Protein Coding	412872	6215	396913	14981	23747, 32513, 41279, 50045, 58811
6061	Protein Coding	412930	6216	402962	14982	23748, 32514, 41280, 50046, 58812
6062	Protein Coding	413214	6217	401941	14983	23749, 32515, 41281, 50047, 58813
6063	Protein Coding	414004	6218	393556	14984	23750, 32516,

						41282, 50048, 58814
6064	Protein Coding	415171	6219	406521	14985	23751, 32517, 41283, 50049, 58815
6065	Protein Coding	415803	6220	400749	14986	23752, 32518, 41284, 50050, 58816
6066	Protein Coding	416168	6221	394529	14987	23753, 32519, 41285, 50051, 58817
6067	Protein Coding	416501	6222	396652	14988	23754, 32520, 41286, 50052, 58818
6068	Protein Coding	416839	6223	404591	14989	23755, 32521, 41287, 50053, 58819
6069	Protein Coding	417734	6224	415273	14990	23756, 32522, 41288, 50054, 58820
6070	Protein Coding	418460	6225	403208	14991	23757, 32523, 41289, 50055, 58821
6071	Protein Coding	418535	6226	404996	14992	23758, 32524, 41290, 50056, 58822
6072	Protein Coding	418749	6227	409722	14993	23759, 32525, 41291, 50057, 58823
6073	Protein Coding	418911	6228	404805	14994	23760, 32526, 41292, 50058, 58824
6074	Protein Coding	419645	6229	407119	14995	23761, 32527, 41293, 50059, 58825
6075	Protein Coding	420532	6230	407508	14996	23762, 32528, 41294, 50060, 58826
6076	Protein Coding	422356	6231	415986	14997	23763, 32529, 41295, 50061, 58827
6077	Protein Coding	422783	6232	404527	14998	23764, 32530, 41296, 50062, 58828
6078	Protein Coding	423962	6233	416780	14999	23765, 32531, 41297, 50063, 58829
6079	Protein Coding	424147	6234	415398	15000	23766, 32532, 41298, 50064, 58830

6080	Protein Coding	424531	6235	393266	15001	23767, 32533, 41299, 50065, 58831
6081	Protein Coding	425051	6236	391855	15002	23768, 32534, 41300, 50066, 58832
6082	Protein Coding	425103	6237	413739	15003	23769, 32535, 41301, 50067, 58833
6083	Protein Coding	425181	6238	393427	15004	23770, 32536, 41302, 50068, 58834
6084	Protein Coding	425471	6239	388857	15005	23771, 32537, 41303, 50069, 58835
6085	Protein Coding	425945	6240	416549	15006	23772, 32538, 41304, 50070, 58836
6086	Protein Coding	426099	6241	396505	15007	23773, 32539, 41305, 50071, 58837
6087	Protein Coding	426268	6242	414493	15008	23774, 32540, 41306, 50072, 58838
6088	Protein Coding	427326	6243	414037	15009	23775, 32541, 41307, 50073, 58839
6089	Protein Coding	427991	6244	400288	15010	23776, 32542, 41308, 50074, 58840
6090	Protein Coding	428628	6245	412889	15011	23777, 32543, 41309, 50075, 58841
6091	Protein Coding	429274	6246	396161	15012	23778, 32544, 41310, 50076, 58842
6092	Protein Coding	429810	6247	393936	15013	23779, 32545, 41311, 50077, 58843
6093	Protein Coding	429979	6248	396935	15014	23780, 32546, 41312, 50078, 58844
6094	Protein Coding	430032	6249	441824	15015	23781, 32547, 41313, 50079, 58845
6095	Protein Coding	430589	6250	440620	15016	23782, 32548, 41314, 50080, 58846
6096	Protein Coding	430695	6251	415795	15017	23783, 32549, 41315, 50081,

						58847
6097	Protein Coding	430975	6252	414977	15018	23784, 32550, 41316, 50082, 58848
6098	Protein Coding	430980	6253	387851	15019	23785, 32551, 41317, 50083, 58849
6099	Protein Coding	431225	6254	403509	15020	23786, 32552, 41318, 50084, 58850
6100	Protein Coding	433366	6255	387828	15021	23787, 32553, 41319, 50085, 58851
6101	Protein Coding	434914	6256	403147	15022	23788, 32554, 41320, 50086, 58852
6102	Protein Coding	435359	6257	388872	15023	23789, 32555, 41321, 50087, 58853
6103	Protein Coding	435732	6258	401381	15024	23790, 32556, 41322, 50088, 58854
6104	Protein Coding	435985	6259	390515	15025	23791, 32557, 41323, 50089, 58855
6105	Protein Coding	436477	6260	403555	15026	23792, 32558, 41324, 50090, 58856
6106	Protein Coding	436884	6261	389985	15027	23793, 32559, 41325, 50091, 58857
6107	Protein Coding	438638	6262	391835	15028	23794, 32560, 41326, 50092, 58858
6108	Protein Coding	439642	6263	414579	15029	23795, 32561, 41327, 50093, 58859
6109	Protein Coding	439965	6264	401102	15030	23796, 32562, 41328, 50094, 58860
6110	Protein Coding	440378	6265	390837	15031	23797, 32563, 41329, 50095, 58861
6111	Protein Coding	440617	6266	387547	15032	23798, 32564, 41330, 50096, 58862
6112	Protein Coding	440738	6267	406216	15033	23799, 32565, 41331, 50097, 58863
6113	Protein Coding	440800	6268	397610	15034	23800, 32566,

						41332, 50098, 58864
6114	Protein Coding	442128	6269	413972	15035	23801, 32567, 41333, 50099, 58865
6115	Protein Coding	442828	6270	396858	15036	23802, 32568, 41334, 50100, 58866
6116	Protein Coding	443310	6271	389482	15037	23803, 32569, 41335, 50101, 58867
6117	Protein Coding	443397	6272	402914	15038	23804, 32570, 41336, 50102, 58868
6118	Protein Coding	443493	6273	410261	15039	23805, 32571, 41337, 50103, 58869
6119	Protein Coding	444002	6274	404840	15040	23806, 32572, 41338, 50104, 58870
6120	Protein Coding	444154	6275	404739	15041	23807, 32573, 41339, 50105, 58871
6121	Protein Coding	444738	6276	415308	15042	23808, 32574, 41340, 50106, 58872
6122	Protein Coding	445871	6277	443987	15043	23809, 32575, 41341, 50107, 58873
6123	Protein Coding	446244	6278	388818	15044	23810, 32576, 41342, 50108, 58874
6124	Protein Coding	446546	6279	408406	15045	23811, 32577, 41343, 50109, 58875
6125	Protein Coding	447140	6280	397618	15046	23812, 32578, 41344, 50110, 58876
6126	Protein Coding	447610	6281	394731	15047	23813, 32579, 41345, 50111, 58877
6127	Protein Coding	448346	6282	401471	15048	23814, 32580, 41346, 50112, 58878
6128	Protein Coding	448373	6283	406459	15049	23815, 32581, 41347, 50113, 58879
6129	Protein Coding	448436	6284	409584	15050	23816, 32582, 41348, 50114, 58880

6130	Protein Coding	450145	6285	409267	15051	23817, 32583, 41349, 50115, 58881
6131	Protein Coding	450856	6286	406904	15052	23818, 32584, 41350, 50116, 58882
6132	Protein Coding	451629	6287	398875	15053	23819, 32585, 41351, 50117, 58883
6133	Protein Coding	452718	6288	405682	15054	23820, 32586, 41352, 50118, 58884
6134	Protein Coding	453873	6289	416795	15055	23821, 32587, 41353, 50119, 58885
6135	Protein Coding	454671	6290	402058	15056	23822, 32588, 41354, 50120, 58886
6136	Protein Coding	454724	6291	392141	15057	23823, 32589, 41355, 50121, 58887
6137	Protein Coding	455163	6292	414366	15058	23824, 32590, 41356, 50122, 58888
6138	Protein Coding	456890	6293	407928	15059	23825, 32591, 41357, 50123, 58889
6139	Protein Coding	458385	6294	409964	15060	23826, 32592, 41358, 50124, 58890
6140	Protein Coding	483725	6295	435150	15061	23827, 32593, 41359, 50125, 58891
6141	Protein Coding	498919	6296	420823	15062	23828, 32594, 41360, 50126, 58892
6142	Protein Coding	500944	6297	443154	15063	23829, 32595, 41361, 50127, 58893
6143	Protein Coding	503082	6298	423741	15064	23830, 32596, 41362, 50128, 58894
6144	Protein Coding	504228	6299	423366	15065	23831, 32597, 41363, 50129, 58895
6145	Protein Coding	504688	6300	424906	15066	23832, 32598, 41364, 50130, 58896
6146	Protein Coding	506983	6301	421746	15067	23833, 32599, 41365, 50131,

						58897
6147	Protein Coding	507531	6302	421741	15068	23834, 32600, 41366, 50132, 58898
6148	Protein Coding	507983	6303	441177	15069	23835, 32601, 41367, 50133, 58899
6149	Protein Coding	508423	6304	426815	15070	23836, 32602, 41368, 50134, 58900
6150	Protein Coding	510164	6305	421061	15071	23837, 32603, 41369, 50135, 58901
6151	Protein Coding	511216	6306	425130	15072	23838, 32604, 41370, 50136, 58902
6152	Protein Coding	511563	6307	423340	15073	23839, 32605, 41371, 50137, 58903
6153	Protein Coding	512728	6308	427701	15074	23840, 32606, 41372, 50138, 58904
6154	Protein Coding	513200	6309	424618	15075	23841, 32607, 41373, 50139, 58905
6155	Protein Coding	517349	6310	428858	15076	23842, 32608, 41374, 50140, 58906
6156	Protein Coding	517562	6311	454561	15077	23843, 32609, 41375, 50141, 58907
6157	Protein Coding	524632	6312	436355	15078	23844, 32610, 41376, 50142, 58908
6158	Protein Coding	528896	6313	436773	15079	23845, 32611, 41377, 50143, 58909, 61539, 61597
6159	Protein Coding	530275	6314	431179	15080	23846, 32612, 41378, 50144, 58910
6160	Protein Coding	532798	6315	457511	15081	23847, 32613, 41379, 50145, 58911
6161	Protein Coding	534925	6316	437501	15082	23848, 32614, 41380, 50146, 58912
6162	Protein Coding	535433	6317	440195	15083	23849, 32615, 41381, 50147, 58913

6163	Protein Coding	535580	6318	441997	15084	23850, 32616, 41382, 50148, 58914
6164	Protein Coding	536004	6319	437976	15085	23851, 32617, 41383, 50149, 58915
6165	Protein Coding	536163	6320	445768	15086	23852, 32618, 41384, 50150, 58916
6166	Protein Coding	536272	6321	440504	15087	23853, 32619, 41385, 50151, 58917
6167	Protein Coding	536450	6322	441807	15088	23854, 32620, 41386, 50152, 58918
6168	Protein Coding	536542	6323	441916	15089	23855, 32621, 41387, 50153, 58919
6169	Protein Coding	536865	6324	444544	15090	23856, 32622, 41388, 50154, 58920
6170	Protein Coding	536986	6325	444170	15091	23857, 32623, 41389, 50155, 58921
6171	Protein Coding	537689	6326	443184	15092	23858, 32624, 41390, 50156, 58922
6172	Protein Coding	538623	6327	439425	15093	23859, 32625, 41391, 50157, 58923
6173	Protein Coding	538975	6328	439628	15094	23860, 32626, 41392, 50158, 58924
6174	Protein Coding	541073	6329	444006	15095	23861, 32627, 41393, 50159, 58925
6175	Protein Coding	541342	6330	444061	15096	23862, 32628, 41394, 50160, 58926
6176	Protein Coding	541421	6331	456026	15097	23863, 32629, 41395, 50161, 58927
6177	Protein Coding	541705	6332	437781	15098	23864, 32630, 41396, 50162, 58928
6178	Protein Coding	542006	6333	443615	15099	23865, 32631, 41397, 50163, 58929
6179	Protein Coding	543188	6334	445749	15100	23866, 32632, 41398, 50164,

						58930
6180	Protein Coding	543827	6335	445996	15101	23867, 32633, 41399, 50165, 58931
6181	Protein Coding	543887	6336	439560	15102	23868, 32634, 41400, 50166, 58932
6182	Protein Coding	543923	6337	441359	15103	23869, 32635, 41401, 50167, 58933
6183	Protein Coding	544071	6338	442465	15104	23870, 32636, 41402, 50168, 58934
6184	Protein Coding	544237	6339	444138	15105	23871, 32637, 41403, 50169, 58935
6185	Protein Coding	544664	6340	442396	15106	23872, 32638, 41404, 50170, 58936
6186	Protein Coding	544825	6341	441995	15107	23873, 32639, 41405, 50171, 58937
6187	Protein Coding	544884	6342	446443	15108	23874, 32640, 41406, 50172, 58938, 61540, 61598
6188	Protein Coding	544930	6343	445288	15109	23875, 32641, 41407, 50173, 58939
6189	Protein Coding	545063	6344	446381	15110	23876, 32642, 41408, 50174, 58940
6190	Protein Coding	545356	6345	445507	15111	23877, 32643, 41409, 50175, 58941
6191	Protein Coding	545452	6346	446137	15112	23878, 32644, 41410, 50176, 58942
6192	Protein Coding	545792	6347	440517	15113	23879, 32645, 41411, 50177, 58943
6193	Protein Coding	546221	6348	446248	15114	23880, 32646, 41412, 50178, 58944
6194	Protein Coding	546451	6349	450204	15115	23881, 32647, 41413, 50179, 58945
6195	Protein Coding	546518	6350	447648	15116	23882, 32648, 41414, 50180, 58946

6196	Protein Coding	546522	6351	446791	15117	23883, 32649, 41415, 50181, 58947
6197	Protein Coding	546574	6352	449466	15118	23884, 32650, 41416, 50182, 58948
6198	Protein Coding	546641	6353	447304	15119	23885, 32651, 41417, 50183, 58949
6199	Protein Coding	546658	6354	446824	15120	23886, 32652, 41418, 50184, 58950
6200	Protein Coding	546691	6355	447598	15121	23887, 32653, 41419, 50185, 58951
6201	Protein Coding	546797	6356	449418	15122	23888, 32654, 41420, 50186, 58952
6202	Protein Coding	546879	6357	450126	15123	23889, 32655, 41421, 50187, 58953
6203	Protein Coding	546994	6358	449405	15124	23890, 32656, 41422, 50188, 58954
6204	Protein Coding	547011	6359	447208	15125	23891, 32657, 41423, 50189, 58955
6205	Protein Coding	547028	6360	447086	15126	23892, 32658, 41424, 50190, 58956
6206	Protein Coding	547037	6361	448898	15127	23893, 32659, 41425, 50191, 58957
6207	Protein Coding	547091	6362	448511	15128	23894, 32660, 41426, 50192, 58958
6208	Protein Coding	547159	6363	448432	15129	23895, 32661, 41427, 50193, 58959
6209	Protein Coding	547162	6364	449646	15130	23896, 32662, 41428, 50194, 58960
6210	Protein Coding	547192	6365	448851	15131	23897, 32663, 41429, 50195, 58961
6211	Protein Coding	547266	6366	448942	15132	23898, 32664, 41430, 50196, 58962
6212	Protein Coding	547277	6367	447768	15133	23899, 32665, 41431, 50197,

						58963
6213	Protein Coding	547354	6368	450075	15134	23900, 32666, 41432, 50198, 58964
6214	Protein Coding	547373	6369	447930	15135	23901, 32667, 41433, 50199, 58965
6215	Protein Coding	547433	6370	446969	15136	23902, 32668, 41434, 50200, 58966
6216	Protein Coding	547467	6371	448974	15137	23903, 32669, 41435, 50201, 58967
6217	Protein Coding	547507	6372	447023	15138	23904, 32670, 41436, 50202, 58968
6218	Protein Coding	547551	6373	448151	15139	23905, 32671, 41437, 50203, 58969
6219	Protein Coding	547601	6374	447415	15140	23906, 32672, 41438, 50204, 58970
6220	Protein Coding	547618	6375	446522	15141	23907, 32673, 41439, 50205, 58971
6221	Protein Coding	547689	6376	449645	15142	23908, 32674, 41440, 50206, 58972
6222	Protein Coding	547707	6377	448928	15143	23909, 32675, 41441, 50207, 58973
6223	Protein Coding	547740	6378	446502	15144	23910, 32676, 41442, 50208, 58974
6224	Protein Coding	547788	6379	449212	15145	23911, 32677, 41443, 50209, 58975
6225	Protein Coding	547811	6380	450115	15146	23912, 32678, 41444, 50210, 58976
6226	Protein Coding	547850	6381	447024	15147	23913, 32679, 41445, 50211, 58977
6227	Protein Coding	547900	6382	447331	15148	23914, 32680, 41446, 50212, 58978
6228	Protein Coding	548004	6383	449735	15149	23915, 32681, 41447, 50213, 58979
6229	Protein Coding	548157	6384	448017	15150	23916, 32682,

						41448, 50214, 58980
6230	Protein Coding	548272	6385	448139	15151	23917, 32683, 41449, 50215, 58981
6231	Protein Coding	548275	6386	446594	15152	23918, 32684, 41450, 50216, 58982
6232	Protein Coding	548321	6387	449947	15153	23919, 32685, 41451, 50217, 58983
6233	Protein Coding	548325	6388	448160	15154	23920, 32686, 41452, 50218, 58984
6234	Protein Coding	548417	6389	449188	15155	23921, 32687, 41453, 50219, 58985
6235	Protein Coding	548459	6390	447223	15156	23922, 32688, 41454, 50220, 58986
6236	Protein Coding	548508	6391	446813	15157	23923, 32689, 41455, 50221, 58987
6237	Protein Coding	548509	6392	448436	15158	23924, 32690, 41456, 50222, 58988
6238	Protein Coding	548510	6393	448751	15159	23925, 32691, 41457, 50223, 58989
6239	Protein Coding	548544	6394	446899	15160	23926, 32692, 41458, 50224, 58990
6240	Protein Coding	548591	6395	447968	15161	23927, 32693, 41459, 50225, 58991
6241	Protein Coding	548606	6396	450213	15162	23928, 32694, 41460, 50226, 58992
6242	Protein Coding	548618	6397	447586	15163	23929, 32695, 41461, 50227, 58993
6243	Protein Coding	548635	6398	448380	15164	23930, 32696, 41462, 50228, 58994
6244	Protein Coding	548699	6399	450290	15165	23931, 32697, 41463, 50229, 58995
6245	Protein Coding	548726	6400	447172	15166	23932, 32698, 41464, 50230, 58996

6246	Protein Coding	548881	6401	449277	15167	23933, 32699, 41465, 50231, 58997
6247	Protein Coding	548976	6402	448914	15168	23934, 32700, 41466, 50232, 58998
6248	Protein Coding	548990	6403	449364	15169	23935, 32701, 41467, 50233, 58999
6249	Protein Coding	548991	6404	448319	15170	23936, 32702, 41468, 50234, 59000
6250	Protein Coding	549059	6405	447840	15171	23937, 32703, 41469, 50235, 59001
6251	Protein Coding	549113	6406	448109	15172	23938, 32704, 41470, 50236, 59002
6252	Protein Coding	549118	6407	449555	15173	23939, 32705, 41471, 50237, 59003
6253	Protein Coding	549186	6408	447071	15174	23940, 32706, 41472, 50238, 59004
6254	Protein Coding	549200	6409	447912	15175	23941, 32707, 41473, 50239, 59005
6255	Protein Coding	549248	6410	447775	15176	23942, 32708, 41474, 50240, 59006
6256	Protein Coding	549331	6411	448446	15177	23943, 32709, 41475, 50241, 59007
6257	Protein Coding	549494	6412	450034	15178	23944, 32710, 41476, 50242, 59008
6258	Protein Coding	549517	6413	447412	15179	23945, 32711, 41477, 50243, 59009
6259	Protein Coding	549536	6414	447283	15180	23946, 32712, 41478, 50244, 59010
6260	Protein Coding	549650	6415	447106	15181	23947, 32713, 41479, 50245, 59011
6261	Protein Coding	549675	6416	448675	15182	23948, 32714, 41480, 50246, 59012
6262	Protein Coding	549708	6417	449465	15183	23949, 32715, 41481, 50247,

						59013
6263	Protein Coding	549802	6418	450062	15184	23950, 32716, 41482, 50248, 59014
6264	Protein Coding	549837	6419	448416	15185	23951, 32717, 41483, 50249, 59015
6265	Protein Coding	549908	6420	449902	15186	23952, 32718, 41484, 50250, 59016
6266	Protein Coding	549991	6421	446808	15187	23953, 32719, 41485, 50251, 59017
6267	Protein Coding	550269	6422	450292	15188	23954, 32720, 41486, 50252, 59018
6268	Protein Coding	550481	6423	449107	15189	23955, 32721, 41487, 50253, 59019
6269	Protein Coding	550667	6424	449916	15190	23956, 32722, 41488, 50254, 59020
6270	Protein Coding	550960	6425	446942	15191	23957, 32723, 41489, 50255, 59021
6271	Protein Coding	550976	6426	448549	15192	23958, 32724, 41490, 50256, 59022
6272	Protein Coding	551022	6427	450388	15193	23959, 32725, 41491, 50257, 59023
6273	Protein Coding	551048	6428	447463	15194	23960, 32726, 41492, 50258, 59024
6274	Protein Coding	551064	6429	448493	15195	23961, 32727, 41493, 50259, 59025
6275	Protein Coding	551342	6430	450335	15196	23962, 32728, 41494, 50260, 59026
6276	Protein Coding	551523	6431	449875	15197	23963, 32729, 41495, 50261, 59027
6277	Protein Coding	551609	6432	448631	15198	23964, 32730, 41496, 50262, 59028
6278	Protein Coding	551668	6433	447681	15199	23965, 32731, 41497, 50263, 59029
6279	Protein Coding	551735	6434	447535	15200	23966, 32732,

						41498, 50264, 59030
6280	Protein Coding	551795	6435	449265	15201	23967, 32733, 41499, 50265, 59031
6281	Protein Coding	551820	6436	448949	15202	23968, 32734, 41500, 50266, 59032
6282	Protein Coding	551891	6437	447350	15203	23969, 32735, 41501, 50267, 59033
6283	Protein Coding	551942	6438	447855	15204	23970, 32736, 41502, 50268, 59034
6284	Protein Coding	551953	6439	447142	15205	23971, 32737, 41503, 50269, 59035
6285	Protein Coding	551990	6440	449099	15206	23972, 32738, 41504, 50270, 59036
6286	Protein Coding	552035	6441	449298	15207	23973, 32739, 41505, 50271, 59037
6287	Protein Coding	552118	6442	446694	15208	23974, 32740, 41506, 50272, 59038
6288	Protein Coding	552148	6443	449568	15209	23975, 32741, 41507, 50273, 59039
6289	Protein Coding	552224	6444	448718	15210	23976, 32742, 41508, 50274, 59040
6290	Protein Coding	552358	6445	448021	15211	23977, 32743, 41509, 50275, 59041
6291	Protein Coding	552359	6446	449285	15212	23978, 32744, 41510, 50276, 59042
6292	Protein Coding	552381	6447	447826	15213	23979, 32745, 41511, 50277, 59043
6293	Protein Coding	552385	6448	448249	15214	23980, 32746, 41512, 50278, 59044
6294	Protein Coding	552476	6449	446958	15215	23981, 32747, 41513, 50279, 59045
6295	Protein Coding	552543	6450	450360	15216	23982, 32748, 41514, 50280, 59046

6296	Protein Coding	552547	6451	449384	15217	23983, 32749, 41515, 50281, 59047
6297	Protein Coding	552607	6452	447114	15218	23984, 32750, 41516, 50282, 59048
6298	Protein Coding	552708	6453	448183	15219	23985, 32751, 41517, 50283, 59049
6299	Protein Coding	552715	6454	446689	15220	23986, 32752, 41518, 50284, 59050
6300	Protein Coding	552722	6455	447130	15221	23987, 32753, 41519, 50285, 59051
6301	Protein Coding	552730	6456	449510	15222	23988, 32754, 41520, 50286, 59052
6302	Protein Coding	552927	6457	448537	15223	23989, 32755, 41521, 50287, 59053
6303	Protein Coding	552988	6458	449582	15224	23990, 32756, 41522, 50288, 59054
6304	Protein Coding	553054	6459	449077	15225	23991, 32757, 41523, 50289, 59055
6305	Protein Coding	553249	6460	448712	15226	23992, 32758, 41524, 50290, 59056
6306	Protein Coding	553250	6461	449063	15227	23993, 32759, 41525, 50291, 59057
6307	Protein Coding	553262	6462	450226	15228	23994, 32760, 41526, 50292, 59058
6308	Protein Coding	554447	6463	452380	15229	23995, 32761, 41527, 50293, 59059
6309	Protein Coding	554658	6464	451522	15230	23996, 32762, 41528, 50294, 59060
6310	Protein Coding	555200	6465	451493	15231	23997, 32763, 41529, 50295, 59061
6311	Protein Coding	557115	6466	452589	15232	23998, 32764, 41530, 50296, 59062
6312	Protein Coding	557565	6467	454657	15233	23999, 32765, 41531, 50297,

						59063
6313	Protein Coding	558026	6468	452662	15234	24000, 32766, 41532, 50298, 59064
6314	Protein Coding	558079	6469	453843	15235	24001, 32767, 41533, 50299, 59065
6315	Protein Coding	558195	6470	453012	15236	24002, 32768, 41534, 50300, 59066
6316	Protein Coding	558378	6471	452943	15237	24003, 32769, 41535, 50301, 59067
6317	Protein Coding	560045	6472	452747	15238	24004, 32770, 41536, 50302, 59068
6318	Protein Coding	561141	6473	452880	15239	24005, 32771, 41537, 50303, 59069
6319	Protein FAM132B	408994	6474	386667	15240	24006, 32772, 41538, 50304, 59070
6320	Protein FAM195B	457257	6475	408827	15241	24007, 32773, 41539, 50305, 59071
6321	Protein FAM205B	455647	6476	398718	15242	24008, 32774, 41540, 50306, 59072
6322	Protein FAM27D1	417276	6477	393138	15243	24009, 32775, 41541, 50307, 59073
6323	Protein FAM27D1	426006	6478	403307	15244	24010, 32776, 41542, 50308, 59074
6324	protein FAM3A isoform 1 precursor	596546	6479	472855	15245	24011, 32777, 41543, 50309, 59075
6325	Protein FRG2	368515	6480	357501	15246	24012, 32778, 41544, 50310, 59076
6326	Protein FRG2-like-2	403385	6481	384730	15247	24013, 32779, 41545, 50311, 59077
6327	protein geranylgeranyltransferase type I, beta subunit	379615	6482	368935	15248	24014, 32780, 41546, 50312, 59078
6328	protein geranylgeranyltransferase type I, beta subunit	419445	6483	404676	15249	24015, 32781, 41547, 50313, 59079
6329	protein interacting with	301039	6484	301039	15250	24016, 32782,

	cyclin A1					41548, 50314, 59080
6330	protein interacting with cyclin A1	415329	6485	406218	15251	24017, 32783, 41549, 50315, 59081
6331	protein interacting with cyclin A1	422880	6486	390058	15252	24018, 32784, 41550, 50316, 59082
6332	protein interacting with cyclin A1	439862	6487	411400	15253	24019, 32785, 41551, 50317, 59083
6333	Protein PCOTH	422229	6488	396192	15254	24020, 32786, 41552, 50318, 59084
6334	protein phosphatase 1 regulatory subunit 17	409146	6489	386459	15255	24021, 32787, 41553, 50319, 59085
6335	protein phosphatase 1 regulatory subunit 3F	596845	6490	470648	15256	24022, 32788, 41554, 50320, 59086
6336	protein phosphatase 1, regulatory subunit 17	342032	6491	340125	15257	24023, 32789, 41555, 50321, 59087
6337	protein phosphatase 1, regulatory subunit 18	383573	6492	373067	15258	24024, 32790, 41556, 50322, 59088
6338	protein phosphatase 1, regulatory subunit 18	400554	6493	383400	15259	24025, 32791, 41557, 50323, 59089
6339	protein phosphatase 1, regulatory subunit 18	412189	6494	399786	15260	24026, 32792, 41558, 50324, 59090
6340	protein phosphatase 1, regulatory subunit 18	435006	6495	411275	15261	24027, 32793, 41559, 50325, 59091
6341	protein phosphatase 1, regulatory subunit 18	435929	6496	387526	15262	24028, 32794, 41560, 50326, 59092
6342	protein phosphatase 1, regulatory subunit 18	455026	6497	416491	15263	24029, 32795, 41561, 50327, 59093
6343	protein phosphatase 1, regulatory subunit 18	548255	6498	446851	15264	24030, 32796, 41562, 50328, 59094
6344	protein phosphatase 1, regulatory subunit 18	550073	6499	447832	15265	24031, 32797, 41563, 50329, 59095
6345	protein phosphatase 1, regulatory subunit 21	281394	6500	281394	15266	24032, 32798, 41564, 50330, 59096

6346	protein phosphatase 1, regulatory subunit 21	294952	6501	294952	15267	24033, 32799, 41565, 50331, 59097
6347	protein phosphatase 1, regulatory subunit 21	449090	6502	415696	15268	24034, 32800, 41566, 50332, 59098
6348	protein phosphatase 1, regulatory subunit 27	330261	6503	331065	15269	24035, 32801, 41567, 50333, 59099
6349	protein phosphatase 1, regulatory subunit 32	338608	6504	344140	15270	24036, 32802, 41568, 50334, 59100
6350	protein phosphatase 1, regulatory subunit 32	432063	6505	391560	15271	24037, 32803, 41569, 50335, 59101
6351	protein phosphatase 1, regulatory subunit 35	292330	6506	292330	15272	24038, 32804, 41570, 50336, 59102
6352	protein phosphatase 1, regulatory subunit 36	298705	6507	298705	15273	24039, 32805, 41571, 50337, 59103
6353	protein phosphatase 1, regulatory subunit 37	221462	6508	221462	15274	24040, 32806, 41572, 50338, 59104
6354	protein phosphatase 1, regulatory subunit 37	421905	6509	390861	15275	24041, 32807, 41573, 50339, 59105
6355	protein phosphatase 1, regulatory subunit 3B	310455	6510	308318	15276	24042, 32808, 41574, 50340, 59106
6356	protein phosphatase 1, regulatory subunit 3B	519699	6511	428642	15277	24043, 32809, 41575, 50341, 59107
6357	protein phosphatase 1, regulatory subunit 42	324682	6512	315035	15278	24044, 32810, 41576, 50342, 59108
6358	protein phosphatase 1, regulatory subunit 42	421742	6513	409797	15279	24045, 32811, 41577, 50343, 59109
6359	protein phosphatase 1, regulatory subunit 42	522909	6514	429721	15280	24046, 32812, 41578, 50344, 59110
6360	protein phosphatase 2 regulatory subunit B" alpha	490467	6515	419344	15281	24047, 32813, 41579, 50345, 59111
6361	protein phosphatase 2, regulatory subunit B", alpha	264977	6516	264977	15282	24048, 32814, 41580, 50346, 59112
6362	protein phosphatase 2, regulatory subunit B", alpha	334546	6517	334748	15283	24049, 32815, 41581, 50347,

						59113
6363	protein phosphatase 2, regulatory subunit B", alpha	492624	6518	417231	15284	24050, 32816, 41582, 50348, 59114
6364	protein phosphatase 2C-like domain containing 1	389050	6519	373702	15285	24051, 32817, 41583, 50349, 59115
6365	protein phosphatase 4, regulatory subunit 1-like	334187	6520	335579	15286	24052, 32818, 41584, 50350, 59116
6366	protein phosphatase, Mg2+/Mn2+ dependent, 1F	263212	6521	263212	15287	24053, 32819, 41585, 50351, 59117
6367	protein phosphatase, Mg2+/Mn2+ dependent, 1F	397495	6522	380632	15288	24054, 32820, 41586, 50352, 59118
6368	protein phosphatase, Mg2+/Mn2+ dependent, 1F	406981	6523	384715	15289	24055, 32821, 41587, 50353, 59119
6369	protein phosphatase, Mg2+/Mn2+ dependent, 1F	407142	6524	384930	15290	24056, 32822, 41588, 50354, 59120
6370	protein phosphatase, Mg2+/Mn2+ dependent, 1F	538191	6525	439915	15291	24057, 32823, 41589, 50355, 59121
6371	protein phosphatase, Mg2+/Mn2+ dependent, 1H	228705	6526	228705	15292	24058, 32824, 41590, 50356, 59122
6372	protein phosphatase, Mg2+/Mn2+ dependent, 1N (putative)	324688	6527	321761	15293	24059, 32825, 41591, 50357, 59123
6373	protein phosphatase, Mg2+/Mn2+ dependent, 1N (putative)	396734	6528	379960	15294	24060, 32826, 41592, 50358, 59124
6374	protein prenyltransferase alpha subunit repeat containing 1	340434	6529	344299	15295	24061, 32827, 41593, 50359, 59125
6375	protein serine kinase H2	276616	6530	276616	15296	24062, 32828, 41594, 50360, 59126
6376	protein tyrosine phosphatase domain containing 1	375360	6531	364509	15297	24063, 32829, 41595, 50361, 59127
6377	protein tyrosine phosphatase domain containing 1	288976	6532	288976	15298	24064, 32830, 41596, 50362, 59128
6378	protein tyrosine phosphatase non-receptor type 20B	581350	6533	462400	15299	24065, 32831, 41597, 50363, 59129
6379	protein tyrosine	583073	6534	463133	15300	24066, 32832,

	phosphatase non-receptor type 20B					41598, 50364, 59130
6380	protein tyrosine phosphatase non-receptor type 20B	584081	6535	464175	15301	24067, 32833, 41599, 50365, 59131
6381	protein tyrosine phosphatase, non-receptor type 20C	316733	6536	313973	15302	24068, 32834, 41600, 50366, 59132
6382	protein tyrosine phosphatase, non-receptor type 20C	428535	6537	414424	15303	24069, 32835, 41601, 50367, 59133
6383	protein tyrosine phosphatase, non-receptor type 20C	455582	6538	388155	15304	24070, 32836, 41602, 50368, 59134
6384	protein tyrosine phosphatase-like A domain containing 1	442729	6539	392491	15305	24071, 32837, 41603, 50369, 59135
6385	PRR5-ARHGAP8 readthrough	352766	6540	262731	15306	24072, 32838, 41604, 50370, 59136
6386	PRR5-ARHGAP8 readthrough	361473	6541	354732	15307	24073, 32839, 41605, 50371, 59137
6387	PRR5-ARHGAP8 readthrough	515632	6542	425026	15308	24074, 32840, 41606, 50372, 59138
6388	pseudouridylate synthase 10	316752	6543	326003	15309	24075, 32841, 41607, 50373, 59139
6389	pseudouridylate synthase 10	407787	6544	386074	15310	24076, 32842, 41608, 50374, 59140
6390	pseudouridylate synthase 10	421319	6545	402185	15311	24077, 32843, 41609, 50375, 59141
6391	pseudouridylate synthase 7 homolog (S. cerevisiae)	356362	6546	348722	15312	24078, 32844, 41610, 50376, 59142
6392	pseudouridylate synthase 7 homolog (S. cerevisiae)	469408	6547	417402	15313	24079, 32845, 41611, 50377, 59143
6393	pseudouridylate synthase 7 homolog (S. cerevisiae)	544995	6548	442995	15314	24080, 32846, 41612, 50378, 59144
6394	pseudouridylate synthase 7 homolog (S. cerevisiae)-like	344862	6549	343081	15315	24081, 32847, 41613, 50379, 59145
6395	pseudouridylate synthase 7 homolog (S. cerevisiae)-like	416848	6550	415899	15316	24082, 32848, 41614, 50380, 59146

6396	pseudouridylate synthase 7 homolog (S. cerevisiae)-like	549868	6551	449502	15317	24083, 32849, 41615, 50381, 59147
6397	pseudouridylate synthase 7 homolog (S. cerevisiae)-like	551923	6552	447706	15318	24084, 32850, 41616, 50382, 59148
6398	pseudouridylate synthase 7 homolog (S. cerevisiae)-like	553166	6553	446865	15319	24085, 32851, 41617, 50383, 59149
6399	pseudouridylate synthase-like 1	379031	6554	368318	15320	24086, 32852, 41618, 50384, 59150
6400	PTPN13-like, Y-linked pseudogene 3	303593	6555	306622	15321	24087, 32853, 41619, 50385, 59151
6401	PTPN13-like, Y-linked pseudogene 3	343584	6556	342409	15322	24088, 32854, 41620, 50386, 59152
6402	PTPN13-like, Y-linked pseudogene 4	306589	6557	303736	15323	24089, 32855, 41621, 50387, 59153
6403	PTPN13-like, Y-linked pseudogene 4	338673	6558	340542	15324	24090, 32856, 41622, 50388, 59154
6404	PTPRF interacting protein binding protein 2 (liprin beta 2)	530181	6559	437321	15325	24091, 32857, 41623, 50389, 59155
6405	PTPRF interacting protein binding protein 2 (liprin beta 2)	533792	6560	436498	15326	24092, 32858, 41624, 50390, 59156
6406	PTPRF interacting protein, binding protein 2 (liprin beta 2)	299492	6561	299492	15327	24093, 32859, 41625, 50391, 59157
6407	PTPRF interacting protein, binding protein 2 (liprin beta 2)	526046	6562	433026	15328	24094, 32860, 41626, 50392, 59158
6408	PTPRF interacting protein, binding protein 2 (liprin beta 2)	526873	6563	434641	15329	24095, 32861, 41627, 50393, 59159
6409	PTPRF interacting protein, binding protein 2 (liprin beta 2)	527790	6564	434981	15330	24096, 32862, 41628, 50394, 59160
6410	PTPRF interacting protein, binding protein 2 (liprin beta 2)	528947	6565	431724	15331	24097, 32863, 41629, 50395, 59161
6411	PTPRF interacting protein, binding protein 2 (liprin beta 2)	537211	6566	444107	15332	24098, 32864, 41630, 50396, 59162
6412	PTPRF interacting protein, binding protein 2 (liprin	537467	6567	442585	15333	24099, 32865, 41631, 50397,

	beta 2)					59163
6413	PTPRF interacting protein, binding protein 2 (liprin beta 2)	541115	6568	441652	15334	24100, 32866, 41632, 50398, 59164
6414	Purkinje cell protein 2	311069	6569	310585	15335	24101, 32867, 41633, 50399, 59165
6415	Purkinje cell protein 4 like 1	504449	6570	426296	15336	24102, 32868, 41634, 50400, 59166
6416	Puromycin-sensitive aminopeptidase-like protein	312412	6571	308540	15337	24103, 32869, 41635, 50401, 59167
6417	Puromycin-sensitive aminopeptidase-like protein	544906	6572	444117	15338	24104, 32870, 41636, 50402, 59168
6418	Putative diacylglycerol O-acyltransferase 2-like protein 7	379421	6573	368732	15339	24105, 32871, 41637, 50403, 59169
6419	Putative eukaryotic translation initiation factor 2 subunit 3-like protein	538173	6574	445077	15340	24106, 32872, 41638, 50404, 59170
6420	Putative gamma-taxilin 2	251749	6575	251749	15341	24107, 32873, 41639, 50405, 59171
6421	Putative gamma-taxilin 2	407724	6576	384233	15342	24108, 32874, 41640, 50406, 59172
6422	Putative gamma-taxilin 2	447202	6577	390079	15343	24109, 32875, 41641, 50407, 59173
6423	Putative gamma-taxilin 2	447520	6578	414498	15344	24110, 32876, 41642, 50408, 59174
6424	Putative gamma-taxilin 2	538014	6579	444200	15345	24111, 32877, 41643, 50409, 59175
6425	Putative gamma-taxilin-like protein CYorf15B	253320	6580	253320	15346	24112, 32878, 41644, 50410, 59176
6426	Putative gamma-taxilin-like protein CYorf15B	382832	6581	372283	15347	24113, 32879, 41645, 50411, 59177
6427	Putative germ cell-specific gene 1-like protein 2	399363	6582	382298	15348	24114, 32880, 41646, 50412, 59178
6428	Putative golgin subfamily A member 6-like protein 11	333156	6583	332482	15349	24115, 32881, 41647, 50413, 59179
6429	Putative golgin subfamily A	414865	6584	403486	15350	24116, 32882,

	member 6-like protein 11					41648, 50414, 59180
6430	Putative golgin subfamily A member 6-like protein 11	426622	6585	416216	15351	24117, 32883, 41649, 50415, 59181
6431	Putative golgin subfamily A member 6-like protein 11	448387	6586	398454	15352	24118, 32884, 41650, 50416, 59182
6432	Putative golgin subfamily A member 6-like protein 11	509311	6587	423159	15353	24119, 32885, 41651, 50417, 59183
6433	Putative KHDC1-like protein	370385	6588	359412	15354	24120, 32886, 41652, 50418, 59184
6434	Putative lung carcinoma-associated protein 10	357566	6589	350178	15355	24121, 32887, 41653, 50419, 59185
6435	Putative methyltransferase KIAA1456	447063	6590	443288	15356	24122, 32888, 41654, 50420, 59186
6436	Putative methyltransferase KIAA1456	524591	6591	432695	15357	24123, 32889, 41655, 50421, 59187
6437	Putative methyltransferase KIAA1456	529978	6592	434752	15358	24124, 32890, 41656, 50422, 59188
6438	putative NPIP-like protein KIAA0220-like	357370	6593	349936	15359	24125, 32891, 41657, 50423, 59189
6439	putative NPIP-like protein KIAA0220-like	415645	6594	404439	15360	24126, 32892, 41658, 50424, 59190
6440	putative NPIP-like protein KIAA0220-like	451409	6595	392155	15361	24127, 32893, 41659, 50425, 59191
6441	putative NPIP-like protein KIAA0220-like	537951	6596	439166	15362	24128, 32894, 41660, 50426, 59192
6442	Putative NPIP-like protein LOC613037	448793	6597	391836	15363	24129, 32895, 41661, 50427, 59193
6443	Putative NPIP-like protein LOC613037	543463	6598	444728	15364	24130, 32896, 41662, 50428, 59194
6444	Putative NPIP-like protein LOC613037	544982	6599	442347	15365	24131, 32897, 41663, 50429, 59195
6445	Putative PERP-like protein	411845	6600	441910	15366	24132, 32898, 41664, 50430, 59196

6446	Putative POM121-like protein 1	427789	6601	393689	15367	24133, 32899, 41665, 50431, 59197
6447	Putative protein FAM27E1	377525	6602	366747	15368	24134, 32900, 41666, 50432, 59198
6448	Putative protein FAM90A2	432515	6603	395848	15369	24135, 32901, 41667, 50433, 59199
6449	Putative protein FAM90A-like	338885	6604	341223	15370	24136, 32902, 41668, 50434, 59200
6450	Putative protein SLC9B1-like 1	331172	6605	331938	15371	24137, 32903, 41669, 50435, 59201
6451	Putative RNA exonuclease NEF-sp	261377	6606	261377	15372	24138, 32904, 41670, 50436, 59202
6452	Putative RNA exonuclease NEF-sp	348433	6607	261378	15373	24139, 32905, 41671, 50437, 59203
6453	Putative scavenger receptor cysteine-rich domain-containing protein LOC619207	356567	6608	348974	15374	24140, 32906, 41672, 50438, 59204
6454	Putative tripartite motif-containing protein 49B	332682	6609	330216	15375	24141, 32907, 41673, 50439, 59205
6455	Putative ubiquitin-like protein FUBI-like protein 310146	309775	6610	310146	15376	24142, 32908, 41674, 50440, 59206
6456	Putative UPF0607 protein FLJ37424	359888	6611	352954	15377	24143, 32909, 41675, 50441, 59207
6457	Putative UPF0633 protein 303136	305709	6612	303136	15378	24144, 32910, 41676, 50442, 59208
6458	PWWP domain containing 2A	307063	6613	305151	15379	24145, 32911, 41677, 50443, 59209
6459	PWWP domain containing 2A	456329	6614	390462	15380	24146, 32912, 41678, 50444, 59210
6460	PWWP domain containing 2A	523662	6615	428143	15381	24147, 32913, 41679, 50445, 59211
6461	PWWP domain containing 2B	305233	6616	306324	15382	24148, 32914, 41680, 50446, 59212
6462	PWWP domain containing	368609	6617	357598	15383	24149, 32915,

	2B					41681, 50447, 59213
6463	PX domain containing 1	380277	6618	369630	15384	24150, 32916, 41682, 50448, 59214
6464	PX domain containing 1	380283	6619	369636	15385	24151, 32917, 41683, 50449, 59215
6465	pyridine nucleotide-disulphide oxidoreductase domain 1	240651	6620	240651	15386	24152, 32918, 41684, 50450, 59216
6466	pyridine nucleotide-disulphide oxidoreductase domain 1	545178	6621	443912	15387	24153, 32919, 41685, 50451, 59217
6467	pyridine nucleotide-disulphide oxidoreductase domain 2	370575	6622	359607	15388	24154, 32920, 41686, 50452, 59218
6468	pyroglutamyl-peptidase I-like	378919	6623	368199	15389	24155, 32921, 41687, 50453, 59219
6469	pyroglutamyl-peptidase I-like	535714	6624	437560	15390	24156, 32922, 41688, 50454, 59220
6470	pyroglutamyl-peptidase I-like	595289	6625	471029	15391	24157, 32923, 41689, 50455, 59221
6471	pyrroline-5-carboxylate reductase-like	220966	6626	220966	15392	24158, 32924, 41690, 50456, 59222
6472	pyrroline-5-carboxylate reductase-like	377579	6627	366802	15393	24159, 32925, 41691, 50457, 59223
6473	R3H domain and coiled-coil containing 1	265806	6628	265806	15394	24160, 32926, 41692, 50458, 59224
6474	R3H domain and coiled-coil containing 1	411463	6629	397555	15395	24161, 32927, 41693, 50459, 59225
6475	R3H domain and coiled-coil containing 1	518454	6630	430607	15396	24162, 32928, 41694, 50460, 59226
6476	R3H domain and coiled-coil containing 1	518840	6631	429604	15397	24163, 32929, 41695, 50461, 59227
6477	R3H domain and coiled-coil containing 1	519952	6632	429417	15398	24164, 32930, 41696, 50462, 59228
6478	R3H domain and coiled-coil containing 1	521588	6633	428395	15399	24165, 32931, 41697, 50463, 59229

6479	R3H domain containing 1	264160	6634	264160	15400	24166, 32932, 41698, 50464, 59230
6480	R3H domain containing 1	329971	6635	331396	15401	24167, 32933, 41699, 50465, 59231
6481	R3H domain containing 4	361574	6636	355385	15402	24168, 32934, 41700, 50466, 59232
6482	RAB member of RAS oncogene family-like 2B	594223	6637	471135	15403	24169, 32935, 41701, 50467, 59233
6483	RAB member of RAS oncogene family-like 2B	595999	6638	470099	15404	24170, 32936, 41702, 50468, 59234
6484	RAB member of RAS oncogene family-like 2B	599205	6639	472993	15405	24171, 32937, 41703, 50469, 59235
6485	RAB, member RAS oncogene family-like 5	315322	6640	320359	15406	24172, 32938, 41704, 50470, 59236
6486	RAB, member RAS oncogene family-like 5	422177	6641	392087	15407	24173, 32939, 41705, 50471, 59237
6487	RAB, member RAS oncogene family-like 5	437644	6642	390770	15408	24174, 32940, 41706, 50472, 59238
6488	RAB, member RAS oncogene family-like 5	498704	6643	429648	15409	24175, 32941, 41707, 50473, 59239
6489	RAB, member RAS oncogene family-like 5	517481	6644	429202	15410	24176, 32942, 41708, 50474, 59240
6490	RAB3A interacting protein (rabin3)-like 1	301773	6645	301773	15411	24177, 32943, 41709, 50475, 59241
6491	RAB3A interacting protein (rabin3)-like 1	394836	6646	378313	15412	24178, 32944, 41710, 50476, 59242
6492	RAB42, member RAS oncogene family	373826	6647	362932	15413	24179, 32945, 41711, 50477, 59243
6493	RAB44, member RAS oncogene family	229824	6648	229824	15414	24180, 32946, 41712, 50478, 59244
6494	RAB5C member RAS oncogene family	565751	6649	457972	15415	24181, 32947, 41713, 50479, 59245
6495	rabphilin 3A-like (without C2 domains)	594863	6650	469993	15416	24182, 32948, 41714, 50480,

						59246
6496	RAD17 homolog (S. pombe)	573405	6651	461592	15417	24183, 32949, 41715, 50481, 59247
6497	RAD17 homolog (S. pombe)	575651	6652	461866	15418	24184, 32950, 41716, 50482, 59248
6498	RAD17 homolog (S. pombe)	576047	6653	458536	15419	24185, 32951, 41717, 50483, 59249
6499	RAD51 associated protein 2	399080	6654	382030	15420	24186, 32952, 41718, 50484, 59250
6500	radial spoke 3 homolog (Chlamydomonas)	252655	6655	252655	15421	24187, 32953, 41719, 50485, 59251
6501	radial spoke 3 homolog (Chlamydomonas)	297262	6656	297262	15422	24188, 32954, 41720, 50486, 59252
6502	radial spoke 3 homolog (Chlamydomonas)	367069	6657	356036	15423	24189, 32955, 41721, 50487, 59253
6503	radial spoke 3 homolog (Chlamydomonas)	449822	6658	393195	15424	24190, 32956, 41722, 50488, 59254
6504	radial spoke head 10 homolog B (Chlamydomonas)	337579	6659	338556	15425	24191, 32957, 41723, 50489, 59255
6505	radial spoke head 10 homolog B (Chlamydomonas)	354951	6660	347037	15426	24192, 32958, 41724, 50490, 59256
6506	radial spoke head 10 homolog B (Chlamydomonas)	404406	6661	384097	15427	24193, 32959, 41725, 50491, 59257
6507	radial spoke head 10 homolog B (Chlamydomonas)	405415	6662	385443	15428	24194, 32960, 41726, 50492, 59258
6508	radial spoke head 10 homolog B (Chlamydomonas)	441023	6663	400988	15429	24195, 32961, 41727, 50493, 59259
6509	radial spoke head 10 homolog B (Chlamydomonas)	455618	6664	390326	15430	24196, 32962, 41728, 50494, 59260
6510	radial spoke head 10 homolog B (Chlamydomonas)	539903	6665	445203	15431	24197, 32963, 41729, 50495, 59261
6511	radial spoke head 10 homolog B (Chlamydomonas)	542644	6666	444512	15432	24198, 32964, 41730, 50496, 59262
6512	radial spoke head 10	297186	6667	297186	15433	24199, 32965,

	homolog B2 (Chlamydomonas)					41731, 50497, 59263
6513	radial spoke head 10 homolog B2 (Chlamydomonas)	359718	6668	352749	15434	24200, 32966, 41732, 50498, 59264
6514	radial spoke head 10 homolog B2 (Chlamydomonas)	403107	6669	384766	15435	24201, 32967, 41733, 50499, 59265
6515	radial spoke head 10 homolog B2 (Chlamydomonas)	404077	6670	386102	15436	24202, 32968, 41734, 50500, 59266
6516	radial spoke head 10 homolog B2 (Chlamydomonas)	418406	6671	395335	15437	24203, 32969, 41735, 50501, 59267
6517	radial spoke head 10 homolog B2 (Chlamydomonas)	433859	6672	416710	15438	24204, 32970, 41736, 50502, 59268
6518	radial spoke head 10 homolog B2 (Chlamydomonas)	435395	6673	396498	15439	24205, 32971, 41737, 50503, 59269
6519	radial spoke head 10 homolog B2 (Chlamydomonas)	540958	6674	441021	15440	24206, 32972, 41738, 50504, 59270
6520	radial spoke head 6 homolog A (Chlamydomonas)	221538	6675	221538	15441	24207, 32973, 41739, 50505, 59271
6521	Ral GTPase activating protein, beta subunit (non-catalytic)	262879	6676	262879	15442	24208, 32974, 41740, 50506, 59272
6522	Ral GTPase activating protein, beta subunit (non-catalytic)	304939	6677	302059	15443	24209, 32975, 41741, 50507, 59273
6523	Ral GTPase activating protein, beta subunit (non-catalytic)	397038	6678	380231	15444	24210, 32976, 41742, 50508, 59274
6524	Ral GTPase activating protein, beta subunit (non-catalytic)	397040	6679	380233	15445	24211, 32977, 41743, 50509, 59275
6525	Ral GTPase activating protein, beta subunit (non-catalytic)	397042	6680	380235	15446	24212, 32978, 41744, 50510, 59276
6526	Ral GTPase activating protein, beta subunit (non-catalytic)	438490	6681	416646	15447	24213, 32979, 41745, 50511, 59277
6527	Ral GTPase activating protein, beta subunit (non-catalytic)	537204	6682	442959	15448	24214, 32980, 41746, 50512, 59278
6528	ral guanine nucleotide dissociation stimulator-like 2	383204	6683	372691	15449	24215, 32981, 41747, 50513, 59279

6529	ral guanine nucleotide dissociation stimulator-like 2	412959	6684	387453	15450	24216, 32982, 41748, 50514, 59280
6530	ral guanine nucleotide dissociation stimulator-like 2	413136	6685	407088	15451	24217, 32983, 41749, 50515, 59281
6531	ral guanine nucleotide dissociation stimulator-like 2	416548	6686	412152	15452	24218, 32984, 41750, 50516, 59282
6532	ral guanine nucleotide dissociation stimulator-like 2	421215	6687	400083	15453	24219, 32985, 41751, 50517, 59283
6533	ral guanine nucleotide dissociation stimulator-like 2	425946	6688	392918	15454	24220, 32986, 41752, 50518, 59284
6534	ral guanine nucleotide dissociation stimulator-like 2	431976	6689	398125	15455	24221, 32987, 41753, 50519, 59285
6535	ral guanine nucleotide dissociation stimulator-like 2	444031	6690	403070	15456	24222, 32988, 41754, 50520, 59286
6536	ral guanine nucleotide dissociation stimulator-like 2	446570	6691	412625	15457	24223, 32989, 41755, 50521, 59287
6537	ral guanine nucleotide dissociation stimulator-like 2	452084	6692	390098	15458	24224, 32990, 41756, 50522, 59288
6538	ral guanine nucleotide dissociation stimulator-like 2	455072	6693	397558	15459	24225, 32991, 41757, 50523, 59289
6539	ral guanine nucleotide dissociation stimulator-like 2	497454	6694	420211	15460	24226, 32992, 41758, 50524, 59290
6540	ral guanine nucleotide dissociation stimulator-like 2	546945	6695	448294	15461	24227, 32993, 41759, 50525, 59291
6541	ral guanine nucleotide dissociation stimulator-like 2	547127	6696	447602	15462	24228, 32994, 41760, 50526, 59292
6542	ral guanine nucleotide dissociation stimulator-like 2	548778	6697	447385	15463	24229, 32995, 41761, 50527, 59293
6543	ral guanine nucleotide dissociation stimulator-like 2	549377	6698	448781	15464	24230, 32996, 41762, 50528, 59294
6544	ral guanine nucleotide dissociation stimulator-like 2	550374	6699	447611	15465	24231, 32997, 41763, 50529, 59295
6545	ral guanine nucleotide dissociation stimulator-like	550921	6700	448604	15466	24232, 32998, 41764, 50530,

	2					59296
6546	ral guanine nucleotide dissociation stimulator-like 2	552204	6701	449763	15467	24233, 32999, 41765, 50531, 59297
6547	ral guanine nucleotide dissociation stimulator-like 2	553067	6702	449417	15468	24234, 33000, 41766, 50532, 59298
6548	ral guanine nucleotide dissociation stimulator-like 3	342684	6703	344665	15469	24235, 33001, 41767, 50533, 59299
6549	ral guanine nucleotide dissociation stimulator-like 3	380456	6704	369823	15470	24236, 33002, 41768, 50534, 59300
6550	ral guanine nucleotide dissociation stimulator-like 3	393423	6705	377075	15471	24237, 33003, 41769, 50535, 59301
6551	ral guanine nucleotide dissociation stimulator-like 3	453604	6706	391460	15472	24238, 33004, 41770, 50536, 59302
6552	RALY RNA binding protein-like	517988	6707	428711	15473	24239, 33005, 41771, 50537, 59303
6553	RALY RNA binding protein-like	521268	6708	430367	15474	24240, 33006, 41772, 50538, 59304
6554	RALY RNA binding protein-like	521695	6709	428667	15475	24241, 33007, 41773, 50539, 59305
6555	RALY RNA binding protein-like	522455	6710	430394	15476	24242, 33008, 41774, 50540, 59306
6556	RALY RNA binding protein-like	522613	6711	427787	15477	24243, 33009, 41775, 50541, 59307
6557	RALY RNA binding protein-like	523850	6712	428807	15478	24244, 33010, 41776, 50542, 59308
6558	Rap guanine nucleotide exchange factor (GEF)-like 1	264644	6713	264644	15479	24245, 33011, 41777, 50543, 59309
6559	Rap guanine nucleotide exchange factor (GEF)-like 1	436615	6714	408322	15480	24246, 33012, 41778, 50544, 59310
6560	Rap guanine nucleotide exchange factor (GEF)-like 1	537255	6715	437874	15481	24247, 33013, 41779, 50545, 59311
6561	Rap guanine nucleotide exchange factor (GEF)-like 1	538884	6716	440006	15482	24248, 33014, 41780, 50546, 59312
6562	Rap guanine nucleotide	538981	6717	441059	15483	24249, 33015,

	exchange factor (GEF)-like 1					41781, 50547, 59313
6563	Rap guanine nucleotide exchange factor (GEF)-like 1	543876	6718	440226	15484	24250, 33016, 41782, 50548, 59314
6564	Ras and Rab interactor-like	340740	6719	340369	15485	24251, 33017, 41783, 50549, 59315
6565	Ras and Rab interactor-like	536520	6720	439962	15486	24252, 33018, 41784, 50550, 59316
6566	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	282884	6721	282884	15487	24253, 33019, 41785, 50551, 59317
6567	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	381352	6722	370756	15488	24254, 33020, 41786, 50552, 59318
6568	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	405154	6723	384491	15489	24255, 33021, 41787, 50553, 59319
6569	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	535907	6724	442036	15490	24256, 33022, 41788, 50554, 59320
6570	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	537946	6725	445434	15491	24257, 33023, 41789, 50555, 59321
6571	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	541218	6726	445970	15492	24258, 33024, 41790, 50556, 59322
6572	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	541490	6727	443096	15493	24259, 33025, 41791, 50557, 59323
6573	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	541934	6728	445860	15494	24260, 33026, 41792, 50558, 59324
6574	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	542004	6729	442485	15495	24261, 33027, 41793, 50559, 59325
6575	Ras association (RalGDS/AF-6) domain family (N-terminal)	542315	6730	441294	15496	24262, 33028, 41794, 50560, 59326

	member 8					
6576	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	542865	6731	439839	15497	24263, 33029, 41795, 50561, 59327
6577	Ras association (RalGDS/AF-6) domain family (N-terminal) member 8	545413	6732	443696	15498	24264, 33030, 41796, 50562, 59328
6578	RAS p21 protein activator 4B	465829	6733	417895	15499	24265, 33031, 41797, 50563, 59329
6579	RAS p21 protein activator 4B	541662	6734	440982	15500	24266, 33032, 41798, 50564, 59330
6580	Ras protein-specific guanine nucleotide-releasing factor 1	394741	6735	378224	15501	24267, 33033, 41799, 50565, 59331
6581	Ras protein-specific guanine nucleotide-releasing factor 1	394745	6736	378228	15502	24268, 33034, 41800, 50566, 59332
6582	Ras protein-specific guanine nucleotide-releasing factor 1	419573	6737	405963	15503	24269, 33035, 41801, 50567, 59333
6583	Ras protein-specific guanine nucleotide-releasing factor 1	558480	6738	452781	15504	24270, 33036, 41802, 50568, 59334
6584	RasGEF domain family, member 1A	374459	6739	363583	15505	24271, 33037, 41803, 50569, 59335
6585	RasGEF domain family, member 1A	395809	6740	379154	15506	24272, 33038, 41804, 50570, 59336
6586	RasGEF domain family, member 1A	395810	6741	379155	15507	24273, 33039, 41805, 50571, 59337
6587	RasGEF domain family, member 1B	264400	6742	264400	15508	24274, 33040, 41806, 50572, 59338
6588	RasGEF domain family, member 1B	335927	6743	338437	15509	24275, 33041, 41807, 50573, 59339
6589	RasGEF domain family, member 1B	395570	6744	378937	15510	24276, 33042, 41808, 50574, 59340
6590	RasGEF domain family, member 1B	436139	6745	398763	15511	24277, 33043, 41809, 50575, 59341
6591	RasGEF domain family, member 1B	509081	6746	425393	15512	24278, 33044, 41810, 50576,

						59342
6592	RasGEF domain family, member 1C	361132	6747	354963	15513	24279, 33045, 41811, 50577, 59343
6593	RasGEF domain family, member 1C	393371	6748	377037	15514	24280, 33046, 41812, 50578, 59344
6594	RAS-like, family 12	220062	6749	220062	15515	24281, 33047, 41813, 50579, 59345
6595	RAS-like, family 12	421977	6750	390028	15516	24282, 33048, 41814, 50580, 59346
6596	RAS-like, family 12	434605	6751	412787	15517	24283, 33049, 41815, 50581, 59347
6597	RCC1 domain containing 1	394258	6752	377801	15518	24284, 33050, 41816, 50582, 59348
6598	RCC1 domain containing 1	556618	6753	451963	15519	24285, 33051, 41817, 50583, 59349
6599	RCSD domain containing 1	361496	6754	355291	15520	24286, 33052, 41818, 50584, 59350
6600	RCSD domain containing 1	367854	6755	356828	15521	24287, 33053, 41819, 50585, 59351
6601	RCSD domain containing 1	537350	6756	439409	15522	24288, 33054, 41820, 50586, 59352
6602	recoverin	226193	6757	226193	15523	24289, 33055, 41821, 50587, 59353
6603	regulation of nuclear pre-mRNA domain containing 1A	319040	6758	314602	15524	24290, 33056, 41822, 50588, 59354
6604	regulation of nuclear pre-mRNA domain containing 1A	337059	6759	337476	15525	24291, 33057, 41823, 50589, 59355
6605	regulation of nuclear pre-mRNA domain containing 1A	357384	6760	349955	15526	24292, 33058, 41824, 50590, 59356
6606	regulation of nuclear pre-mRNA domain containing 1A	399022	6761	381984	15527	24293, 33059, 41825, 50591, 59357
6607	regulation of nuclear pre-mRNA domain containing 1B	373433	6762	362532	15528	24294, 33060, 41826, 50592, 59358
6608	regulation of nuclear pre-	369067	6763	358063	15529	24295, 33061,

	mRNA domain containing 2					41827, 50593, 59359
6609	regulation of nuclear pre-mRNA domain containing 2	369068	6764	358064	15530	24296, 33062, 41828, 50594, 59360
6610	regulation of nuclear pre-mRNA domain containing 2	401000	6765	383785	15531	24297, 33063, 41829, 50595, 59361
6611	regulation of nuclear pre-mRNA domain containing 2	539519	6766	445482	15532	24298, 33064, 41830, 50596, 59362
6612	regulator of G-protein signaling like 1	294854	6767	457748	15533	24299, 33065, 41831, 50597, 59363
6613	regulatory subunit of type II PKA R-subunit (RIIa) domain containing 1	326413	6768	420280	15534	24300, 33066, 41832, 50598, 59364
6614	required for meiotic nuclear division 5 homolog A (S. cerevisiae)	283632	6769	283632	15535	24301, 33067, 41833, 50599, 59365
6615	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	313386	6770	320623	15536	24302, 33068, 41834, 50600, 59366
6616	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	502814	6771	424928	15537	24303, 33069, 41835, 50601, 59367
6617	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	507457	6772	425920	15538	24304, 33070, 41836, 50602, 59368
6618	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	508647	6773	426588	15539	24305, 33071, 41837, 50603, 59369
6619	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	515098	6774	420875	15540	24306, 33072, 41838, 50604, 59370
6620	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	542098	6775	437630	15541	24307, 33073, 41839, 50605, 59371
6621	RERG/RAS-like	229002	6776	229002	15542	24308, 33074, 41840, 50606, 59372
6622	ret finger protein-like 4A	434937	6777	392936	15543	24309, 33075, 41841, 50607, 59373
6623	ret finger protein-like 4B	441065	6778	423391	15544	24310, 33076, 41842, 50608, 59374
6624	retinal degeneration 3-like	557640	6779	455434	15545	24311, 33077, 41843, 50609, 59375

6625	retrotransposon gag domain containing 1	465301	6780	419786	15546	24312, 33078, 41844, 50610, 59376
6626	retrotransposon gag domain containing 1	520821	6781	430395	15547	24313, 33079, 41845, 50611, 59377
6627	retrotransposon gag domain containing 1	540313	6782	441452	15548	24314, 33080, 41846, 50612, 59378
6628	retrotransposon gag domain containing 1	540483	6783	440938	15549	24315, 33081, 41847, 50613, 59379
6629	retrotransposon gag domain containing 4	479991	6784	418667	15550	24316, 33082, 41848, 50614, 59380
6630	retrotransposon gag domain containing 4	545866	6785	441366	15551	24317, 33083, 41849, 50615, 59381
6631	REX1, RNA exonuclease 1 homolog (S. cerevisiae)-like 2, pseudogene	425429	6786	405038	15552	24318, 33084, 41850, 50616, 59382
6632	REX1, RNA exonuclease 1 homolog (S. cerevisiae)-like 2, pseudogene	540724	6787	444777	15553	24319, 33085, 41851, 50617, 59383
6633	Rho GTPase activating protein 33	7510	6788	7510	15554	24320, 33086, 41852, 50618, 59384, 61541, 61599
6634	Rho GTPase activating protein 33	221905	6789	221905	15555	24321, 33087, 41853, 50619, 59385
6635	Rho GTPase activating protein 33	314737	6790	320038	15556	24322, 33088, 41854, 50620, 59386
6636	Rho GTPase activating protein 33	378944	6791	368227	15557	24323, 33089, 41855, 50621, 59387
6637	Rho GTPase activating protein 42	298815	6792	298815	15558	24324, 33090, 41856, 50622, 59388
6638	rho GTPase-activating protein 27 isoform a	546802	6793	446550	15559	24325, 33091, 41857, 50623, 59389
6639	rho GTPase-activating protein 27 isoform a	547264	6794	449024	15560	24326, 33092, 41858, 50624, 59390
6640	rho GTPase-activating protein 27 isoform a	548772	6795	448920	15561	24327, 33093, 41859, 50625, 59391
6641	rho GTPase-activating	549653	6796	447150	15562	24328, 33094,

	protein 27 isoform a					41860, 50626, 59392
6642	rho GTPase-activating protein 27 isoform a	550209	6797	447624	15563	24329, 33095, 41861, 50627, 59393
6643	Rho guanine nucleotide exchange factor (GEF) 15	361926	6798	355026	15564	24330, 33096, 41862, 50628, 59394
6644	Rho guanine nucleotide exchange factor (GEF) 15	421050	6799	412505	15565	24331, 33097, 41863, 50629, 59395
6645	Rho guanine nucleotide exchange factor (GEF) 15	455564	6800	413324	15566	24332, 33098, 41864, 50630, 59396
6646	Rho guanine nucleotide exchange factor (GEF) 26	356448	6801	348828	15567	24333, 33099, 41865, 50631, 59397
6647	Rho guanine nucleotide exchange factor (GEF) 26	465093	6802	423418	15568	24334, 33100, 41866, 50632, 59398
6648	Rho guanine nucleotide exchange factor (GEF) 26	465817	6803	423295	15569	24335, 33101, 41867, 50633, 59399
6649	Rho guanine nucleotide exchange factor (GEF) 26	496710	6804	424446	15570	24336, 33102, 41868, 50634, 59400
6650	Rho guanine nucleotide exchange factor (GEF) 33	398800	6805	381780	15571	24337, 33103, 41869, 50635, 59401
6651	Rho guanine nucleotide exchange factor (GEF) 33	536934	6806	445586	15572	24338, 33104, 41870, 50636, 59402
6652	Rho guanine nucleotide exchange factor (GEF) 33	409978	6807	387020	15573	24339, 33105, 41871, 50637, 59403
6653	Rho guanine nucleotide exchange factor (GEF) 35	378115	6808	367355	15574	24340, 33106, 41872, 50638, 59404
6654	Rho guanine nucleotide exchange factor (GEF) 35	543357	6809	438502	15575	24341, 33107, 41873, 50639, 59405
6655	rhomboid domain containing 2	574493	6810	458798	15576	24342, 33108, 41874, 50640, 59406
6656	rhophilin, Rho GTPase binding protein 1	289013	6811	289013	15577	24343, 33109, 41875, 50641, 59407
6657	RIB43A domain with coiled-coils 1	329209	6812	332142	15578	24344, 33110, 41876, 50642, 59408

6658	RIB43A domain with coiled-coils 1	375327	6813	364476	15579	24345, 33111, 41877, 50643, 59409
6659	RIB43A domain with coiled-coils 1	414955	6814	401463	15580	24346, 33112, 41878, 50644, 59410
6660	RIB43A domain with coiled-coils 1	457095	6815	402080	15581	24347, 33113, 41879, 50645, 59411
6661	RIB43A domain with coiled-coils 2	342894	6816	342529	15582	24348, 33114, 41880, 50646, 59412
6662	RIB43A domain with coiled-coils 2	538017	6817	444196	15583	24349, 33115, 41881, 50647, 59413
6663	ribonuclease, RNase A family, 11 (non-active)	413502	6818	415954	15584	24350, 33116, 41882, 50648, 59414, 61542, 61600
6664	ribosomal protein L17	579248	6819	462023	15585	24351, 33117, 41883, 50649, 59415
6665	ribosomal protein L17	581373	6820	462944	15586	24352, 33118, 41884, 50650, 59416
6666	ribosomal protein L17	583637	6821	462203	15587	24353, 33119, 41885, 50651, 59417
6667	ribosomal protein S9	573353	6822	461356	15588	24354, 33120, 41886, 50652, 59418
6668	ribosomal protein SA pseudogene 58	354585	6823	346598	15589	24355, 33121, 41887, 50653, 59419
6669	ribosomal RNA processing 7 homolog A (S. cerevisiae)	323013	6824	321449	15590	24356, 33122, 41888, 50654, 59420
6670	Ribosomal RNA small subunit methyltransferase NEP1	599672	6825	470560	15591	24357, 33123, 41889, 50655, 59421
6671	Rieske (Fe-S) domain containing	311364	6826	309229	15592	24358, 33124, 41890, 50656, 59422
6672	Rieske (Fe-S) domain containing	380005	6827	369341	15593	24359, 33125, 41891, 50657, 59423
6673	Rieske (Fe-S) domain containing	458310	6828	413592	15594	24360, 33126, 41892, 50658, 59424
6674	Rieske (Fe-S) domain	511684	6829	422520	15595	24361, 33127,

	containing					41893, 50659, 59425
6675	ring finger protein 113A	371442	6830	360497	15596	24362, 33128, 41894, 50660, 59426
6676	ring finger protein 113B	267291	6831	267291	15597	24363, 33129, 41895, 50661, 59427
6677	ring finger protein 125	217740	6832	217740	15598	24364, 33130, 41896, 50662, 59428
6678	ring finger protein 126	292363	6833	292363	15599	24365, 33131, 41897, 50663, 59429
6679	ring finger protein 126	340092	6834	341380	15600	24366, 33132, 41898, 50664, 59430
6680	ring finger protein 138	257190	6835	257190	15601	24367, 33133, 41899, 50665, 59431
6681	ring finger protein 138	261593	6836	261593	15602	24368, 33134, 41900, 50666, 59432
6682	ring finger protein 141	265981	6837	265981	15603	24369, 33135, 41901, 50667, 59433
6683	ring finger protein 141	533412	6838	435086	15604	24370, 33136, 41902, 50668, 59434
6684	ring finger protein 157	269391	6839	269391	15605	24371, 33137, 41903, 50669, 59435
6685	ring finger protein 157	301610	6840	301610	15606	24372, 33138, 41904, 50670, 59436
6686	ring finger protein 157	319945	6841	321837	15607	24373, 33139, 41905, 50671, 59437
6687	ring finger protein 165	269439	6842	269439	15608	24374, 33140, 41906, 50672, 59438
6688	ring finger protein 165	543885	6843	444285	15609	24375, 33141, 41907, 50673, 59439
6689	ring finger protein 165	586604	6844	468365	15610	24376, 33142, 41908, 50674, 59440
6690	ring finger protein 166	312838	6845	326095	15611	24377, 33143, 41909, 50675, 59441

6691	ring finger protein 166	537718	6846	446301	15612	24378, 33144, 41910, 50676, 59442
6692	ring finger protein 166	541206	6847	440454	15613	24379, 33145, 41911, 50677, 59443
6693	ring finger protein 166	567844	6848	457336	15614	24380, 33146, 41912, 50678, 59444
6694	ring finger protein 169	299563	6849	299563	15615	24381, 33147, 41913, 50679, 59445
6695	ring finger protein 169	527301	6850	436339	15616	24382, 33148, 41914, 50680, 59446
6696	ring finger protein 183	297894	6851	417943	15617	24383, 33149, 41915, 50681, 59447
6697	ring finger protein 183	416588	6852	420740	15618	24384, 33150, 41916, 50682, 59448
6698	ring finger protein 183	441031	6853	417176	15619	24385, 33151, 41917, 50683, 59449
6699	ring finger protein 183	478815	6854	419454	15620	24386, 33152, 41918, 50684, 59450
6700	ring finger protein 207	377939	6855	367173	15621	24387, 33153, 41919, 50685, 59451
6701	ring finger protein 207	377948	6856	367183	15622	24388, 33154, 41920, 50686, 59452
6702	ring finger protein 208	391553	6857	375397	15623	24389, 33155, 41921, 50687, 59453
6703	ring finger protein 208	392827	6858	376572	15624	24390, 33156, 41922, 50688, 59454
6704	ring finger protein 214	300650	6859	300650	15625	24391, 33157, 41923, 50689, 59455
6705	ring finger protein 214	531452	6860	431643	15626	24392, 33158, 41924, 50690, 59456
6706	ring finger protein 214	534428	6861	434186	15627	24393, 33159, 41925, 50691, 59457
6707	ring finger protein 219	282003	6862	282003	15628	24394, 33160, 41926, 50692,

						59458
6708	ring finger protein 222	344001	6863	343799	15629	24395, 33161, 41927, 50693, 59459
6709	ring finger protein 222	399398	6864	382330	15630	24396, 33162, 41928, 50694, 59460
6710	ring finger protein 224	445101	6865	406665	15631	24397, 33163, 41929, 50695, 59461
6711	ring finger protein 41	345093	6866	342755	15632	24398, 33164, 41930, 50696, 59462
6712	ring finger protein 41	394013	6867	377581	15633	24399, 33165, 41931, 50697, 59463
6713	ring finger protein 41	448057	6868	409919	15634	24400, 33166, 41932, 50698, 59464
6714	ring finger protein 41	549038	6869	446595	15635	24401, 33167, 41933, 50699, 59465
6715	ring finger protein 41	551711	6870	450164	15636	24402, 33168, 41934, 50700, 59466
6716	ring finger protein 41	552244	6871	448187	15637	24403, 33169, 41935, 50701, 59467
6717	ring finger protein 41	552656	6872	447303	15638	24404, 33170, 41936, 50702, 59468
6718	ring finger protein 44	274811	6873	274811	15639	24405, 33171, 41937, 50703, 59469
6719	ring finger protein 44	537487	6874	440352	15640	24406, 33172, 41938, 50704, 59470
6720	RIO kinase 1 (yeast)	379834	6875	369162	15641	24407, 33173, 41939, 50705, 59471
6721	RIO kinase 2 (yeast)	283109	6876	283109	15642	24408, 33174, 41940, 50706, 59472
6722	RIO kinase 2 (yeast)	508447	6877	420932	15643	24409, 33175, 41941, 50707, 59473
6723	RIO kinase 3 (yeast)	339486	6878	341874	15644	24410, 33176, 41942, 50708, 59474
6724	RMI1, RecQ mediated	445877	6879	402433	15645	24411, 33177,

	genome instability 1, homolog (S. cerevisiae)					41943, 50709, 59475
6725	RNA (guanine-9-) methyltransferase domain containing 2	273962	6880	273962	15646	24412, 33178, 41944, 50710, 59476
6726	RNA (guanine-9-) methyltransferase domain containing 2	394876	6881	378342	15647	24413, 33179, 41945, 50711, 59477
6727	RNA (guanine-9-) methyltransferase domain containing 2	394877	6882	378343	15648	24414, 33180, 41946, 50712, 59478
6728	RNA (guanine-9-) methyltransferase domain containing 2	455368	6883	397551	15649	24415, 33181, 41947, 50713, 59479
6729	RNA (guanine-9-) methyltransferase domain containing 2	514547	6884	423628	15650	24416, 33182, 41948, 50714, 59480
6730	RNA (guanine-9-) methyltransferase domain containing 3	297994	6885	297994	15651	24417, 33183, 41949, 50715, 59481
6731	RNA (guanine-9-) methyltransferase domain containing 3	377753	6886	366982	15652	24418, 33184, 41950, 50716, 59482
6732	RNA (guanine-9-) methyltransferase domain containing 3	537911	6887	444997	15653	24419, 33185, 41951, 50717, 59483
6733	RNA binding motif (RNP1 RRM) protein 3	598825	6888	470199	15654	24420, 33186, 41952, 50718, 59484
6734	RNA binding motif protein 11	400577	6889	383421	15655	24421, 33187, 41953, 50719, 59485
6735	RNA binding motif protein 12B	399300	6890	382239	15656	24422, 33188, 41954, 50720, 59486
6736	RNA binding motif protein 12B	517700	6891	427729	15657	24423, 33189, 41955, 50721, 59487
6737	RNA binding motif protein 12B	518597	6892	428269	15658	24424, 33190, 41956, 50722, 59488
6738	RNA binding motif protein 12B	519109	6893	430474	15659	24425, 33191, 41957, 50723, 59489
6739	RNA binding motif protein 12B	520560	6894	429807	15660	24426, 33192, 41958, 50724, 59490
6740	RNA binding motif protein 12B	521947	6895	430466	15661	24427, 33193, 41959, 50725, 59491

6741	RNA binding motif protein 18	417201	6896	409315	15662	24428, 33194, 41960, 50726, 59492
6742	RNA binding motif protein 26	267229	6897	267229	15663	24429, 33195, 41961, 50727, 59493
6743	RNA binding motif protein 26	327303	6898	327080	15664	24430, 33196, 41962, 50728, 59494
6744	RNA binding motif protein 26	438724	6899	390222	15665	24431, 33197, 41963, 50729, 59495
6745	RNA binding motif protein 33	287912	6900	287912	15666	24432, 33198, 41964, 50730, 59496
6746	RNA binding motif protein 33	341148	6901	341583	15667	24433, 33199, 41965, 50731, 59497
6747	RNA binding motif protein 33	401878	6902	384160	15668	24434, 33200, 41966, 50732, 59498
6748	RNA binding motif protein 33	438356	6903	405793	15669	24435, 33201, 41967, 50733, 59499
6749	RNA binding motif protein 34	366606	6904	355565	15670	24436, 33202, 41968, 50734, 59500
6750	RNA binding motif protein 41	203616	6905	203616	15671	24437, 33203, 41969, 50735, 59501
6751	RNA binding motif protein 41	372479	6906	361557	15672	24438, 33204, 41970, 50736, 59502
6752	RNA binding motif protein 41	372482	6907	361560	15673	24439, 33205, 41971, 50737, 59503
6753	RNA binding motif protein 41	372487	6908	361565	15674	24440, 33206, 41972, 50738, 59504
6754	RNA binding motif protein 41	434854	6909	405522	15675	24441, 33207, 41973, 50739, 59505
6755	RNA binding motif protein 44	316997	6910	321179	15676	24442, 33208, 41974, 50740, 59506
6756	RNA binding motif protein 44	409864	6911	386727	15677	24443, 33209, 41975, 50741, 59507
6757	RNA binding motif protein 46	281722	6912	281722	15678	24444, 33210, 41976, 50742,

						59508
6758	RNA binding motif protein 48	265732	6913	265732	15679	24445, 33211, 41977, 50743, 59509
6759	RNA binding motif protein 48	450580	6914	401920	15680	24446, 33212, 41978, 50744, 59510
6760	RNA binding motif protein 48	509224	6915	442073	15681	24447, 33213, 41979, 50745, 59511
6761	RNA binding motif protein, X-linked 2	305536	6916	339090	15682	24448, 33214, 41980, 50746, 59512
6762	RNA binding motif protein, X-linked 2	370947	6917	359985	15683	24449, 33215, 41981, 50747, 59513
6763	RNA binding motif protein, X-linked 2	538614	6918	437425	15684	24450, 33216, 41982, 50748, 59514
6764	RNA binding motif protein, X-linked-like 3	424776	6919	417451	15685	24451, 33217, 41983, 50749, 59515
6765	RNA binding motif protein, Y-linked, family 1, member B	383020	6920	372484	15686	24452, 33218, 41984, 50750, 59516
6766	RNA binding motif protein, Y-linked, family 1, member D	382677	6921	372124	15687	24453, 33219, 41985, 50751, 59517
6767	RNA binding motif protein, Y-linked, family 1, member D	382680	6922	372127	15688	24454, 33220, 41986, 50752, 59518
6768	RNA binding motif protein, Y-linked, family 1, member D	418956	6923	399181	15689	24455, 33221, 41987, 50753, 59519
6769	RNA binding motif protein, Y-linked, family 1, member E	382658	6924	372104	15690	24456, 33222, 41988, 50754, 59520
6770	RNA binding motif protein, Y-linked, family 1, member E	382659	6925	372105	15691	24457, 33223, 41989, 50755, 59521
6771	RNA binding motif protein, Y-linked, family 1, member E	382673	6926	372119	15692	24458, 33224, 41990, 50756, 59522
6772	RNA binding protein with multiple splicing 2	300069	6927	300069	15693	24459, 33225, 41991, 50757, 59523
6773	RNA polymerase I transcription factor homolog (S. cerevisiae) pseudogene 2	219758	6928	219758	15694	24460, 33226, 41992, 50758, 59524

6774	RNA polymerase I transcription factor homolog (S. cerevisiae) pseudogene 2	415221	6929	398187	15695	24461, 33227, 41993, 50759, 59525
6775	RNA polymerase I transcription factor homolog (S. cerevisiae) pseudogene 2	427965	6930	398611	15696	24462, 33228, 41994, 50760, 59526
6776	RNA pseudouridylate synthase domain containing 1	7264	6931	7264	15697	24463, 33229, 41995, 50761, 59527, 61543, 61601
6777	RNA pseudouridylate synthase domain containing 2	315616	6932	323288	15698	24464, 33230, 41996, 50762, 59528
6778	RNA pseudouridylate synthase domain containing 2	417769	6933	388146	15699	24465, 33231, 41997, 50763, 59529
6779	RNA pseudouridylate synthase domain containing 3	383820	6934	373331	15700	24466, 33232, 41998, 50764, 59530
6780	RNA pseudouridylate synthase domain containing 3	433535	6935	398921	15701	24467, 33233, 41999, 50765, 59531
6781	rogdi homolog (Drosophila)	322048	6936	322832	15702	24468, 33234, 42000, 50766, 59532
6782	rotatin	255674	6937	255674	15703	24469, 33235, 42001, 50767, 59533
6783	rotatin	437017	6938	399520	15704	24470, 33236, 42002, 50768, 59534
6784	rotatin	454359	6939	402352	15705	24471, 33237, 42003, 50769, 59535
6785	RPA interacting protein	327154	6940	315069	15706	24472, 33238, 42004, 50770, 59536
6786	RPA interacting protein	381208	6941	370605	15707	24473, 33239, 42005, 50771, 59537
6787	RPA interacting protein	381209	6942	370606	15708	24474, 33240, 42006, 50772, 59538
6788	RPA interacting protein	405578	6943	385814	15709	24475, 33241, 42007, 50773, 59539
6789	RPA interacting protein	536255	6944	439939	15710	24476, 33242, 42008, 50774,

						59540
6790	RPA interacting protein	539417	6945	446453	15711	24477, 33243, 42009, 50775, 59541
6791	RPA interacting protein	540734	6946	445229	15712	24478, 33244, 42010, 50776, 59542
6792	RUN and FYVE domain containing 2	265865	6947	265865	15713	24479, 33245, 42011, 50777, 59543
6793	RUN and FYVE domain containing 2	342616	6948	341727	15714	24480, 33246, 42012, 50778, 59544
6794	RUN and FYVE domain containing 2	388768	6949	373420	15715	24481, 33247, 42013, 50779, 59545
6795	RUN and FYVE domain containing 2	399200	6950	382151	15716	24482, 33248, 42014, 50780, 59546
6796	RUN and FYVE domain containing 2	454950	6951	404986	15717	24483, 33249, 42015, 50781, 59547
6797	RUN and FYVE domain containing 3	226328	6952	226328	15718	24484, 33250, 42016, 50782, 59548
6798	RUN and FYVE domain containing 3	417478	6953	399771	15719	24485, 33251, 42017, 50783, 59549
6799	RUN and FYVE domain containing 3	514898	6954	426165	15720	24486, 33252, 42018, 50784, 59550
6800	RUN and FYVE domain containing 3	536664	6955	443652	15721	24487, 33253, 42019, 50785, 59551
6801	RUN and FYVE domain containing 3	381006	6956	370394	15722	24488, 33254, 42020, 50786, 59552
6802	RUN and FYVE domain containing 4	344321	6957	345900	15723	24489, 33255, 42021, 50787, 59553
6803	RUN and FYVE domain containing 4	374155	6958	363270	15724	24490, 33256, 42022, 50788, 59554
6804	RUN and FYVE domain containing 4	441828	6959	388839	15725	24491, 33257, 42023, 50789, 59555
6805	RUN domain containing 1	361677	6960	354622	15726	24492, 33258, 42024, 50790, 59556
6806	RUN domain containing 3B	338056	6961	337732	15727	24493, 33259,

						42025, 50791, 59557
6807	RUN domain containing 3B	394654	6962	378149	15728	24494, 33260, 42026, 50792, 59558
6808	RUN domain containing 3B	493037	6963	420394	15729	24495, 33261, 42027, 50793, 59559
6809	RWD domain containing 1	368590	6964	429070	15730	24496, 33262, 42028, 50794, 59560
6810	RWD domain containing 1	392526	6965	376311	15731	24497, 33263, 42029, 50795, 59561
6811	RWD domain containing 1	466444	6966	420357	15732	24498, 33264, 42030, 50796, 59562
6812	RWD domain containing 1	468204	6967	428704	15733	24499, 33265, 42031, 50797, 59563
6813	RWD domain containing 1	487832	6968	428778	15734	24500, 33266, 42032, 50798, 59564
6814	RWD domain containing 1	518117	6969	429942	15735	24501, 33267, 42033, 50799, 59565
6815	RWD domain containing 2A	369724	6970	358739	15736	24502, 33268, 42034, 50800, 59566
6816	RWD domain containing 2A	539997	6971	442731	15737	24503, 33269, 42035, 50801, 59567
6817	RWD domain containing 2B	493196	6972	418693	15738	24504, 33270, 42036, 50802, 59568
6818	RWD domain containing 4	326397	6973	388920	15739	24505, 33271, 42037, 50803, 59569
6819	RWD domain containing 4	327570	6974	332177	15740	24506, 33272, 42038, 50804, 59570
6820	S1 RNA binding domain 1	263736	6975	263736	15741	24507, 33273, 42039, 50805, 59571
6821	S1 RNA binding domain 1	535761	6976	441272	15742	24508, 33274, 42040, 50806, 59572
6822	S100 calcium binding protein A7-like 2	368724	6977	357713	15743	24509, 33275, 42041, 50807, 59573

6823	S100 calcium binding protein A7-like 2	368725	6978	357714	15744	24510, 33276, 42042, 50808, 59574
6824	S100 calcium binding protein A7-like 2	453814	6979	405610	15745	24511, 33277, 42043, 50809, 59575
6825	sarcoma antigen 1	324447	6980	323191	15746	24512, 33278, 42044, 50810, 59576
6826	sarcoma antigen 1	370709	6981	359743	15747	24513, 33279, 42045, 50811, 59577
6827	sarcoma antigen 1	535938	6982	445959	15748	24514, 33280, 42046, 50812, 59578
6828	sarcoma antigen 1	537770	6983	438276	15749	24515, 33281, 42047, 50813, 59579
6829	sarcoma antigen 1	601197	6984	473003	15750	24516, 33282, 42048, 50814, 59580
6830	Sarcoma antigen NY-SAR-79	400396	6985	383246	15751	24517, 33283, 42049, 50815, 59581
6831	SCAN domain containing 3	508341	6986	420877	15752	24518, 33284, 42050, 50816, 59582
6832	schlafen family member 12	304905	6987	302077	15753	24519, 33285, 42051, 50817, 59583
6833	schlafen family member 12	394562	6988	378063	15754	24520, 33286, 42052, 50818, 59584
6834	schlafen family member 12	428476	6989	407689	15755	24521, 33287, 42053, 50819, 59585
6835	schlafen family member 12	445092	6990	404175	15756	24522, 33288, 42054, 50820, 59586
6836	schlafen family member 12	447040	6991	398315	15757	24523, 33289, 42055, 50821, 59587
6837	schlafen family member 12	452764	6992	394903	15758	24524, 33290, 42056, 50822, 59588
6838	schlafen family member 12-like	361112	6993	354412	15759	24525, 33291, 42057, 50823, 59589
6839	schlafen family member 12-like	449046	6994	389348	15760	24526, 33292, 42058, 50824,

						59590
6840	schlafen family member 13	285013	6995	285013	15761	24527, 33293, 42059, 50825, 59591
6841	schlafen family member 13	360502	6996	353692	15762	24528, 33294, 42060, 50826, 59592
6842	schlafen family member 13	524511	6997	433181	15763	24529, 33295, 42061, 50827, 59593
6843	schlafen family member 13	526861	6998	434439	15764	24530, 33296, 42062, 50828, 59594
6844	schlafen family member 13	534689	6999	435442	15765	24531, 33297, 42063, 50829, 59595
6845	schlafen family member 13	542635	7000	444016	15766	24532, 33298, 42064, 50830, 59596
6846	schlafen family member 14	415846	7001	391101	15767	24533, 33299, 42065, 50831, 59597
6847	schlafen family member 5	299977	7002	299977	15768	24534, 33300, 42066, 50832, 59598
6848	schlafen family member 5	542451	7003	440537	15769	24535, 33301, 42067, 50833, 59599
6849	schlafen-like 1	302946	7004	304401	15770	24536, 33302, 42068, 50834, 59600
6850	schlafen-like 1	359345	7005	352299	15771	24537, 33303, 42069, 50835, 59601
6851	schlafen-like 1	372611	7006	361694	15772	24538, 33304, 42070, 50836, 59602
6852	schlafen-like 1	372613	7007	361696	15773	24539, 33305, 42071, 50837, 59603
6853	schlafen-like 1	397197	7008	380381	15774	24540, 33306, 42072, 50838, 59604
6854	schlafen-like 1	439569	7009	398938	15775	24541, 33307, 42073, 50839, 59605
6855	sec1 family domain containing 2	388940	7010	373592	15776	24542, 33308, 42074, 50840, 59606
6856	sec1 family domain	401642	7011	384182	15777	24543, 33309,

	containing 2					42075, 50841, 59607
6857	SEC24 family, member C (S. cerevisiae)	546025	7012	446333	15778	24544, 33310, 42076, 50842, 59608
6858	secernin 2	290216	7013	290216	15779	24545, 33311, 42077, 50843, 59609
6859	secernin 2	407215	7014	383935	15780	24546, 33312, 42078, 50844, 59610
6860	secernin 3	272732	7015	272732	15781	24547, 33313, 42079, 50845, 59611
6861	secernin 3	424069	7016	402086	15782	24548, 33314, 42080, 50846, 59612
6862	secernin 3	427038	7017	408376	15783	24549, 33315, 42081, 50847, 59613
6863	secernin 3	435964	7018	394024	15784	24550, 33316, 42082, 50848, 59614
6864	secernin 3	458563	7019	396884	15785	24551, 33317, 42083, 50849, 59615
6865	secernin 3	548031	7020	446727	15786	24552, 33318, 42084, 50850, 59616
6866	secernin 3	409673	7021	387142	15787	24553, 33319, 42085, 50851, 59617
6867	SECIS binding protein 2-like	261847	7022	261847	15788	24554, 33320, 42086, 50852, 59618
6868	SECIS binding protein 2-like	559471	7023	453854	15789	24555, 33321, 42087, 50853, 59619
6869	secretoglobin family 1C member 1-like precursor	595228	7024	471646	15790	24556, 33322, 42088, 50854, 59620
6870	seizure threshold 2 homolog (mouse)	310739	7025	312234	15791	24557, 33323, 42089, 50855, 59621
6871	seizure threshold 2 homolog (mouse)	357658	7026	361525	15792	24558, 33324, 42090, 50856, 59622
6872	seizure threshold 2 homolog (mouse)	372442	7027	361519	15793	24559, 33325, 42091, 50857, 59623

6873	seizure threshold 2 homolog (mouse)	372450	7028	361528	15794	24560, 33326, 42092, 50858, 59624
6874	seizure threshold 2 homolog (mouse)	562955	7029	457168	15795	24561, 33327, 42093, 50859, 59625
6875	Sel1 repeat containing 1	371538	7030	360593	15796	24562, 33328, 42094, 50860, 59626
6876	Selenoprotein K	495461	7031	418813	15797	24563, 33329, 42095, 50861, 59627
6877	Selenoprotein K	541726	7032	443164	15798	24564, 33330, 42096, 50862, 59628
6878	Selenoprotein M	400299	7033	383155	15799	24565, 33331, 42097, 50863, 59629
6879	Selenoprotein M	402395	7034	384564	15800	24566, 33332, 42098, 50864, 59630
6880	Selenoprotein O	380903	7035	370288	15801	24567, 33333, 42099, 50865, 59631
6881	Selenoprotein T	471696	7036	418910	15802	24568, 33334, 42100, 50866, 59632
6882	selenoprotein V	335426	7037	333956	15803	24569, 33335, 42101, 50867, 59633
6883	selenoprotein V	423711	7038	412508	15804	24570, 33336, 42102, 50868, 59634
6884	sema domain immunoglobulin domain (Ig) short basic domain secreted (semaphorin) 3B	575064	7039	461497	15805	24571, 33337, 42103, 50869, 59635
6885	sentan, cilia apical structure protein	343837	7040	341442	15806	24572, 33338, 42104, 50870, 59636
6886	septin 7-like	239730	7041	239730	15807	24573, 33339, 42105, 50871, 59637
6887	septin 7-like	328105	7042	363679	15808	24574, 33340, 42106, 50872, 59638
6888	septin 9	571241	7043	460993	15809	24575, 33341, 42107, 50873, 59639
6889	septin 9	574362	7044	459494	15810	24576, 33342,

						42108, 50874, 59640
6890	septin 9	575088	7045	458668	15811	24577, 33343, 42109, 50875, 59641
6891	septin 9	576977	7046	460394	15812	24578, 33344, 42110, 50876, 59642
6892	serine incorporator 2	564235	7047	455505	15813	24579, 33345, 42111, 50877, 59643
6893	serine peptidase inhibitor, Kazal type 8 (putative)	434006	7048	407497	15814	24580, 33346, 42112, 50878, 59644
6894	serine/arginine repetitive matrix 3	326382	7049	325298	15815	24581, 33347, 42113, 50879, 59645
6895	serine/arginine repetitive matrix 3	388802	7050	373454	15816	24582, 33348, 42114, 50880, 59646
6896	serine/arginine repetitive matrix 3	571189	7051	460576	15817	24583, 33349, 42115, 50881, 59647
6897	serine/arginine repetitive matrix 3	574979	7052	458336	15818	24584, 33350, 42116, 50882, 59648
6898	serine/arginine repetitive matrix 5	417606	7053	414512	15819	24585, 33351, 42117, 50883, 59649
6899	serine/arginine repetitive matrix 5	526798	7054	432514	15820	24586, 33352, 42118, 50884, 59650
6900	serine/threonine kinase 32A	397936	7055	381030	15821	24587, 33353, 42119, 50885, 59651
6901	serine/threonine kinase 32A	398521	7056	381533	15822	24588, 33354, 42120, 50886, 59652
6902	serine/threonine kinase 32A	541094	7057	443156	15823	24589, 33355, 42121, 50887, 59653
6903	serine/threonine kinase 32B	282908	7058	282908	15824	24590, 33356, 42122, 50888, 59654
6904	serine/threonine kinase 32B	510398	7059	420984	15825	24591, 33357, 42123, 50889, 59655
6905	serine/threonine kinase 32C	298630	7060	298630	15826	24592, 33358, 42124, 50890, 59656

6906	serine/threonine kinase 32C	368619	7061	357608	15827	24593, 33359, 42125, 50891, 59657
6907	serine/threonine kinase 32C	368620	7062	357609	15828	24594, 33360, 42126, 50892, 59658
6908	serine/threonine kinase 32C	368622	7063	357611	15829	24595, 33361, 42127, 50893, 59659
6909	serine/threonine kinase 32C	368625	7064	357614	15830	24596, 33362, 42128, 50894, 59660
6910	serine/threonine kinase 32C	456004	7065	389112	15831	24597, 33363, 42129, 50895, 59661
6911	serine/threonine/tyrosine interacting-like 1	248600	7066	248600	15832	24598, 33364, 42130, 50896, 59662
6912	serine/threonine/tyrosine interacting-like 1	340062	7067	343383	15833	24599, 33365, 42131, 50897, 59663
6913	serine/threonine/tyrosine interacting-like 1	359697	7068	352726	15834	24600, 33366, 42132, 50898, 59664
6914	serine/threonine/tyrosine interacting-like 1	360591	7069	353798	15835	24601, 33367, 42133, 50899, 59665
6915	serine/threonine/tyrosine interacting-like 1	404050	7070	385904	15836	24602, 33368, 42134, 50900, 59666
6916	serine/threonine/tyrosine interacting-like 1	431581	7071	392221	15837	24603, 33369, 42135, 50901, 59667
6917	serine/threonine/tyrosine interacting-like 1	574630	7072	460994	15838	24604, 33370, 42136, 50902, 59668
6918	Serine/threonine-protein kinase NIM1	326035	7073	313572	15839	24605, 33371, 42137, 50903, 59669
6919	Serine/threonine-protein kinase NIM1	512796	7074	420849	15840	24606, 33372, 42138, 50904, 59670
6920	serpin peptidase inhibitor, clade B (ovalbumin), member 1	380739	7075	370115	15841	24607, 33373, 42139, 50905, 59671, 61544, 61602
6921	serpin peptidase inhibitor, clade B (ovalbumin), member 1	537185	7076	444543	15842	24608, 33374, 42140, 50906, 59672, 61545, 61603

6922	serpin peptidase inhibitor, clade B (ovalbumin), member 1	542771	7077	446467	15843	24609, 33375, 42141, 50907, 59673, 61546, 61604
6923	serpin peptidase inhibitor, clade B (ovalbumin), member 11 (gene/pseudogene)	536691	7078	441708	15844	24610, 33376, 42142, 50908, 59674
6924	serpin peptidase inhibitor, clade B (ovalbumin), member 11 (gene/pseudogene)	538847	7079	440795	15845	24611, 33377, 42143, 50909, 59675
6925	serpin peptidase inhibitor, clade B (ovalbumin), member 11 (gene/pseudogene)	544088	7080	441497	15846	24612, 33378, 42144, 50910, 59676
6926	SERTA domain containing 4	367012	7081	355979	15847	24613, 33379, 42145, 50911, 59677
6927	SET and MYND domain containing 3	391836	7082	375712	15848	24614, 33380, 42146, 50912, 59678
6928	SET and MYND domain containing 3	453676	7083	408122	15849	24615, 33381, 42147, 50913, 59679
6929	SET and MYND domain containing 3	455277	7084	394281	15850	24616, 33382, 42148, 50914, 59680
6930	SET and MYND domain containing 3	490107	7085	419184	15851	24617, 33383, 42149, 50915, 59681
6931	SET and MYND domain containing 3	541742	7086	444184	15852	24618, 33384, 42150, 50916, 59682
6932	SET and MYND domain containing 3	544586	7087	443400	15853	24619, 33385, 42151, 50917, 59683
6933	SET and MYND domain containing 4	305513	7088	304360	15854	24620, 33386, 42152, 50918, 59684
6934	SET domain containing (lysine methyltransferase) 8	330479	7089	332995	15855	24621, 33387, 42153, 50919, 59685
6935	SET domain containing (lysine methyltransferase) 8	402868	7090	384629	15856	24622, 33388, 42154, 50920, 59686
6936	SET domain containing 4	332131	7091	329189	15857	24623, 33389, 42155, 50921, 59687
6937	SET domain containing 4	399201	7092	382152	15858	24624, 33390,

						42156, 50922, 59688
6938	SET domain containing 4	399205	7093	382156	15859	24625, 33391, 42157, 50923, 59689
6939	SET domain containing 4	399207	7094	382158	15860	24626, 33392, 42158, 50924, 59690
6940	SET domain containing 4	399208	7095	382159	15861	24627, 33393, 42159, 50925, 59691
6941	SET domain containing 4	399212	7096	382161	15862	24628, 33394, 42160, 50926, 59692
6942	SET domain containing 4	399215	7097	382163	15863	24629, 33395, 42161, 50927, 59693
6943	SET domain containing 4	424303	7098	399998	15864	24630, 33396, 42162, 50928, 59694
6944	SET domain containing 4	429161	7099	396837	15865	24631, 33397, 42163, 50929, 59695
6945	SET domain containing 4	442559	7100	394822	15866	24632, 33398, 42164, 50930, 59696
6946	SET domain containing 4	443703	7101	392463	15867	24633, 33399, 42165, 50931, 59697
6947	SET domain containing 4	446166	7102	413318	15868	24634, 33400, 42166, 50932, 59698
6948	SET domain containing 5	302463	7103	302028	15869	24635, 33401, 42167, 50933, 59699
6949	SET domain containing 5	402198	7104	385852	15870	24636, 33402, 42168, 50934, 59700
6950	SET domain containing 5	402466	7105	384429	15871	24637, 33403, 42169, 50935, 59701
6951	SET domain containing 5	406341	7106	383939	15872	24638, 33404, 42170, 50936, 59702
6952	SET domain containing 5	450326	7107	413786	15873	24639, 33405, 42171, 50937, 59703
6953	SH2 domain containing 3A	245908	7108	245908	15874	24640, 33406, 42172, 50938, 59704

6954	SH2 domain containing 3A	437152	7109	393303	15875	24641, 33407, 42173, 50939, 59705
6955	SH2 domain containing 4B	313455	7110	314242	15876	24642, 33408, 42174, 50940, 59706
6956	SH2 domain containing 4B	339284	7111	345295	15877	24643, 33409, 42175, 50941, 59707
6957	SH2 domain containing 4B	372147	7112	361220	15878	24644, 33410, 42176, 50942, 59708
6958	SH2 domain containing 4B	470604	7113	417953	15879	24645, 33411, 42177, 50943, 59709
6959	SH2 domain containing 5	375031	7114	364171	15880	24646, 33412, 42178, 50944, 59710
6960	SH2 domain containing 5	444387	7115	406026	15881	24647, 33413, 42179, 50945, 59711
6961	SH2 domain containing 5	517430	7116	428656	15882	24648, 33414, 42180, 50946, 59712
6962	SH2 domain containing 5	518294	7117	428153	15883	24649, 33415, 42181, 50947, 59713
6963	SH2 domain containing 5	519434	7118	430115	15884	24650, 33416, 42182, 50948, 59714
6964	SH2 domain containing 6	340326	7119	341867	15885	24651, 33417, 42183, 50949, 59715
6965	SH2 domain containing 6	389938	7120	374588	15886	24652, 33418, 42184, 50950, 59716
6966	SH2B adaptor protein 2	306803	7121	304701	15887	24653, 33419, 42185, 50951, 59717
6967	SH2B adaptor protein 2	432527	7122	415306	15888	24654, 33420, 42186, 50952, 59718
6968	SH2B adaptor protein 2	444095	7123	401883	15889	24655, 33421, 42187, 50953, 59719
6969	SH2B adaptor protein 2	536178	7124	440273	15890	24656, 33422, 42188, 50954, 59720
6970	SH2B adaptor protein 2	563740	7125	455175	15891	24657, 33423, 42189, 50955,

						59721
6971	SH3 and cysteine rich domain 2	333461	7126	327509	15892	24658, 33424, 42190, 50956, 59722
6972	SH3 and cysteine rich domain 3	332782	7127	329200	15893	24659, 33425, 42191, 50957, 59723
6973	SH3 and cysteine rich domain 3	553489	7128	452299	15894	24660, 33426, 42192, 50958, 59724
6974	SH3 and cysteine rich domain 3	554578	7129	452068	15895	24661, 33427, 42193, 50959, 59725
6975	SH3 and multiple ankyrin repeat domains protein 2 isoform 1	601391	7130	471204	15896	24662, 33428, 42194, 50960, 59726
6976	SH3 domain and tetratricopeptide repeats 1	245105	7131	245105	15897	24663, 33429, 42195, 50961, 59727
6977	SH3 domain and tetratricopeptide repeats 1	382516	7132	371956	15898	24664, 33430, 42196, 50962, 59728
6978	SH3 domain and tetratricopeptide repeats 1	457650	7133	390311	15899	24665, 33431, 42197, 50963, 59729
6979	SH3 domain and tetratricopeptide repeats 1	535265	7134	443971	15900	24666, 33432, 42198, 50964, 59730
6980	SH3 domain and tetratricopeptide repeats 1	539824	7135	441045	15901	24667, 33433, 42199, 50965, 59731
6981	SH3 domain containing 21	312808	7136	321936	15902	24668, 33434, 42200, 50966, 59732
6982	SH3 domain containing 21	426732	7137	408613	15903	24669, 33435, 42201, 50967, 59733
6983	SH3 domain containing 21	453908	7138	403476	15904	24670, 33436, 42202, 50968, 59734
6984	SH3 domain containing 21	505871	7139	421294	15905	24671, 33437, 42203, 50969, 59735
6985	SH3 domain containing ring finger 3	309415	7140	309186	15906	24672, 33438, 42204, 50970, 59736
6986	SH3 domain containing ring finger 3	418513	7141	414997	15907	24673, 33439, 42205, 50971, 59737
6987	SH3 domain containing	444352	7142	390685	15908	24674, 33440,

	ring finger 3					42206, 50972, 59738
6988	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	356150	7143	348471	15909	24675, 33441, 42207, 50973, 59739
6989	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	403657	7144	385668	15910	24676, 33442, 42208, 50974, 59740
6990	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	403658	7145	383928	15911	24677, 33443, 42209, 50975, 59741
6991	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	403712	7146	384276	15912	24678, 33444, 42210, 50976, 59742
6992	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	405430	7147	384269	15913	24679, 33445, 42211, 50977, 59743
6993	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	415006	7148	404143	15914	24680, 33446, 42212, 50978, 59744
6994	SH3 domain containing, Ysc84-like 1 (S. cerevisiae)	415368	7149	410235	15915	24681, 33447, 42213, 50979, 59745
6995	SH3-binding domain kinase family member 2	413299	7150	389015	15916	24682, 33448, 42214, 50980, 59746
6996	SH3-binding domain kinase family, member 2	344158	7151	345044	15917	24683, 33449, 42215, 50981, 59747
6997	SH3-binding domain protein 5-like	366472	7152	355428	15918	24684, 33450, 42216, 50982, 59748
6998	SH3-binding domain protein 5-like	411742	7153	412203	15919	24685, 33451, 42217, 50983, 59749
6999	SHC SH2-domain binding protein 1-like	287709	7154	287709	15920	24686, 33452, 42218, 50984, 59750
7000	SHC SH2-domain binding protein 1-like	367547	7155	356518	15921	24687, 33453, 42219, 50985, 59751
7001	SHC SH2-domain binding protein 1-like	423786	7156	397308	15922	24688, 33454, 42220, 50986, 59752
7002	shisa homolog 7 (Xenopus laevis)	376325	7157	365503	15923	24689, 33455, 42221, 50987, 59753
7003	short chain dehydrogenase/reductase family 39U, member 1	336353	7158	336854	15924	24690, 33456, 42222, 50988, 59754

7004	short chain dehydrogenase/reductase family 39U, member 1	399390	7159	382322	15925	24691, 33457, 42223, 50989, 59755
7005	short chain dehydrogenase/reductase family 39U, member 1	399395	7160	382327	15926	24692, 33458, 42224, 50990, 59756
7006	short chain dehydrogenase/reductase family 42E, member 2	330898	7161	330812	15927	24693, 33459, 42225, 50991, 59757
7007	shroom family member 4	600171	7162	472407	15928	24694, 33460, 42226, 50992, 59758
7008	sialic acid binding Ig-like lectin 16 (gene/pseudogene)	417280	7163	396157	15929	24695, 33461, 42227, 50993, 59759
7009	sialic acid binding Ig-like lectin 16 (gene/pseudogene)	456956	7164	416930	15930	24696, 33462, 42228, 50994, 59760
7010	Signal peptide peptidase-like 2B	382189	7165	371624	15931	24697, 33463, 42229, 50995, 59761
7011	Signal peptide peptidase-like 2B	452401	7166	404539	15932	24698, 33464, 42230, 50996, 59762
7012	signal sequence receptor delta	594475	7167	471489	15933	24699, 33465, 42231, 50997, 59763
7013	signal sequence receptor delta	599490	7168	470405	15934	24700, 33466, 42232, 50998, 59764
7014	signal sequence receptor delta	599757	7169	473104	15935	24701, 33467, 42233, 50999, 59765
7015	signal-induced proliferation-associated 1 like 3	222345	7170	222345	15936	24702, 33468, 42234, 51000, 59766
7016	single-stranded DNA binding protein 1 mitochondrial	570667	7171	460028	15937	24703, 33469, 42235, 51001, 59767
7017	single-stranded DNA binding protein 1 mitochondrial	571430	7172	459367	15938	24704, 33470, 42236, 51002, 59768
7018	single-stranded DNA binding protein 1 mitochondrial	576311	7173	460161	15939	24705, 33471, 42237, 51003, 59769
7019	single-stranded DNA binding protein 1 mitochondrial	576834	7174	459208	15940	24706, 33472, 42238, 51004, 59770
7020	SLAIN motif family, member 1	314070	7175	314443	15941	24707, 33473, 42239, 51005,

						59771
7021	SLAIN motif family, member 1	351546	7176	314546	15942	24708, 33474, 42240, 51006, 59772
7022	SLAIN motif family, member 1	358679	7177	351507	15943	24709, 33475, 42241, 51007, 59773
7023	SLAIN motif family, member 1	377236	7178	366444	15944	24710, 33476, 42242, 51008, 59774
7024	SLAIN motif family, member 1	389459	7179	374110	15945	24711, 33477, 42243, 51009, 59775
7025	SLAIN motif family, member 1	418532	7180	400921	15946	24712, 33478, 42244, 51010, 59776
7026	SLAIN motif family, member 1	441784	7181	403056	15947	24713, 33479, 42245, 51011, 59777
7027	SLAIN motif family, member 1	466548	7182	419730	15948	24714, 33480, 42246, 51012, 59778
7028	SLAIN motif family, member 1	474663	7183	419436	15949	24715, 33481, 42247, 51013, 59779
7029	SLAIN motif family, member 1	481614	7184	418053	15950	24716, 33482, 42248, 51014, 59780
7030	SLAIN motif family, member 1	488699	7185	418707	15951	24717, 33483, 42249, 51015, 59781
7031	SLAIN motif family, member 1	496045	7186	420619	15952	24718, 33484, 42250, 51016, 59782
7032	SLIT and NTRK-like family member 2	596854	7187	472699	15953	24719, 33485, 42251, 51017, 59783
7033	SLIT and NTRK-like family member 2	597957	7188	468887	15954	24720, 33486, 42252, 51018, 59784
7034	SLIT and NTRK-like family member 2	597981	7189	469687	15955	24721, 33487, 42253, 51019, 59785
7035	small EDRK-rich factor 1B (centromeric)	380750	7190	370126	15956	24722, 33488, 42254, 51020, 59786
7036	small EDRK-rich factor 1B (centromeric)	380751	7191	370127	15957	24723, 33489, 42255, 51021, 59787
7037	small glutamine-rich	381007	7192	370395	15958	24724, 33490,

	tetratricopeptide repeat (TPR)-containing, beta					42256, 51022, 59788
7038	small glutamine-rich tetratricopeptide repeat (TPR)-containing, beta	506816	7193	421447	15959	24725, 33491, 42257, 51023, 59789
7039	small integral membrane protein 1	444870	7194	457386	15960	24726, 33492, 42258, 51024, 59790
7040	small integral membrane protein 6	579469	7195	463361	15961	24727, 33493, 42259, 51025, 59791
7041	small nuclear ribonucleoprotein polypeptide E pseudogene 2	338402	7196	356177	15962	24728, 33494, 42260, 51026, 59792
7042	small nucleolar RNA host gene 15 (non-protein coding)	438705	7197	399428	15963	24729, 33495, 42261, 51027, 59793
7043	Smith-Magenis syndrome chromosome region, candidate 5 (non-protein coding)	543475	7198	438627	15964	24730, 33496, 42262, 51028, 59794
7044	Smith-Magenis syndrome chromosome region, candidate 8	406438	7199	385025	15965	24731, 33497, 42263, 51029, 59795
7045	smoothelin-like 2	338859	7200	345143	15966	24732, 33498, 42264, 51030, 59796
7046	smoothelin-like 2	389313	7201	373964	15967	24733, 33499, 42265, 51031, 59797
7047	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae)	314523	7202	400886	15968	24734, 33500, 42266, 51032, 59798
7048	SMT3 suppressor of mif two 3 homolog 2 (S. cerevisiae)	420826	7203	405965	15969	24735, 33501, 42267, 51033, 59799
7049	SMYD family member 5	389501	7204	374152	15970	24736, 33502, 42268, 51034, 59800
7050	SNRPN upstream reading frame-like	309296	7205	311181	15971	24737, 33503, 42269, 51035, 59801
7051	solute carrier family 12 (potassium/chloride transporters), member 8	314584	7206	323632	15972	24738, 33504, 42270, 51036, 59802
7052	solute carrier family 12 (potassium/chloride transporters), member 8	423114	7207	404243	15973	24739, 33505, 42271, 51037, 59803
7053	solute carrier family 12 (potassium/chloride	430155	7208	415713	15974	24740, 33506, 42272, 51038,

	transporters), member 8					59804
7054	solute carrier family 15, member 4	544112	7209	439946	15975	24741, 33507, 42273, 51039, 59805
7055	solute carrier family 16 member 6 (monocarboxylic acid transporter 7)	571465	7210	458703	15976	24742, 33508, 42274, 51040, 59806
7056	solute carrier family 22 (organic cation transporter), member 18 antisense	455942	7211	434027	15977	24743, 33509, 42275, 51041, 59807
7057	solute carrier family 22 (organic cation transporter), member 18 antisense	526203	7212	435592	15978	24744, 33510, 42276, 51042, 59808
7058	solute carrier family 22 (organic cation transporter), member 18 antisense	533594	7213	433282	15979	24745, 33511, 42277, 51043, 59809
7059	solute carrier family 25 (S-adenosylmethionine carrier) member 26	566782	7214	456546	15980	24746, 33512, 42278, 51044, 59810
7060	solute carrier family 35, member G4	424015	7215	408366	15981	24747, 33513, 42279, 51045, 59811
7061	solute carrier family 35, member G6	412468	7216	396523	15982	24748, 33514, 42280, 51046, 59812
7062	solute carrier family 38, member 8	299709	7217	299709	15983	24749, 33515, 42281, 51047, 59813
7063	solute carrier family 45, member 4	24061	7218	24061	15984	24750, 33516, 42282, 51048, 59814, 61547, 61605
7064	solute carrier family 45, member 4	433583	7219	400799	15985	24751, 33517, 42283, 51049, 59815
7065	solute carrier family 45, member 4	517878	7220	428137	15986	24752, 33518, 42284, 51050, 59816
7066	solute carrier family 45, member 4	519067	7221	429059	15987	24753, 33519, 42285, 51051, 59817
7067	solute carrier family 52 riboflavin transporter member 2	562273	7222	456755	15988	24754, 33520, 42286, 51052, 59818
7068	solute carrier family 52 riboflavin transporter member 2	563713	7223	457799	15989	24755, 33521, 42287, 51053, 59819
7069	solute carrier family 52 riboflavin transporter member 2	567429	7224	455251	15990	24756, 33522, 42288, 51054, 59820

7070	solute carrier organic anion transporter family, member 1B7 (non-functional)	421593	7225	394168	15991	24757, 33523, 42289, 51055, 59821
7071	solute carrier organic anion transporter family, member 1B7 (non-functional)	554957	7226	452013	15992	24758, 33524, 42290, 51056, 59822
7072	sorting nexin 11	359238	7227	352175	15993	24759, 33525, 42291, 51057, 59823
7073	sorting nexin 11	393405	7228	377059	15994	24760, 33526, 42292, 51058, 59824
7074	sorting nexin 11	439357	7229	407369	15995	24761, 33527, 42293, 51059, 59825
7075	sorting nexin 11	452859	7230	396790	15996	24762, 33528, 42294, 51060, 59826
7076	sorting nexin 12	276105	7231	276105	15997	24763, 33529, 42295, 51061, 59827
7077	sorting nexin 12	374274	7232	363392	15998	24764, 33530, 42296, 51062, 59828
7078	sorting nexin 29	219090	7233	219090	15999	24765, 33531, 42297, 51063, 59829
7079	sorting nexin 29	268271	7234	268271	16000	24766, 33532, 42298, 51064, 59830
7080	sorting nexin 29	306030	7235	306940	16001	24767, 33533, 42299, 51065, 59831
7081	sorting nexin 29	323433	7236	322226	16002	24768, 33534, 42300, 51066, 59832
7082	sorting nexin 29 pseudogene 2	356328	7237	348682	16003	24769, 33535, 42301, 51067, 59833
7083	sorting nexin 29 pseudogene 2	398878	7238	381853	16004	24770, 33536, 42302, 51068, 59834
7084	sorting nexin 29 pseudogene 2	507381	7239	425679	16005	24771, 33537, 42303, 51069, 59835
7085	sorting nexin 29 pseudogene 2	509141	7240	424721	16006	24772, 33538, 42304, 51070, 59836
7086	sorting nexin 31	311812	7241	312368	16007	24773, 33539, 42305, 51071,

						59837
7087	sorting nexin 31	428383	7242	405024	16008	24774, 33540, 42306, 51072, 59838
7088	sorting nexin 32	308342	7243	310620	16009	24775, 33541, 42307, 51073, 59839
7089	sorting nexin 32	536740	7244	440891	16010	24776, 33542, 42308, 51074, 59840
7090	sorting nexin 33	308527	7245	311427	16011	24777, 33543, 42309, 51075, 59841
7091	SPANX family member B1	598204	7246	469053	16012	24778, 33544, 42310, 51076, 59842
7092	SPANX family member D	597815	7247	472247	16013	24779, 33545, 42311, 51077, 59843
7093	SPANX family, member N1	370493	7248	359524	16014	24780, 33546, 42312, 51078, 59844
7094	SPANX family, member N2	370498	7249	359529	16015	24781, 33547, 42313, 51079, 59845
7095	SPANX family, member N3	370503	7250	359534	16016	24782, 33548, 42314, 51080, 59846
7096	SPANX family, member N4	446864	7251	405210	16017	24783, 33549, 42315, 51081, 59847
7097	SPANX family, member N5	375511	7252	364661	16018	24784, 33550, 42316, 51082, 59848
7098	speedy homolog E1 (Xenopus laevis)	258704	7253	258704	16019	24785, 33551, 42317, 51083, 59849
7099	speedy homolog E2 (Xenopus laevis)	341656	7254	342628	16020	24786, 33552, 42318, 51084, 59850
7100	speedy homolog E2 (Xenopus laevis)	432940	7255	395689	16021	24787, 33553, 42319, 51085, 59851
7101	speedy homolog E2 (Xenopus laevis)	507918	7256	421686	16022	24788, 33554, 42320, 51086, 59852
7102	speedy homolog E3 (Xenopus laevis)	332397	7257	329565	16023	24789, 33555, 42321, 51087, 59853
7103	speedy homolog E3	437326	7258	401147	16024	24790, 33556,

	(Xenopus laevis)					42322, 51088, 59854
7104	speedy homolog E4 (Xenopus laevis)	328794	7259	329522	16025	24791, 33557, 42323, 51089, 59855
7105	speedy homolog E6 (Xenopus laevis)	436228	7260	440393	16026	24792, 33558, 42324, 51090, 59856
7106	speedy homolog E6 (Xenopus laevis)	455020	7261	414338	16027	24793, 33559, 42325, 51091, 59857
7107	speedy homolog E6 (Xenopus laevis)	507450	7262	424058	16028	24794, 33560, 42326, 51092, 59858
7108	sperm flagellar 2	282469	7263	282469	16029	24795, 33561, 42327, 51093, 59859
7109	sperm flagellar 2	303129	7264	303843	16030	24796, 33562, 42328, 51094, 59860
7110	sperm flagellar 2	356031	7265	348314	16031	24797, 33563, 42329, 51095, 59861
7111	spermatogenesis associated 21	335496	7266	335612	16032	24798, 33564, 42330, 51096, 59862
7112	spermatogenesis associated 21	375577	7267	364727	16033	24799, 33565, 42331, 51097, 59863
7113	spermatogenesis associated 21	540400	7268	440046	16034	24800, 33566, 42332, 51098, 59864
7114	spermatogenesis associated 22	268981	7269	268981	16035	24801, 33567, 42333, 51099, 59865
7115	spermatogenesis associated 22	355380	7270	347541	16036	24802, 33568, 42334, 51100, 59866
7116	spermatogenesis associated 22	397168	7271	380354	16037	24803, 33569, 42335, 51101, 59867
7117	spermatogenesis associated 22	541913	7272	441920	16038	24804, 33570, 42336, 51102, 59868
7118	spermatogenesis associated 22	572969	7273	460187	16039	24805, 33571, 42337, 51103, 59869
7119	spermatogenesis associated 22	573128	7274	459580	16040	24806, 33572, 42338, 51104, 59870

7120	spermatogenesis associated 2-like	289805	7275	289805	16041	24807, 33573, 42339, 51105, 59871
7121	spermatogenesis associated 2-like	335360	7276	334006	16042	24808, 33574, 42340, 51106, 59872
7122	spermatogenesis associated 3	355662	7277	347884	16043	24809, 33575, 42341, 51107, 59873
7123	spermatogenesis associated 3	424440	7278	399514	16044	24810, 33576, 42342, 51108, 59874
7124	spermatogenesis associated 3	433428	7279	403804	16045	24811, 33577, 42343, 51109, 59875
7125	spermatogenesis associated 3	452881	7280	388895	16046	24812, 33578, 42344, 51110, 59876
7126	spermatogenesis associated 3	455816	7281	388741	16047	24813, 33579, 42345, 51111, 59877
7127	spermatogenesis associated 3	495639	7282	436378	16048	24814, 33580, 42346, 51112, 59878
7128	spermatogenesis associated 6-like	475086	7283	417063	16049	24815, 33581, 42347, 51113, 59879
7129	spermatogenesis associated, serine-rich 1	288390	7284	424400	16050	24816, 33582, 42348, 51114, 59880
7130	spermatogenesis associated, serine-rich 1	323108	7285	437552	16051	24817, 33583, 42349, 51115, 59881
7131	spermidine/spermine N1-acetyl transferase-like 1	332921	7286	329115	16052	24818, 33584, 42350, 51116, 59882
7132	spermidine/spermine N1-acetyl transferase-like 1	395409	7287	378804	16053	24819, 33585, 42351, 51117, 59883
7133	spermidine/spermine N1-acetyl transferase-like 1	509231	7288	425421	16054	24820, 33586, 42352, 51118, 59884
7134	S-phase response (cyclin related)	366688	7289	355649	16055	24821, 33587, 42353, 51119, 59885
7135	Sphingosine 1-phosphate receptor 2	590320	7290	466933	16056	24822, 33588, 42354, 51120, 59886
7136	Spi-B transcription factor (Spi-1/PU.1 related)	595883	7291	471921	16057	24823, 33589, 42355, 51121,

						59887
7137	spindle and kinetochore associated complex subunit 1	571751	7292	458992	16058	24824, 33590, 42356, 51122, 59888
7138	spindle and kinetochore associated complex subunit 2-like	425592	7293	407425	16059	24825, 33591, 42357, 51123, 59889
7139	spindlin family, member 2A	374906	7294	364041	16060	24826, 33592, 42358, 51124, 59890
7140	spindlin family, member 2A	374908	7295	364043	16061	24827, 33593, 42359, 51125, 59891
7141	spindlin family, member 3	374915	7296	364050	16062	24828, 33594, 42360, 51126, 59892
7142	spindlin family, member 3	374919	7297	364054	16063	24829, 33595, 42361, 51127, 59893
7143	spindlin family, member 4	335144	7298	334163	16064	24830, 33596, 42362, 51128, 59894
7144	spindlin family, member 4	374884	7299	364018	16065	24831, 33597, 42363, 51129, 59895
7145	splA/ryanodine receptor domain and SOCS box containing 2	597925	7300	470303	16066	24832, 33598, 42364, 51130, 59896
7146	splA/ryanodine receptor domain and SOCS box containing 2	598262	7301	469611	16067	24833, 33599, 42365, 51131, 59897
7147	spondin 1 extracellular matrix protein	576479	7302	460236	16068	24834, 33600, 42366, 51132, 59898
7148	SPRY domain containing 3	301463	7303	301463	16069	24835, 33601, 42367, 51133, 59899
7149	SPRY domain containing 5	449290	7304	395086	16070	24836, 33602, 42368, 51134, 59900
7150	SPRY domain containing 7	361840	7305	354774	16071	24837, 33603, 42369, 51135, 59901
7151	SPRY domain containing 7	378195	7306	367437	16072	24838, 33604, 42370, 51136, 59902
7152	SPT2, Suppressor of Ty, domain containing 1 (S. cerevisiae)	333429	7307	331447	16073	24839, 33605, 42371, 51137, 59903
7153	SPT2, Suppressor of Ty,	336349	7308	337991	16074	24840, 33606,

	domain containing 1 (S. cerevisiae)					42372, 51138, 59904
7154	Src homology 2 domain containing E	304760	7309	307369	16075	24841, 33607, 42373, 51139, 59905
7155	Src homology 2 domain containing F	290894	7310	290894	16076	24842, 33608, 42374, 51140, 59906
7156	Src homology 2 domain containing F	318390	7311	315978	16077	24843, 33609, 42375, 51141, 59907
7157	Src homology 2 domain containing F	361989	7312	355004	16078	24844, 33610, 42376, 51142, 59908
7158	Src homology 2 domain containing F	413198	7313	387573	16079	24845, 33611, 42377, 51143, 59909
7159	Src homology 2 domain containing transforming protein D	221852	7314	221852	16080	24846, 33612, 42378, 51144, 59910
7160	Src homology 2 domain containing transforming protein D	543264	7315	446058	16081	24847, 33613, 42379, 51145, 59911
7161	SRC kinase signaling inhibitor 1	264659	7316	264659	16082	24848, 33614, 42380, 51146, 59912
7162	SRC kinase signaling inhibitor 1	398579	7317	381584	16083	24849, 33615, 42381, 51147, 59913
7163	SRC kinase signaling inhibitor 1	542707	7318	445368	16084	24850, 33616, 42382, 51148, 59914
7164	src-related kinase lacking C-terminal regulatory tyrosine and N-terminal myristylation sites	217188	7319	217188	16085	24851, 33617, 42383, 51149, 59915
7165	SREK1-interacting protein 1	513458	7320	427401	16086	24852, 33618, 42384, 51150, 59916
7166	SRSF protein kinase 3	370101	7321	359119	16087	24853, 33619, 42385, 51151, 59917
7167	SRSF protein kinase 3	393786	7322	377376	16088	24854, 33620, 42386, 51152, 59918
7168	ssu-2 homolog (C. elegans)	420394	7323	390328	16089	24855, 33621, 42387, 51153, 59919
7169	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	319914	7324	318445	16090	24856, 33622, 42388, 51154,

						59920, 61548, 61606
7170	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	399640	7325	414073	16091	24857, 33623, 42389, 51155, 59921, 61549, 61607
7171	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	519924	7326	430135	16092	24858, 33624, 42390, 51156, 59922, 61550, 61608
7172	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	521180	7327	428540	16093	24859, 33625, 42391, 51157, 59923, 61551, 61609
7173	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	522652	7328	430515	16094	24860, 33626, 42392, 51158, 59924, 61552, 61610
7174	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	523634	7329	429936	16095	24861, 33627, 42393, 51159, 59925, 61553, 61611
7175	ST3 beta-galactoside alpha-2,3-sialyltransferase 1	523855	7330	427786	16096	24862, 33628, 42394, 51160, 59926, 61554, 61612
7176	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	169298	7331	169298	16097	24863, 33629, 42395, 51161, 59927, 61555, 61613
7177	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	416235	7332	414504	16098	24864, 33630, 42396, 51162, 59928, 61556, 61614
7178	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	417392	7333	407631	16099	24865, 33631, 42397, 51163, 59929, 61557, 61615
7179	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	423451	7334	411518	16100	24866, 33632, 42398, 51164, 59930, 61558, 61616
7180	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	430309	7335	399525	16101	24867, 33633, 42399, 51165, 59931, 61559, 61617
7181	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	438590	7336	416163	16102	24868, 33634, 42400, 51166, 59932, 61560, 61618

7182	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	440338	7337	388928	16103	24869, 33635, 42401, 51167, 59933, 61561, 61619
7183	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	446170	7338	388789	16104	24870, 33636, 42402, 51168, 59934, 61562, 61620
7184	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	448044	7339	389337	16105	24871, 33637, 42403, 51169, 59935, 61563, 61621
7185	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	448408	7340	390793	16106	24872, 33638, 42404, 51170, 59936, 61564, 61622
7186	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	457772	7341	412221	16107	24873, 33639, 42405, 51171, 59937, 61565, 61623
7187	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	458216	7342	400547	16108	24874, 33640, 42406, 51172, 59938, 61566, 61624
7188	StAR-related lipid transfer (START) domain containing 10	334805	7343	335247	16109	24875, 33641, 42407, 51173, 59939
7189	StAR-related lipid transfer (START) domain containing 10	536290	7344	443523	16110	24876, 33642, 42408, 51174, 59940
7190	StAR-related lipid transfer (START) domain containing 10	537947	7345	445657	16111	24877, 33643, 42409, 51175, 59941
7191	StAR-related lipid transfer (START) domain containing 10	540587	7346	440302	16112	24878, 33644, 42410, 51176, 59942
7192	StAR-related lipid transfer (START) domain containing 10	542989	7347	443597	16113	24879, 33645, 42411, 51177, 59943
7193	StAR-related lipid transfer (START) domain containing 10	543304	7348	438792	16114	24880, 33646, 42412, 51178, 59944
7194	StAR-related lipid transfer (START) domain containing 10	546314	7349	445886	16115	24881, 33647, 42413, 51179, 59945
7195	StAR-related lipid transfer (START) domain containing 9	290607	7350	290607	16116	24882, 33648, 42414, 51180, 59946
7196	stathmin-like 4	265770	7351	265770	16117	24883, 33649, 42415, 51181,

						59947
7197	stathmin-like 4	350889	7352	342538	16118	24884, 33650, 42416, 51182, 59948
7198	STE20-related kinase adaptor alpha	582137	7353	462922	16119	24885, 33651, 42417, 51183, 59949
7199	sterile alpha and TIR motif containing 1	3834	7354	3834	16120	24886, 33652, 42418, 51184, 59950, 61567, 61625
7200	sterile alpha and TIR motif containing 1	457710	7355	406738	16121	24887, 33653, 42419, 51185, 59951
7201	sterile alpha motif domain containing 14	330175	7356	329144	16122	24888, 33654, 42420, 51186, 59952
7202	sterile alpha motif domain containing 14	503131	7357	424474	16123	24889, 33655, 42421, 51187, 59953
7203	sterile alpha motif domain containing 14	511964	7358	423479	16124	24890, 33656, 42422, 51188, 59954
7204	sterile alpha motif domain containing 15	216471	7359	216471	16125	24891, 33657, 42423, 51189, 59955
7205	sterile alpha motif domain containing 3	324172	7360	324874	16126	24892, 33658, 42424, 51190, 59956
7206	sterile alpha motif domain containing 3	368134	7361	357116	16127	24893, 33659, 42425, 51191, 59957
7207	sterile alpha motif domain containing 3	437477	7362	391163	16128	24894, 33660, 42426, 51192, 59958
7208	sterile alpha motif domain containing 3	439090	7363	403565	16129	24895, 33661, 42427, 51193, 59959
7209	sterile alpha motif domain containing 3	531544	7364	435875	16130	24896, 33662, 42428, 51194, 59960
7210	sterile alpha motif domain containing 4B	314471	7365	317224	16131	24897, 33663, 42429, 51195, 59961
7211	sterile alpha motif domain containing 4B	429637	7366	387732	16132	24898, 33664, 42430, 51196, 59962
7212	sterile alpha motif domain containing 5	367474	7367	356444	16133	24899, 33665, 42431, 51197, 59963

7213	sterile alpha motif domain containing 7	335556	7368	334668	16134	24900, 33666, 42432, 51198, 59964
7214	sterile alpha motif domain containing 7	428432	7369	391299	16135	24901, 33667, 42433, 51199, 59965
7215	storkhead box 2	308497	7370	311257	16136	24902, 33668, 42434, 51200, 59966
7216	storkhead box 2	438269	7371	390127	16137	24903, 33669, 42435, 51201, 59967
7217	strawberry notch homolog 2 (Drosophila)	250872	7372	250872	16138	24904, 33670, 42436, 51202, 59968
7218	strawberry notch homolog 2 (Drosophila)	361757	7373	354733	16139	24905, 33671, 42437, 51203, 59969
7219	strawberry notch homolog 2 (Drosophila)	438103	7374	400762	16140	24906, 33672, 42438, 51204, 59970
7220	stromal antigen 3-like 4	416602	7375	408597	16141	24907, 33673, 42439, 51205, 59971
7221	stromal antigen 3-like 4	437742	7376	398690	16142	24908, 33674, 42440, 51206, 59972
7222	sulfotransferase family, cytosolic, 1B, member 1	310613	7377	308770	16143	24909, 33675, 42441, 51207, 59973
7223	sulfotransferase family, cytosolic, 1B, member 1	510821	7378	425464	16144	24910, 33676, 42442, 51208, 59974
7224	SUMO/sentrin specific peptidase family member 8	340912	7379	340505	16145	24911, 33677, 42443, 51209, 59975
7225	SUMO/sentrin specific peptidase family member 8	542035	7380	446057	16146	24912, 33678, 42444, 51210, 59976
7226	SUMO/sentrin specific peptidase family member 8	544171	7381	439415	16147	24913, 33679, 42445, 51211, 59977
7227	SUMO/sentrin specific peptidase family member 8	544411	7382	441753	16148	24914, 33680, 42446, 51212, 59978
7228	suppression of tumorigenicity 7 like	343210	7383	345312	16149	24915, 33681, 42447, 51213, 59979
7229	suppression of tumorigenicity 7 like	358039	7384	350734	16150	24916, 33682, 42448, 51214,

						59980
7230	suppression of tumorigenicity 7 like	360743	7385	353972	16151	24917, 33683, 42449, 51215, 59981
7231	suppression of tumorigenicity 7 like	369664	7386	358678	16152	24918, 33684, 42450, 51216, 59982
7232	suppression of tumorigenicity 7 like	369665	7387	358679	16153	24919, 33685, 42451, 51217, 59983
7233	suppression of tumorigenicity 7 like	369666	7388	358680	16154	24920, 33686, 42452, 51218, 59984
7234	suppression of tumorigenicity 7 like	369668	7389	358682	16155	24921, 33687, 42453, 51219, 59985
7235	suppression of tumorigenicity 7 like	369669	7390	358683	16156	24922, 33688, 42454, 51220, 59986
7236	suppression of tumorigenicity 7 like	369673	7391	358687	16157	24923, 33689, 42455, 51221, 59987
7237	suppression of tumorigenicity 7 like	418497	7392	413718	16158	24924, 33690, 42456, 51222, 59988
7238	suppression of tumorigenicity 7 like	490067	7393	417140	16159	24925, 33691, 42457, 51223, 59989
7239	suppression of tumorigenicity 7 like	538187	7394	444021	16160	24926, 33692, 42458, 51224, 59990
7240	suppression of tumorigenicity 7 like	543570	7395	444088	16161	24927, 33693, 42459, 51225, 59991
7241	suppression of tumorigenicity 7 like	544629	7396	445499	16162	24928, 33694, 42460, 51226, 59992
7242	suppressor APC domain containing 1	383205	7397	372692	16163	24929, 33695, 42461, 51227, 59993
7243	suppressor APC domain containing 1	415669	7398	411948	16164	24930, 33696, 42462, 51228, 59994
7244	suppressor APC domain containing 1	425286	7399	414539	16165	24931, 33697, 42463, 51229, 59995
7245	suppressor APC domain containing 1	425424	7400	413372	16166	24932, 33698, 42464, 51230, 59996
7246	suppressor APC domain	427166	7401	410585	16167	24933, 33699,

	containing 1					42465, 51231, 59997
7247	suppressor APC domain containing 1	433778	7402	408918	16168	24934, 33700, 42466, 51232, 59998
7248	suppressor APC domain containing 1	436320	7403	412154	16169	24935, 33701, 42467, 51233, 59999
7249	suppressor APC domain containing 1	443153	7404	403687	16170	24936, 33702, 42468, 51234, 60000
7250	suppressor APC domain containing 1	447852	7405	403346	16171	24937, 33703, 42469, 51235, 60001
7251	suppressor APC domain containing 1	449857	7406	387942	16172	24938, 33704, 42470, 51236, 60002
7252	suppressor APC domain containing 1	449925	7407	414654	16173	24939, 33705, 42471, 51237, 60003
7253	suppressor APC domain containing 1	457185	7408	405513	16174	24940, 33706, 42472, 51238, 60004
7254	suppressor APC domain containing 1	547662	7409	447344	16175	24941, 33707, 42473, 51239, 60005
7255	suppressor APC domain containing 1	548003	7410	450332	16176	24942, 33708, 42474, 51240, 60006
7256	suppressor APC domain containing 1	548987	7411	448208	16177	24943, 33709, 42475, 51241, 60007
7257	suppressor APC domain containing 1	551778	7412	450257	16178	24944, 33710, 42476, 51242, 60008
7258	suppressor APC domain containing 1	552302	7413	446749	16179	24945, 33711, 42477, 51243, 60009
7259	suppressor of G2 allele of SKP1 (S. cerevisiae) pseudogene 3	304932	7414	304545	16180	24946, 33712, 42478, 51244, 60010
7260	suppressor of G2 allele of SKP1 (S. cerevisiae) pseudogene 3	456963	7415	415153	16181	24947, 33713, 42479, 51245, 60011
7261	suppressor of glucose autophagy associated 1	237536	7416	237536	16182	24948, 33714, 42480, 51246, 60012
7262	suppressor of glucose autophagy associated 1	279034	7417	279034	16183	24949, 33715, 42481, 51247, 60013

7263	suppressor of glucose autophagy associated 1	357779	7418	350424	16184	24950, 33716, 42482, 51248, 60014
7264	suppressor of glucose autophagy associated 1	456801	7419	413886	16185	24951, 33717, 42483, 51249, 60015
7265	surfactant associated 2	448586	7420	409248	16186	24952, 33718, 42484, 51250, 60016
7266	SWIM-type zinc finger 7 associated protein 1	312423	7421	310008	16187	24953, 33719, 42485, 51251, 60017
7267	SWT1 RNA endoribonuclease homolog (S. cerevisiae)	367500	7422	356470	16188	24954, 33720, 42486, 51252, 60018
7268	SWT1 RNA endoribonuclease homolog (S. cerevisiae)	367501	7423	356471	16189	24955, 33721, 42487, 51253, 60019
7269	SWT1 RNA endoribonuclease homolog (S. cerevisiae)	450350	7424	401413	16190	24956, 33722, 42488, 51254, 60020
7270	synapsin II	540660	7425	442512	16191	24957, 33723, 42489, 51255, 60021
7271	synaptonemal complex central element protein 1-like	378644	7426	367911	16192	24958, 33724, 42490, 51256, 60022
7272	synaptonemal complex central element protein 3	406915	7427	385480	16193	24959, 33725, 42491, 51257, 60023
7273	synaptophysin	599440	7428	473186	16194	24960, 33726, 42492, 51258, 60024
7274	synaptotagmin XV	578496	7429	463584	16195	24961, 33727, 42493, 51259, 60025
7275	synaptotagmin-like 3	297239	7430	297239	16196	24962, 33728, 42494, 51260, 60026
7276	synaptotagmin-like 3	360448	7431	353631	16197	24963, 33729, 42495, 51261, 60027
7277	synaptotagmin-like 3	367081	7432	356048	16198	24964, 33730, 42496, 51262, 60028
7278	synaptotagmin-like 3	543689	7433	439453	16199	24965, 33731, 42497, 51263, 60029
7279	synaptotagmin-like 5	297875	7434	297875	16200	24966, 33732, 42498, 51264,

						60030
7280	synaptotagmin-like 5	357972	7435	350657	16201	24967, 33733, 42499, 51265, 60031
7281	synaptotagmin-like 5	456733	7436	395220	16202	24968, 33734, 42500, 51266, 60032
7282	synemin isoform B	594047	7437	472953	16203	24969, 33735, 42501, 51267, 60033
7283	synemin, intermediate filament protein	328642	7438	330469	16204	24970, 33736, 42502, 51268, 60034
7284	synemin, intermediate filament protein	336292	7439	336775	16205	24971, 33737, 42503, 51269, 60035
7285	synovial sarcoma X breakpoint 5	596327	7440	472588	16206	24972, 33738, 42504, 51270, 60036
7286	syntaxin 19	315099	7441	320679	16207	24973, 33739, 42505, 51271, 60037
7287	T cell receptor beta variable 20/OR9-2Uncharacterized protein	558219	7442	453565	16208	24974, 33740, 42506, 51272, 60038
7288	T cell receptor beta variable 23/OR9-2	558144	7443	452755	16209	24975, 33741, 42507, 51273, 60039
7289	T cell receptor beta variable 25/OR9-2 (pseudogene)	438417	7444	403609	16210	24976, 33742, 42508, 51274, 60040
7290	TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa	372978	7445	362069	16211	24977, 33743, 42509, 51275, 60041
7291	TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa	372982	7446	362073	16212	24978, 33744, 42510, 51276, 60042
7292	TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa	456846	7447	411900	16213	24979, 33745, 42511, 51277, 60043
7293	TAF8 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 43kDa	494547	7448	417867	16214	24980, 33746, 42512, 51278, 60044
7294	TAF9 RNA polymerase II TATA box binding protein (TBP)-associated factor	577094	7449	460768	16215	24981, 33747, 42513, 51279, 60045

	32kDa					
7295	target of myb1-like 2 (chicken)	318094	7450	312860	16216	24982, 33748, 42514, 51280, 60046
7296	target of myb1-like 2 (chicken)	379504	7451	368818	16217	24983, 33749, 42515, 51281, 60047
7297	target of myb1-like 2 (chicken)	395739	7452	379088	16218	24984, 33750, 42516, 51282, 60048
7298	target of myb1-like 2 (chicken)	535933	7453	438621	16219	24985, 33751, 42517, 51283, 60049
7299	target of myb1-like 2 (chicken)	537091	7454	446407	16220	24986, 33752, 42518, 51284, 60050
7300	target of myb1-like 2 (chicken)	540946	7455	437655	16221	24987, 33753, 42519, 51285, 60051
7301	target of myb1-like 2 (chicken)	542206	7456	445188	16222	24988, 33754, 42520, 51286, 60052
7302	target of myb1-like 2 (chicken)	581396	7457	464297	16223	24989, 33755, 42521, 51287, 60053
7303	TBC1 (tre-2/USP6, BUB2, cdc16) domain family, member 1	510573	7458	421641	16224	24990, 33756, 42522, 51288, 60054
7304	TBC1 domain containing kinase	273980	7459	273980	16225	24991, 33757, 42523, 51289, 60055
7305	TBC1 domain containing kinase	361687	7460	355338	16226	24992, 33758, 42524, 51290, 60056
7306	TBC1 domain containing kinase	394706	7461	378196	16227	24993, 33759, 42525, 51291, 60057
7307	TBC1 domain containing kinase	394708	7462	378198	16228	24994, 33760, 42526, 51292, 60058
7308	TBC1 domain containing kinase	432496	7463	405847	16229	24995, 33761, 42527, 51293, 60059
7309	TBC1 domain containing kinase	507696	7464	423637	16230	24996, 33762, 42528, 51294, 60060
7310	TBC1 domain containing kinase	509532	7465	420985	16231	24997, 33763, 42529, 51295, 60061
7311	TBC1 domain containing	509862	7466	425197	16232	24998, 33764,

	kinase					42530, 51296, 60062
7312	TBC1 domain family member 26	437605	7467	410111	16233	24999, 33765, 42531, 51297, 60063
7313	TBC1 domain family member 29	580161	7468	462799	16234	25000, 33766, 42532, 51298, 60064
7314	TBC1 domain family member 30	539867	7469	440207	16235	25001, 33767, 42533, 51299, 60065
7315	TBC1 domain family member 5	446818	7470	402935	16236	25002, 33768, 42534, 51300, 60066
7316	TBC1 domain family, member 12	225235	7471	225235	16237	25003, 33769, 42535, 51301, 60067
7317	TBC1 domain family, member 13	223865	7472	223865	16238	25004, 33770, 42536, 51302, 60068
7318	TBC1 domain family, member 13	372648	7473	361731	16239	25005, 33771, 42537, 51303, 60069
7319	TBC1 domain family, member 13	539497	7474	437751	16240	25006, 33772, 42538, 51304, 60070
7320	TBC1 domain family, member 14	409757	7475	386921	16241	25007, 33773, 42539, 51305, 60071
7321	TBC1 domain family, member 14	427736	7476	411760	16242	25008, 33774, 42540, 51306, 60072
7322	TBC1 domain family, member 14	444368	7477	414951	16243	25009, 33775, 42541, 51307, 60073
7323	TBC1 domain family, member 14	446947	7478	405875	16244	25010, 33776, 42542, 51308, 60074
7324	TBC1 domain family, member 14	448507	7479	404041	16245	25011, 33777, 42543, 51309, 60075
7325	TBC1 domain family, member 14	451522	7480	388886	16246	25012, 33778, 42544, 51310, 60076
7326	TBC1 domain family, member 16	310924	7481	309794	16247	25013, 33779, 42545, 51311, 60077
7327	TBC1 domain family, member 16	340848	7482	341517	16248	25014, 33780, 42546, 51312, 60078

7328	TBC1 domain family, member 17	221543	7483	221543	16249	25015, 33781, 42547, 51313, 60079
7329	TBC1 domain family, member 17	535102	7484	446323	16250	25016, 33782, 42548, 51314, 60080
7330	TBC1 domain family, member 19	264866	7485	264866	16251	25017, 33783, 42549, 51315, 60081
7331	TBC1 domain family, member 19	511789	7486	425569	16252	25018, 33784, 42550, 51316, 60082
7332	TBC1 domain family, member 21	300504	7487	300504	16253	25019, 33785, 42551, 51317, 60083
7333	TBC1 domain family, member 21	535547	7488	439325	16254	25020, 33786, 42552, 51318, 60084
7334	TBC1 domain family, member 22A	337137	7489	336724	16255	25021, 33787, 42553, 51319, 60085
7335	TBC1 domain family, member 22A	355704	7490	347932	16256	25022, 33788, 42554, 51320, 60086
7336	TBC1 domain family, member 22A	380995	7491	370383	16257	25023, 33789, 42555, 51321, 60087
7337	TBC1 domain family, member 22A	406733	7492	385634	16258	25024, 33790, 42556, 51322, 60088
7338	TBC1 domain family, member 22A	407381	7493	384036	16259	25025, 33791, 42557, 51323, 60089
7339	TBC1 domain family, member 22B	373491	7494	362590	16260	25026, 33792, 42558, 51324, 60090
7340	TBC1 domain family, member 23	344949	7495	340693	16261	25027, 33793, 42559, 51325, 60091
7341	TBC1 domain family, member 23	394144	7496	377700	16262	25028, 33794, 42560, 51326, 60092
7342	TBC1 domain family, member 23	475134	7497	418059	16263	25029, 33795, 42561, 51327, 60093
7343	TBC1 domain family, member 26	469477	7498	434391	16264	25030, 33796, 42562, 51328, 60094
7344	TBC1 domain family, member 28	345096	7499	339973	16265	25031, 33797, 42563, 51329,

						60095
7345	TBC1 domain family, member 28	405044	7500	385821	16266	25032, 33798, 42564, 51330, 60096
7346	TBC1 domain family, member 29	329040	7501	330052	16267	25033, 33799, 42565, 51331, 60097
7347	TBC1 domain family, member 29	378698	7502	367970	16268	25034, 33800, 42566, 51332, 60098
7348	TBC1 domain family, member 2B	300584	7503	300584	16269	25035, 33801, 42567, 51333, 60099
7349	TBC1 domain family, member 2B	409931	7504	387165	16270	25036, 33802, 42568, 51334, 60100
7350	TBC1 domain family, member 30	229088	7505	229088	16271	25037, 33803, 42569, 51335, 60101
7351	TBC1 domain family, member 30	411580	7506	394004	16272	25038, 33804, 42570, 51336, 60102
7352	TBC1 domain family, member 30	455166	7507	415850	16273	25039, 33805, 42571, 51337, 60103
7353	TBC1 domain family, member 5	253692	7508	253692	16274	25040, 33806, 42572, 51338, 60104
7354	TBC1 domain family, member 5	415814	7509	396239	16275	25041, 33807, 42573, 51339, 60105
7355	TBC1 domain family, member 5	429383	7510	398127	16276	25042, 33808, 42574, 51340, 60106
7356	TBC1 domain family, member 5	507877	7511	424998	16277	25043, 33809, 42575, 51341, 60107
7357	TBC1 domain family, member 8 (with GRAM domain)	376840	7512	366036	16278	25044, 33810, 42576, 51342, 60108
7358	TBC1 domain family, member 8 (with GRAM domain)	409318	7513	386856	16279	25045, 33811, 42577, 51343, 60109
7359	TBC1 domain family, member 8B (with GRAM domain)	310452	7514	310675	16280	25046, 33812, 42578, 51344, 60110
7360	TBC1 domain family, member 8B (with GRAM domain)	357242	7515	349781	16281	25047, 33813, 42579, 51345, 60111
7361	TBC1 domain family,	394972	7516	378423	16282	25048, 33814,

	member 8B (with GRAM domain)					42580, 51346, 60112
7362	TBC1 domain family, member 9 (with GRAM domain)	442267	7517	411197	16283	25049, 33815, 42581, 51347, 60113
7363	TBK1 binding protein 1	361722	7518	354777	16284	25050, 33816, 42582, 51348, 60114
7364	TBK1 binding protein 1	537587	7519	446365	16285	25051, 33817, 42583, 51349, 60115
7365	t-complex 10-like 2	366832	7520	355797	16286	25052, 33818, 42584, 51350, 60116
7366	t-complex 11 (mouse)-like 1	324357	7521	316279	16287	25053, 33819, 42585, 51351, 60117
7367	t-complex 11 (mouse)-like 1	334274	7522	335595	16288	25054, 33820, 42586, 51352, 60118
7368	t-complex 11 (mouse)-like 1	432887	7523	395070	16289	25055, 33821, 42587, 51353, 60119
7369	t-complex 11 (mouse)-like 1	528898	7524	435870	16290	25056, 33822, 42588, 51354, 60120
7370	t-complex 11 (mouse)-like 1	530419	7525	436428	16291	25057, 33823, 42589, 51355, 60121
7371	t-complex 11 (mouse)-like 1	531632	7526	433067	16292	25058, 33824, 42590, 51356, 60122
7372	t-complex 11 (mouse)-like 2	299045	7527	299045	16293	25059, 33825, 42591, 51357, 60123
7373	t-complex 11 (mouse)-like 2	548428	7528	447457	16294	25060, 33826, 42592, 51358, 60124
7374	t-complex 11 (mouse)-like 2	551228	7529	449844	16295	25061, 33827, 42593, 51359, 60125
7375	t-complex 11 (mouse)-like 2	551802	7530	447174	16296	25062, 33828, 42594, 51360, 60126
7376	t-complex 11 (mouse)-like 2	553098	7531	448629	16297	25063, 33829, 42595, 51361, 60127
7377	t-complex 11 (mouse)-like 2	553143	7532	447416	16298	25064, 33830, 42596, 51362, 60128

7378	Tctex1 domain containing 1	282670	7533	282670	16299	25065, 33831, 42597, 51363, 60129
7379	Tctex1 domain containing 2	325318	7534	324323	16300	25066, 33832, 42598, 51364, 60130
7380	Tctex1 domain containing 2	545438	7535	445150	16301	25067, 33833, 42599, 51365, 60131
7381	TDP-glucose 4,6-dehydratase	261296	7536	261296	16302	25068, 33834, 42600, 51366, 60132
7382	tectonin beta-propeller repeat containing 2	359520	7537	352510	16303	25069, 33835, 42601, 51367, 60133
7383	tectonin beta-propeller repeat containing 2	380088	7538	369428	16304	25070, 33836, 42602, 51368, 60134
7384	tectonin beta-propeller repeat containing 2	558678	7539	453671	16305	25071, 33837, 42603, 51369, 60135
7385	testis expressed 22	451127	7540	397002	16306	25072, 33838, 42604, 51370, 60136
7386	testis expressed 38	334122	7541	455854	16307	25073, 33839, 42605, 51371, 60137
7387	testis expressed 9	352903	7542	342169	16308	25074, 33840, 42606, 51372, 60138
7388	testis expressed 9	537232	7543	438745	16309	25075, 33841, 42607, 51373, 60139
7389	testis specific 13	582211	7544	462005	16310	25076, 33842, 42608, 51374, 60140
7390	testis specific protein, Y-linked 10	428845	7545	406407	16311	25077, 33843, 42609, 51375, 60141
7391	testis specific protein, Y-linked 10	429039	7546	414049	16312	25078, 33844, 42610, 51376, 60142
7392	testis specific protein, Y-linked 10	444056	7547	397151	16313	25079, 33845, 42611, 51377, 60143
7393	testis specific protein, Y-linked 2	320701	7548	314077	16314	25080, 33846, 42612, 51378, 60144
7394	testis specific protein, Y-linked 3	383010	7549	372473	16315	25081, 33847, 42613, 51379,

						60145
7395	testis specific protein, Y-linked 3	427871	7550	396987	16316	25082, 33848, 42614, 51380, 60146
7396	testis specific protein, Y-linked 3	440483	7551	406010	16317	25083, 33849, 42615, 51381, 60147
7397	testis specific protein, Y-linked 3	457222	7552	398163	16318	25084, 33850, 42616, 51382, 60148
7398	testis specific protein, Y-linked 4	383008	7553	372471	16319	25085, 33851, 42617, 51383, 60149
7399	testis specific protein, Y-linked 4	426950	7554	399668	16320	25086, 33852, 42618, 51384, 60150
7400	testis specific protein, Y-linked 8	287721	7555	287721	16321	25087, 33853, 42619, 51385, 60151
7401	testis specific protein, Y-linked 8	330628	7556	327984	16322	25088, 33854, 42620, 51386, 60152
7402	testis specific protein, Y-linked 8	383000	7557	372462	16323	25089, 33855, 42621, 51387, 60153
7403	testis specific protein, Y-linked 8	383005	7558	372467	16324	25090, 33856, 42622, 51388, 60154
7404	testis specific protein, Y-linked 8	537415	7559	439701	16325	25091, 33857, 42623, 51389, 60155
7405	testis specific, 13	356588	7560	348996	16326	25092, 33858, 42624, 51390, 60156
7406	testis specific, 13	438346	7561	407352	16327	25093, 33859, 42625, 51391, 60157
7407	testis specific, 13	443954	7562	415856	16328	25094, 33860, 42626, 51392, 60158
7408	testis specific, 13	456951	7563	406047	16329	25095, 33861, 42627, 51393, 60159
7409	testis-expressed sequence 13A protein	600991	7564	471604	16330	25096, 33862, 42628, 51394, 60160
7410	tet methylcytosine dioxygenase 3	233310	7565	233310	16331	25097, 33863, 42629, 51395, 60161
7411	tet methylcytosine	409262	7566	386869	16332	25098, 33864,

	dioxygenase 3					42630, 51396, 60162
7412	tetra-peptide repeat homeobox-like	326972	7567	322097	16333	25099, 33865, 42631, 51397, 60163
7413	tetra-peptide repeat homeobox-like	424053	7568	400448	16334	25100, 33866, 42632, 51398, 60164
7414	tetra-peptide repeat homeobox-like	429201	7569	400824	16335	25101, 33867, 42633, 51399, 60165
7415	tetra-peptide repeat homeobox-like	524375	7570	435219	16336	25102, 33868, 42634, 51400, 60166
7416	tetra-peptide repeat homeobox-like	528040	7571	435511	16337	25103, 33869, 42635, 51401, 60167
7417	tetra-peptide repeat homeobox-like	528067	7572	435438	16338	25104, 33870, 42636, 51402, 60168
7418	tetra-peptide repeat homeobox-like	528312	7573	435227	16339	25105, 33871, 42637, 51403, 60169
7419	tetra-peptide repeat homeobox-like	529129	7574	436919	16340	25106, 33872, 42638, 51404, 60170
7420	tetra-peptide repeat homeobox-like	530586	7575	435853	16341	25107, 33873, 42639, 51405, 60171
7421	tetra-peptide repeat homeobox-like	532880	7576	437227	16342	25108, 33874, 42640, 51406, 60172
7422	tetra-peptide repeat homeobox-like	532924	7577	432662	16343	25109, 33875, 42641, 51407, 60173
7423	tetraspanin 19	532498	7578	433816	16344	25110, 33876, 42642, 51408, 60174
7424	tetraspanin 19	547836	7579	446898	16345	25111, 33877, 42643, 51409, 60175
7425	tetratricopeptide repeat and ankyrin repeat containing 1	301807	7580	301807	16346	25112, 33878, 42644, 51410, 60176
7426	tetratricopeptide repeat and ankyrin repeat containing 1	428977	7581	416826	16347	25113, 33879, 42645, 51411, 60177
7427	tetratricopeptide repeat and ankyrin repeat containing 1	429976	7582	416168	16348	25114, 33880, 42646, 51412, 60178

7428	tetratricopeptide repeat domain 13	366661	7583	355621	16349	25115, 33881, 42647, 51413, 60179
7429	tetratricopeptide repeat domain 13	366662	7584	355622	16350	25116, 33882, 42648, 51414, 60180
7430	tetratricopeptide repeat domain 13	414259	7585	416631	16351	25117, 33883, 42649, 51415, 60181
7431	tetratricopeptide repeat domain 14	296015	7586	296015	16352	25118, 33884, 42650, 51416, 60182
7432	tetratricopeptide repeat domain 14	382584	7587	372027	16353	25119, 33885, 42651, 51417, 60183
7433	tetratricopeptide repeat domain 14	412756	7588	413743	16354	25120, 33886, 42652, 51418, 60184
7434	tetratricopeptide repeat domain 16	316259	7589	319048	16355	25121, 33887, 42653, 51419, 60185
7435	tetratricopeptide repeat domain 16	373288	7590	362385	16356	25122, 33888, 42654, 51420, 60186
7436	tetratricopeptide repeat domain 16	373289	7591	362386	16357	25123, 33889, 42655, 51421, 60187
7437	tetratricopeptide repeat domain 16	393748	7592	377349	16358	25124, 33890, 42656, 51422, 60188
7438	tetratricopeptide repeat domain 17	39989	7593	39989	16359	25125, 33891, 42657, 51423, 60189, 61568, 61626
7439	tetratricopeptide repeat domain 17	299240	7594	299240	16360	25126, 33892, 42658, 51424, 60190
7440	tetratricopeptide repeat domain 18	310715	7595	310829	16361	25127, 33893, 42659, 51425, 60191
7441	tetratricopeptide repeat domain 18	340329	7596	343650	16362	25128, 33894, 42660, 51426, 60192
7442	tetratricopeptide repeat domain 18	355577	7597	347781	16363	25129, 33895, 42661, 51427, 60193
7443	tetratricopeptide repeat domain 18	372928	7598	362019	16364	25130, 33896, 42662, 51428, 60194
7444	tetratricopeptide repeat	394862	7599	378331	16365	25131, 33897,

	domain 18					42663, 51429, 60195
7445	tetratricopeptide repeat domain 18	394865	7600	378334	16366	25132, 33898, 42664, 51430, 60196
7446	tetratricopeptide repeat domain 18	401621	7601	384479	16367	25133, 33899, 42665, 51431, 60197
7447	tetratricopeptide repeat domain 18	433268	7602	409527	16368	25134, 33900, 42666, 51432, 60198
7448	tetratricopeptide repeat domain 21A	301819	7603	301819	16369	25135, 33901, 42667, 51433, 60199
7449	tetratricopeptide repeat domain 21A	424305	7604	393800	16370	25136, 33902, 42668, 51434, 60200
7450	tetratricopeptide repeat domain 21A	431162	7605	398211	16371	25137, 33903, 42669, 51435, 60201
7451	tetratricopeptide repeat domain 21A	440121	7606	410882	16372	25138, 33904, 42670, 51436, 60202
7452	tetratricopeptide repeat domain 22	371274	7607	360321	16373	25139, 33905, 42671, 51437, 60203
7453	tetratricopeptide repeat domain 22	371276	7608	360323	16374	25140, 33906, 42672, 51438, 60204
7454	tetratricopeptide repeat domain 23	262074	7609	262074	16375	25141, 33907, 42673, 51439, 60205
7455	tetratricopeptide repeat domain 23	394130	7610	377688	16376	25142, 33908, 42674, 51440, 60206
7456	tetratricopeptide repeat domain 23	394132	7611	377690	16377	25143, 33909, 42675, 51441, 60207
7457	tetratricopeptide repeat domain 23	394135	7612	377692	16378	25144, 33910, 42676, 51442, 60208
7458	tetratricopeptide repeat domain 23	394136	7613	377693	16379	25145, 33911, 42677, 51443, 60209
7459	tetratricopeptide repeat domain 23	558078	7614	453673	16380	25146, 33912, 42678, 51444, 60210
7460	tetratricopeptide repeat domain 23	558613	7615	453054	16381	25147, 33913, 42679, 51445, 60211

7461	tetratricopeptide repeat domain 23	558663	7616	452923	16382	25148, 33914, 42680, 51446, 60212
7462	tetratricopeptide repeat domain 23	560235	7617	452882	16383	25149, 33915, 42681, 51447, 60213
7463	tetratricopeptide repeat domain 23	560279	7618	454017	16384	25150, 33916, 42682, 51448, 60214
7464	tetratricopeptide repeat domain 23	560772	7619	453862	16385	25151, 33917, 42683, 51449, 60215
7465	tetratricopeptide repeat domain 23	560860	7620	453419	16386	25152, 33918, 42684, 51450, 60216
7466	tetratricopeptide repeat domain 23	561365	7621	454175	16387	25153, 33919, 42685, 51451, 60217
7467	tetratricopeptide repeat domain 23	596370	7622	469746	16388	25154, 33920, 42686, 51452, 60218
7468	tetratricopeptide repeat domain 23	597233	7623	473031	16389	25155, 33921, 42687, 51453, 60219
7469	tetratricopeptide repeat domain 23	598575	7624	472257	16390	25156, 33922, 42688, 51454, 60220
7470	tetratricopeptide repeat domain 23	599529	7625	470324	16391	25157, 33923, 42689, 51455, 60221
7471	tetratricopeptide repeat domain 23-like	505624	7626	422188	16392	25158, 33924, 42690, 51456, 60222
7472	tetratricopeptide repeat domain 23-like	535797	7627	443536	16393	25159, 33925, 42691, 51457, 60223
7473	tetratricopeptide repeat domain 24	340086	7628	339487	16394	25160, 33926, 42692, 51458, 60224
7474	tetratricopeptide repeat domain 24	368236	7629	357219	16395	25161, 33927, 42693, 51459, 60225
7475	tetratricopeptide repeat domain 24	368237	7630	357220	16396	25162, 33928, 42694, 51460, 60226
7476	tetratricopeptide repeat domain 24	413282	7631	400414	16397	25163, 33929, 42695, 51461, 60227
7477	tetratricopeptide repeat domain 25	569541	7632	458114	16398	25164, 33930, 42696, 51462,

						60228
7478	tetratricopeptide repeat domain 26	430935	7633	410655	16399	25165, 33931, 42697, 51463, 60229
7479	tetratricopeptide repeat domain 26	464848	7634	419279	16400	25166, 33932, 42698, 51464, 60230
7480	tetratricopeptide repeat domain 26	343187	7635	339135	16401	25167, 33933, 42699, 51465, 60231
7481	tetratricopeptide repeat domain 27	317907	7636	313953	16402	25168, 33934, 42700, 51466, 60232
7482	tetratricopeptide repeat domain 28	397906	7637	381003	16403	25169, 33935, 42701, 51467, 60233
7483	tetratricopeptide repeat domain 29	325106	7638	316740	16404	25170, 33936, 42702, 51468, 60234
7484	tetratricopeptide repeat domain 29	398883	7639	381858	16405	25171, 33937, 42703, 51469, 60235
7485	tetratricopeptide repeat domain 29	398886	7640	381861	16406	25172, 33938, 42704, 51470, 60236
7486	tetratricopeptide repeat domain 29	502319	7641	425665	16407	25173, 33939, 42705, 51471, 60237
7487	tetratricopeptide repeat domain 29	504425	7642	425778	16408	25174, 33940, 42706, 51472, 60238
7488	tetratricopeptide repeat domain 29	513335	7643	423505	16409	25175, 33941, 42707, 51473, 60239
7489	tetratricopeptide repeat domain 29	515315	7644	423646	16410	25176, 33942, 42708, 51474, 60240
7490	tetratricopeptide repeat domain 30A	355689	7645	347915	16411	25177, 33943, 42709, 51475, 60241
7491	tetratricopeptide repeat domain 30A	545660	7646	440603	16412	25178, 33944, 42710, 51476, 60242
7492	tetratricopeptide repeat domain 30B	408939	7647	386181	16413	25179, 33945, 42711, 51477, 60243
7493	tetratricopeptide repeat domain 30B	500357	7648	440462	16414	25180, 33946, 42712, 51478, 60244
7494	tetratricopeptide repeat	435361	7649	397652	16415	25181, 33947,

	domain 31					42713, 51479, 60245
7495	tetratricopeptide repeat domain 31	441635	7650	413183	16416	25182, 33948, 42714, 51480, 60246
7496	tetratricopeptide repeat domain 31	442235	7651	416823	16417	25183, 33949, 42715, 51481, 60247
7497	tetratricopeptide repeat domain 31	545977	7652	443950	16418	25184, 33950, 42716, 51482, 60248
7498	tetratricopeptide repeat domain 31	233623	7653	233623	16419	25185, 33951, 42717, 51483, 60249
7499	tetratricopeptide repeat domain 32	333610	7654	333018	16420	25186, 33952, 42718, 51484, 60250
7500	tetratricopeptide repeat domain 33	337702	7655	338533	16421	25187, 33953, 42719, 51485, 60251
7501	tetratricopeptide repeat domain 34	401095	7656	383873	16422	25188, 33954, 42720, 51486, 60252
7502	tetratricopeptide repeat domain 36	302783	7657	307640	16423	25189, 33955, 42721, 51487, 60253
7503	tetratricopeptide repeat domain 36	539546	7658	442513	16424	25190, 33956, 42722, 51488, 60254
7504	tetratricopeptide repeat domain 37	358746	7659	351596	16425	25191, 33957, 42723, 51489, 60255
7505	tetratricopeptide repeat domain 37	513823	7660	425403	16426	25192, 33958, 42724, 51490, 60256
7506	tetratricopeptide repeat domain 38	445282	7661	393960	16427	25193, 33959, 42725, 51491, 60257
7507	tetratricopeptide repeat domain 38	381031	7662	370419	16428	25194, 33960, 42726, 51492, 60258
7508	tetratricopeptide repeat domain 39A	262676	7663	262676	16429	25195, 33961, 42727, 51493, 60259
7509	tetratricopeptide repeat domain 39A	371750	7664	360815	16430	25196, 33962, 42728, 51494, 60260
7510	tetratricopeptide repeat domain 39A	413473	7665	406144	16431	25197, 33963, 42729, 51495, 60261

7511	tetratricopeptide repeat domain 39A	447632	7666	393952	16432	25198, 33964, 42730, 51496, 60262
7512	tetratricopeptide repeat domain 39A	451380	7667	397207	16433	25199, 33965, 42731, 51497, 60263
7513	tetratricopeptide repeat domain 39A	525906	7668	436659	16434	25200, 33966, 42732, 51498, 60264
7514	tetratricopeptide repeat domain 39A	530004	7669	431228	16435	25201, 33967, 42733, 51499, 60265
7515	tetratricopeptide repeat domain 39C	304621	7670	306598	16436	25202, 33968, 42734, 51500, 60266
7516	tetratricopeptide repeat domain 39C	317571	7671	323645	16437	25203, 33969, 42735, 51501, 60267
7517	tetratricopeptide repeat domain 39C	540918	7672	443016	16438	25204, 33970, 42736, 51502, 60268
7518	tetratricopeptide repeat domain 39C	584250	7673	464344	16439	25205, 33971, 42737, 51503, 60269
7519	tetratricopeptide repeat domain 40	263170	7674	263170	16440	25206, 33972, 42738, 51504, 60270
7520	tetratricopeptide repeat domain 40	368582	7675	357571	16441	25207, 33973, 42739, 51505, 60271
7521	tetratricopeptide repeat domain 40	368585	7676	357574	16442	25208, 33974, 42740, 51506, 60272
7522	tetratricopeptide repeat domain 40	368586	7677	357575	16443	25209, 33975, 42741, 51507, 60273
7523	tetratricopeptide repeat domain 6	267368	7678	267368	16444	25210, 33976, 42742, 51508, 60274
7524	tetratricopeptide repeat domain 6	382320	7679	371757	16445	25211, 33977, 42743, 51509, 60275
7525	tetratricopeptide repeat domain 6	476979	7680	417788	16446	25212, 33978, 42744, 51510, 60276
7526	tetratricopeptide repeat domain 7B	328459	7681	336127	16447	25213, 33979, 42745, 51511, 60277
7527	tetratricopeptide repeat domain 7B	357056	7682	349564	16448	25214, 33980, 42746, 51512,

						60278
7528	tetratricopeptide repeat domain 7B	540938	7683	441787	16449	25215, 33981, 42747, 51513, 60279
7529	tetratricopeptide repeat domain 7B	553972	7684	451440	16450	25216, 33982, 42748, 51514, 60280
7530	tetratricopeptide repeat domain 9B	311308	7685	311760	16451	25217, 33983, 42749, 51515, 60281
7531	tetratricopeptide repeat domain 9C	316461	7686	325266	16452	25218, 33984, 42750, 51516, 60282
7532	tetratricopeptide repeat domain 9C	513247	7687	444031	16453	25219, 33985, 42751, 51517, 60283
7533	tetratricopeptide repeat domain 9C	530625	7688	435282	16454	25220, 33986, 42752, 51518, 60284
7534	tetratricopeptide repeat domain 9C	532583	7689	434340	16455	25221, 33987, 42753, 51519, 60285
7535	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2	389520	7690	374171	16456	25222, 33988, 42754, 51520, 60286
7536	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 2	424789	7691	387593	16457	25223, 33989, 42755, 51521, 60287
7537	TGIF2-C20orf24 protein	558530	7692	454021	16458	25224, 33990, 42756, 51522, 60288
7538	theg spermatid protein-like	512175	7693	456850	16459	25225, 33991, 42757, 51523, 60289
7539	thiamine triphosphatase	554789	7694	450459	16460	25226, 33992, 42758, 51524, 60290
7540	thioesterase superfamily member 5	453881	7695	406809	16461	25227, 33993, 42759, 51525, 60291
7541	thioredoxin reductase 3 neighbor	383572	7696	373066	16462	25228, 33994, 42760, 51526, 60292
7542	thioredoxin reductase 3 neighbor	404489	7697	384071	16463	25229, 33995, 42761, 51527, 60293
7543	thiosulfate sulfurtransferase (rhodanese)-like domain containing 2	341170	7698	342499	16464	25230, 33996, 42762, 51528, 60294
7544	thiosulfate sulfurtransferase	354801	7699	346856	16465	25231, 33997,

	(rhodanese)-like domain containing 2					42763, 51529, 60295
7545	thiosulfate sulfurtransferase (rhodanese)-like domain containing 2	375163	7700	364306	16466	25232, 33998, 42764, 51530, 60296
7546	thiosulfate sulfurtransferase (rhodanese)-like domain containing 2	375165	7701	364308	16467	25233, 33999, 42765, 51531, 60297
7547	thiosulfate sulfurtransferase (rhodanese)-like domain containing 2	375172	7702	364315	16468	25234, 34000, 42766, 51532, 60298
7548	thiosulfate sulfurtransferase (rhodanese)-like domain containing 2	375173	7703	364316	16469	25235, 34001, 42767, 51533, 60299
7549	three prime repair exonuclease 2	596889	7704	469756	16470	25236, 34002, 42768, 51534, 60300
7550	threonine synthase-like 1 (S. cerevisiae)	376356	7705	365534	16471	25237, 34003, 42769, 51535, 60301
7551	threonine synthase-like 1 (S. cerevisiae)	524413	7706	434887	16472	25238, 34004, 42770, 51536, 60302
7552	threonyl-tRNA synthetase-like 2	539112	7707	439899	16473	25239, 34005, 42771, 51537, 60303
7553	thrombospondin, type I, domain containing 7B	272643	7708	272643	16474	25240, 34006, 42772, 51538, 60304
7554	thrombospondin, type I, domain containing 7B	413152	7709	413841	16475	25241, 34007, 42773, 51539, 60305
7555	thrombospondin, type I, domain containing 7B	543459	7710	443370	16476	25242, 34008, 42774, 51540, 60306
7556	THUMP domain containing 1	381337	7711	370741	16477	25243, 34009, 42775, 51541, 60307
7557	THUMP domain containing 1	396083	7712	379392	16478	25244, 34010, 42776, 51542, 60308
7558	THUMP domain containing 1	431224	7713	392282	16479	25245, 34011, 42777, 51543, 60309
7559	THUMP domain containing 3	345094	7714	339532	16480	25246, 34012, 42778, 51544, 60310
7560	THUMP domain containing 3	417036	7715	402968	16481	25247, 34013, 42779, 51545, 60311

7561	THUMP domain containing 3	419437	7716	411126	16482	25248, 34014, 42780, 51546, 60312
7562	THUMP domain containing 3	452837	7717	395893	16483	25249, 34015, 42781, 51547, 60313
7563	THUMP domain containing 3	515662	7718	424064	16484	25250, 34016, 42782, 51548, 60314
7564	thymocyte expressed positive selection associated 1	449076	7719	400892	16485	25251, 34017, 42783, 51549, 60315
7565	thymocyte expressed positive selection associated 1	524622	7720	435622	16486	25252, 34018, 42784, 51550, 60316
7566	thymocyte expressed positive selection associated 1	524668	7721	436635	16487	25253, 34019, 42785, 51551, 60317
7567	thymocyte expressed positive selection associated 1	533607	7722	433895	16488	25254, 34020, 42786, 51552, 60318
7568	thymosin beta 15B	419165	7723	456121	16489	25255, 34021, 42787, 51553, 60319
7569	tigger transposable element derived 1-like 2	451672	7724	414891	16490	25256, 34022, 42788, 51554, 60320
7570	TLC domain containing 2	330676	7725	331965	16491	25257, 34023, 42789, 51555, 60321
7571	TLR9	494383	7726	417517	16492	25258, 34024, 42790, 51556, 60322
7572	TMEM189-UBE2V1 readthrough	341698	7727	344166	16493	25259, 34025, 42791, 51557, 60323
7573	TNFAIP3 interacting protein 3	57513	7728	57513	16494	25260, 34026, 42792, 51558, 60324, 61569, 61627
7574	TNFAIP3 interacting protein 3	454328	7729	411817	16495	25261, 34027, 42793, 51559, 60325
7575	TNFAIP3 interacting protein 3	507879	7730	427106	16496	25262, 34028, 42794, 51560, 60326
7576	tocopherol (alpha) transfer protein-like	262605	7731	262605	16497	25263, 34029, 42795, 51561, 60327
7577	tocopherol (alpha) transfer	372904	7732	361995	16498	25264, 34030,

	protein-like					42796, 51562, 60328
7578	tocopherol (alpha) transfer protein-like	456317	7733	412720	16499	25265, 34031, 42797, 51563, 60329
7579	TP53 target 3	569420	7734	457452	16500	25266, 34032, 42798, 51564, 60330
7580	TP53-target gene 3 protein-like	398664	7735	455596	16501	25267, 34033, 42799, 51565, 60331
7581	TraB domain containing	303434	7736	305664	16502	25268, 34034, 42800, 51566, 60332
7582	TraB domain containing	380909	7737	370295	16503	25269, 34035, 42801, 51567, 60333
7583	TraB domain containing	395827	7738	379171	16504	25270, 34036, 42802, 51568, 60334
7584	TraB domain containing 2B	371865	7739	456730	16505	25271, 34037, 42803, 51569, 60335
7585	TRAF-interacting protein with forkhead-associated domain	361717	7740	354911	16506	25272, 34038, 42804, 51570, 60336
7586	TRAF-interacting protein with forkhead-associated domain	438746	7741	388946	16507	25273, 34039, 42805, 51571, 60337
7587	TRAF-interacting protein with forkhead-associated domain	500655	7742	424231	16508	25274, 34040, 42806, 51572, 60338
7588	transcription elongation factor A (SII)-like 6	598476	7743	468830	16509	25275, 34041, 42807, 51573, 60339
7589	transcription elongation factor B polypeptide 3C-like 2	591973	7744	468046	16510	25276, 34042, 42808, 51574, 60340
7590	transcription elongation regulator 1-like	368642	7745	357631	16511	25277, 34043, 42809, 51575, 60341
7591	transcription factor 24	563496	7746	455444	16512	25278, 34044, 42810, 51576, 60342
7592	transformation/transcription domain-associated protein	565218	7747	457834	16513	25279, 34045, 42811, 51577, 60343
7593	transforming growth factor beta receptor III-like	565886	7748	457962	16514	25280, 34046, 42812, 51578, 60344

7594	transgelin 3	273368	7749	273368	16515	25281, 34047, 42813, 51579, 60345
7595	transgelin 3	393917	7750	377494	16516	25282, 34048, 42814, 51580, 60346
7596	transgelin 3	455401	7751	391160	16517	25283, 34049, 42815, 51581, 60347
7597	transgelin 3	478951	7752	419105	16518	25284, 34050, 42816, 51582, 60348
7598	transgelin 3	540095	7753	439890	16519	25285, 34051, 42817, 51583, 60349
7599	transient receptor potential cation channel subfamily V member 1	572705	7754	459962	16520	25286, 34052, 42818, 51584, 60350
7600	transketolase-like 1	596987	7755	472763	16521	25287, 34053, 42819, 51585, 60351
7601	transmembrane and coiled-coil domains 6	252100	7756	252100	16522	25288, 34054, 42820, 51586, 60352
7602	transmembrane and coiled-coil domains 6	394671	7757	378166	16523	25289, 34055, 42821, 51587, 60353
7603	transmembrane and coiled-coil domains 6	511410	7758	422154	16524	25290, 34056, 42822, 51588, 60354
7604	transmembrane and coiled-coil domains 6	537378	7759	444474	16525	25291, 34057, 42823, 51589, 60355
7605	transmembrane protein 158 (gene/pseudogene)	503771	7760	422431	16526	25292, 34058, 42824, 51590, 60356
7606	transmembrane protein 159	233047	7761	233047	16527	25293, 34059, 42825, 51591, 60357
7607	transmembrane protein 159	261388	7762	261388	16528	25294, 34060, 42826, 51592, 60358
7608	transmembrane protein 159	451578	7763	409879	16529	25295, 34061, 42827, 51593, 60359
7609	transmembrane protein 178B	565468	7764	456594	16530	25296, 34062, 42828, 51594, 60360
7610	transmembrane protein 185A	316916	7765	359449	16531	25297, 34063, 42829, 51595,

						60361
7611	transmembrane protein 185A	536359	7766	443119	16532	25298, 34064, 42830, 51596, 60362
7612	transmembrane protein 185A	543618	7767	440270	16533	25299, 34065, 42831, 51597, 60363
7613	transmembrane protein 194B	409150	7768	386292	16534	25300, 34066, 42832, 51598, 60364
7614	transmembrane protein 202	341689	7769	340212	16535	25301, 34067, 42833, 51599, 60365
7615	transmembrane protein 212	334567	7770	334072	16536	25302, 34068, 42834, 51600, 60366
7616	transmembrane protein 212	450693	7771	393684	16537	25303, 34069, 42835, 51601, 60367
7617	transmembrane protein 221	341130	7772	342162	16538	25304, 34070, 42836, 51602, 60368
7618	transmembrane protein 236	569785	7773	457455	16539	25305, 34071, 42837, 51603, 60369
7619	transmembrane protein 238	444469	7774	416154	16540	25306, 34072, 42838, 51604, 60370
7620	transmembrane protein 239	361033	7775	354312	16541	25307, 34073, 42839, 51605, 60371
7621	transmembrane protein 239	554164	7776	452175	16542	25308, 34074, 42840, 51606, 60372
7622	transmembrane protein 239	380585	7777	369959	16543	25309, 34075, 42841, 51607, 60373
7623	transmembrane protein 25	596699	7778	469390	16544	25310, 34076, 42842, 51608, 60374
7624	transmembrane protein 25	597742	7779	471941	16545	25311, 34077, 42843, 51609, 60375
7625	Transmembrane protein 343375	434431	7780	388684	16546	25312, 34078, 42844, 51610, 60376
7626	transmembrane protein 44	273580	7781	273580	16547	25313, 34079, 42845, 51611, 60377
7627	transmembrane protein 44	330115	7782	328300	16548	25314, 34080,

						42846, 51612, 60378
7628	transmembrane protein 44	347147	7783	333355	16549	25315, 34081, 42847, 51613, 60379
7629	transmembrane protein 44	381975	7784	371402	16550	25316, 34082, 42848, 51614, 60380
7630	transmembrane protein 44	392432	7785	376227	16551	25317, 34083, 42849, 51615, 60381
7631	transmembrane protein 44	473092	7786	418674	16552	25318, 34084, 42850, 51616, 60382
7632	transmembrane protein 50B	573374	7787	460121	16553	25319, 34085, 42851, 51617, 60383
7633	transmembrane protein 71	356838	7788	349296	16554	25320, 34086, 42852, 51618, 60384
7634	transmembrane protein 71	377901	7789	367133	16555	25321, 34087, 42853, 51619, 60385
7635	transmembrane protein 71	519187	7790	429873	16556	25322, 34088, 42854, 51620, 60386
7636	transmembrane protein 71	519304	7791	430239	16557	25323, 34089, 42855, 51621, 60387
7637	transmembrane protein 8C	339996	7792	419712	16558	25324, 34090, 42856, 51622, 60388
7638	transmembrane protein 95	330767	7793	331466	16559	25325, 34091, 42857, 51623, 60389
7639	transmembrane protein 95	389982	7794	374632	16560	25326, 34092, 42858, 51624, 60390
7640	trehalase precursor	602002	7795	471255	16561	25327, 34093, 42859, 51625, 60391
7641	trichohyalin-like 1	368806	7796	357796	16562	25328, 34094, 42860, 51626, 60392
7642	TRIM39-RPP21 readthrough	513556	7797	424048	16563	25329, 34095, 42861, 51627, 60393
7643	trinucleotide repeat containing 18	327499	7798	330383	16564	25330, 34096, 42862, 51628, 60394

7644	trinucleotide repeat containing 18	399537	7799	382452	16565	25331, 34097, 42863, 51629, 60395
7645	trinucleotide repeat containing 18	399544	7800	382459	16566	25332, 34098, 42864, 51630, 60396
7646	trinucleotide repeat containing 18	415160	7801	388161	16567	25333, 34099, 42865, 51631, 60397
7647	trinucleotide repeat containing 18	430969	7802	395538	16568	25334, 34100, 42866, 51632, 60398
7648	triosephosphate isomerase 1	598287	7803	469966	16569	25335, 34101, 42867, 51633, 60399
7649	tripartite motif containing 15	259930	7804	259930	16570	25336, 34102, 42868, 51634, 60400
7650	tripartite motif containing 15	376688	7805	365878	16571	25337, 34103, 42869, 51635, 60401
7651	tripartite motif containing 15	376694	7806	365884	16572	25338, 34104, 42870, 51636, 60402
7652	tripartite motif containing 15	376695	7807	365885	16573	25339, 34105, 42871, 51637, 60403
7653	tripartite motif containing 15	414873	7808	415480	16574	25340, 34106, 42872, 51638, 60404
7654	tripartite motif containing 15	421984	7809	413961	16575	25341, 34107, 42873, 51639, 60405
7655	tripartite motif containing 15	423220	7810	400174	16576	25342, 34108, 42874, 51640, 60406
7656	tripartite motif containing 15	424597	7811	403836	16577	25343, 34109, 42875, 51641, 60407
7657	tripartite motif containing 15	425255	7812	391673	16578	25344, 34110, 42876, 51642, 60408
7658	tripartite motif containing 15	426765	7813	389858	16579	25345, 34111, 42877, 51643, 60409
7659	tripartite motif containing 15	427091	7814	411683	16580	25346, 34112, 42878, 51644, 60410
7660	tripartite motif containing 15	427952	7815	392768	16581	25347, 34113, 42879, 51645,

						60411
7661	tripartite motif containing 15	429524	7816	409605	16582	25348, 34114, 42880, 51646, 60412
7662	tripartite motif containing 15	430090	7817	398224	16583	25349, 34115, 42881, 51647, 60413
7663	tripartite motif containing 15	431059	7818	403221	16584	25350, 34116, 42882, 51648, 60414
7664	tripartite motif containing 15	433744	7819	398285	16585	25351, 34117, 42883, 51649, 60415
7665	tripartite motif containing 15	440260	7820	402326	16586	25352, 34118, 42884, 51650, 60416
7666	tripartite motif containing 15	444157	7821	412755	16587	25353, 34119, 42885, 51651, 60417
7667	tripartite motif containing 15	546888	7822	447004	16588	25354, 34120, 42886, 51652, 60418
7668	tripartite motif containing 15	548212	7823	450319	16589	25355, 34121, 42887, 51653, 60419
7669	tripartite motif containing 15	548642	7824	449949	16590	25356, 34122, 42888, 51654, 60420
7670	tripartite motif containing 15	548653	7825	447232	16591	25357, 34123, 42889, 51655, 60421
7671	tripartite motif containing 15	548732	7826	449583	16592	25358, 34124, 42890, 51656, 60422
7672	tripartite motif containing 15	549109	7827	448650	16593	25359, 34125, 42891, 51657, 60423
7673	tripartite motif containing 15	550400	7828	447500	16594	25360, 34126, 42892, 51658, 60424
7674	tripartite motif containing 15	550694	7829	450011	16595	25361, 34127, 42893, 51659, 60425
7675	tripartite motif containing 15	550702	7830	448772	16596	25362, 34128, 42894, 51660, 60426
7676	tripartite motif containing 15	550969	7831	447725	16597	25363, 34129, 42895, 51661, 60427
7677	tripartite motif containing	551636	7832	446761	16598	25364, 34130,

	15					42896, 51662, 60428
7678	tripartite motif containing 15	552062	7833	448307	16599	25365, 34131, 42897, 51663, 60429
7679	tripartite motif containing 15	552676	7834	449686	16600	25366, 34132, 42898, 51664, 60430
7680	tripartite motif containing 15	552836	7835	449617	16601	25367, 34133, 42899, 51665, 60431
7681	tripartite motif containing 17	295033	7836	295033	16602	25368, 34134, 42900, 51666, 60432
7682	tripartite motif containing 17	355586	7837	347794	16603	25369, 34135, 42901, 51667, 60433
7683	tripartite motif containing 17	366697	7838	355658	16604	25370, 34136, 42902, 51668, 60434
7684	tripartite motif containing 17	366698	7839	355659	16605	25371, 34137, 42903, 51669, 60435
7685	tripartite motif containing 17	456946	7840	403312	16606	25372, 34138, 42904, 51670, 60436
7686	tripartite motif containing 17	520264	7841	429555	16607	25373, 34139, 42905, 51671, 60437
7687	tripartite motif containing 38	349458	7842	230099	16608	25374, 34140, 42906, 51672, 60438
7688	tripartite motif containing 38	357085	7843	349596	16609	25375, 34141, 42907, 51673, 60439
7689	tripartite motif containing 38	540262	7844	443976	16610	25376, 34142, 42908, 51674, 60440
7690	tripartite motif containing 40	307859	7845	308310	16611	25377, 34143, 42909, 51675, 60441
7691	tripartite motif containing 40	376724	7846	365914	16612	25378, 34144, 42910, 51676, 60442
7692	tripartite motif containing 40	383610	7847	373105	16613	25379, 34145, 42911, 51677, 60443
7693	tripartite motif containing 40	396581	7848	379826	16614	25380, 34146, 42912, 51678, 60444

7694	tripartite motif containing 40	400651	7849	383492	16615	25381, 34147, 42913, 51679, 60445
7695	tripartite motif containing 40	418267	7850	415169	16616	25382, 34148, 42914, 51680, 60446
7696	tripartite motif containing 40	421981	7851	403025	16617	25383, 34149, 42915, 51681, 60447
7697	tripartite motif containing 40	425845	7852	414258	16618	25384, 34150, 42916, 51682, 60448
7698	tripartite motif containing 40	429471	7853	393674	16619	25385, 34151, 42917, 51683, 60449
7699	tripartite motif containing 40	430485	7854	414769	16620	25386, 34152, 42918, 51684, 60450
7700	tripartite motif containing 40	431397	7855	402617	16621	25387, 34153, 42919, 51685, 60451
7701	tripartite motif containing 40	433713	7856	389607	16622	25388, 34154, 42920, 51686, 60452
7702	tripartite motif containing 40	434151	7857	388460	16623	25389, 34155, 42921, 51687, 60453
7703	tripartite motif containing 40	436951	7858	416663	16624	25390, 34156, 42922, 51688, 60454
7704	tripartite motif containing 40	437563	7859	416950	16625	25391, 34157, 42923, 51689, 60455
7705	tripartite motif containing 40	445004	7860	399450	16626	25392, 34158, 42924, 51690, 60456
7706	tripartite motif containing 40	456884	7861	394748	16627	25393, 34159, 42925, 51691, 60457
7707	tripartite motif containing 40	547289	7862	446663	16628	25394, 34160, 42926, 51692, 60458
7708	tripartite motif containing 40	548672	7863	448384	16629	25395, 34161, 42927, 51693, 60459
7709	tripartite motif containing 40	549728	7864	447016	16630	25396, 34162, 42928, 51694, 60460
7710	tripartite motif containing 40	552119	7865	448967	16631	25397, 34163, 42929, 51695,

						60461
7711	tripartite motif containing 42	286349	7866	286349	16632	25398, 34164, 42930, 51696, 60462
7712	tripartite motif containing 43	272395	7867	272395	16633	25399, 34165, 42931, 51697, 60463
7713	tripartite motif containing 46	334634	7868	334657	16634	25400, 34166, 42932, 51698, 60464
7714	tripartite motif containing 46	368382	7869	357366	16635	25401, 34167, 42933, 51699, 60465
7715	tripartite motif containing 46	368383	7870	357367	16636	25402, 34168, 42934, 51700, 60466
7716	tripartite motif containing 46	368385	7871	357369	16637	25403, 34169, 42935, 51701, 60467
7717	tripartite motif containing 46	392451	7872	376245	16638	25404, 34170, 42936, 51702, 60468
7718	tripartite motif containing 46	430513	7873	408696	16639	25405, 34171, 42937, 51703, 60469
7719	tripartite motif containing 46	543729	7874	442719	16640	25406, 34172, 42938, 51704, 60470
7720	tripartite motif containing 46	545012	7875	440254	16641	25407, 34173, 42939, 51705, 60471
7721	tripartite motif containing 48	417545	7876	402414	16642	25408, 34174, 42940, 51706, 60472
7722	tripartite motif containing 49	329758	7877	327604	16643	25409, 34175, 42941, 51707, 60473
7723	tripartite motif containing 49-like 2	432771	7878	396557	16644	25410, 34176, 42942, 51708, 60474
7724	tripartite motif containing 49-like 2	448984	7879	388299	16645	25411, 34177, 42943, 51709, 60475
7725	tripartite motif containing 52	327767	7880	332152	16646	25412, 34178, 42944, 51710, 60476
7726	tripartite motif containing 58	366481	7881	355437	16647	25413, 34179, 42945, 51711, 60477
7727	tripartite motif containing	341062	7882	343765	16648	25414, 34180,

	60					42946, 51712, 60478
7728	tripartite motif containing 60	507119	7883	421784	16649	25415, 34181, 42947, 51713, 60479
7729	tripartite motif containing 60	508504	7884	426496	16650	25416, 34182, 42948, 51714, 60480
7730	tripartite motif containing 60	512596	7885	421142	16651	25417, 34183, 42949, 51715, 60481
7731	tripartite motif containing 61	329314	7886	332288	16652	25418, 34184, 42950, 51716, 60482
7732	tripartite motif containing 62	291416	7887	291416	16653	25419, 34185, 42951, 51717, 60483
7733	tripartite motif containing 62	373430	7888	362529	16654	25420, 34186, 42952, 51718, 60484
7734	tripartite motif containing 62	373432	7889	362531	16655	25421, 34187, 42953, 51719, 60485
7735	tripartite motif containing 62	482586	7890	432294	16656	25422, 34188, 42954, 51720, 60486
7736	tripartite motif containing 62	543586	7891	441173	16657	25423, 34189, 42955, 51721, 60487
7737	tripartite motif containing 64B	329862	7892	332969	16658	25424, 34190, 42956, 51722, 60488
7738	tripartite motif containing 64C	530230	7893	431987	16659	25425, 34191, 42957, 51723, 60489
7739	tripartite motif containing 65	269383	7894	269383	16660	25426, 34192, 42958, 51724, 60490
7740	tripartite motif family-like 1	332517	7895	327738	16661	25427, 34193, 42959, 51725, 60491
7741	tripartite motif family-like 2	512729	7896	422581	16662	25428, 34194, 42960, 51726, 60492
7742	tripartite motif family-like 2	536972	7897	441236	16663	25429, 34195, 42961, 51727, 60493
7743	TRM1 tRNA methyltransferase 1-like	367504	7898	356474	16664	25430, 34196, 42962, 51728, 60494

7744	TRM1 tRNA methyltransferase 1-like	367506	7899	356476	16665	25431, 34197, 42963, 51729, 60495
7745	TRM1 tRNA methyltransferase 1-like	458395	7900	414339	16666	25432, 34198, 42964, 51730, 60496
7746	tRNA methyltransferase 11 homolog (S. cerevisiae)	334379	7901	333934	16667	25433, 34199, 42965, 51731, 60497
7747	tRNA methyltransferase 11 homolog (S. cerevisiae)	368332	7902	357316	16668	25434, 34200, 42966, 51732, 60498
7748	tRNA methyltransferase 11 homolog (S. cerevisiae)	444121	7903	406230	16669	25435, 34201, 42967, 51733, 60499
7749	tRNA methyltransferase 11 homolog (S. cerevisiae)	446681	7904	415724	16670	25436, 34202, 42968, 51734, 60500
7750	tRNA methyltransferase 11 homolog (S. cerevisiae)	450358	7905	405140	16671	25437, 34203, 42969, 51735, 60501
7751	tRNA methyltransferase 11 homolog (S. cerevisiae)	453993	7906	410498	16672	25438, 34204, 42970, 51736, 60502
7752	tRNA methyltransferase 11-2 homolog (S. cerevisiae)	544844	7907	438349	16673	25439, 34205, 42971, 51737, 60503
7753	tRNA methyltransferase 12 homolog (S. cerevisiae)	328599	7908	329858	16674	25440, 34206, 42972, 51738, 60504
7754	tRNA methyltransferase 61 homolog B (S. cerevisiae)	306108	7909	302801	16675	25441, 34207, 42973, 51739, 60505
7755	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	571364	7910	460819	16676	25442, 34208, 42974, 51740, 60506
7756	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	572746	7911	459858	16677	25443, 34209, 42975, 51741, 60507
7757	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	593507	7912	470873	16678	25444, 34210, 42976, 51742, 60508
7758	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	595421	7913	468875	16679	25445, 34211, 42977, 51743, 60509
7759	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	597962	7914	471027	16680	25446, 34212, 42978, 51744, 60510
7760	tRNA splicing endonuclease 34 homolog	598602	7915	471526	16681	25447, 34213, 42979, 51745,

	(S. cerevisiae)					60511
7761	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	598883	7916	472812	16682	25448, 34214, 42980, 51746, 60512
7762	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	599816	7917	469088	16683	25449, 34215, 42981, 51747, 60513
7763	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	600856	7918	469743	16684	25450, 34216, 42982, 51748, 60514
7764	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	600870	7919	471131	16685	25451, 34217, 42983, 51749, 60515
7765	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	601248	7920	469131	16686	25452, 34218, 42984, 51750, 60516
7766	tRNA splicing endonuclease 34 homolog (S. cerevisiae)	601721	7921	470924	16687	25453, 34219, 42985, 51751, 60517
7767	tRNA-yW synthesizing protein 1 homolog (S. cerevisiae)	359626	7922	352645	16688	25454, 34220, 42986, 51752, 60518
7768	tRNA-yW synthesizing protein 1 homolog (S. cerevisiae)	389196	7923	373848	16689	25455, 34221, 42987, 51753, 60519
7769	tRNA-yW synthesizing protein 1 homolog (S. cerevisiae)	445198	7924	414367	16690	25456, 34222, 42988, 51754, 60520
7770	tRNA-yW synthesizing protein 3 homolog (S. cerevisiae)	370867	7925	359904	16691	25457, 34223, 42989, 51755, 60521
7771	tRNA-yW synthesizing protein 3 homolog (S. cerevisiae)	421739	7926	409336	16692	25458, 34224, 42990, 51756, 60522
7772	tRNA-yW synthesizing protein 3 homolog (S. cerevisiae)	457880	7927	407025	16693	25459, 34225, 42991, 51757, 60523
7773	tRNA-yW synthesizing protein 5	354611	7928	346627	16694	25460, 34226, 42992, 51758, 60524
7774	tryptase beta 2 (gene/pseudogene)	430512	7929	412409	16695	25461, 34227, 42993, 51759, 60525
7775	TSC22 domain family, member 2	361136	7930	354893	16696	25462, 34228, 42994, 51760, 60526
7776	TSC22 domain family, member 2	361875	7931	354543	16697	25463, 34229, 42995, 51761, 60527
7777	TSC22 domain family,	543241	7932	443954	16698	25464, 34230,

	member 2					42996, 51762, 60528
7778	TSR2, 20S rRNA accumulation, homolog (S. cerevisiae)	375151	7933	364293	16699	25465, 34231, 42997, 51763, 60529
7779	tubulin tyrosine ligase-like family, member 12	216129	7934	216129	16700	25466, 34232, 42998, 51764, 60530
7780	tubulin tyrosine ligase-like family, member 12	357017	7935	349521	16701	25467, 34233, 42999, 51765, 60531
7781	tubulin tyrosine ligase-like family, member 13	339615	7936	345294	16702	25468, 34234, 43000, 51766, 60532
7782	tubulin tyrosine ligase-like family, member 13	438251	7937	413362	16703	25469, 34235, 43001, 51767, 60533
7783	tubulin tyrosine ligase-like family, member 2	239587	7938	239587	16704	25470, 34236, 43002, 51768, 60534
7784	tubulin tyrosine ligase-like family, member 2	540954	7939	440649	16705	25471, 34237, 43003, 51769, 60535
7785	tubulin tyrosine ligase-like family, member 7	370703	7940	359737	16706	25472, 34238, 43004, 51770, 60536
7786	tubulin tyrosine ligase-like family, member 7	370704	7941	359738	16707	25473, 34239, 43005, 51771, 60537
7787	tudor domain containing 10	368480	7942	357465	16708	25474, 34240, 43006, 51772, 60538
7788	tudor domain containing 10	368482	7943	357467	16709	25475, 34241, 43007, 51773, 60539
7789	tudor domain containing 12	421545	7944	390621	16710	25476, 34242, 43008, 51774, 60540
7790	tudor domain containing 12	444215	7945	416248	16711	25477, 34243, 43009, 51775, 60541
7791	tumor necrosis factor, alpha-induced protein 8-like 1	327473	7946	331827	16712	25478, 34244, 43010, 51776, 60542
7792	tumor necrosis factor, alpha-induced protein 8-like 1	536716	7947	444215	16713	25479, 34245, 43011, 51777, 60543
7793	tumor necrosis factor, alpha-induced protein 8-like 3	327536	7948	328016	16714	25480, 34246, 43012, 51778, 60544

7794	tumor protein D52-like 3	314556	7949	318665	16715	25481, 34247, 43013, 51779, 60545
7795	tumor protein D52-like 3	344545	7950	341677	16716	25482, 34248, 43014, 51780, 60546
7796	tumor protein D52-like 3	381428	7951	370836	16717	25483, 34249, 43015, 51781, 60547
7797	tumor protein p53 inducible protein 3	238721	7952	238721	16718	25484, 34250, 43016, 51782, 60548
7798	tumor protein p53 inducible protein 3	313482	7953	322298	16719	25485, 34251, 43017, 51783, 60549
7799	tumor protein p53 inducible protein 3	335934	7954	337834	16720	25486, 34252, 43018, 51784, 60550
7800	tumor protein p53 inducible protein 3	413037	7955	389620	16721	25487, 34253, 43019, 51785, 60551
7801	tumor protein p53 regulated apoptosis inducing protein 1	458238	7956	390694	16722	25488, 34254, 43020, 51786, 60552
7802	tumor protein p53 regulated apoptosis inducing protein 1	530777	7957	432908	16723	25489, 34255, 43021, 51787, 60553
7803	Type III iodothyronine deiodinase	359323	7958	352273	16724	25490, 34256, 43022, 51788, 60554
7804	Tyrosine-protein kinase SgK223	330777	7959	330930	16725	25491, 34257, 43023, 51789, 60555
7805	Tyrosine-protein kinase SgK223	520004	7960	428054	16726	25492, 34258, 43024, 51790, 60556
7806	U2 small nuclear RNA auxiliary factor 2	450554	7961	388475	16727	25493, 34259, 43025, 51791, 60557
7807	ubiquilin-like	538889	7962	445178	16728	25494, 34260, 43026, 51792, 60558
7808	ubiquilin-like	380184	7963	369531	16729	25495, 34261, 43027, 51793, 60559
7809	ubiquitin associated protein 1-like	502113	7964	440243	16730	25496, 34262, 43028, 51794, 60560
7810	ubiquitin associated protein 1-like	559089	7965	454012	16731	25497, 34263, 43029, 51795,

						60561
7811	ubiquitin associated protein 2	351580	7966	259602	16732	25498, 34264, 43030, 51796, 60562
7812	ubiquitin associated protein 2	360802	7967	354039	16733	25499, 34265, 43031, 51797, 60563
7813	ubiquitin associated protein 2	379225	7968	368527	16734	25500, 34266, 43032, 51798, 60564
7814	ubiquitin associated protein 2	379235	7969	368537	16735	25501, 34267, 43033, 51799, 60565
7815	ubiquitin associated protein 2	379238	7970	368540	16736	25502, 34268, 43034, 51800, 60566
7816	ubiquitin associated protein 2	379239	7971	368541	16737	25503, 34269, 43035, 51801, 60567
7817	ubiquitin associated protein 2	379260	7972	368562	16738	25504, 34270, 43036, 51802, 60568
7818	ubiquitin associated protein 2	412543	7973	414800	16739	25505, 34271, 43037, 51803, 60569
7819	ubiquitin associated protein 2	418786	7974	404436	16740	25506, 34272, 43038, 51804, 60570
7820	ubiquitin associated protein 2	421278	7975	412954	16741	25507, 34273, 43039, 51805, 60571
7821	ubiquitin associated protein 2	431417	7976	414684	16742	25508, 34274, 43040, 51806, 60572
7822	ubiquitin associated protein 2	449054	7977	416932	16743	25509, 34275, 43041, 51807, 60573
7823	ubiquitin associated protein 2	539807	7978	439329	16744	25510, 34276, 43042, 51808, 60574
7824	Ubiquitin carboxyl-terminal hydrolase 17	421288	7979	390759	16745	25511, 34277, 43043, 51809, 60575
7825	ubiquitin domain containing 1	370664	7980	359698	16746	25512, 34278, 43044, 51810, 60576
7826	ubiquitin family domain containing 1	219638	7981	219638	16747	25513, 34279, 43045, 51811, 60577
7827	ubiquitin family domain	395878	7982	379217	16748	25514, 34280,

	containing 1					43046, 51812, 60578
7828	ubiquitin family domain containing 1	399462	7983	402391	16749	25515, 34281, 43047, 51813, 60579
7829	ubiquitin protein ligase E3B	280774	7984	280774	16750	25516, 34282, 43048, 51814, 60580
7830	ubiquitin protein ligase E3B	340074	7985	342614	16751	25517, 34283, 43049, 51815, 60581
7831	ubiquitin protein ligase E3B	342494	7986	340596	16752	25518, 34284, 43050, 51816, 60582
7832	ubiquitin protein ligase E3B	434735	7987	391529	16753	25519, 34285, 43051, 51817, 60583
7833	ubiquitin protein ligase E3B	535089	7988	442276	16754	25520, 34286, 43052, 51818, 60584
7834	ubiquitin protein ligase E3B	536398	7989	440585	16755	25521, 34287, 43053, 51819, 60585
7835	ubiquitin protein ligase E3B	538070	7990	446233	16756	25522, 34288, 43054, 51820, 60586
7836	ubiquitin protein ligase E3B	539599	7991	443131	16757	25523, 34289, 43055, 51821, 60587
7837	ubiquitin protein ligase E3B	540230	7992	443565	16758	25524, 34290, 43056, 51822, 60588
7838	ubiquitin specific peptidase 15	280377	7993	280377	16759	25525, 34291, 43057, 51823, 60589
7839	ubiquitin specific peptidase 15	353364	7994	258123	16760	25526, 34292, 43058, 51824, 60590
7840	ubiquitin specific peptidase 15	393654	7995	377264	16761	25527, 34293, 43059, 51825, 60591
7841	ubiquitin specific peptidase 15	312635	7996	309240	16762	25528, 34294, 43060, 51826, 60592
7842	ubiquitin specific peptidase 29	254181	7997	254181	16763	25529, 34295, 43061, 51827, 60593
7843	ubiquitin specific peptidase 31	219689	7998	219689	16764	25530, 34296, 43062, 51828, 60594

7844	ubiquitin specific peptidase 31	381162	7999	370554	16765	25531, 34297, 43063, 51829, 60595
7845	ubiquitin specific peptidase 34	263989	8000	263989	16766	25532, 34298, 43064, 51830, 60596
7846	ubiquitin specific peptidase 34	398569	8001	381575	16767	25533, 34299, 43065, 51831, 60597
7847	ubiquitin specific peptidase 34	398571	8002	381577	16768	25534, 34300, 43066, 51832, 60598
7848	ubiquitin specific peptidase 35	441408	8003	400825	16769	25535, 34301, 43067, 51833, 60599
7849	ubiquitin specific peptidase 35	529308	8004	431876	16770	25536, 34302, 43068, 51834, 60600
7850	ubiquitin specific peptidase 38	307017	8005	303434	16771	25537, 34303, 43069, 51835, 60601
7851	ubiquitin specific peptidase 40	251722	8006	251722	16772	25538, 34304, 43070, 51836, 60602
7852	ubiquitin specific peptidase 40	409945	8007	386664	16773	25539, 34305, 43071, 51837, 60603
7853	ubiquitin specific peptidase 40	427112	8008	387898	16774	25540, 34306, 43072, 51838, 60604
7854	ubiquitin specific peptidase 40	435959	8009	398914	16775	25541, 34307, 43073, 51839, 60605
7855	ubiquitin specific peptidase 40	450966	8010	415434	16776	25542, 34308, 43074, 51840, 60606
7856	ubiquitin specific peptidase 41	454608	8011	414922	16777	25543, 34309, 43075, 51841, 60607
7857	ubiquitin specific peptidase 42	306177	8012	301962	16778	25544, 34310, 43076, 51842, 60608
7858	ubiquitin specific peptidase 43	285199	8013	285199	16779	25545, 34311, 43077, 51843, 60609
7859	ubiquitin specific peptidase 43	570475	8014	458963	16780	25546, 34312, 43078, 51844, 60610
7860	ubiquitin specific peptidase 45	327681	8015	333376	16781	25547, 34313, 43079, 51845,

						60611
7861	ubiquitin specific peptidase 45	329966	8016	330540	16782	25548, 34314, 43080, 51846, 60612
7862	ubiquitin specific peptidase 45	369231	8017	358234	16783	25549, 34315, 43081, 51847, 60613
7863	ubiquitin specific peptidase 45	392738	8018	376495	16784	25550, 34316, 43082, 51848, 60614
7864	ubiquitin specific peptidase 45	472914	8019	423993	16785	25551, 34317, 43083, 51849, 60615
7865	ubiquitin specific peptidase 45	500704	8020	424372	16786	25552, 34318, 43084, 51850, 60616
7866	ubiquitin specific peptidase 45	508908	8021	426861	16787	25553, 34319, 43085, 51851, 60617
7867	ubiquitin specific peptidase 45	539675	8022	439569	16788	25554, 34320, 43086, 51852, 60618
7868	ubiquitin specific peptidase 49	297229	8023	297229	16789	25555, 34321, 43087, 51853, 60619
7869	ubiquitin specific peptidase 49	373006	8024	362097	16790	25556, 34322, 43088, 51854, 60620
7870	ubiquitin specific peptidase 49	373009	8025	362100	16791	25557, 34323, 43089, 51855, 60621
7871	ubiquitin specific peptidase 49	394253	8026	377797	16792	25558, 34324, 43090, 51856, 60622
7872	ubiquitin specific peptidase 49	423567	8027	411603	16793	25559, 34325, 43091, 51857, 60623
7873	ubiquitin specific peptidase 49	437061	8028	410003	16794	25560, 34326, 43092, 51858, 60624
7874	ubiquitin specific peptidase 50	532404	8029	434676	16795	25561, 34327, 43093, 51859, 60625
7875	ubiquitin specific peptidase 51	500968	8030	423333	16796	25562, 34328, 43094, 51860, 60626
7876	ubiquitin specific peptidase 53	274030	8031	274030	16797	25563, 34329, 43095, 51861, 60627
7877	ubiquitin specific peptidase	450251	8032	409906	16798	25564, 34330,

	53					43096, 51862, 60628
7878	ubiquitin specific peptidase 54	319786	8033	326547	16799	25565, 34331, 43097, 51863, 60629
7879	ubiquitin specific peptidase 54	339859	8034	345216	16800	25566, 34332, 43098, 51864, 60630
7880	ubiquitin specific peptidase 54	394811	8035	378290	16801	25567, 34333, 43099, 51865, 60631
7881	ubiquitin specific peptidase 54	408019	8036	386080	16802	25568, 34334, 43100, 51866, 60632
7882	ubiquitin specific peptidase 54	413442	8037	404710	16803	25569, 34335, 43101, 51867, 60633
7883	ubiquitin specific peptidase 54	422491	8038	407368	16804	25570, 34336, 43102, 51868, 60634
7884	ubiquitin specific peptidase 54	428547	8039	408714	16805	25571, 34337, 43103, 51869, 60635
7885	ubiquitin specific peptidase 54	433394	8040	407245	16806	25572, 34338, 43104, 51870, 60636
7886	ubiquitin specific peptidase like 1	255304	8041	255304	16807	25573, 34339, 43105, 51871, 60637
7887	ubiquitin-conjugating enzyme E2D 2	253815	8042	253815	16808	25574, 34340, 43106, 51872, 60638
7888	ubiquitin-conjugating enzyme E2D 2	398733	8043	381717	16809	25575, 34341, 43107, 51873, 60639
7889	ubiquitin-conjugating enzyme E2D 2	398734	8044	381718	16810	25576, 34342, 43108, 51874, 60640
7890	ubiquitin-conjugating enzyme E2D 2	505548	8045	424941	16811	25577, 34343, 43109, 51875, 60641
7891	ubiquitin-conjugating enzyme E2D 4 (putative)	222402	8046	222402	16812	25578, 34344, 43110, 51876, 60642, 61560, 61628
7892	ubiquitin-conjugating enzyme E2D 4 (putative)	394798	8047	378277	16813	25579, 34345, 43111, 51877, 60643
7893	ubiquitin-conjugating enzyme E2F (putative)	272930	8048	272930	16814	25580, 34346, 43112, 51878,

						60644
7894	ubiquitin-conjugating enzyme E2F (putative)	414443	8049	399183	16815	25581, 34347, 43113, 51879, 60645
7895	ubiquitin-conjugating enzyme E2F (putative)	434655	8050	406113	16816	25582, 34348, 43114, 51880, 60646
7896	ubiquitin-conjugating enzyme E2G 1	396981	8051	380178	16817	25583, 34349, 43115, 51881, 60647
7897	ubiquitin-conjugating enzyme E2M	253023	8052	253023	16818	25584, 34350, 43116, 51882, 60648
7898	ubiquitin-conjugating enzyme E2O	319380	8053	323687	16819	25585, 34351, 43117, 51883, 60649
7899	ubiquitin-conjugating enzyme E2Q family member 1	292211	8054	292211	16820	25586, 34352, 43118, 51884, 60650
7900	ubiquitin-conjugating enzyme E2Q family-like 1	399816	8055	382713	16821	25587, 34353, 43119, 51885, 60651
7901	ubiquitin-conjugating enzyme E2U (putative)	371076	8056	360116	16822	25588, 34354, 43120, 51886, 60652
7902	ubiquitin-conjugating enzyme E2U (putative)	371077	8057	360117	16823	25589, 34355, 43121, 51887, 60653
7903	ubiquitin-fold modifier conjugating enzyme 1	368003	8058	356982	16824	25590, 34356, 43122, 51888, 60654
7904	ubiquitin-like modifier activating enzyme 1	335972	8059	338413	16825	25591, 34357, 43123, 51889, 60655
7905	ubiquitin-like modifier activating enzyme 1	377269	8060	366481	16826	25592, 34358, 43124, 51890, 60656
7906	ubiquitin-like modifier activating enzyme 1	377351	8061	366568	16827	25593, 34359, 43125, 51891, 60657
7907	ubiquitin-like modifier activating enzyme 1	412206	8062	415033	16828	25594, 34360, 43126, 51892, 60658
7908	ubiquitin-like modifier activating enzyme 1	427561	8063	397816	16829	25595, 34361, 43127, 51893, 60659
7909	ubiquitin-like modifier activating enzyme 1	442035	8064	389583	16830	25596, 34362, 43128, 51894, 60660
7910	ubiquitin-like modifier	451702	8065	401101	16831	25597, 34363,

	activating enzyme 1					43129, 51895, 60661
7911	ubiquitin-like modifier activating enzyme 1	457753	8066	404796	16832	25598, 34364, 43130, 51896, 60662
7912	UBX domain protein 10	375099	8067	364240	16833	25599, 34365, 43131, 51897, 60663
7913	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6 (core 3 synthase)	354301	8068	346256	16834	25600, 34366, 43132, 51898, 60664
7914	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6 (core 3 synthase)	421061	8069	403463	16835	25601, 34367, 43133, 51899, 60665
7915	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6 (core 3 synthase)	528622	8070	435628	16836	25602, 34368, 43134, 51900, 60666
7916	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 6 (core 3 synthase)	533140	8071	435352	16837	25603, 34369, 43135, 51901, 60667
7917	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase-like 1	320865	8072	319979	16838	25604, 34370, 43136, 51902, 60668
7918	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	328957	8073	329846	16839	25605, 34371, 43137, 51903, 60669
7919	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	397325	8074	380488	16840	25606, 34372, 43138, 51904, 60670
7920	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	535228	8075	439745	16841	25607, 34373, 43139, 51905, 60671
7921	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	538356	8076	444709	16842	25608, 34374, 43140, 51906, 60672
7922	UDP-N-acetyl-alpha-D-galactosamine:polypeptide	541995	8077	440544	16843	25609, 34375, 43141, 51907,

	N-acetylgalactosaminyltransferase 9 (GalNAc-T9)					60673
7923	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	542942	8078	438221	16844	25610, 34376, 43142, 51908, 60674
7924	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	562730	8079	455804	16845	25611, 34377, 43143, 51909, 60675
7925	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 9 (GalNAc-T9)	566593	8080	457075	16846	25612, 34378, 43144, 51910, 60676
7926	UDP-N-acteylglucosamine pyrophosphorylase 1-like 1	360271	8081	353409	16847	25613, 34379, 43145, 51911, 60677
7927	UDP-N-acteylglucosamine pyrophosphorylase 1-like 1	409858	8082	386935	16848	25614, 34380, 43146, 51912, 60678
7928	UHRF1 binding protein 1	192788	8083	192788	16849	25615, 34381, 43147, 51913, 60679
7929	UHRF1 binding protein 1	452449	8084	400628	16850	25616, 34382, 43148, 51914, 60680
7930	UHRF1 binding protein 1-like	279907	8085	279907	16851	25617, 34383, 43149, 51915, 60681
7931	UHRF1 binding protein 1-like	356828	8086	349285	16852	25618, 34384, 43150, 51916, 60682
7932	unc-119 homolog B (C. elegans)	344651	8087	344942	16853	25619, 34385, 43151, 51917, 60683
7933	unc-119 homolog B (C. elegans)	537794	8088	438905	16854	25620, 34386, 43152, 51918, 60684
7934	unc-51-like kinase 4 (C. elegans)	301831	8089	301831	16855	25621, 34387, 43153, 51919, 60685
7935	unc-51-like kinase 4 (C. elegans) pseudogene 1	321578	8090	314827	16856	25622, 34388, 43154, 51920, 60686
7936	unc-51-like kinase 4 (C. elegans) pseudogene 3	341955	8091	345449	16857	25623, 34389, 43155, 51921,

						60687
7937	unc-79 homolog (C. elegans)	256339	8092	256339	16858	25624, 34390, 43156, 51922, 60688
7938	unc-79 homolog (C. elegans)	393151	8093	376858	16859	25625, 34391, 43157, 51923, 60689
7939	unc-79 homolog (C. elegans)	393153	8094	376860	16860	25626, 34392, 43158, 51924, 60690
7940	unc-79 homolog (C. elegans)	553484	8095	451360	16861	25627, 34393, 43159, 51925, 60691
7941	Uncharacterized membrane protein C19orf24	416408	8096	407816	16862	25628, 34394, 43160, 51926, 60692
7942	Uncharacterized protein	295844	8097	295844	16863	25629, 34395, 43161, 51927, 60693
7943	Uncharacterized protein	304488	8098	304875	16864	25630, 34396, 43162, 51928, 60694
7944	Uncharacterized protein	307499	8099	306241	16865	25631, 34397, 43163, 51929, 60695
7945	Uncharacterized protein	313865	8100	325519	16866	25632, 34398, 43164, 51930, 60696
7946	Uncharacterized protein	314552	8101	321316	16867	25633, 34399, 43165, 51931, 60697
7947	Uncharacterized protein	317008	8102	408302	16868	25634, 34400, 43166, 51932, 60698
7948	Uncharacterized protein	318117	8103	313363	16869	25635, 34401, 43167, 51933, 60699
7949	Uncharacterized protein	318245	8104	317235	16870	25636, 34402, 43168, 51934, 60700
7950	Uncharacterized protein	318959	8105	320221	16871	25637, 34403, 43169, 51935, 60701
7951	Uncharacterized protein	321930	8106	415462	16872	25638, 34404, 43170, 51936, 60702
7952	Uncharacterized protein	325811	8107	316959	16873	25639, 34405, 43171, 51937, 60703
7953	Uncharacterized protein	325845	8108	449128	16874	25640, 34406,

						43172, 51938, 60704
7954	Uncharacterized protein	326780	8109	317768	16875	25641, 34407, 43173, 51939, 60705
7955	Uncharacterized protein	327607	8110	330326	16876	25642, 34408, 43174, 51940, 60706
7956	Uncharacterized protein	329793	8111	331460	16877	25643, 34409, 43175, 51941, 60707
7957	Uncharacterized protein	333110	8112	333711	16878	25644, 34410, 43176, 51942, 60708
7958	Uncharacterized protein	334973	8113	334143	16879	25645, 34411, 43177, 51943, 60709
7959	Uncharacterized protein	335083	8114	334090	16880	25646, 34412, 43178, 51944, 60710
7960	Uncharacterized protein	335616	8115	334077	16881	25647, 34413, 43179, 51945, 60711
7961	Uncharacterized protein	339120	8116	339793	16882	25648, 34414, 43180, 51946, 60712
7962	Uncharacterized protein	339303	8117	445812	16883	25649, 34415, 43181, 51947, 60713
7963	Uncharacterized protein	340249	8118	344295	16884	25650, 34416, 43182, 51948, 60714
7964	Uncharacterized protein	342888	8119	341237	16885	25651, 34417, 43183, 51949, 60715
7965	Uncharacterized protein	354563	8120	346572	16886	25652, 34418, 43184, 51950, 60716
7966	Uncharacterized protein	356801	8121	349255	16887	25653, 34419, 43185, 51951, 60717
7967	Uncharacterized protein	358748	8122	351598	16888	25654, 34420, 43186, 51952, 60718
7968	Uncharacterized protein	360625	8123	397372	16889	25655, 34421, 43187, 51953, 60719
7969	Uncharacterized protein	369190	8124	358191	16890	25656, 34422, 43188, 51954, 60720

7970	Uncharacterized protein	369365	8125	358372	16891	25657, 34423, 43189, 51955, 60721
7971	Uncharacterized protein	369372	8126	358379	16892	25658, 34424, 43190, 51956, 60722
7972	Uncharacterized protein	369373	8127	358380	16893	25659, 34425, 43191, 51957, 60723
7973	Uncharacterized protein	369654	8128	358668	16894	25660, 34426, 43192, 51958, 60724
7974	Uncharacterized protein	369655	8129	358669	16895	25661, 34427, 43193, 51959, 60725
7975	Uncharacterized protein	369657	8130	358671	16896	25662, 34428, 43194, 51960, 60726
7976	Uncharacterized protein	371162	8131	360204	16897	25663, 34429, 43195, 51961, 60727
7977	Uncharacterized protein	374258	8132	363376	16898	25664, 34430, 43196, 51962, 60728
7978	Uncharacterized protein	374976	8133	364115	16899	25665, 34431, 43197, 51963, 60729
7979	Uncharacterized protein	377296	8134	366511	16900	25666, 34432, 43198, 51964, 60730
7980	Uncharacterized protein	377540	8135	366763	16901	25667, 34433, 43199, 51965, 60731
7981	Uncharacterized protein	377571	8136	366794	16902	25668, 34434, 43200, 51966, 60732
7982	Uncharacterized protein	378337	8137	407866	16903	25669, 34435, 43201, 51967, 60733
7983	Uncharacterized protein	379336	8138	395075	16904	25670, 34436, 43202, 51968, 60734
7984	Uncharacterized protein	379458	8139	368771	16905	25671, 34437, 43203, 51969, 60735
7985	Uncharacterized protein	381466	8140	370875	16906	25672, 34438, 43204, 51970, 60736
7986	Uncharacterized protein	383040	8141	372510	16907	25673, 34439, 43205, 51971,

						60737
7987	Uncharacterized protein	383146	8142	384224	16908	25674, 34440, 43206, 51972, 60738
7988	Uncharacterized protein	383535	8143	373027	16909	25675, 34441, 43207, 51973, 60739
7989	Uncharacterized protein	391366	8144	375174	16910	25676, 34442, 43208, 51974, 60740
7990	Uncharacterized protein	391405	8145	375222	16911	25677, 34443, 43209, 51975, 60741
7991	Uncharacterized protein	392227	8146	376061	16912	25678, 34444, 43210, 51976, 60742
7992	Uncharacterized protein	392468	8147	376261	16913	25679, 34445, 43211, 51977, 60743
7993	Uncharacterized protein	396489	8148	379747	16914	25680, 34446, 43212, 51978, 60744
7994	Uncharacterized protein	397190	8149	380374	16915	25681, 34447, 43213, 51979, 60745
7995	Uncharacterized protein	398726	8150	381711	16916	25682, 34448, 43214, 51980, 60746
7996	Uncharacterized protein	398832	8151	381813	16917	25683, 34449, 43215, 51981, 60747
7997	Uncharacterized protein	398875	8152	381850	16918	25684, 34450, 43216, 51982, 60748
7998	Uncharacterized protein	398976	8153	381948	16919	25685, 34451, 43217, 51983, 60749
7999	Uncharacterized protein	399086	8154	382036	16920	25686, 34452, 43218, 51984, 60750
8000	Uncharacterized protein	399087	8155	382037	16921	25687, 34453, 43219, 51985, 60751
8001	Uncharacterized protein	399342	8156	382280	16922	25688, 34454, 43220, 51986, 60752
8002	Uncharacterized protein	399576	8157	382486	16923	25689, 34455, 43221, 51987, 60753
8003	Uncharacterized protein	400449	8158	383299	16924	25690, 34456,

						43222, 51988, 60754
8004	Uncharacterized protein	400512	8159	383356	16925	25691, 34457, 43223, 51989, 60755
8005	Uncharacterized protein	400514	8160	383358	16926	25692, 34458, 43224, 51990, 60756
8006	Uncharacterized protein	400592	8161	383435	16927	25693, 34459, 43225, 51991, 60757
8007	Uncharacterized protein	400676	8162	383515	16928	25694, 34460, 43226, 51992, 60758
8008	Uncharacterized protein	400678	8163	383517	16929	25695, 34461, 43227, 51993, 60759
8009	Uncharacterized protein	400681	8164	383520	16930	25696, 34462, 43228, 51994, 60760
8010	Uncharacterized protein	400840	8165	383640	16931	25697, 34463, 43229, 51995, 60761
8011	Uncharacterized protein	404649	8166	385364	16932	25698, 34464, 43230, 51996, 60762
8012	Uncharacterized protein	406767	8167	385758	16933	25699, 34465, 43231, 51997, 60763
8013	Uncharacterized protein	407042	8168	383952	16934	25700, 34466, 43232, 51998, 60764
8014	Uncharacterized protein	407384	8169	384049	16935	25701, 34467, 43233, 51999, 60765
8015	Uncharacterized protein	407600	8170	385341	16936	25702, 34468, 43234, 52000, 60766
8016	Uncharacterized protein	412624	8171	404564	16937	25703, 34469, 43235, 52001, 60767
8017	Uncharacterized protein	413283	8172	405556	16938	25704, 34470, 43236, 52002, 60768
8018	Uncharacterized protein	414155	8173	392262	16939	25705, 34471, 43237, 52003, 60769
8019	Uncharacterized protein	415643	8174	407755	16940	25706, 34472, 43238, 52004, 60770

8020	Uncharacterized protein	418788	8175	443195	16941	25707, 34473, 43239, 52005, 60771
8021	Uncharacterized protein	419755	8176	398526	16942	25708, 34474, 43240, 52006, 60772
8022	Uncharacterized protein	420338	8177	411125	16943	25709, 34475, 43241, 52007, 60773
8023	Uncharacterized protein	421555	8178	412038	16944	25710, 34476, 43242, 52008, 60774
8024	Uncharacterized protein	423459	8179	391091	16945	25711, 34477, 43243, 52009, 60775
8025	Uncharacterized protein	424538	8180	387845	16946	25712, 34478, 43244, 52010, 60776
8026	Uncharacterized protein	424958	8181	389658	16947	25713, 34479, 43245, 52011, 60777
8027	Uncharacterized protein	425159	8182	411291	16948	25714, 34480, 43246, 52012, 60778
8028	Uncharacterized protein	425566	8183	400635	16949	25715, 34481, 43247, 52013, 60779
8029	Uncharacterized protein	426571	8184	405228	16950	25716, 34482, 43248, 52014, 60780
8030	Uncharacterized protein	429672	8185	414638	16951	25717, 34483, 43249, 52015, 60781
8031	Uncharacterized protein	429930	8186	440385	16952	25718, 34484, 43250, 52016, 60782
8032	Uncharacterized protein	431326	8187	406579	16953	25719, 34485, 43251, 52017, 60783
8033	Uncharacterized protein	432570	8188	411109	16954	25720, 34486, 43252, 52018, 60784
8034	Uncharacterized protein	433279	8189	392610	16955	25721, 34487, 43253, 52019, 60785
8035	Uncharacterized protein	436381	8190	397111	16956	25722, 34488, 43254, 52020, 60786
8036	Uncharacterized protein	436832	8191	401500	16957	25723, 34489, 43255, 52021,

						60787
8037	Uncharacterized protein	436901	8192	391536	16958	25724, 34490, 43256, 52022, 60788
8038	Uncharacterized protein	436914	8193	393682	16959	25725, 34491, 43257, 52023, 60789
8039	Uncharacterized protein	437887	8194	409748	16960	25726, 34492, 43258, 52024, 60790
8040	Uncharacterized protein	438078	8195	395413	16961	25727, 34493, 43259, 52025, 60791
8041	Uncharacterized protein	438516	8196	400918	16962	25728, 34494, 43260, 52026, 60792
8042	Uncharacterized protein	440990	8197	395811	16963	25729, 34495, 43261, 52027, 60793
8043	Uncharacterized protein	442514	8198	439057	16964	25730, 34496, 43262, 52028, 60794
8044	Uncharacterized protein	445770	8199	416897	16965	25731, 34497, 43263, 52029, 60795
8045	Uncharacterized protein	448136	8200	394384	16966	25732, 34498, 43264, 52030, 60796
8046	Uncharacterized protein	448615	8201	403936	16967	25733, 34499, 43265, 52031, 60797
8047	Uncharacterized protein	449355	8202	411673	16968	25734, 34500, 43266, 52032, 60798
8048	Uncharacterized protein	450789	8203	415825	16969	25735, 34501, 43267, 52033, 60799
8049	Uncharacterized protein	450958	8204	392350	16970	25736, 34502, 43268, 52034, 60800
8050	Uncharacterized protein	451356	8205	391622	16971	25737, 34503, 43269, 52035, 60801
8051	Uncharacterized protein	453326	8206	392879	16972	25738, 34504, 43270, 52036, 60802
8052	Uncharacterized protein	453638	8207	443634	16973	25739, 34505, 43271, 52037, 60803
8053	Uncharacterized protein	454258	8208	401894	16974	25740, 34506,

						43272, 52038, 60804
8054	Uncharacterized protein	456544	8209	391134	16975	25741, 34507, 43273, 52039, 60805
8055	Uncharacterized protein	457364	8210	392851	16976	25742, 34508, 43274, 52040, 60806
8056	Uncharacterized protein	457728	8211	416075	16977	25743, 34509, 43275, 52041, 60807
8057	Uncharacterized protein	466655	8212	445695	16978	25744, 34510, 43276, 52042, 60808
8058	Uncharacterized protein	502413	8213	443359	16979	25745, 34511, 43277, 52043, 60809
8059	Uncharacterized protein	510574	8214	427681	16980	25746, 34512, 43278, 52044, 60810
8060	Uncharacterized protein	512626	8215	426691	16981	25747, 34513, 43279, 52045, 60811
8061	Uncharacterized protein	523795	8216	431198	16982	25748, 34514, 43280, 52046, 60812
8062	Uncharacterized protein	535113	8217	445093	16983	25749, 34515, 43281, 52047, 60813
8063	Uncharacterized protein	535339	8218	441891	16984	25750, 34516, 43282, 52048, 60814
8064	Uncharacterized protein	536432	8219	437400	16985	25751, 34517, 43283, 52049, 60815
8065	Uncharacterized protein	536896	8220	442451	16986	25752, 34518, 43284, 52050, 60816
8066	Uncharacterized protein	538264	8221	438251	16987	25753, 34519, 43285, 52051, 60817
8067	Uncharacterized protein	538519	8222	437917	16988	25754, 34520, 43286, 52052, 60818
8068	Uncharacterized protein	538668	8223	445522	16989	25755, 34521, 43287, 52053, 60819
8069	Uncharacterized protein	538795	8224	437481	16990	25756, 34522, 43288, 52054, 60820

8070	Uncharacterized protein	539033	8225	437563	16991	25757, 34523, 43289, 52055, 60821
8071	Uncharacterized protein	539278	8226	441047	16992	25758, 34524, 43290, 52056, 60822
8072	Uncharacterized protein	539422	8227	438970	16993	25759, 34525, 43291, 52057, 60823
8073	Uncharacterized protein	541917	8228	437957	16994	25760, 34526, 43292, 52058, 60824
8074	Uncharacterized protein	542270	8229	445063	16995	25761, 34527, 43293, 52059, 60825
8075	Uncharacterized protein	543012	8230	446256	16996	25762, 34528, 43294, 52060, 60826
8076	Uncharacterized protein	543801	8231	441072	16997	25763, 34529, 43295, 52061, 60827
8077	Uncharacterized protein	544678	8232	439791	16998	25764, 34530, 43296, 52062, 60828
8078	Uncharacterized protein	545087	8233	443317	16999	25765, 34531, 43297, 52063, 60829
8079	Uncharacterized protein	546494	8234	447984	17000	25766, 34532, 43298, 52064, 60830
8080	Uncharacterized protein	547001	8235	446532	17001	25767, 34533, 43299, 52065, 60831
8081	Uncharacterized protein	547334	8236	449885	17002	25768, 34534, 43300, 52066, 60832
8082	Uncharacterized protein	547599	8237	448890	17003	25769, 34535, 43301, 52067, 60833
8083	Uncharacterized protein	548061	8238	450354	17004	25770, 34536, 43302, 52068, 60834
8084	Uncharacterized protein	548094	8239	448906	17005	25771, 34537, 43303, 52069, 60835
8085	Uncharacterized protein	548471	8240	449401	17006	25772, 34538, 43304, 52070, 60836
8086	Uncharacterized protein	548600	8241	447785	17007	25773, 34539, 43305, 52071,

						60837
8087	Uncharacterized protein	548794	8242	446488	17008	25774, 34540, 43306, 52072, 60838
8088	Uncharacterized protein	549001	8243	447430	17009	25775, 34541, 43307, 52073, 60839
8089	Uncharacterized protein	549105	8244	449424	17010	25776, 34542, 43308, 52074, 60840
8090	Uncharacterized protein	549322	8245	447960	17011	25777, 34543, 43309, 52075, 60841
8091	Uncharacterized protein	549619	8246	447490	17012	25778, 34544, 43310, 52076, 60842
8092	Uncharacterized protein	549634	8247	449852	17013	25779, 34545, 43311, 52077, 60843
8093	Uncharacterized protein	549783	8248	449076	17014	25780, 34546, 43312, 52078, 60844
8094	Uncharacterized protein	549873	8249	446545	17015	25781, 34547, 43313, 52079, 60845
8095	Uncharacterized protein	550392	8250	450066	17016	25782, 34548, 43314, 52080, 60846
8096	Uncharacterized protein	550982	8251	447982	17017	25783, 34549, 43315, 52081, 60847
8097	Uncharacterized protein	551166	8252	449840	17018	25784, 34550, 43316, 52082, 60848
8098	Uncharacterized protein	551239	8253	448306	17019	25785, 34551, 43317, 52083, 60849
8099	Uncharacterized protein	551289	8254	447264	17020	25786, 34552, 43318, 52084, 60850
8100	Uncharacterized protein	551364	8255	449288	17021	25787, 34553, 43319, 52085, 60851
8101	Uncharacterized protein	551390	8256	447850	17022	25788, 34554, 43320, 52086, 60852
8102	Uncharacterized protein	551700	8257	446649	17023	25789, 34555, 43321, 52087, 60853
8103	Uncharacterized protein	551904	8258	447201	17024	25790, 34556,

						43322, 52088, 60854
8104	Uncharacterized protein	552021	8259	446588	17025	25791, 34557, 43323, 52089, 60855
8105	Uncharacterized protein	552152	8260	449197	17026	25792, 34558, 43324, 52090, 60856
8106	Uncharacterized protein	552264	8261	449155	17027	25793, 34559, 43325, 52091, 60857
8107	Uncharacterized protein	552373	8262	447103	17028	25794, 34560, 43326, 52092, 60858
8108	Uncharacterized protein	552647	8263	447642	17029	25795, 34561, 43327, 52093, 60859
8109	Uncharacterized protein	552653	8264	450129	17030	25796, 34562, 43328, 52094, 60860
8110	Uncharacterized protein	552661	8265	449816	17031	25797, 34563, 43329, 52095, 60861
8111	Uncharacterized protein	552733	8266	448271	17032	25798, 34564, 43330, 52096, 60862
8112	Uncharacterized protein	553258	8267	450349	17033	25799, 34565, 43331, 52097, 60863
8113	Uncharacterized protein	557851	8268	454133	17034	25800, 34566, 43332, 52098, 60864
8114	Uncharacterized protein	558425	8269	453044	17035	25801, 34567, 43333, 52099, 60865
8115	Uncharacterized protein	558636	8270	452832	17036	25802, 34568, 43334, 52100, 60866
8116	Uncharacterized protein	558962	8271	453190	17037	25803, 34569, 43335, 52101, 60867
8117	Uncharacterized protein	560426	8272	453187	17038	25804, 34570, 43336, 52102, 60868
8118	Uncharacterized protein 244321	244321	8273	244321	17039	25805, 34571, 43337, 52103, 60869
8119	Uncharacterized protein 372125	382678	8274	372125	17040	25806, 34572, 43338, 52104, 60870

8120	Uncharacterized protein 382042	399091	8275	382042	17041	25807, 34573, 43339, 52105, 60871
8121	Uncharacterized protein 382042	399093	8276	382044	17042	25808, 34574, 43340, 52106, 60872
8122	Uncharacterized protein 382042	428928	8277	395460	17043	25809, 34575, 43341, 52107, 60873
8123	Uncharacterized protein 382042	443876	8278	404934	17044	25810, 34576, 43342, 52108, 60874
8124	uncharacterized protein C14orf162	599174	8279	469474	17045	25811, 34577, 43343, 52109, 60875
8125	Uncharacterized protein C14orf167	354854	8280	346918	17046	25812, 34578, 43344, 52110, 60876
8126	Uncharacterized protein C16orf95	253461	8281	253461	17047	25813, 34579, 43345, 52111, 60877
8127	Uncharacterized protein DKFZp434B061	391545	8282	375387	17048	25814, 34580, 43346, 52112, 60878
8128	Uncharacterized protein FLJ43738	344062	8283	342380	17049	25815, 34581, 43347, 52113, 60879
8129	Uncharacterized protein FLJ43738	508239	8284	424951	17050	25816, 34582, 43348, 52114, 60880
8130	Uncharacterized protein FLJ43738	511204	8285	422463	17051	25817, 34583, 43349, 52115, 60881
8131	Uncharacterized protein FLJ45252	339092	8286	341274	17052	25818, 34584, 43350, 52116, 60882
8132	Uncharacterized protein KIAA0040	546143	8287	464226	17053	25819, 34585, 43351, 52117, 60883
8133	Uncharacterized protein KIAA1456	445495	8288	441960	17054	25820, 34586, 43352, 52118, 60884
8134	uncharacterized protein LOC100128071	432622	8289	455971	17055	25821, 34587, 43353, 52119, 60885
8135	uncharacterized protein LOC100130480	584361	8290	462415	17056	25822, 34588, 43354, 52120, 60886
8136	uncharacterized protein LOC100131094	381796	8291	371215	17057	25823, 34589, 43355, 52121,

						60887
8137	uncharacterized protein LOC100287177	593161	8292	464956	17058	25824, 34590, 43356, 52122, 60888
8138	uncharacterized protein LOC100287482	462322	8293	454370	17059	25825, 34591, 43357, 52123, 60889
8139	uncharacterized protein LOC100288814	445307	8294	403980	17060	25826, 34592, 43358, 52124, 60890
8140	uncharacterized protein LOC100506650	441889	8295	411112	17061	25827, 34593, 43359, 52125, 60891
8141	Uncharacterized protein LOC113230	269720	8296	269720	17062	25828, 34594, 43360, 52126, 60892
8142	uncharacterized protein LOC145788	569691	8297	456337	17063	25829, 34595, 43361, 52127, 60893
8143	uncharacterized protein LOC147646	574814	8298	458772	17064	25830, 34596, 43362, 52128, 60894
8144	uncharacterized protein LOC147670	598409	8299	471126	17065	25831, 34597, 43363, 52129, 60895
8145	uncharacterized protein LOC284385	587536	8300	464846	17066	25832, 34598, 43364, 52130, 60896
8146	uncharacterized protein LOC388276	562818	8301	454664	17067	25833, 34599, 43365, 52131, 60897
8147	uncharacterized protein LOC388849	540078	8302	445668	17068	25834, 34600, 43366, 52132, 60898
8148	uncharacterized protein LOC389831	400890	8303	383683	17069	25835, 34601, 43367, 52133, 60899
8149	uncharacterized protein LOC399693	563590	8304	457438	17070	25836, 34602, 43368, 52134, 60900
8150	uncharacterized protein LOC400818	581201	8305	463341	17071	25837, 34603, 43369, 52135, 60901
8151	uncharacterized protein LOC440335 isoform 1	586440	8306	465037	17072	25838, 34604, 43370, 52136, 60902
8152	uncharacterized protein LOC440335 isoform 1	589327	8307	468237	17073	25839, 34605, 43371, 52137, 60903
8153	uncharacterized protein	589721	8308	465660	17074	25840, 34606,

	LOC440335 isoform 1					43372, 52138, 60904
8154	uncharacterized protein LOC646498	545770	8309	454903	17075	25841, 34607, 43373, 52139, 60905
8155	uncharacterized protein LOC647589	419717	8310	409950	17076	25842, 34608, 43374, 52140, 60906
8156	uncharacterized protein LOC729059	566855	8311	457161	17077	25843, 34609, 43375, 52141, 60907
8157	Uncharacterized protein; cDNA FLJ58975	565422	8312	454770	17078	25844, 34610, 43376, 52142, 60908
8158	Uncharacterized proteincDNA FLJ12988 fis, clone NT2RP3000080	435356	8313	399248	17079	25845, 34611, 43377, 52143, 60909
8159	Uncharacterized proteincDNA FLJ26048 fis, clone PRS02384	376775	8314	365967	17080	25846, 34612, 43378, 52144, 60910
8160	Uncharacterized proteincDNA FLJ26336 fis, clone HRT02842	381778	8315	371197	17081	25847, 34613, 43379, 52145, 60911
8161	Uncharacterized proteincDNA FLJ26472 fis, clone KDN04506	357132	8316	349651	17082	25848, 34614, 43380, 52146, 60912
8162	Uncharacterized proteincDNA FLJ26718 fis, clone PNC03325	398957	8317	381930	17083	25849, 34615, 43381, 52147, 60913
8163	Uncharacterized proteincDNA FLJ26728 fis, clone PNC06635	378347	8318	367598	17084	25850, 34616, 43382, 52148, 60914
8164	Uncharacterized proteincDNA FLJ27030 fis, clone SLV07741	369474	8319	358486	17085	25851, 34617, 43383, 52149, 60915
8165	Uncharacterized proteincDNA FLJ27422 fis, clone WMC08087	398387	8320	381423	17086	25852, 34618, 43384, 52150, 60916
8166	Uncharacterized proteincDNA FLJ34594 fis, clone KIDNE2009109	314040	8321	320396	17087	25853, 34619, 43385, 52151, 60917
8167	Uncharacterized proteincDNA FLJ34815 fis, clone NT2NE2007786	313266	8322	316098	17088	25854, 34620, 43386, 52152, 60918
8168	Uncharacterized proteincDNA FLJ35776 fis, clone TESTI2005326	317114	8323	319936	17089	25855, 34621, 43387, 52153, 60919
8169	Uncharacterized proteincDNA FLJ36032 fis, clone TESTI2017069	442233	8324	437574	17090	25856, 34622, 43388, 52154, 60920

8170	Uncharacterized proteincDNA FLJ37627 fis, clone BRCOC2014833	551838	8325	450113	17091	25857, 34623, 43389, 52155, 60921
8171	Uncharacterized proteincDNA FLJ37627 fis, clone BRCOC2014833	552923	8326	448540	17092	25858, 34624, 43390, 52156, 60922
8172	Uncharacterized proteincDNA FLJ39396 fis, clone PLACE6008640	319426	8327	385877	17093	25859, 34625, 43391, 52157, 60923
8173	Uncharacterized proteincDNA FLJ40032 fis, clone STOMA2009256	358234	8328	350969	17094	25860, 34626, 43392, 52158, 60924
8174	Uncharacterized proteincDNA FLJ40144 fis, clone TESTI2013012	326348	8329	320657	17095	25861, 34627, 43393, 52159, 60925
8175	Uncharacterized proteincDNA FLJ40589 fis, clone THYMU2009596	450721	8330	414919	17096	25862, 34628, 43394, 52160, 60926
8176	Uncharacterized proteincDNA FLJ42076 fis, clone SYNOV2018921	377652	8331	366880	17097	25863, 34629, 43395, 52161, 60927
8177	Uncharacterized proteincDNA FLJ43318 fis, clone NT2RI2018311	382426	8332	371863	17098	25864, 34630, 43396, 52162, 60928
8178	Uncharacterized proteincDNA FLJ43696 fis, clone TBAES2007964	372387	8333	361463	17099	25865, 34631, 43397, 52163, 60929
8179	Uncharacterized proteincDNA FLJ43763 fis, clone TESTI2048603	381078	8334	370468	17100	25866, 34632, 43398, 52164, 60930
8180	Uncharacterized proteincDNA FLJ43818 fis, clone TESTI4001923	382313	8335	371750	17101	25867, 34633, 43399, 52165, 60931
8181	Uncharacterized proteincDNA FLJ45526 fis, clone BRTHA2027227	538868	8336	439259	17102	25868, 34634, 43400, 52166, 60932
8182	Uncharacterized proteincDNA FLJ46220 fis, clone TESTI4013774	536898	8337	437610	17103	25869, 34635, 43401, 52167, 60933
8183	Uncharacterized proteincDNA FLJ46261 fis, clone TESTI4025062	356374	8338	348738	17104	25870, 34636, 43402, 52168, 60934
8184	Uncharacterized proteincDNA FLJ46300 fis, clone TESTI4035989	341866	8339	340261	17105	25871, 34637, 43403, 52169, 60935
8185	Uncharacterized proteincDNA FLJ46557 fis, clone THYMU3039846	371390	8340	360443	17106	25872, 34638, 43404, 52170, 60936
8186	Uncharacterized proteincDNA FLJ46600 fis,	374945	8341	364083	17107	25873, 34639, 43405, 52171,

	clone THYMU3047144					60937
8187	Uncharacterized proteincDNA FLJ50038	543018	8342	441588	17108	25874, 34640, 43406, 52172, 60938
8188	Uncharacterized proteincDNA FLJ52611	435655	8343	387512	17109	25875, 34641, 43407, 52173, 60939
8189	Uncharacterized proteincDNA FLJ52611	453651	8344	408206	17110	25876, 34642, 43408, 52174, 60940
8190	Uncharacterized proteincDNA FLJ52623	539023	8345	444973	17111	25877, 34643, 43409, 52175, 60941
8191	Uncharacterized proteincDNA FLJ52625	415412	8346	406242	17112	25878, 34644, 43410, 52176, 60942
8192	Uncharacterized proteincDNA FLJ53535	429169	8347	412792	17113	25879, 34645, 43411, 52177, 60943
8193	Uncharacterized proteincDNA FLJ53548	537896	8348	440866	17114	25880, 34646, 43412, 52178, 60944
8194	Uncharacterized proteincDNA FLJ54282, highly similar to Protein FAM44C	420277	8349	442342	17115	25881, 34647, 43413, 52179, 60945
8195	Uncharacterized proteincDNA FLJ56974, moderately similar to Myeloid cell surface antigen CD33	305812	8350	303760	17116	25882, 34648, 43414, 52180, 60946
8196	Uncharacterized proteincDNA FLJ56974, moderately similar to Myeloid cell surface antigen CD33	341811	8351	341295	17117	25883, 34649, 43415, 52181, 60947
8197	Uncharacterized proteincDNA FLJ57407, weakly similar to Mus musculus leucine rich repeat containing 29 (Lrrc29), mRNA	454102	8352	388531	17118	25884, 34650, 43416, 52182, 60948
8198	Uncharacterized proteincDNA FLJ57652, highly similar to Ephrin-A3	505139	8353	426741	17119	25885, 34651, 43417, 52183, 60949
8199	Uncharacterized proteincDNA FLJ58069	419182	8354	416229	17120	25886, 34652, 43418, 52184, 60950
8200	Uncharacterized proteincDNA FLJ58508,	554914	8355	451145	17121	25887, 34653, 43419, 52185,

	highly similar to Transcription factor SOX-7					60951
8201	Uncharacterized proteincDNA FLJ59044, highly similar to LINE-1 reverse transcriptase homolog	392385	8356	442163	17122	25888, 34654, 43420, 52186, 60952
8202	Uncharacterized proteincDNA FLJ59053	547426	8357	450194	17123	25889, 34655, 43421, 52187, 60953
8203	Uncharacterized proteincDNA FLJ59053	552911	8358	447197	17124	25890, 34656, 43422, 52188, 60954
8204	Uncharacterized proteincDNA FLJ60005, moderately similar to Homo sapiens pleckstrin homology domain containing, family M member 1, mRNA	397718	8359	380830	17125	25891, 34657, 43423, 52189, 60955
8205	Uncharacterized proteincDNA FLJ60005, moderately similar to Homo sapiens pleckstrin homology domain containing, family M member 1, mRNA	440036	8360	396883	17126	25892, 34658, 43424, 52190, 60956
8206	Uncharacterized proteincDNA FLJ60024, highly similar to Cytochrome P450 4F12	412610	8361	389636	17127	25893, 34659, 43425, 52191, 60957
8207	Uncharacterized proteincDNA FLJ60082, weakly similar to Uro-adherence factor A	419587	8362	391551	17128	25894, 34660, 43426, 52192, 60958
8208	Uncharacterized proteincDNA FLJ60524	454512	8363	402720	17129	25895, 34661, 43427, 52193, 60959
8209	Uncharacterized proteincDNA FLJ61769	435144	8364	400907	17130	25896, 34662, 43428, 52194, 60960
8210	Uncharacterized proteincDNA, FLJ78869	456304	8365	400644	17131	25897, 34663, 43429, 52195, 60961
8211	Uncharacterized proteinUncharacterized protein	326333	8366	319235	17132	25898, 34664, 43430, 52196, 60962
8212	Uncharacterized proteinValyl-tRNA synthetase like	425563	8367	415752	17133	25899, 34665, 43431, 52197, 60963

8213	Uncharacterized proteinValyl-tRNA synthetase like	428577	8368	396754	17134	25900, 34666, 43432, 52198, 60964
8214	Uncharacterized proteinValyl-tRNA synthetase like	443384	8369	407946	17135	25901, 34667, 43433, 52199, 60965
8215	Uncharacterized proteinValyl-tRNA synthetase like	547340	8370	447478	17136	25902, 34668, 43434, 52200, 60966
8216	Uncharacterized proteinValyl-tRNA synthetase like	548165	8371	447179	17137	25903, 34669, 43435, 52201, 60967
8217	Uncharacterized proteinValyl-tRNA synthetase like	548842	8372	449456	17138	25904, 34670, 43436, 52202, 60968
8218	Uncharacterized proteinValyl-tRNA synthetase like	550112	8373	449047	17139	25905, 34671, 43437, 52203, 60969
8219	Uncharacterized proteinZNF668 protein	417110	8374	391989	17140	25906, 34672, 43438, 52204, 60970
8220	Uncharacterized serine/threonine-protein kinase SgK494	301037	8375	301037	17141	25907, 34673, 43439, 52205, 60971
8221	Uncharacterized serine/threonine-protein kinase SgK494	378976	8376	368259	17142	25908, 34674, 43440, 52206, 60972
8222	Uncharacterized serine/threonine-protein kinase SgK494	481916	8377	436369	17143	25909, 34675, 43441, 52207, 60973
8223	Uncharacterized serine/threonine-protein kinase SgK494	534850	8378	437573	17144	25910, 34676, 43442, 52208, 60974
8224	unconventional SNARE in the ER 1 homolog (S. cerevisiae)	379776	8379	369101	17145	25911, 34677, 43443, 52209, 60975
8225	unconventional SNARE in the ER 1 homolog (S. cerevisiae)	445667	8380	390287	17146	25912, 34678, 43444, 52210, 60976
8226	unkempt homolog (Drosophila)	293218	8381	293218	17147	25913, 34679, 43445, 52211, 60977
8227	UPF0627 protein 341061/339743	434336	8382	408511	17148	25914, 34680, 43446, 52212, 60978
8228	UPF0627 protein 358171	369173	8383	358171	17149	25915, 34681, 43447, 52213, 60979
8229	UPF0638 protein B	420135	8384	389043	17150	25916, 34682, 43448, 52214,

						60980
8230	vacuolar protein sorting 13 homolog B (yeast)	355155	8385	347281	17151	25917, 34683, 43449, 52215, 60981
8231	vacuolar protein sorting 13 homolog B (yeast)	357162	8386	349685	17152	25918, 34684, 43450, 52216, 60982
8232	vacuolar protein sorting 13 homolog B (yeast)	358544	8387	351346	17153	25919, 34685, 43451, 52217, 60983
8233	vacuolar protein sorting 13 homolog B (yeast)	395996	8388	379318	17154	25920, 34686, 43452, 52218, 60984
8234	vacuolar protein sorting 13 homolog B (yeast)	441350	8389	398472	17155	25921, 34687, 43453, 52219, 60985
8235	vacuolar protein sorting 13 homolog C (S. cerevisiae)	249837	8390	249837	17156	25922, 34688, 43454, 52220, 60986
8236	vacuolar protein sorting 13 homolog C (S. cerevisiae)	261517	8391	261517	17157	25923, 34689, 43455, 52221, 60987
8237	vacuolar protein sorting 13 homolog C (S. cerevisiae)	395896	8392	379233	17158	25924, 34690, 43456, 52222, 60988
8238	vacuolar protein sorting 13 homolog C (S. cerevisiae)	395898	8393	379235	17159	25925, 34691, 43457, 52223, 60989
8239	vacuolar protein sorting 13 homolog D (S. cerevisiae)	356315	8394	348666	17160	25926, 34692, 43458, 52224, 60990
8240	vacuolar protein sorting 13 homolog D (S. cerevisiae)	358136	8395	350854	17161	25927, 34693, 43459, 52225, 60991
8241	vacuolar protein sorting 13 homolog D (S. cerevisiae)	543710	8396	444120	17162	25928, 34694, 43460, 52226, 60992
8242	vacuolar protein sorting 13 homolog D (S. cerevisiae)	543766	8397	441122	17163	25929, 34695, 43461, 52227, 60993
8243	vacuolar protein sorting 52 homolog (S. cerevisiae)	421357	8398	398367	17164	25930, 34696, 43462, 52228, 60994
8244	vacuolar protein sorting 52 homolog (S. cerevisiae)	462479	8399	435031	17165	25931, 34697, 43463, 52229, 60995
8245	vacuolar protein sorting 52 homolog (S. cerevisiae)	547753	8400	446712	17166	25932, 34698, 43464, 52230, 60996
8246	vacuolar protein sorting 52	548038	8401	449778	17167	25933, 34699,

	homolog (S. cerevisiae)					43465, 52231, 60997
8247	vacuolar protein sorting 52 homolog (S. cerevisiae)	549202	8402	450381	17168	25934, 34700, 43466, 52232, 60998
8248	vacuolar protein sorting 52 homolog (S. cerevisiae)	549702	8403	448063	17169	25935, 34701, 43467, 52233, 60999
8249	vacuolar protein sorting 52 homolog (S. cerevisiae)	549825	8404	449494	17170	25936, 34702, 43468, 52234, 61000
8250	vacuolar protein sorting 52 homolog (S. cerevisiae)	551499	8405	449758	17171	25937, 34703, 43469, 52235, 61001
8251	vacuolar protein sorting 53 homolog (S. cerevisiae)	291074	8406	291074	17172	25938, 34704, 43470, 52236, 61002
8252	vacuolar protein sorting 53 homolog (S. cerevisiae)	389040	8407	373692	17173	25939, 34705, 43471, 52237, 61003
8253	vacuolar protein sorting 53 homolog (S. cerevisiae)	401468	8408	384294	17174	25940, 34706, 43472, 52238, 61004
8254	vacuolar protein sorting 53 homolog (S. cerevisiae)	437048	8409	401435	17175	25941, 34707, 43473, 52239, 61005
8255	vacuolar protein sorting 53 homolog (S. cerevisiae)	446250	8410	394386	17176	25942, 34708, 43474, 52240, 61006
8256	vacuolar protein sorting 53 homolog (S. cerevisiae)	541903	8411	442480	17177	25943, 34709, 43475, 52241, 61007
8257	vacuolar protein sorting 54 homolog (S. cerevisiae)	272322	8412	272322	17178	25944, 34710, 43476, 52242, 61008
8258	vacuolar protein sorting 54 homolog (S. cerevisiae)	394400	8413	377923	17179	25945, 34711, 43477, 52243, 61009
8259	vacuolar protein sorting 54 homolog (S. cerevisiae)	409558	8414	386980	17180	25946, 34712, 43478, 52244, 61010
8260	vacuolar protein sorting 54 homolog (S. cerevisiae)	483277	8415	445040	17181	25947, 34713, 43479, 52245, 61011
8261	vacuolar protein sorting 8 homolog (S. cerevisiae)	287546	8416	287546	17182	25948, 34714, 43480, 52246, 61012
8262	vacuolar protein sorting 8 homolog (S. cerevisiae)	422105	8417	415161	17183	25949, 34715, 43481, 52247, 61013

8263	vacuolar protein sorting 8 homolog (S. cerevisiae)	436792	8418	404704	17184	25950, 34716, 43482, 52248, 61014
8264	vacuolar protein sorting 8 homolog (S. cerevisiae)	437079	8419	397879	17185	25951, 34717, 43483, 52249, 61015
8265	vacuolar protein sorting 8 homolog (S. cerevisiae)	441141	8420	409957	17186	25952, 34718, 43484, 52250, 61016
8266	vacuolar protein sorting 8 homolog (S. cerevisiae)	445089	8421	416150	17187	25953, 34719, 43485, 52251, 61017
8267	vacuolar protein sorting 8 homolog (S. cerevisiae)	446204	8422	405483	17188	25954, 34720, 43486, 52252, 61018
8268	vacuolar protein sorting 8 homolog (S. cerevisiae)	453056	8423	394018	17189	25955, 34721, 43487, 52253, 61019
8269	variable charge X-linked 3B	381032	8424	370420	17190	25956, 34722, 43488, 52254, 61020
8270	variable charge, Y-linked 1B	250825	8425	250825	17191	25957, 34723, 43489, 52255, 61021
8271	vertebrae development homolog (pig)	256362	8426	256362	17192	25958, 34724, 43490, 52256, 61022
8272	vertebrae development homolog (pig)	557177	8427	452158	17193	25959, 34725, 43491, 52257, 61023
8273	vesicle amine transport protein 1 homolog (T. californica)-like	302536	8428	303129	17194	25960, 34726, 43492, 52258, 61024
8274	vesicle-trafficking protein SEC22b precursor	578049	8429	463393	17195	25961, 34727, 43493, 52259, 61025
8275	vestigial like 4 (Drosophila)	273038	8430	273038	17196	25962, 34728, 43494, 52260, 61026
8276	vestigial like 4 (Drosophila)	404339	8431	384705	17197	25963, 34729, 43495, 52261, 61027
8277	vestigial like 4 (Drosophila)	417206	8432	391932	17198	25964, 34730, 43496, 52262, 61028
8278	vestigial like 4 (Drosophila)	418000	8433	394439	17199	25965, 34731, 43497, 52263, 61029
8279	vestigial like 4 (Drosophila)	419541	8434	395557	17200	25966, 34732, 43498, 52264,

						61030
8280	vestigial like 4 (Drosophila)	430365	8435	404251	17201	25967, 34733, 43499, 52265, 61031
8281	vestigial like 4 (Drosophila)	445411	8436	412923	17202	25968, 34734, 43500, 52266, 61032
8282	vestigial like 4 (Drosophila)	424529	8437	402878	17203	25969, 34735, 43501, 52267, 61033
8283	vestigial like 4 (Drosophila)	451674	8438	416615	17204	25970, 34736, 43502, 52268, 61034
8284	vomeronasal 1 receptor 4	311170	8439	310856	17205	25971, 34737, 43503, 52269, 61035
8285	von Willebrand factor A domain containing 2	298715	8440	298715	17206	25972, 34738, 43504, 52270, 61036
8286	von Willebrand factor A domain containing 3B	358269	8441	351009	17207	25973, 34739, 43505, 52271, 61037
8287	von Willebrand factor A domain containing 3B	435344	8442	401959	17208	25974, 34740, 43506, 52272, 61038
8288	von Willebrand factor A domain containing 3B	451075	8443	389463	17209	25975, 34741, 43507, 52273, 61039
8289	von Willebrand factor A domain containing 3B	477737	8444	417955	17210	25976, 34742, 43508, 52274, 61040
8290	von Willebrand factor A domain containing 5B2	426955	8445	398688	17211	25977, 34743, 43509, 52275, 61041
8291	von Willebrand factor A domain containing 7	452630	8446	411804	17212	25978, 34744, 43510, 52276, 61042
8292	von Willebrand factor A domain containing 7	550291	8447	447965	17213	25979, 34745, 43511, 52277, 61043
8293	von Willebrand factor A domain containing 7	550450	8448	450313	17214	25980, 34746, 43512, 52278, 61044
8294	von Willebrand factor D and EGF domains	536307	8449	439861	17215	25981, 34747, 43513, 52279, 61045
8295	von Willebrand factor D and EGF domains	541006	8450	439347	17216	25982, 34748, 43514, 52280, 61046
8296	Vpr (HIV-1) binding	563997	8451	454540	17217	25983, 34749,

	protein					43515, 52281, 61047
8297	Vpr (HIV-1) binding protein	566027	8452	456445	17218	25984, 34750, 43516, 52282, 61048
8298	V-set and immunoglobulin domain containing 2	326621	8453	318684	17219	25985, 34751, 43517, 52283, 61049
8299	V-set and immunoglobulin domain containing 2	403470	8454	385013	17220	25986, 34752, 43518, 52284, 61050
8300	V-set and immunoglobulin domain containing 7	559480	8455	453358	17221	25987, 34753, 43519, 52285, 61051
8301	V-set and transmembrane domain containing 2 like	373458	8456	362557	17222	25988, 34754, 43520, 52286, 61052
8302	V-set and transmembrane domain containing 2 like	373461	8457	362560	17223	25989, 34755, 43521, 52287, 61053
8303	V-set and transmembrane domain containing 2 like	448944	8458	406537	17224	25990, 34756, 43522, 52288, 61054
8304	V-set and transmembrane domain containing 2B	335523	8459	335038	17225	25991, 34757, 43523, 52289, 61055
8305	WD and tetratricopeptide repeats 1	319394	8460	317971	17226	25992, 34758, 43524, 52290, 61056
8306	WD and tetratricopeptide repeats 1	361771	8461	355317	17227	25993, 34759, 43525, 52291, 61057
8307	WD repeat and FYVE domain containing 2	298125	8462	298125	17228	25994, 34760, 43526, 52292, 61058
8308	WD repeat and SOCS box containing 1	262394	8463	262394	17229	25995, 34761, 43527, 52293, 61059
8309	WD repeat and SOCS box containing 1	348811	8464	327055	17230	25996, 34762, 43528, 52294, 61060
8310	WD repeat and SOCS box containing 1	427287	8465	416112	17231	25997, 34763, 43529, 52295, 61061
8311	WD repeat and SOCS box containing 2	315436	8466	319474	17232	25998, 34764, 43530, 52296, 61062
8312	WD repeat and SOCS box containing 2	542304	8467	445941	17233	25999, 34765, 43531, 52297, 61063

8313	WD repeat and SOCS box containing 2	544233	8468	444431	17234	26000, 34766, 43532, 52298, 61064
8314	WD repeat domain 13	599106	8469	470871	17235	26001, 34767, 43533, 52299, 61065
8315	WD repeat domain 18	251289	8470	251289	17236	26002, 34768, 43534, 52300, 61066
8316	WD repeat domain 20	335263	8471	335434	17237	26003, 34769, 43535, 52301, 61067
8317	WD repeat domain 20	342702	8472	341037	17238	26004, 34770, 43536, 52302, 61068
8318	WD repeat domain 20	401892	8473	385755	17239	26005, 34771, 43537, 52303, 61069
8319	WD repeat domain 20	424963	8474	395793	17240	26006, 34772, 43538, 52304, 61070
8320	WD repeat domain 20	454394	8475	406084	17241	26007, 34773, 43539, 52305, 61071
8321	WD repeat domain 20	499851	8476	443641	17242	26008, 34774, 43540, 52306, 61072
8322	WD repeat domain 20	545563	8477	437927	17243	26009, 34775, 43541, 52307, 61073
8323	WD repeat domain 20	556511	8478	451633	17244	26010, 34776, 43542, 52308, 61074
8324	WD repeat domain 20	322340	8479	314209	17245	26011, 34777, 43543, 52309, 61075
8325	WD repeat domain 20	556807	8480	450636	17246	26012, 34778, 43544, 52310, 61076
8326	WD repeat domain 24	248142	8481	248142	17247	26013, 34779, 43545, 52311, 61077
8327	WD repeat domain 24	293883	8482	293883	17248	26014, 34780, 43546, 52312, 61078
8328	WD repeat domain 25	335290	8483	334148	17249	26015, 34781, 43547, 52313, 61079
8329	WD repeat domain 25	402312	8484	385540	17250	26016, 34782, 43548, 52314,

						61080
8330	WD repeat domain 25	542471	8485	441903	17251	26017, 34783, 43549, 52315, 61081
8331	WD repeat domain 25	554998	8486	450661	17252	26018, 34784, 43550, 52316, 61082
8332	WD repeat domain 27	333572	8487	330265	17253	26019, 34785, 43551, 52317, 61083
8333	WD repeat domain 27	420344	8488	406114	17254	26020, 34786, 43552, 52318, 61084
8334	WD repeat domain 27	423258	8489	397869	17255	26021, 34787, 43553, 52319, 61085
8335	WD repeat domain 27	448612	8490	416289	17256	26022, 34788, 43554, 52320, 61086
8336	WD repeat domain 27	474018	8491	449696	17257	26023, 34789, 43555, 52321, 61087
8337	WD repeat domain 31	341761	8492	345027	17258	26024, 34790, 43556, 52322, 61088
8338	WD repeat domain 31	374193	8493	363308	17259	26025, 34791, 43557, 52323, 61089
8339	WD repeat domain 31	374195	8494	363310	17260	26026, 34792, 43558, 52324, 61090
8340	WD repeat domain 33	322313	8495	325377	17261	26027, 34793, 43559, 52325, 61091, 61571, 61629
8341	WD repeat domain 33	393006	8496	376730	17262	26028, 34794, 43560, 52326, 61092, 61572, 61630
8342	WD repeat domain 33	408998	8497	386861	17263	26029, 34795, 43561, 52327, 61093, 61573, 61631
8343	WD repeat domain 33	409658	8498	387186	17264	26030, 34796, 43562, 52328, 61094, 61574, 61632
8344	WD repeat domain 37	263150	8499	263150	17265	26031, 34797, 43563, 52329, 61095

8345	WD repeat domain 37	358220	8500	350954	17266	26032, 34798, 43564, 52330, 61096
8346	WD repeat domain 37	381329	8501	370730	17267	26033, 34799, 43565, 52331, 61097
8347	WD repeat domain 37	436154	8502	404346	17268	26034, 34800, 43566, 52332, 61098
8348	WD repeat domain 38	373574	8503	362677	17269	26035, 34801, 43567, 52333, 61099
8349	WD repeat domain 41	296679	8504	296679	17270	26036, 34802, 43568, 52334, 61100
8350	WD repeat domain 41	414719	8505	392931	17271	26037, 34803, 43569, 52335, 61101
8351	WD repeat domain 45	598033	8506	471414	17272	26038, 34804, 43570, 52336, 61102
8352	WD repeat domain 46	374617	8507	363746	17273	26039, 34805, 43571, 52337, 61103
8353	WD repeat domain 46	383208	8508	372695	17274	26040, 34806, 43572, 52338, 61104
8354	WD repeat domain 46	416777	8509	406835	17275	26041, 34807, 43573, 52339, 61105
8355	WD repeat domain 46	432609	8510	402869	17276	26042, 34808, 43574, 52340, 61106
8356	WD repeat domain 46	432933	8511	399454	17277	26043, 34809, 43575, 52341, 61107
8357	WD repeat domain 46	443102	8512	407066	17278	26044, 34810, 43576, 52342, 61108
8358	WD repeat domain 46	444176	8513	405568	17279	26045, 34811, 43577, 52343, 61109
8359	WD repeat domain 46	450918	8514	412069	17280	26046, 34812, 43578, 52344, 61110
8360	WD repeat domain 46	456332	8515	408651	17281	26047, 34813, 43579, 52345, 61111
8361	WD repeat domain 46	457382	8516	405614	17282	26048, 34814, 43580, 52346,

						61112
8362	WD repeat domain 47	357672	8517	350301	17283	26049, 34815, 43581, 52347, 61113
8363	WD repeat domain 47	361054	8518	354339	17284	26050, 34816, 43582, 52348, 61114
8364	WD repeat domain 47	369962	8519	358979	17285	26051, 34817, 43583, 52349, 61115
8365	WD repeat domain 47	369965	8520	358982	17286	26052, 34818, 43584, 52350, 61116
8366	WD repeat domain 47	400794	8521	383599	17287	26053, 34819, 43585, 52351, 61117
8367	WD repeat domain 47	528747	8522	433452	17288	26054, 34820, 43586, 52352, 61118
8368	WD repeat domain 47	530772	8523	434289	17289	26055, 34821, 43587, 52353, 61119
8369	WD repeat domain 49	308378	8524	311343	17290	26056, 34822, 43588, 52354, 61120
8370	WD repeat domain 49	453925	8525	410863	17291	26057, 34823, 43589, 52355, 61121
8371	WD repeat domain 52	295868	8526	295868	17292	26058, 34824, 43590, 52356, 61122
8372	WD repeat domain 52	308346	8527	311497	17293	26059, 34825, 43591, 52357, 61123
8373	WD repeat domain 52	393845	8528	377428	17294	26060, 34826, 43592, 52358, 61124
8374	WD repeat domain 52	473143	8529	419671	17295	26061, 34827, 43593, 52359, 61125
8375	WD repeat domain 53	332629	8530	328079	17296	26062, 34828, 43594, 52360, 61126
8376	WD repeat domain 53	425888	8531	396248	17297	26063, 34829, 43595, 52361, 61127
8377	WD repeat domain 53	456677	8532	408087	17298	26064, 34830, 43596, 52362, 61128
8378	WD repeat domain 54	348227	8533	6526	17299	26065, 34831,

						43597, 52363, 61129
8379	WD repeat domain 59	262144	8534	262144	17300	26066, 34832, 43598, 52364, 61130
8380	WD repeat domain 59	536050	8535	441109	17301	26067, 34833, 43599, 52365, 61131
8381	WD repeat domain 5B	330689	8536	330381	17302	26068, 34834, 43600, 52366, 61132
8382	WD repeat domain 60	407559	8537	384290	17303	26069, 34835, 43601, 52367, 61133
8383	WD repeat domain 61	267973	8538	267973	17304	26070, 34836, 43602, 52368, 61134
8384	WD repeat domain 61	558311	8539	453801	17305	26071, 34837, 43603, 52369, 61135
8385	WD repeat domain 61	560569	8540	453902	17306	26072, 34838, 43604, 52370, 61136
8386	WD repeat domain 63	294664	8541	294664	17307	26073, 34839, 43605, 52371, 61137
8387	WD repeat domain 63	326813	8542	317463	17308	26074, 34840, 43606, 52372, 61138
8388	WD repeat domain 63	370596	8543	359628	17309	26075, 34841, 43607, 52373, 61139
8389	WD repeat domain 64	366552	8544	355510	17310	26076, 34842, 43608, 52374, 61140
8390	WD repeat domain 64	437684	8545	402446	17311	26077, 34843, 43609, 52375, 61141
8391	WD repeat domain 66	288912	8546	288912	17312	26078, 34844, 43610, 52376, 61142
8392	WD repeat domain 66	397454	8547	380595	17313	26079, 34845, 43611, 52377, 61143
8393	WD repeat domain 69	309931	8548	311899	17314	26080, 34846, 43612, 52378, 61144
8394	WD repeat domain 69	545118	8549	437887	17315	26081, 34847, 43613, 52379, 61145

8395	WD repeat domain 70	265107	8550	265107	17316	26082, 34848, 43614, 52380, 61146
8396	WD repeat domain 73	434634	8551	387982	17317	26083, 34849, 43615, 52381, 61147
8397	WD repeat domain 76	263795	8552	263795	17318	26084, 34850, 43616, 52382, 61148
8398	WD repeat domain 76	381246	8553	370645	17319	26085, 34851, 43617, 52383, 61149
8399	WD repeat domain 78	371023	8554	360062	17320	26086, 34852, 43618, 52384, 61150
8400	WD repeat domain 78	371026	8555	360065	17321	26087, 34853, 43619, 52385, 61151
8401	WD repeat domain 78	431318	8556	393182	17322	26088, 34854, 43620, 52386, 61152
8402	WD repeat domain 81	309182	8557	312074	17323	26089, 34855, 43621, 52387, 61153
8403	WD repeat domain 81	354680	8558	346710	17324	26090, 34856, 43622, 52388, 61154
8404	WD repeat domain 81	437219	8559	391074	17325	26091, 34857, 43623, 52389, 61155
8405	WD repeat domain 81	545662	8560	442726	17326	26092, 34858, 43624, 52390, 61156
8406	WD repeat domain 81	409644	8561	386609	17327	26093, 34859, 43625, 52391, 61157
8407	WD repeat domain 81	419248	8562	407845	17328	26094, 34860, 43626, 52392, 61158
8408	WD repeat domain 86	477459	8563	417512	17329	26095, 34861, 43627, 52393, 61159
8409	WD repeat domain 86	334493	8564	335522	17330	26096, 34862, 43628, 52394, 61160
8410	WD repeat domain 87	303868	8565	368025	17331	26097, 34863, 43629, 52395, 61161
8411	WD repeat domain 87	447313	8566	405012	17332	26098, 34864, 43630, 52396,

						61162
8412	WD repeat domain 88	355868	8567	348129	17333	26099, 34865, 43631, 52397, 61163
8413	WD repeat domain 88	361680	8568	355148	17334	26100, 34866, 43632, 52398, 61164
8414	WD repeat domain 89	267522	8569	267522	17335	26101, 34867, 43633, 52399, 61165
8415	WD repeat domain 89	394942	8570	378399	17336	26102, 34868, 43634, 52400, 61166
8416	WD repeat domain 90	315764	8571	322808	17337	26103, 34869, 43635, 52401, 61167
8417	WD repeat domain 90	293879	8572	293879	17338	26104, 34870, 43636, 52402, 61168
8418	WD repeat domain 91	344400	8573	340877	17339	26105, 34871, 43637, 52403, 61169
8419	WD repeat domain 91	354475	8574	346466	17340	26106, 34872, 43638, 52404, 61170
8420	WD repeat domain 96	278064	8575	278064	17341	26107, 34873, 43639, 52405, 61171
8421	WD repeat domain 96	357060	8576	349568	17342	26108, 34874, 43640, 52406, 61172
8422	WD repeat domain 96	369719	8577	358733	17343	26109, 34875, 43641, 52407, 61173
8423	WD repeat domain 96	369720	8578	358734	17344	26110, 34876, 43642, 52408, 61174
8424	WD repeat domain 96	428666	8579	400289	17345	26111, 34877, 43643, 52409, 61175
8425	WD repeat domain 96	434629	8580	391364	17346	26112, 34878, 43644, 52410, 61176
8426	WD repeat domain 96	457071	8581	394274	17347	26113, 34879, 43645, 52411, 61177
8427	Wilms tumor 1 interacting protein	270288	8582	270288	17348	26114, 34880, 43646, 52412, 61178
8428	WNK lysine deficient	598300	8583	472115	17349	26115, 34881,

	protein kinase 3					43647, 52413, 61179
8429	WNT1 inducible signaling pathway protein 3	582958	8584	464005	17350	26116, 34882, 43648, 52414, 61180
8430	WW and C2 domain containing 2	378925	8585	368205	17351	26117, 34883, 43649, 52415, 61181
8431	WW and C2 domain containing 2	403733	8586	384222	17352	26118, 34884, 43650, 52416, 61182
8432	WW and C2 domain containing 2	448232	8587	398577	17353	26119, 34885, 43651, 52417, 61183
8433	WW and C2 domain containing 2	508747	8588	420835	17354	26120, 34886, 43652, 52418, 61184
8434	WW and C2 domain containing 2	513834	8589	425054	17355	26121, 34887, 43653, 52419, 61185
8435	WW domain binding protein 5	372656	8590	361740	17356	26122, 34888, 43654, 52420, 61186
8436	WW domain binding protein 5	372661	8591	361745	17357	26123, 34889, 43655, 52421, 61187
8437	WWC family member 3	380861	8592	370242	17358	26124, 34890, 43656, 52422, 61188
8438	WWC family member 3	398613	8593	381614	17359	26125, 34891, 43657, 52423, 61189
8439	WWC family member 3	454666	8594	399584	17360	26126, 34892, 43658, 52424, 61190
8440	WWC family member 3	543293	8595	446203	17361	26127, 34893, 43659, 52425, 61191
8441	WWC family member 3	543412	8596	437675	17362	26128, 34894, 43660, 52426, 61192
8442	X antigen family member 1A	597405	8597	470080	17363	26129, 34895, 43661, 52427, 61193
8443	X antigen family member 1A	600138	8598	469109	17364	26130, 34896, 43662, 52428, 61194
8444	X antigen family member 1B	594178	8599	470774	17365	26131, 34897, 43663, 52429, 61195

8445	X antigen family member 1B	600638	8600	469147	17366	26132, 34898, 43664, 52430, 61196
8446	X antigen family member 3	598948	8601	472053	17367	26133, 34899, 43665, 52431, 61197
8447	X antigen family member 3	601427	8602	471401	17368	26134, 34900, 43666, 52432, 61198
8448	X antigen family member 5	601552	8603	471543	17369	26135, 34901, 43667, 52433, 61199
8449	X antigen family, member 1D	375578	8604	364728	17370	26136, 34902, 43668, 52434, 61200
8450	X antigen family, member 1D	396497	8605	379755	17371	26137, 34903, 43669, 52435, 61201
8451	X antigen family, member 1D	438079	8606	389220	17372	26138, 34904, 43670, 52436, 61202
8452	X antigen family, member 2	330906	8607	333775	17373	26139, 34905, 43671, 52437, 61203
8453	X antigen family, member 2B	286049	8608	286049	17374	26140, 34906, 43672, 52438, 61204
8454	X antigen family, member 5	351072	8609	342240	17375	26141, 34907, 43673, 52439, 61205
8455	X antigen family, member 5	375501	8610	364651	17376	26142, 34908, 43674, 52440, 61206
8456	X antigen family, member 5	375503	8611	364653	17377	26143, 34909, 43675, 52441, 61207
8457	X antigen family, member 5	425386	8612	392864	17378	26144, 34910, 43676, 52442, 61208
8458	XK, Kell blood group complex subunit-related family, member 9	519350	8613	428904	17379	26145, 34911, 43677, 52443, 61209
8459	Yae1 domain containing 1	223273	8614	223273	17380	26146, 34912, 43678, 52444, 61210
8460	Yae1 domain containing 1	432096	8615	395777	17381	26147, 34913, 43679, 52445, 61211
8461	YdjC homolog (bacterial)	292778	8616	292778	17382	26148, 34914, 43680, 52446,

						61212
8462	YdjC homolog (bacterial)	398873	8617	381847	17383	26149, 34915, 43681, 52447, 61213
8463	YjeF N-terminal domain containing 3	397179	8618	380364	17384	26150, 34916, 43682, 52448, 61214
8464	YjeF N-terminal domain containing 3	436027	8619	398520	17385	26151, 34917, 43683, 52449, 61215
8465	YjeF N-terminal domain containing 3	510139	8620	423979	17386	26152, 34918, 43684, 52450, 61216
8466	YjeF N-terminal domain containing 3	514277	8621	426964	17387	26153, 34919, 43685, 52451, 61217
8467	YjeF N-terminal domain containing 3	553705	8622	451799	17388	26154, 34920, 43686, 52452, 61218
8468	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	315513	8623	321160	17389	26155, 34921, 43687, 52453, 61219
8469	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	358371	8624	351140	17390	26156, 34922, 43688, 52454, 61220
8470	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	375844	8625	365004	17391	26157, 34923, 43689, 52455, 61221
8471	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	375845	8626	365005	17392	26158, 34924, 43690, 52456, 61222
8472	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	392917	8627	376649	17393	26159, 34925, 43691, 52457, 61223
8473	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	392918	8628	376650	17394	26160, 34926, 43692, 52458, 61224
8474	YSK4 Sps1/Ste20-related kinase homolog (S. cerevisiae)	437365	8629	392827	17395	26161, 34927, 43693, 52459, 61225
8475	YTH domain containing 2	161863	8630	161863	17396	26162, 34928, 43694, 52460, 61226, 61575, 61633
8476	YTH domain containing 2	511372	8631	425272	17397	26163, 34929, 43695, 52461, 61227
8477	YTH domain family, member 1	342761	8632	339489	17398	26164, 34930, 43696, 52462, 61228

8478	YTH domain family, member 1	370333	8633	359358	17399	26165, 34931, 43697, 52463, 61229
8479	YTH domain family, member 1	370339	8634	359364	17400	26166, 34932, 43698, 52464, 61230
8480	ZHX1-C8ORF76 readthrough	357082	8635	349593	17401	26167, 34933, 43699, 52465, 61231
8481	zinc finger AN1-type domain 1	519523	8636	429167	17402	26168, 34934, 43700, 52466, 61232
8482	zinc finger AN1-type domain 1	523096	8637	430736	17403	26169, 34935, 43701, 52467, 61233
8483	zinc finger and AT hook domain containing	520727	8638	427831	17404	26170, 34936, 43702, 52468, 61234
8484	zinc finger and BTB domain containing 22	383196	8639	372683	17405	26171, 34937, 43703, 52469, 61235
8485	zinc finger and BTB domain containing 22	416097	8640	393514	17406	26172, 34938, 43704, 52470, 61236
8486	zinc finger and BTB domain containing 22	418540	8641	388191	17407	26173, 34939, 43705, 52471, 61237
8487	zinc finger and BTB domain containing 22	426244	8642	412427	17408	26174, 34940, 43706, 52472, 61238
8488	zinc finger and BTB domain containing 22	448500	8643	391135	17409	26175, 34941, 43707, 52473, 61239
8489	zinc finger and BTB domain containing 22	454866	8644	394349	17410	26176, 34942, 43708, 52474, 61240
8490	zinc finger and BTB domain containing 22	547592	8645	448158	17411	26177, 34943, 43709, 52475, 61241
8491	zinc finger and BTB domain containing 22	548019	8646	447113	17412	26178, 34944, 43710, 52476, 61242
8492	zinc finger and BTB domain containing 22	552144	8647	449511	17413	26179, 34945, 43711, 52477, 61243
8493	zinc finger and BTB domain containing 33	599507	8648	471279	17414	26180, 34946, 43712, 52478, 61244
8494	zinc finger and BTB domain containing 44	338191	8649	341618	17415	26181, 34947, 43713, 52479,

						61245
8495	zinc finger and BTB domain containing 44	357899	8650	350574	17416	26182, 34948, 43714, 52480, 61246
8496	zinc finger and BTB domain containing 44	397753	8651	380861	17417	26183, 34949, 43715, 52481, 61247
8497	zinc finger and BTB domain containing 44	445008	8652	408079	17418	26184, 34950, 43716, 52482, 61248
8498	zinc finger and BTB domain containing 44	525842	8653	433457	17419	26185, 34951, 43717, 52483, 61249
8499	zinc finger and BTB domain containing 44	530205	8654	434177	17420	26186, 34952, 43718, 52484, 61250
8500	zinc finger and BTB domain containing 8 opposite strand	341885	8655	343760	17421	26187, 34953, 43719, 52485, 61251
8501	zinc finger and BTB domain containing 8 opposite strand	373501	8656	362600	17422	26188, 34954, 43720, 52486, 61252
8502	zinc finger and BTB domain containing 8 opposite strand	436661	8657	413485	17423	26189, 34955, 43721, 52487, 61253
8503	zinc finger and BTB domain containing 8 opposite strand	468695	8658	417677	17424	26190, 34956, 43722, 52488, 61254
8504	zinc finger and SCAN domain containing 5B	358992	8659	351883	17425	26191, 34957, 43723, 52489, 61255
8505	zinc finger and SCAN domain containing 5C	376267	8660	365443	17426	26192, 34958, 43724, 52490, 61256
8506	zinc finger and SCAN domain containing 5C	534327	8661	435234	17427	26193, 34959, 43725, 52491, 61257
8507	zinc finger B-box domain containing	392764	8662	376517	17428	26194, 34960, 43726, 52492, 61258
8508	zinc finger BED-type containing 5	413761	8663	415939	17429	26195, 34961, 43727, 52493, 61259
8509	zinc finger BED-type containing 5	432999	8664	398106	17430	26196, 34962, 43728, 52494, 61260
8510	zinc finger CCCH-type containing 10	257940	8665	257940	17431	26197, 34963, 43729, 52495, 61261
8511	zinc finger CCCH-type	546903	8666	448881	17432	26198, 34964,

	containing 10					43730, 52496, 61262
8512	zinc finger CCCH-type containing 10	551880	8667	448309	17433	26199, 34965, 43731, 52497, 61263
8513	zinc finger CCCH-type containing 10	552345	8668	450122	17434	26200, 34966, 43732, 52498, 61264
8514	zinc finger CCCH-type containing 12B	218172	8669	218172	17435	26201, 34967, 43733, 52499, 61265
8515	zinc finger CCCH-type containing 12B	338957	8670	340839	17436	26202, 34968, 43734, 52500, 61266
8516	zinc finger CCCH-type containing 12B	423889	8671	408077	17437	26203, 34969, 43735, 52501, 61267
8517	zinc finger CCCH-type containing 12C	278590	8672	278590	17438	26204, 34970, 43736, 52502, 61268
8518	zinc finger CCCH-type containing 13	242848	8673	242848	17439	26205, 34971, 43737, 52503, 61269
8519	zinc finger CCCH-type containing 13	282007	8674	282007	17440	26206, 34972, 43738, 52504, 61270
8520	zinc finger CCCH-type containing 13	378921	8675	368201	17441	26207, 34973, 43739, 52505, 61271
8521	zinc finger CCCH-type containing 13	428921	8676	416238	17442	26208, 34974, 43740, 52506, 61272
8522	zinc finger CCCH-type containing 13	431251	8677	391064	17443	26209, 34975, 43741, 52507, 61273
8523	zinc finger CCCH-type containing 4	253048	8678	253048	17444	26210, 34976, 43742, 52508, 61274
8524	zinc finger CCCH-type containing 6	343936	8679	340298	17445	26211, 34977, 43743, 52509, 61275
8525	zinc finger CCCH-type containing 6	409871	8680	386764	17446	26212, 34978, 43744, 52510, 61276
8526	zinc finger CCCH-type containing 6	542974	8681	439726	17447	26213, 34979, 43745, 52511, 61277
8527	zinc finger CCCH-type, antiviral 1-like	275766	8682	275766	17448	26214, 34980, 43746, 52512, 61278

8528	zinc finger CCCH-type, antiviral 1-like	358573	8683	351381	17449	26215, 34981, 43747, 52513, 61279
8529	zinc finger CW type with PWWP domain 1	360951	8684	354210	17450	26216, 34982, 43748, 52514, 61280
8530	Zinc finger domain-related protein TSRM	433518	8685	389543	17451	26217, 34983, 43749, 52515, 61281
8531	zinc finger family member 788	397755	8686	380862	17452	26218, 34984, 43750, 52516, 61282
8532	zinc finger FYVE domain containing 19	564258	8687	457617	17453	26219, 34985, 43751, 52517, 61283
8533	zinc finger imprinted 2	601070	8688	470326	17454	26220, 34986, 43752, 52518, 61284
8534	zinc finger MYND-type containing 11	565311	8689	457248	17455	26221, 34987, 43753, 52519, 61285
8535	zinc finger protein 182	601062	8690	470287	17456	26222, 34988, 43754, 52520, 61286
8536	zinc finger protein 185 (LIM domain)	594503	8691	469017	17457	26223, 34989, 43755, 52521, 61287
8537	zinc finger protein 2	295210	8692	295210	17458	26224, 34990, 43756, 52522, 61288
8538	zinc finger protein 252	355436	8693	347611	17459	26225, 34991, 43757, 52523, 61289
8539	zinc finger protein 252	544285	8694	439232	17460	26226, 34992, 43758, 52524, 61290
8540	zinc finger protein 302	423823	8695	405219	17461	26227, 34993, 43759, 52525, 61291
8541	zinc finger protein 302	446502	8696	396379	17462	26228, 34994, 43760, 52526, 61292
8542	zinc finger protein 302	457781	8697	391067	17463	26229, 34995, 43761, 52527, 61293
8543	zinc finger protein 302	505163	8698	421696	17464	26230, 34996, 43762, 52528, 61294
8544	zinc finger protein 302	505242	8699	421028	17465	26231, 34997, 43763, 52529,

						61295
8545	zinc finger protein 302	506901	8700	424292	17466	26232, 34998, 43764, 52530, 61296
8546	zinc finger protein 302	507959	8701	421201	17467	26233, 34999, 43765, 52531, 61297
8547	zinc finger protein 311	458265	8702	398440	17468	26234, 35000, 43766, 52532, 61298
8548	zinc finger protein 311	552406	8703	447119	17469	26235, 35001, 43767, 52533, 61299
8549	zinc finger protein 321, pseudogene	391777	8704	375656	17470	26236, 35002, 43768, 52534, 61300
8550	zinc finger protein 322	595473	8705	471308	17471	26237, 35003, 43769, 52535, 61301
8551	zinc finger protein 323	446474	8706	402937	17472	26238, 35004, 43770, 52536, 61302
8552	zinc finger protein 404	324394	8707	319479	17473	26239, 35005, 43771, 52537, 61303
8553	zinc finger protein 415	243643	8708	243643	17474	26240, 35006, 43772, 52538, 61304
8554	zinc finger protein 415	421033	8709	395055	17475	26241, 35007, 43773, 52539, 61305
8555	zinc finger protein 415	440291	8710	414601	17476	26242, 35008, 43774, 52540, 61306
8556	zinc finger protein 415	448501	8711	396492	17477	26243, 35009, 43775, 52541, 61307
8557	zinc finger protein 415	455735	8712	388787	17478	26244, 35010, 43776, 52542, 61308
8558	zinc finger protein 415	500065	8713	439435	17479	26245, 35011, 43777, 52543, 61309
8559	zinc finger protein 428	300811	8714	300811	17480	26246, 35012, 43778, 52544, 61310
8560	zinc finger protein 428	391964	8715	375826	17481	26247, 35013, 43779, 52545, 61311
8561	zinc finger protein 43	599986	8716	471644	17482	26248, 35014,

						43780, 52546, 61312
8562	zinc finger protein 474	296600	8717	296600	17483	26249, 35015, 43781, 52547, 61313
8563	zinc finger protein 474	504912	8718	422285	17484	26250, 35016, 43782, 52548, 61314
8564	zinc finger protein 474	505843	8719	424794	17485	26251, 35017, 43783, 52549, 61315
8565	zinc finger protein 518A	572626	8720	459452	17486	26252, 35018, 43784, 52550, 61316
8566	zinc finger protein 527	317566	8721	325231	17487	26253, 35019, 43785, 52551, 61317
8567	zinc finger protein 527	356178	8722	348501	17488	26254, 35020, 43786, 52552, 61318
8568	zinc finger protein 527	436120	8723	390179	17489	26255, 35021, 43787, 52553, 61319
8569	zinc finger protein 529	334116	8724	334695	17490	26256, 35022, 43788, 52554, 61320
8570	zinc finger protein 529	591340	8725	465578	17491	26257, 35023, 43789, 52555, 61321
8571	zinc finger protein 558	576358	8726	461645	17492	26258, 35024, 43790, 52556, 61322
8572	zinc finger protein 578	435691	8727	454104	17493	26259, 35025, 43791, 52557, 61323
8573	zinc finger protein 578	553364	8728	451773	17494	26260, 35026, 43792, 52558, 61324
8574	zinc finger protein 578	421239	8729	459216	17495	26261, 35027, 43793, 52559, 61325
8575	zinc finger protein 595	526473	8730	437878	17496	26262, 35028, 43794, 52560, 61326
8576	zinc finger protein 598	431526	8731	411409	17497	26263, 35029, 43795, 52561, 61327
8577	zinc finger protein 598	563630	8732	455882	17498	26264, 35030, 43796, 52562, 61328

8578	zinc finger protein 608	306315	8733	307746	17499	26265, 35031, 43797, 52563, 61329
8579	zinc finger protein 608	504926	8734	427657	17500	26266, 35032, 43798, 52564, 61330
8580	zinc finger protein 608	509799	8735	423279	17501	26267, 35033, 43799, 52565, 61331
8581	zinc finger protein 608	513986	8736	421899	17502	26268, 35034, 43800, 52566, 61332
8582	Zinc finger protein 676	340708	8737	342595	17503	26269, 35035, 43801, 52567, 61333
8583	zinc finger protein 704	327835	8738	331462	17504	26270, 35036, 43802, 52568, 61334
8584	zinc finger protein 704	519936	8739	427715	17505	26271, 35037, 43803, 52569, 61335
8585	zinc finger protein 705B	400120	8740	382987	17506	26272, 35038, 43804, 52570, 61336
8586	zinc finger protein 705B	443676	8741	411618	17507	26273, 35039, 43805, 52571, 61337
8587	zinc finger protein 705G	400078	8742	445477	17508	26274, 35040, 43806, 52572, 61338
8588	zinc finger protein 705G	400156	8743	383020	17509	26275, 35041, 43807, 52573, 61339
8589	zinc finger protein 706	311212	8744	311768	17510	26276, 35042, 43808, 52574, 61340
8590	zinc finger protein 706	517844	8745	428227	17511	26277, 35043, 43809, 52575, 61341
8591	zinc finger protein 706	518336	8746	428696	17512	26278, 35044, 43810, 52576, 61342
8592	zinc finger protein 706	519882	8747	428985	17513	26279, 35045, 43811, 52577, 61343
8593	zinc finger protein 706	520347	8748	430823	17514	26280, 35046, 43812, 52578, 61344
8594	zinc finger protein 706	520454	8749	430090	17515	26281, 35047, 43813, 52579,

						61345
8595	zinc finger protein 706	520984	8750	427761	17516	26282, 35048, 43814, 52580, 61346
8596	zinc finger protein 706	521272	8751	430165	17517	26283, 35049, 43815, 52581, 61347
8597	zinc finger protein 706	523922	8752	429260	17518	26284, 35050, 43816, 52582, 61348
8598	zinc finger protein 707	563379	8753	457652	17519	26285, 35051, 43817, 52583, 61349
8599	zinc finger protein 707	567310	8754	455926	17520	26286, 35052, 43818, 52584, 61350
8600	zinc finger protein 714	291770	8755	291770	17521	26287, 35053, 43819, 52585, 61351
8601	zinc finger protein 714	343332	8756	345389	17522	26288, 35054, 43820, 52586, 61352
8602	zinc finger protein 714	596143	8757	472368	17523	26289, 35055, 43821, 52587, 61353
8603	zinc finger protein 716	418732	8758	387687	17524	26290, 35056, 43822, 52588, 61354
8604	zinc finger protein 716	420713	8759	394248	17525	26291, 35057, 43823, 52589, 61355
8605	zinc finger protein 717	400845	8760	383643	17526	26292, 35058, 43824, 52590, 61356
8606	zinc finger protein 717	422325	8761	409514	17527	26293, 35059, 43825, 52591, 61357
8607	zinc finger protein 720	316491	8762	319222	17528	26294, 35060, 43826, 52592, 61358
8608	zinc finger protein 720	398696	8763	443758	17529	26295, 35061, 43827, 52593, 61359
8609	zinc finger protein 720	399681	8764	440701	17530	26296, 35062, 43828, 52594, 61360
8610	zinc finger protein 724, pseudogene	418100	8765	413411	17531	26297, 35063, 43829, 52595, 61361
8611	zinc finger protein 727	550760	8766	447987	17532	26298, 35064,

						43830, 52596, 61362
8612	zinc finger protein 728	594710	8767	471593	17533	26299, 35065, 43831, 52597, 61363
8613	zinc finger protein 729	357491	8768	350085	17534	26300, 35066, 43832, 52598, 61364
8614	zinc finger protein 729	596562	8769	470161	17535	26301, 35067, 43833, 52599, 61365
8615	zinc finger protein 747	252799	8770	252799	17536	26302, 35068, 43834, 52600, 61366
8616	zinc finger protein 747	395094	8771	378528	17537	26303, 35069, 43835, 52601, 61367
8617	zinc finger protein 747	535210	8772	441702	17538	26304, 35070, 43836, 52602, 61368
8618	zinc finger protein 777	247930	8773	247930	17539	26305, 35071, 43837, 52603, 61369
8619	zinc finger protein 777	314683	8774	323730	17540	26306, 35072, 43838, 52604, 61370
8620	zinc finger protein 781	358582	8775	351391	17541	26307, 35073, 43839, 52605, 61371
8621	zinc finger protein 781	545586	8776	441465	17542	26308, 35074, 43840, 52606, 61372
8622	zinc finger protein 793	322299	8777	318811	17543	26309, 35075, 43841, 52607, 61373
8623	zinc finger protein 793	418827	8778	408471	17544	26310, 35076, 43842, 52608, 61374
8624	zinc finger protein 793	445217	8779	396402	17545	26311, 35077, 43843, 52609, 61375
8625	zinc finger protein 793	542455	8780	444355	17546	26312, 35078, 43844, 52610, 61376
8626	zinc finger protein 804B	333190	8781	329638	17547	26313, 35079, 43845, 52611, 61377
8627	zinc finger protein 81	599945	8782	472283	17548	26314, 35080, 43846, 52612, 61378

8628	zinc finger protein 812	457674	8783	395629	17549	26315, 35081, 43847, 52613, 61379
8629	zinc finger protein 814	376205	8784	365378	17550	26316, 35082, 43848, 52614, 61380
8630	zinc finger protein 814	435989	8785	410545	17551	26317, 35083, 43849, 52615, 61381
8631	zinc finger protein 821	313565	8786	313822	17552	26318, 35084, 43850, 52616, 61382
8632	zinc finger protein 821	425432	8787	398089	17553	26319, 35085, 43851, 52617, 61383
8633	zinc finger protein 821	446827	8788	405908	17554	26320, 35086, 43852, 52618, 61384
8634	zinc finger protein 821	564134	8789	455738	17555	26321, 35087, 43853, 52619, 61385
8635	zinc finger protein 821	565601	8790	455648	17556	26322, 35088, 43854, 52620, 61386
8636	zinc finger protein 835	342088	8791	341756	17557	26323, 35089, 43855, 52621, 61387
8637	zinc finger protein 835	537055	8792	444747	17558	26324, 35090, 43856, 52622, 61388
8638	zinc finger protein 839	262236	8793	262236	17559	26325, 35091, 43857, 52623, 61389
8639	zinc finger protein 839	398436	8794	381463	17560	26326, 35092, 43858, 52624, 61390
8640	zinc finger protein 839	442396	8795	399863	17561	26327, 35093, 43859, 52625, 61391
8641	zinc finger protein 839	558850	8796	453363	17562	26328, 35094, 43860, 52626, 61392
8642	zinc finger protein 839	559185	8797	453109	17563	26329, 35095, 43861, 52627, 61393
8643	zinc finger protein 843	315678	8798	322899	17564	26330, 35096, 43862, 52628, 61394
8644	zinc finger protein 85	571716	8799	459635	17565	26331, 35097, 43863, 52629,

						61395
8645	zinc finger protein 850	591344	8800	464976	17566	26332, 35098, 43864, 52630, 61396
8646	zinc finger protein 852	313378	8801	322569	17567	26333, 35099, 43865, 52631, 61397
8647	zinc finger protein 852	436261	8802	389841	17568	26334, 35100, 43866, 52632, 61398
8648	zinc finger protein 853	457543	8803	455585	17569	26335, 35101, 43867, 52633, 61399
8649	zinc finger protein 865	568956	8804	457715	17570	26336, 35102, 43868, 52634, 61400
8650	zinc finger protein 878	547628	8805	447931	17571	26337, 35103, 43869, 52635, 61401
8651	zinc finger protein 880	344085	8806	343625	17572	26338, 35104, 43870, 52636, 61402
8652	zinc finger protein 880	422689	8807	406318	17573	26339, 35105, 43871, 52637, 61403
8653	zinc finger protein 891	397313	8808	380480	17574	26340, 35106, 43872, 52638, 61404
8654	zinc finger RNA binding protein 2	262961	8809	262961	17575	26341, 35107, 43873, 52639, 61405
8655	zinc finger RNA binding protein 2	438164	8810	388974	17576	26342, 35108, 43874, 52640, 61406
8656	zinc finger RNA binding protein 2	439086	8811	388567	17577	26343, 35109, 43875, 52641, 61407
8657	zinc finger with UFM1-specific peptidase domain	368573	8812	357562	17578	26344, 35110, 43876, 52642, 61408
8658	zinc finger with UFM1-specific peptidase domain	368576	8813	357565	17579	26345, 35111, 43877, 52643, 61409
8659	zinc finger, AN1-type domain 1	220669	8814	220669	17580	26346, 35112, 43878, 52644, 61410
8660	zinc finger, AN1-type domain 1	517450	8815	427811	17581	26347, 35113, 43879, 52645, 61411
8661	zinc finger, AN1-type	518419	8816	428527	17582	26348, 35114,

	domain 1					43880, 52646, 61412
8662	zinc finger, AN1-type domain 1	520076	8817	430719	17583	26349, 35115, 43881, 52647, 61413
8663	zinc finger, AN1-type domain 1	520604	8818	428101	17584	26350, 35116, 43882, 52648, 61414
8664	zinc finger, AN1-type domain 1	520635	8819	428278	17585	26351, 35117, 43883, 52649, 61415
8665	zinc finger, AN1-type domain 1	521287	8820	428139	17586	26352, 35118, 43884, 52650, 61416
8666	zinc finger, AN1-type domain 1	521742	8821	430405	17587	26353, 35119, 43885, 52651, 61417
8667	zinc finger, AN1-type domain 1	522520	8822	429999	17588	26354, 35120, 43886, 52652, 61418
8668	zinc finger, AN1-type domain 1	523361	8823	427957	17589	26355, 35121, 43887, 52653, 61419
8669	zinc finger, AN1-type domain 4	335258	8824	335586	17590	26356, 35122, 43888, 52654, 61420
8670	zinc finger, AN1-type domain 4	344646	8825	339484	17591	26357, 35123, 43889, 52655, 61421
8671	zinc finger, AN1-type domain 4	374366	8826	363486	17592	26358, 35124, 43890, 52656, 61422
8672	zinc finger, AN1-type domain 4	374370	8827	363490	17593	26359, 35125, 43891, 52657, 61423
8673	zinc finger, AN1-type domain 4	374371	8828	363491	17594	26360, 35126, 43892, 52658, 61424
8674	zinc finger, AN1-type domain 4	374376	8829	363496	17595	26361, 35127, 43893, 52659, 61425
8675	zinc finger, AN1-type domain 6	558087	8830	453888	17596	26362, 35128, 43894, 52660, 61426
8676	zinc finger, B-box domain containing	307529	8831	305065	17597	26363, 35129, 43895, 52661, 61427
8677	zinc finger, B-box domain containing	392766	8832	376519	17598	26364, 35130, 43896, 52662, 61428

8678	zinc finger, B-box domain containing	392767	8833	376520	17599	26365, 35131, 43897, 52663, 61429
8679	zinc finger, B-box domain containing	455345	8834	390232	17600	26366, 35132, 43898, 52664, 61430
8680	zinc finger, B-box domain containing	474464	8835	419307	17601	26367, 35133, 43899, 52665, 61431
8681	zinc finger, BED-type containing 2	317012	8836	321370	17602	26368, 35134, 43900, 52666, 61432
8682	zinc finger, BED-type containing 3	255198	8837	255198	17603	26369, 35135, 43901, 52667, 61433
8683	zinc finger, BED-type containing 3	511587	8838	427487	17604	26370, 35136, 43902, 52668, 61434
8684	zinc finger, C3H1-type containing	378743	8839	368017	17605	26371, 35137, 43903, 52669, 61435
8685	zinc finger, C3H1-type containing	548100	8840	450044	17606	26372, 35138, 43904, 52670, 61436
8686	zinc finger, C4H2 domain containing	337990	8841	338650	17607	26373, 35139, 43905, 52671, 61437
8687	zinc finger, C4H2 domain containing	374839	8842	363972	17608	26374, 35140, 43906, 52672, 61438
8688	zinc finger, C4H2 domain containing	447788	8843	399126	17609	26375, 35141, 43907, 52673, 61439
8689	zinc finger, C4H2 domain containing	545618	8844	440840	17610	26376, 35142, 43908, 52674, 61440
8690	zinc finger, CCHC domain containing 10	324170	8845	324274	17611	26377, 35143, 43909, 52675, 61441
8691	zinc finger, CCHC domain containing 13	339534	8846	345633	17612	26378, 35144, 43910, 52676, 61442
8692	zinc finger, CCHC domain containing 14	268616	8847	268616	17613	26379, 35145, 43911, 52677, 61443
8693	zinc finger, CCHC domain containing 16	340433	8848	340590	17614	26380, 35146, 43912, 52678, 61444
8694	zinc finger, CCHC domain containing 24	372333	8849	361408	17615	26381, 35147, 43913, 52679,

						61445
8695	zinc finger, CCHC domain containing 24	372336	8850	361411	17616	26382, 35148, 43914, 52680, 61446
8696	zinc finger, CCHC domain containing 3	382352	8851	371789	17617	26383, 35149, 43915, 52681, 61447
8697	zinc finger, CCHC domain containing 5	321110	8852	316794	17618	26384, 35150, 43916, 52682, 61448
8698	zinc finger, CCHC domain containing 6	277141	8853	277141	17619	26385, 35151, 43917, 52683, 61449
8699	zinc finger, CCHC domain containing 6	375947	8854	365114	17620	26386, 35152, 43918, 52684, 61450
8700	zinc finger, CCHC domain containing 6	375948	8855	365115	17621	26387, 35153, 43919, 52685, 61451
8701	zinc finger, CCHC domain containing 6	375957	8856	365124	17622	26388, 35154, 43920, 52686, 61452
8702	zinc finger, CCHC domain containing 6	375960	8857	365127	17623	26389, 35155, 43921, 52687, 61453
8703	zinc finger, CCHC domain containing 6	375961	8858	365128	17624	26390, 35156, 43922, 52688, 61454
8704	zinc finger, CCHC domain containing 6	375963	8859	365130	17625	26391, 35157, 43923, 52689, 61455
8705	zinc finger, CCHC domain containing 6	427388	8860	409441	17626	26392, 35158, 43924, 52690, 61456
8706	zinc finger, CCHC domain containing 7	322831	8861	316365	17627	26393, 35159, 43925, 52691, 61457
8707	zinc finger, CCHC domain containing 7	336755	8862	337839	17628	26394, 35160, 43926, 52692, 61458
8708	zinc finger, CCHC domain containing 7	534928	8863	443113	17629	26395, 35161, 43927, 52693, 61459
8709	zinc finger, CCHC domain containing 8	336229	8864	337313	17630	26396, 35162, 43928, 52694, 61460
8710	zinc finger, CCHC domain containing 8	536306	8865	441423	17631	26397, 35163, 43929, 52695, 61461
8711	zinc finger, CCHC domain	540586	8866	440234	17632	26398, 35164,

	containing 8					43930, 52696, 61462
8712	zinc finger, CCHC domain containing 8	543897	8867	438993	17633	26399, 35165, 43931, 52697, 61463
8713	zinc finger, CCHC domain containing 9	254037	8868	254037	17634	26400, 35166, 43932, 52698, 61464
8714	zinc finger, CCHC domain containing 9	380199	8869	369546	17635	26401, 35167, 43933, 52699, 61465
8715	zinc finger, CCHC domain containing 9	407610	8870	385047	17636	26402, 35168, 43934, 52700, 61466
8716	zinc finger, CCHC domain containing 9	438268	8871	412637	17637	26403, 35169, 43935, 52701, 61467
8717	zinc finger, CW type with PWWP domain 1	324725	8872	314880	17638	26404, 35170, 43936, 52702, 61468
8718	zinc finger, CW type with PWWP domain 1	379559	8873	368877	17639	26405, 35171, 43937, 52703, 61469
8719	zinc finger, CW type with PWWP domain 1	398027	8874	381109	17640	26406, 35172, 43938, 52704, 61470
8720	zinc finger, CW type with PWWP domain 2	383768	8875	373278	17641	26407, 35173, 43939, 52705, 61471
8721	zinc finger, CW type with PWWP domain 2	420223	8876	395930	17642	26408, 35174, 43940, 52706, 61472
8722	zinc finger, CW type with PWWP domain 2	421010	8877	412386	17643	26409, 35175, 43941, 52707, 61473
8723	zinc finger, DBF-type containing 2	374423	8878	363545	17644	26410, 35176, 43942, 52708, 61474
8724	zinc finger, DHHC-type containing 11B	382776	8879	445280	17645	26411, 35177, 43943, 52709, 61475
8725	zinc finger, FYVE domain containing 19	299173	8880	299173	17646	26412, 35178, 43944, 52710, 61476
8726	zinc finger, FYVE domain containing 19	336455	8881	337824	17647	26413, 35179, 43945, 52711, 61477
8727	zinc finger, FYVE domain containing 19	355341	8882	347498	17648	26414, 35180, 43946, 52712, 61478

8728	zinc finger, HIT-type containing 1	305105	8883	304593	17649	26415, 35181, 43947, 52713, 61479
8729	zinc finger, HIT-type containing 6	370574	8884	359606	17650	26416, 35182, 43948, 52714, 61480
8730	zinc finger, HIT-type containing 6	431532	8885	414344	17651	26417, 35183, 43949, 52715, 61481
8731	zinc finger, MYM-type 4	314607	8886	322915	17652	26418, 35184, 43950, 52716, 61482
8732	zinc finger, MYM-type 4	373297	8887	362394	17653	26419, 35185, 43951, 52717, 61483
8733	zinc finger, MYM-type 4	441447	8888	397524	17654	26420, 35186, 43952, 52718, 61484
8734	zinc finger, MYM-type 4	457946	8889	400506	17655	26421, 35187, 43953, 52719, 61485
8735	zinc finger, MYND-type containing 12	372565	8890	361646	17656	26422, 35188, 43954, 52720, 61486
8736	zinc finger, MYND-type containing 12	433602	8891	398340	17657	26423, 35189, 43955, 52721, 61487
8737	zinc finger, MYND-type containing 17	299432	8892	299432	17658	26424, 35190, 43956, 52722, 61488
8738	zinc finger, MYND-type containing 17	372912	8893	362003	17659	26425, 35191, 43957, 52723, 61489
8739	zinc finger, RAN-binding domain containing 3	264159	8894	264159	17660	26426, 35192, 43958, 52724, 61490
8740	zinc finger, RAN-binding domain containing 3	283060	8895	283060	17661	26427, 35193, 43959, 52725, 61491
8741	zinc finger, RAN-binding domain containing 3	397448	8896	380590	17662	26428, 35194, 43960, 52726, 61492
8742	zinc finger, RAN-binding domain containing 3	401392	8897	383979	17663	26429, 35195, 43961, 52727, 61493
8743	zinc finger, RAN-binding domain containing 3	412849	8898	404015	17664	26430, 35196, 43962, 52728, 61494
8744	zinc finger, RAN-binding domain containing 3	536680	8899	441320	17665	26431, 35197, 43963, 52729,

						61495
8745	zinc finger, RAN-binding domain containing 3	538542	8900	443455	17666	26432, 35198, 43964, 52730, 61496
8746	zinc finger, SWIM-type containing 2	295131	8901	295131	17667	26433, 35199, 43965, 52731, 61497
8747	zinc finger, SWIM-type containing 3	255152	8902	255152	17668	26434, 35200, 43966, 52732, 61498
8748	zinc finger, SWIM-type containing 3	454862	8903	406313	17669	26435, 35201, 43967, 52733, 61499
8749	zinc finger, SWIM-type containing 4	254323	8904	254323	17670	26436, 35202, 43968, 52734, 61500
8750	zinc finger, SWIM-type containing 4	440752	8905	405278	17671	26437, 35203, 43969, 52735, 61501
8751	zinc finger, SWIM-type containing 5	359600	8906	352614	17672	26438, 35204, 43970, 52736, 61502
8752	zinc finger, SWIM-type containing 6	252744	8907	252744	17673	26439, 35205, 43971, 52737, 61503
8753	zinc finger, ZZ-type with EF-hand domain 1	381638	8908	371051	17674	26440, 35206, 43972, 52738, 61504
8754	ZNF503 antisense RNA 2 (non-protein coding)	425916	8909	412272	17675	26441, 35207, 43973, 52739, 61505
8755	zonadhesin	538115	8910	445091	17676	26442, 35208, 43974, 52740, 61506
8756	zonadhesin	542585	8911	444427	17677	26443, 35209, 43975, 52741, 61507
8757	zonadhesin	546213	8912	441117	17678	26444, 35210, 43976, 52742, 61508
8758	zonadhesin	546292	8913	445943	17679	26445, 35211, 43977, 52743, 61509
8759	zyg-11 homolog A (C. elegans)	371528	8914	360583	17680	26446, 35212, 43978, 52744, 61510
8760	zyg-11 homolog A (C. elegans)	371532	8915	360587	17681	26447, 35213, 43979, 52745, 61511
8761	zyg-11 homolog B (C.	294353	8916	294353	17682	26448, 35214,

	elegans)					43980, 52746, 61512
8762	zyg-11 homolog B (C. elegans)	443756	8917	400522	17683	26449, 35215, 43981, 52747, 61513
8763	zyg-11 homolog B (C. elegans)	545132	8918	441315	17684	26450, 35216, 43982, 52748, 61514
8764	zygote arrest 1-like	345108	8919	344616	17685	26451, 35217, 43983, 52749, 61515
8765	zygote arrest 1-like	533490	8920	437289	17686	26452, 35218, 43984, 52750, 61516
8766	zymogen granule protein 16 homolog (rat)	400752	8921	383563	17687	26453, 35219, 43985, 52751, 61517

Protein Cleavage Signals and Sites

[000230] In one embodiment, the polypeptides of the present invention may include at least one protein cleavage signal containing at least one protein cleavage site. The protein cleavage site may be located at the N-terminus, the C-terminus, at any space between the N- and the C- termini such as, but not limited to, half-way between the N- and C-termini, between the N-terminus and the half way point, between the half way point and the C-terminus, and combinations thereof.

[000231] The polypeptides of the present invention may include, but is not limited to, a proprotein convertase (or prohormone convertase), thrombin or Factor Xa protein cleavage signal. Proprotein convertases are a family of nine proteinases, comprising seven basic amino acid-specific subtilisin-like serine proteinases related to yeast kexin, known as prohormone convertase 1/3 (PC1/3), PC2, furin, PC4, PC5/6, paired basic amino-acid cleaving enzyme 4 (PACE4) and PC7, and two other subtilases that cleave at non-basic residues, called subtilisin kexin isozyme 1 (SKI-1) and proprotein convertase subtilisin kexin 9 (PCSK9). Non-limiting examples of protein cleavage signal amino acid sequences are listing in Table 7. In Table 7, "X" refers to any amino acid, "n" may be 0, 2, 4 or 6 amino acids and "*" refers to the protein cleavage site. In Table 7, SEQ ID NO: 61636 refers to when n=4 and SEQ ID NO: 61637 refers to when n=6.

Table 7. Protein Cleavage Site Sequences

Protein Cleavage Signal	Amino Acid Cleavage Sequence	SEQ ID NO
Proprotein convertase	R-X-X-R*	61634
	R-X-K/R-R*	61635
	K/R-Xn-K/R*	61636 or 61637
Thrombin	L-V-P-R*-G-S	61638
	L-V-P-R*	61639
	A/F/G/I/L/T/V/M-A/F/G/I/L/T/V/W-P-R*	61640
Factor Xa	I-E-G-R*	61641
	I-D-G-R*	61642
	A-E-G-R*	61643
	A/F/G/I/L/T/V/M-D/E-G-R*	61644

[000232] In one embodiment, the primary constructs and the mmRNA of the present invention may be engineered such that the primary construct or mmRNA contains at least one encoded protein cleavage signal. The encoded protein cleavage signal may be located before the start codon, after the start codon, before the coding region, within the coding region such as, but not limited to, half way in the coding region, between the start codon and the half way point, between the half way point and the stop codon, after the coding region, before the stop codon, between two stop codons, after the stop codon and combinations thereof.

[000233] In one embodiment, the primary constructs or mmRNA of the present invention may include at least one encoded protein cleavage signal containing at least one protein cleavage site. The encoded protein cleavage signal may include, but is not limited to, a proprotein convertase (or prohormone convertase), thrombin and/or Factor Xa protein cleavage signal. One of skill in the art may use Table 1 above or other known methods to determine the appropriate encoded protein cleavage signal to include in the primary constructs or mmRNA of the present invention. For example, starting with the signal of Table 7 and considering the codons of Table 1 one can design a signal for the primary construct which can produce a protein signal in the resulting polypeptide.

[000234] In one embodiment, the polypeptides of the present invention include at least one protein cleavage signal and/or site.

[000235] As a non-limiting example, U.S. Pat. No. 7,374,930 and U.S. Pub. No. 20090227660, herein incorporated by reference in their entireties, use a furin cleavage

site to cleave the N-terminal methionine of GLP-1 in the expression product from the Golgi apparatus of the cells. In one embodiment, the polypeptides of the present invention include at least one protein cleavage signal and/or site with the proviso that the polypeptide is not GLP-1.

[000236] In one embodiment, the primary constructs or mmRNA of the present invention includes at least one encoded protein cleavage signal and/or site.

[000237] In one embodiment, the primary constructs or mmRNA of the present invention includes at least one encoded protein cleavage signal and/or site with the proviso that the primary construct or mmRNA does not encode GLP-1.

[000238] In one embodiment, the primary constructs or mmRNA of the present invention may include more than one coding region. Where multiple coding regions are present in the primary construct or mmRNA of the present invention, the multiple coding regions may be separated by encoded protein cleavage sites. As a non-limiting example, the primary construct or mmRNA may be signed in an ordered pattern. On such pattern follows AXBY form where A and B are coding regions which may be the same or different coding regions and/or may encode the same or different polypeptides, and X and Y are encoded protein cleavage signals which may encode the same or different protein cleavage signals. A second such pattern follows the form AXYBZ where A and B are coding regions which may be the same or different coding regions and/or may encode the same or different polypeptides, and X, Y and Z are encoded protein cleavage signals which may encode the same or different protein cleavage signals. A third pattern follows the form ABXCY where A, B and C are coding regions which may be the same or different coding regions and/or may encode the same or different polypeptides, and X and Y are encoded protein cleavage signals which may encode the same or different protein cleavage signals.

[000239] In one embodiment, the polypeptides, primary constructs and mmRNA can also contain sequences that encode protein cleavage sites so that the polypeptides, primary constructs and mmRNA can be released from a carrier region or a fusion partner by treatment with a specific protease for said protein cleavage site.

[000240] In one embodiment, the polypeptides, primary constructs and mmRNA of the present invention may include a sequence encoding the 2A peptide. In one embodiment,

this sequence may be used to separate the coding region of two or more polypeptides of interest. As a non-limiting example, the sequence encoding the 2A peptide may be between coding region A and coding region B (A-2Apep-B). The presence of the 2A peptide would result in the cleavage of one long protein into protein A, protein B and the 2A peptide. Protein A and protein B may be the same or different polypeptides of interest. In another embodiment, the 2A peptide may be used in the polynucleotides, primary constructs and/or mmRNA of the present invention to produce two, three, four, five, six, seven, eight, nine, ten or more proteins.

Incorporating Post Transcriptional Control Modulators

[000241] In one embodiment, the polynucleotides, primary constructs and/or mmRNA of the present invention may include at least one post transcriptional control modulator. These post transcriptional control modulators may be, but are not limited to, small molecules, compounds and regulatory sequences. As a non-limiting example, post transcriptional control may be achieved using small molecules identified by PTC Therapeutics Inc. (South Plainfield, NJ) using their GEMS™ (Gene Expression Modulation by Small-Moleclues) screening technology.

[000242] The post transcriptional control modulator may be a gene expression modulator which is screened by the method detailed in or a gene expression modulator described in International Publication No. WO2006022712, herein incorporated by reference in its entirety. Methods identifying RNA regulatory sequences involved in translational control are described in International Publication No. WO2004067728, herein incorporated by reference in its entirety; methods identifying compounds that modulate untranslated region dependent expression of a gene are described in International Publication No. WO2004065561, herein incorporated by reference in its entirety.

[000243] In one embodiment, the polynucleotides, primary constructs and/or mmRNA of the present invention may include at least one post transcriptional control modulator is located in the 5' and/or the 3' untranslated region of the polynucleotides, primary constructs and/or mmRNA of the present invention

[000244] In another embodiment, the polynucleotides, primary constructs and/or mmRNA of the present invention may include at least one post transcription control

modulator to modulate premature translation termination. The post transcription control modulators may be compounds described in or a compound found by methods outlined in International Publication Nso. WO2004010106, WO2006044456, WO2006044682, WO2006044503 and WO2006044505, each of which is herein incorporated by reference in its entirety. As a non-limiting example, the compound may bind to a region of the 28S ribosomal RNA in order to modulate premature translation termination (See e.g., WO2004010106, herein incorporated by reference in its entirety).

[000245] In one embodiment, polynucleotides, primary constructs and/or mmRNA of the present invention may include at least one post transcription control modulator to alter protein expression. As a non-limiting example, the expression of VEGF may be regulated using the compounds described in or a compound found by the methods described in International Publication Nos. WO2005118857, WO2006065480, WO2006065479 and WO2006058088, each of which is herein incorporated by reference in its entirety.

[000246] The polynucleotides, primary constructs and/or mmRNA of the present invention may include at least one post transcription control modulator to control translation. In one embodiment, the post transcription control modulator may be a RNA regulatory sequence. As a non-limiting example, the RNA regulatory sequence may be identified by the methods described in International Publication No. WO2006071903, herein incorporated by reference in its entirety.

III. Modifications

[000247] Herein, in a polynucleotide (such as a primary construct or an mRNA molecule), the terms "modification" or, as appropriate, "modified" refer to modification with respect to A, G, U or C ribonucleotides. Generally, herein, these terms are not intended to refer to the ribonucleotide modifications in naturally occurring 5′-terminal mRNA cap moieties. In a polypeptide, the term "modification" refers to a modification as compared to the canonical set of 20 amino acids, moiety)

[000248] The modifications may be various distinct modifications. In some embodiments, the coding region, the flanking regions and/or the terminal regions may contain one, two, or more (optionally different) nucleoside or nucleotide modifications. In some embodiments, a modified polynucleotide, primary construct, or mmRNA

introduced to a cell may exhibit reduced degradation in the cell, as compared to an unmodified polynucleotide, primary construct, or mmRNA.

[000249] The polynucleotides, primary constructs, and mmRNA can include any useful modification, such as to the sugar, the nucleobase, or the internucleoside linkage (*e.g.* to a linking phosphate / to a phosphodiester linkage / to the phosphodiester backbone). One or more atoms of a pyrimidine nucleobase may be replaced or substituted with optionally substituted amino, optionally substituted thiol, optionally substituted alkyl (e.g., methyl or ethyl), or halo (e.g., chloro or fluoro). In certain embodiments, modifications (e.g., one or more modifications) are present in each of the sugar and the internucleoside linkage. Modifications according to the present invention may be modifications of ribonucleic acids (RNAs) to deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof). Additional modifications are described herein.

[000250] As described herein, the polynucleotides, primary constructs, and mmRNA of the invention do not substantially induce an innate immune response of a cell into which the mRNA is introduced. Featues of an induced innate immune response include 1) increased expression of pro-inflammatory cytokines, 2) activation of intracellular PRRs (RIG-I, MDA5, etc, and/or 3) termination or reduction in protein translation.

[000251] In certain embodiments, it may desirable to intracellularly degrade a modified nucleic acid molecule introduced into the cell. For example, degradation of a modified nucleic acid molecule may be preferable if precise timing of protein production is desired. Thus, in some embodiments, the invention provides a modified nucleic acid molecule containing a degradation domain, which is capable of being acted on in a directed manner within a cell. In another aspect, the present disclosure provides polynucleotides comprising a nucleoside or nucleotide that can disrupt the binding of a major groove interacting, e.g. binding, partner with the polynucleotide (e.g., where the modified nucleotide has decreased binding affinity to major groove interacting partner, as compared to an unmodified nucleotide).

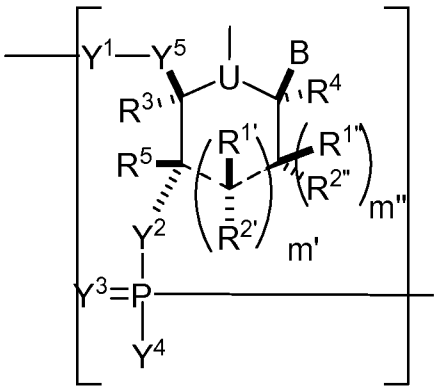
[000252] The polynucleotides, primary constructs, and mmRNA can optionally include other agents (e.g., RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix

formation, aptamers, vectors, etc.). In some embodiments, the polynucleotides, primary constructs, or mmRNA may include one or more messenger RNAs (mRNAs) and one or more modified nucleoside or nucleotides (e.g., mmRNA molecules). Details for these polynucleotides, primary constructs, and mmRNA follow.

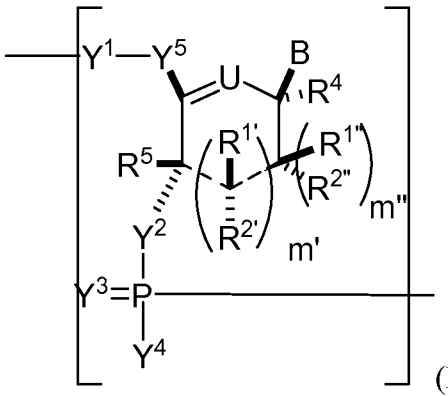
Polynucleotides and Primary Constructs

[000253] The polynucleotides, primary constructs, and mmRNA of the invention includes a first region of linked nucleosides encoding a polypeptide of interest, a first flanking region located at the 5′ terminus of the first region, and a second flanking region located at the 3′ terminus of the first region.

[000254] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) includes n number of linked nucleosides having Formula (Ia) or Formula (Ia-1):



(Ia)



(Ia-1) or a

pharmaceutically acceptable salt or stereoisomer thereof,

[000255] wherein

[000256] U is O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

[000257] --- is a single bond or absent;

[000258] each of $R^{1'}$, $R^{2'}$, $R^{1''}$, $R^{2''}$, R^1, R^2, R^3, R^4, and R^5 is, independently, if present, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl,or absent; wherein the combination of R3 with one or more of

R1', R1", R2′, R2", or R5 (e.g., the combination of R1' and R3, the combination of R1" and R3, the combination of R2' and R3, the combination of R2" and R3, or the combination of R5 and R3) can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl); wherein the combination of R5 with one or more of R1', R1", R2′, or R2" (e.g., the combination of R1' and R5, the combination of R1" and R5, the combination of R2′ and R5, or the combination of R2" and R5) can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl); and wherein the combination of R^4 and one or more of $R^{1'}$, $R^{1"}$, $R^{2'}$, $R^{2"}$, R^3, or R^5 can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl);each of m' and m" is, independently, an integer from 0 to 3 (e.g., from 0 to 2, from 0 to 1, from 1 to 3, or from 1 to 2);

[000259] each of Y^1, Y^2, and Y^3, is, independently, O, S, Se, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or absent;

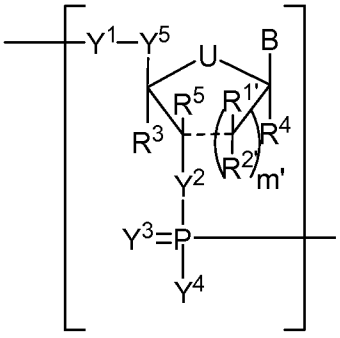
[000260] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000261] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

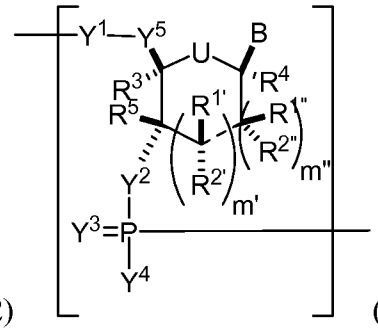
[000262] n is an integer from 1 to 100,000; and

[000263] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof), wherein the combination of B and $R^{1'}$, the combination of B and $R^{2'}$, the combination of B and

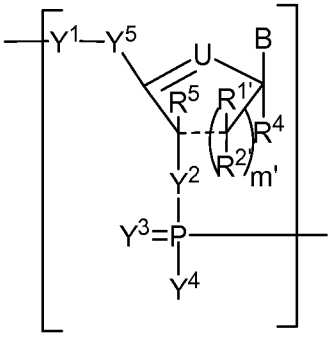
$R^{1"}$, or the combination of B and $R^{2"}$ can, taken together with the carbons to which they are attached, optionally form a bicyclic group (e.g., a bicyclic heterocyclyl) or wherein the combination of B, $R^{1"}$, and R^3 or the combination of B, $R^{2"}$, and R^3 can optionally form a tricyclic or tetracyclic group (e.g., a tricyclic or tetracyclic heterocyclyl, such as in Formula (IIo)-(IIp) herein).In some embodiments, the polynucleotide, primary construct, or mmRNA includes a modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (Ia-2)-(Ia-5) or a pharmaceutically acceptable salt or stereoisomer thereof.



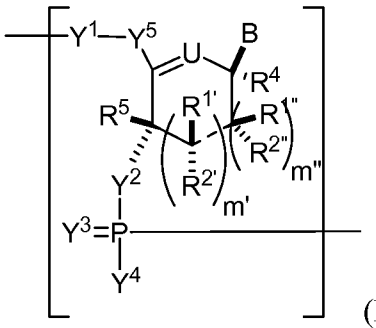
(Ia-2)



(Ia-3)

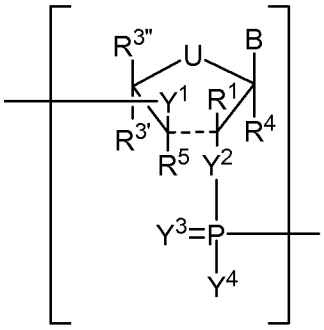


(Ia-4),

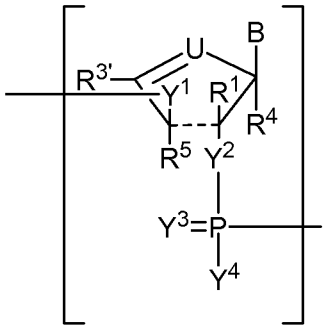


(Ia-5).

[000264] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (Ib) or Formula (Ib-1):



(Ib),



(Ib-1) or a pharmaceutically acceptable salt or stereoisomer thereof,

[000265] wherein

[000266] U is O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

[000267] --- is a single bond or absent;

[000268] each of R^1, $R^{3'}$, $R^{3"}$, and R^4 is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or absent; and wherein the combination of R^1 and $R^{3'}$ or the combination of R^1 and $R^{3"}$ can be taken together to form optionally substituted alkylene or optionally substituted heteroalkylene (e.g., to produce a locked nucleic acid);

[000269] each R^5 is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, or absent;

[000270] each of Y^1, Y^2, and Y^3 is, independently, O, S, Se, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl;

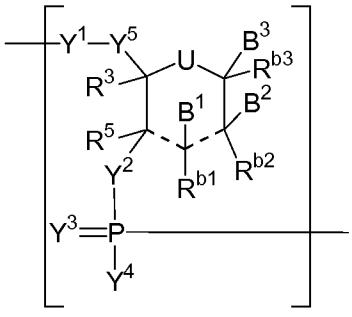
[000271] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted

alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000272] n is an integer from 1 to 100,000; and

[000273] B is a nucleobase.

[000274] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) includes n number of linked nucleosides having Formula (Ic):



(Ic), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000275] wherein

[000276] U is O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

[000277] --- is a single bond or absent;

[000278] each of B^1, B^2, and B^3 is, independently, a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof, as described herein), H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl, wherein one and only one of B^1, B^2, and B^3 is a nucleobase;

[000279] each of R^{b1}, R^{b2}, R^{b3}, R^3, and R^5 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally

substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl or optionally substituted aminoalkynyl;

[000280] each Y^1, Y^2, and Y^3, is, independently, O, S, Se, -NR^{N1}-, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl;

[000281] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

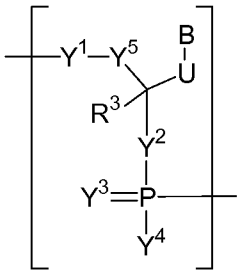
[000282] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000283] n is an integer from 1 to 100,000; and

[000284] wherein the ring including U can include one or more double bonds.

[000285] In particular embodiments, the ring including U does not have a double bond between U-CB^3R^{b3} or between CB^3R^{b3}-$C^{B2}R^{b2}$.

[000286] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) includes n number of linked nucleosides having Formula (Id):



(Id), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000287] wherein

[000288] U is O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

[000289] each R^3 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy,

optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl;

[000290] each of Y^1, Y^2, and Y^3, is, independently, O, S, Se, -NR^{N1}-, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl;

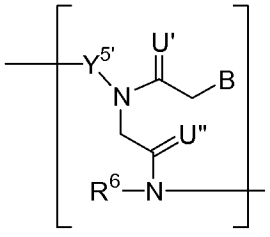
[000291] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000292] each Y^5 is, independently, O, S, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000293] n is an integer from 1 to 100,000; and

[000294] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000295] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) includes n number of linked nucleosides having Formula (Ie):



(Ie), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000296] wherein

[000297] each of U' and U" is, independently, O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

[000298] each R^6 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy,

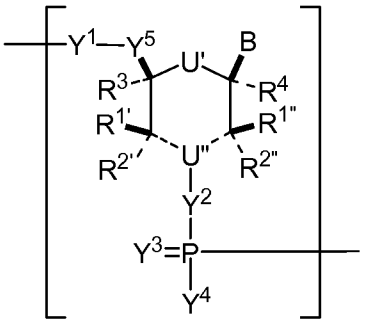
optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl;

[000299] each $Y^{5'}$ is, independently, O, S, optionally substituted alkylene (e.g., methylene or ethylene), or optionally substituted heteroalkylene;

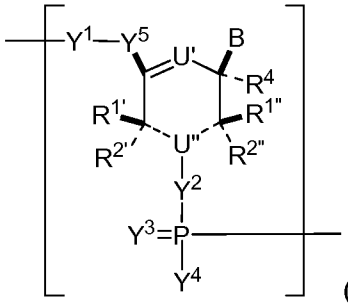
[000300] n is an integer from 1 to 100,000; and

[000301] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000302] In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) includes n number of linked nucleosides having Formula (If) or (If-1):



(If),



(If-1), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000303] wherein

[000304] each of U' and U" is, independently, O, S, N, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U' is O and U" is N);

[000305] --- is a single bond or absent;

[000306] each of $R^{1'}$, $R^{2'}$, $R^{1"}$, $R^{2"}$, R^3, and R^4 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or absent; and wherein the combination of $R^{1'}$ and R^3, the combination of $R^{1"}$ and R^3, the combination of $R^{2'}$ and R^3, or the combination of $R^{2"}$ and R^3 can be taken together to form optionally substituted alkylene or optionally substituted heteroalkylene (e.g., to produce a locked

nucleic acid);each of m' and m" is, independently, an integer from 0 to 3 (e.g., from 0 to 2, from 0 to 1, from 1 to 3, or from 1 to 2);

[000307] each of Y^1, Y^2, and Y^3, is, independently, O, S, Se, -NR^{N1}-, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or absent;

[000308] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000309] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000310] n is an integer from 1 to 100,000; and

[000311] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000312] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia), (Ia-1)-(Ia-3), (Ib)-(If), and (IIa)-(IIp)), the ring including U has one or two double bonds.

[000313] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each of R^1, $R^{1'}$, and $R^{1"}$, if present, is H. In further embodiments, each of R^2, $R^{2'}$, and $R^{2"}$, if present, is, independently, H, halo (e.g., fluoro), hydroxy, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy. In particular embodiments, alkoxyalkoxy is -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl). In some embodiments, s2 is 0, s1 is 1 or 2, s3 is 0 or 1, and R' is C_{1-6} alkyl.

[000314] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each of R^2, $R^{2'}$, and $R^{2"}$, if present, is H. In further

embodiments, each of R^1, $R^{1'}$, and $R^{1''}$, if present, is, independently, H, halo (e.g., fluoro), hydroxy, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy. In particular embodiments, alkoxyalkoxy is -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl). In some embodiments, s2 is 0, s1 is 1 or 2, s3 is 0 or 1, and R' is C_{1-6} alkyl.

[000315] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each of R^3, R^4, and R^5 is, independently, H, halo (e.g., fluoro), hydroxy, optionally substituted alkyl, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy. In particular embodiments, R^3 is H, R^4 is H, R^5 is H, or R^3, R^4, and R^5 are all H. In particular embodiments, R^3 is C_{1-6} alkyl, R^4 is C_{1-6} alkyl, R^5 is C_{1-6} alkyl, or R^3, R^4, and R^5 are all C_{1-6} alkyl. In particular embodiments, R^3 and R^4 are both H, and R^5 is C_{1-6} alkyl.

[000316] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), R^3 and R^5 join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl, such as trans-3',4' analogs, wherein R^3 and R^5 join together to form heteroalkylene (e.g., -$(CH_2)_{b1}O(CH_2)_{b2}O(CH_2)_{b3}$-, wherein each of b1, b2, and b3 are, independently, an integer from 0 to 3).

[000317] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), R^3 and one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, $R^{2''}$, or R^5 join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl, R^3 and one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, $R^{2''}$, or R^5 join together to form heteroalkylene (e.g., -

$(CH_2)_{b1}O(CH_2)_{b2}O(CH_2)_{b3}$-, wherein each of b1, b2, and b3 are, independently, an integer from 0 to 3).

[000318] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), R^5 and one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, or $R^{2''}$ join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl (e.g., a bicyclic, tricyclic, or tetracyclic heterocyclyl, R^5 and one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, or $R^{2''}$ join together to form heteroalkylene (e.g., -$(CH_2)_{b1}O(CH_2)_{b2}O(CH_2)_{b3}$-, wherein each of b1, b2, and b3 are, independently, an integer from 0 to 3).

[000319] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each Y^2 is, independently, O, S, or -NR^{N1}-, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl. In particular embodiments, Y^2 is NR^{N1}-, wherein R^{N1} is H or optionally substituted alkyl (e.g., C_{1-6} alkyl, such as methyl, ethyl, isopropyl, or n-propyl).

[000320] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each Y^3 is, independently, O or S.

[000321] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), R^1 is H; each R^2 is, independently, H, halo (e.g., fluoro), hydroxy, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}$OR', wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, such as wherein s2 is 0, s1 is 1 or 2, s3 is 0 or 1, and R' is C_{1-6} alkyl); each Y^2 is, independently, O or -NR^{N1}-, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or

optionally substituted aryl (e.g., wherein R^{N1} is H or optionally substituted alkyl (e.g., C_{1-6} alkyl, such as methyl, ethyl, isopropyl, or n-propyl)); and each Y^3 is, independently, O or S (e.g., S). In further embodiments, R^3 is H, halo (e.g., fluoro), hydroxy, optionally substituted alkyl, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy. In yet further embodiments, each Y^1 is , independently, O or -NR^{N1}-, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl (e.g., wherein R^{N1} is H or optionally substituted alkyl (e.g., C_{1-6} alkyl, such as methyl, ethyl, isopropyl, or n-propyl)); and each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino.

[000322] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), each R^1 is, independently, H, halo (e.g., fluoro), hydroxy, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, such as wherein s2 is 0, s1 is 1 or 2, s3 is 0 or 1, and R' is C_{1-6} alkyl); R^2 is H; each Y^2 is, independently, O or -NR^{N1}-, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl (e.g., wherein R^{N1} is H or optionally substituted alkyl (e.g., C_{1-6} alkyl, such as methyl, ethyl, isopropyl, or n-propyl)); and each Y^3 is, independently, O or S (e.g., S). In further embodiments, R^3 is H, halo (e.g., fluoro), hydroxy, optionally substituted alkyl, optionally substituted alkoxy (e.g., methoxy or ethoxy), or optionally substituted alkoxyalkoxy. In yet further embodiments, each Y^1 is , independently, O or -NR^{N1}-, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl (e.g., wherein R^{N1} is H or optionally substituted alkyl (e.g., C_{1-6} alkyl, such as methyl, ethyl, isopropyl, or n-propyl)); and each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl,

optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino.

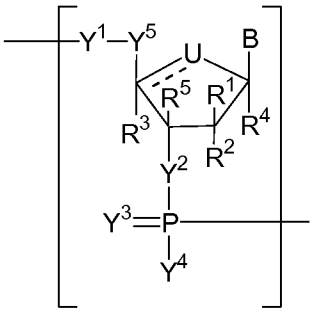
[000323] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), the ring including U is in the β-D (e.g., β-D-ribo) configuration.

[000324] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), the ring including U is in the α-L (e.g., α-L-ribo) configuration.

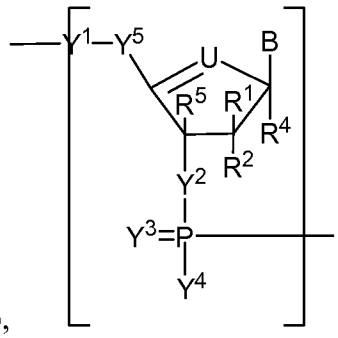
[000325] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), one or more B is not pseudouridine (ψ) or 5-methyl-cytidine (m^5C). In some embodiments, about 10% to about 100% of n number of B nucleobases is not ψ or m^5C (e.g., from 10% to 20%, from 10% to 35%, from 10% to 50%, from 10% to 60%, from 10% to 75%, from 10% to 90%, from 10% to 95%, from 10% to 98%, from 10% to 99%, from 20% to 35%, from 20% to 50%, from 20% to 60%, from 20% to 75%, from 20% to 90%, from 20% to 95%, from 20% to 98%, from 20% to 99%, from 20% to 100%, from 50% to 60%, from 50% to 75%, from 50% to 90%, from 50% to 95%, from 50% to 98%, from 50% to 99%, from 50% to 100%, from 75% to 90%, from 75% to 95%, from 75% to 98%, from 75% to 99%, and from 75% to 100% of n number of B is not ψ or m^5C). In some embodiments, B is not ψ or m^5C.

[000326] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), when B is an unmodified nucleobase selected from cytosine, guanine, uracil and adenine, then at least one of Y^1, Y^2, or Y^3 is not O.

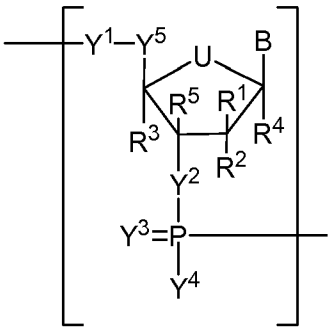
[000327] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IIa)-(IIc):



(IIa),

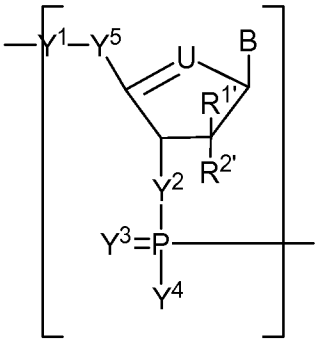


(IIb), or

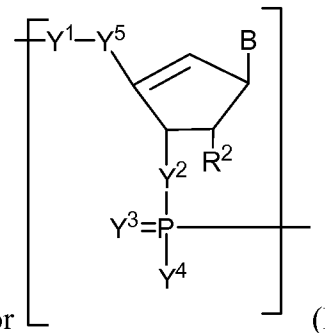


(IIc), or a pharmaceutically acceptable salt or stereoisomer thereof. In particular embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In other embodiments, each of R^1, R^2, R^3, R^4, and R^5 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or absent (e.g., each R^1 and R^2 is, independently, H, halo, hydroxy, optionally substituted alkyl, or optionally substituted alkoxy; each R^3 and R^4 is, independently, H or optionally substituted alkyl; and R^5 is H or hydroxy), and ___ is a single bond or double bond.

[000328] In particular embodiments, the polynucleotidesor mmRNA includes n number of linked nucleosides having Formula (IIb-1)-(IIb-2):

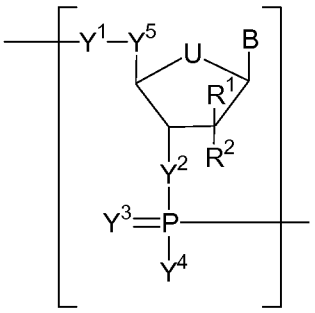


(IIb-1) or

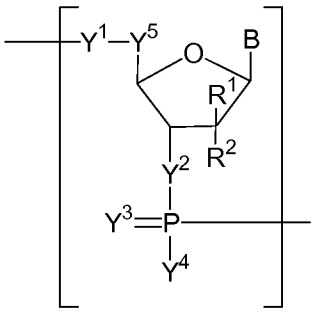


(IIb-2) or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In other embodiments, each of R^1 and R^2 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or absent (e.g., each R^1 and R^2 is, independently, H, halo, hydroxy, optionally substituted alkyl, or optionally substituted alkoxy, e.g., H, halo, hydroxy, alkyl, or alkoxy). In particular embodiments, R^2 is hydroxy or optionally substituted alkoxy (e.g., methoxy, ethoxy, or any described herein).

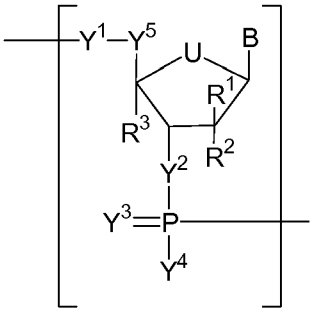
[000329] In particular embodiments, the polynucleotide, primary construct, or mmRNA includes n number of linked nucleosides having Formula (IIc-1)-(IIc-4):



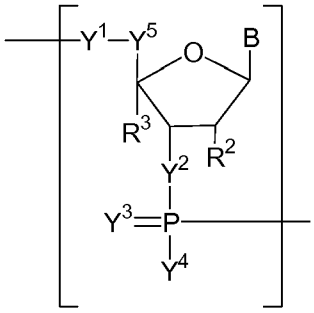
(IIc-1),



(IIc-2),

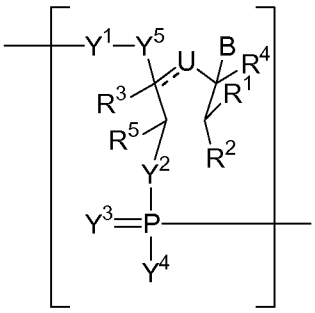
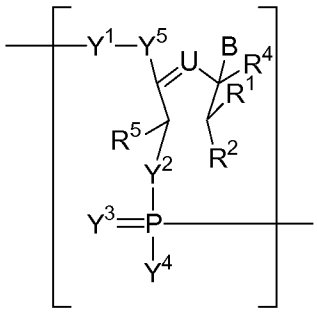
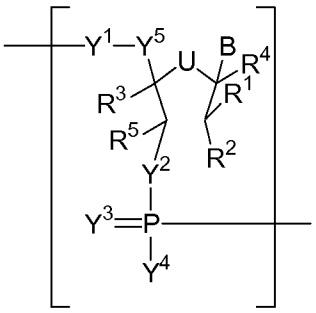


(IIc-3), or

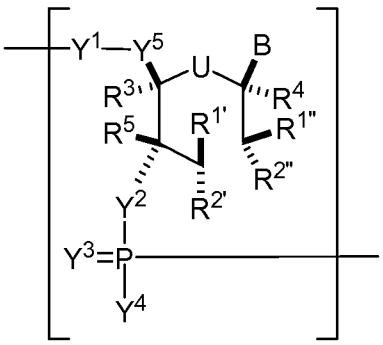
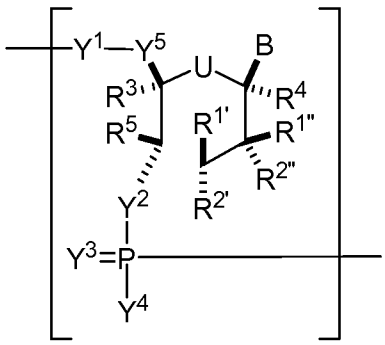
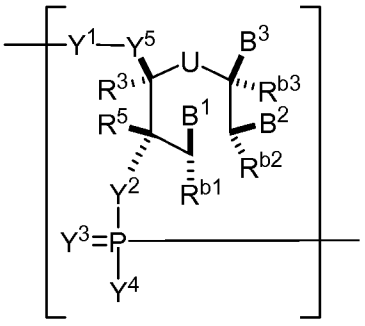
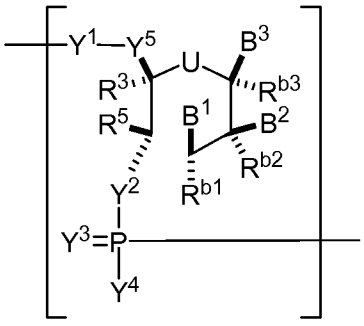


(IIc-4), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In some embodiments, each of R^1, R^2, and R^3 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or absent (e.g., each R^1 and R^2 is, independently, H, halo, hydroxy, optionally substituted alkyl, or optionally substituted alkoxy, e.g., H, halo, hydroxy, alkyl, or alkoxy; and each R^3 is, independently, H or optionally substituted alkyl)). In particular embodiments, R^2 is optionally substituted alkoxy (e.g., methoxy or ethoxy, or any described herein). In particular embodiments, R^1 is optionally substituted alkyl, and R^2 is hydroxy. In other embodiments, R^1 is hydroxy, and R^2 is optionally substituted alkyl. In further embodiments, R^3 is optionally substituted alkyl.

[000330] In some embodiments, the polynucleotide, primary construct, or mmRNA includes an acyclic modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IId)-(IIf):

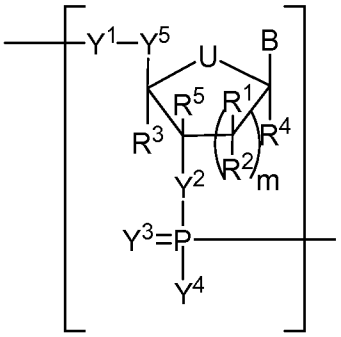

(IId),

(IIe), or

(IIf), or a pharmaceutically acceptable salt or stereoisomer thereof.

[000331] In some embodiments, the polynucleotide, primary construct, or mmRNA includes an acyclic modified hexitol. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides Formula (IIg)-(IIj):

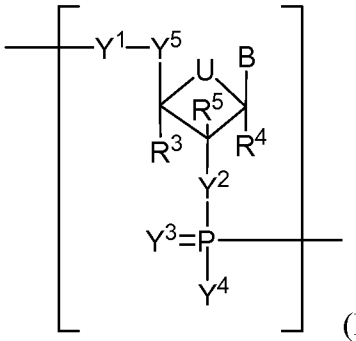

(IIg),

(IIh),

(IIi), or

(IIj), or a pharmaceutically acceptable salt or stereoisomer thereof.

[000332] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a sugar moiety having a contracted or an expanded ribose ring. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula

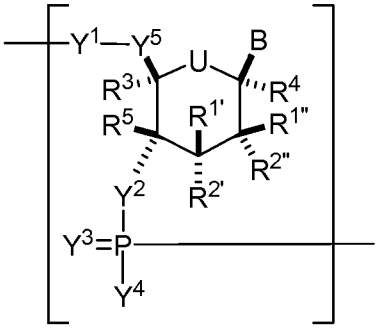
(IIk)-(IIm):



(IIk),

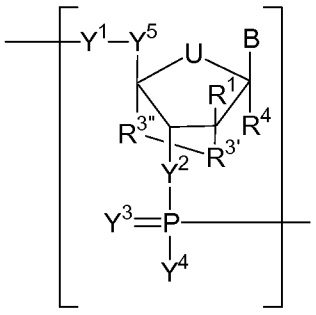


(III), or



(IIm),or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each of $R^{1'}$, $R^{1''}$, $R^{2'}$, and $R^{2''}$ is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, or absent; and wherein the combination of $R^{2'}$ and R^3 or the combination of $R^{2''}$ and R^3 can be taken together to form optionally substituted alkylene or optionally substituted heteroalkylene.

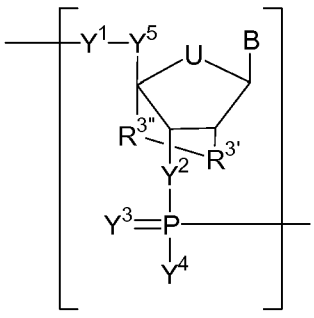
[000333] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a locked modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IIn):



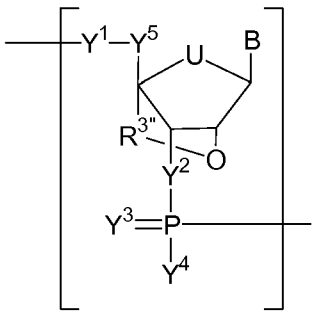
(IIn), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{3'}$ is O, S, or $-NR^{N1}-$, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted

aryl and $R^{3"}$ is optionally substituted alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$) or optionally substituted heteroalkylene (e.g., $-CH_2NH-$, $-CH_2CH_2NH-$, $-CH_2OCH_2-$, or $-CH_2CH_2OCH_2-$)(e.g., $R^{3'}$ is O and $R^{3"}$ is optionally substituted alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$)).

[000334] In some embodiments, the polynucleotide, primary construct, or mmRNA includes n number of linked nucleosides having Formula (IIn-1)-(II-n2):

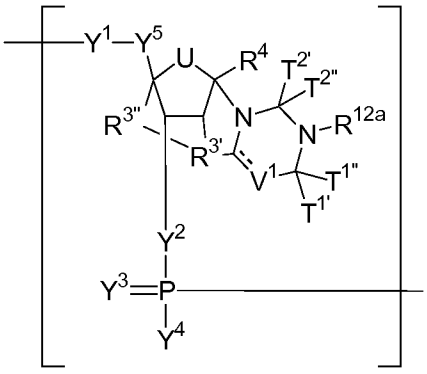


(IIn-1) or

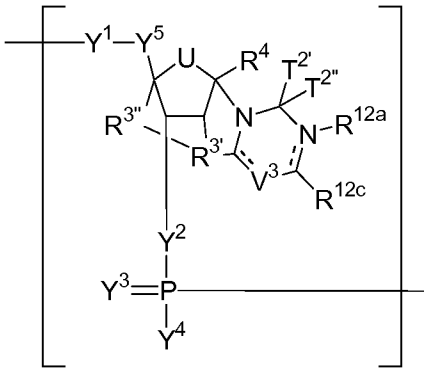


(IIn-2), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{3'}$ is O, S, or $-NR^{N1}-$, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl and $R^{3"}$ is optionally substituted alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$) or optionally substituted heteroalkylene (e.g., $-CH_2NH-$, $-CH_2CH_2NH-$, $-CH_2OCH_2-$, or $-CH_2CH_2OCH_2-$) (e.g., $R^{3'}$ is O and $R^{3"}$ is optionally substituted alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$, or $-CH_2CH_2CH_2-$)).

[000335] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a locked modified ribose that forms a tetracyclic heterocyclyl. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IIo):



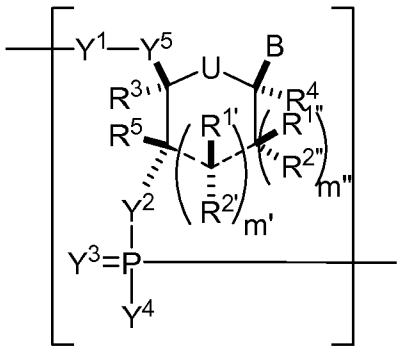
(IIo) or



(IIp), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein R^{12a}, R^{12c}, $T^{1'}$, $T^{1''}$,$T^{2'}$, $T^{2''}$, V^1, and V^3 are as described herein.

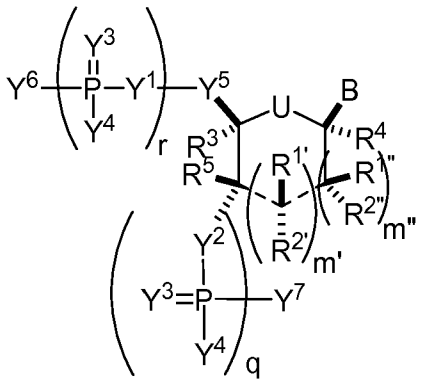
[000336] Any of the formulas for the polynucleotides, primary constructs, or mmRNA can include one or more nucleobases described herein (e.g., Formulas (b1)-(b43)).

[000337] In one embodiment, the present invention provides methods of preparing a polynucleotide, primary construct, or mmRNA, wherein the polynucleotide comprises n number of nucleosides having Formula (Ia), as defined herein:



(Ia),

the method comprising reacting a compound of Formula (IIIa), as defined herein:

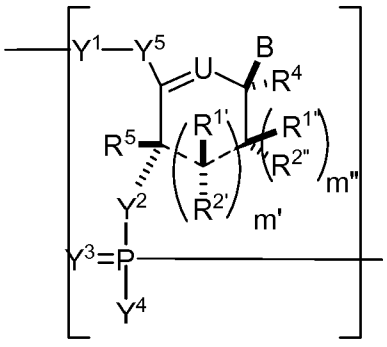


(IIIa),

with an RNA polymerase, and a cDNA template.

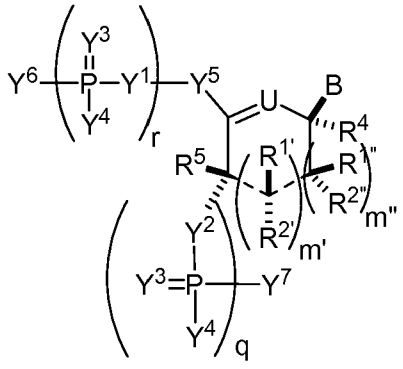
[000338] In a further embodiment, the present invention provides methods of amplifying a polynucleotide, primary construct, or mmRNA comprising at least one nucleotide (e.g., mmRNA molecule), the method comprising: reacting a compound of Formula (IIIa), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

[000339] In one embodiment, the present invention provides methods of preparing a polynucleotide, primary construct, or mmRNA comprising at least one nucleotide (e.g., mmRNA molecule), wherein the polynucleotide comprises n number of nucleosides having Formula (Ia), as defined herein:



(Ia-1),

the method comprising reacting a compound of Formula (IIIa-1), as defined herein:



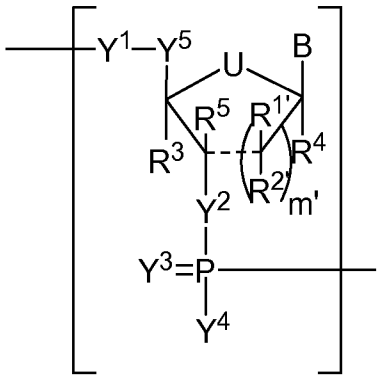
(IIIa-1),

with an RNA polymerase, and a cDNA template.

[000340] In a further embodiment, the present invention provides methods of amplifying a polynucleotide, primary construct, or mmRNA comprising at least one nucleotide (e.g., mmRNA molecule), the method comprising:

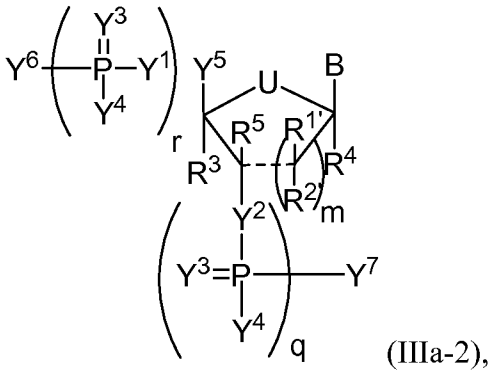
[000341] reacting a compound of Formula (IIIa-1), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

[000342] In one embodiment, the present invention provides methods of preparing a modified mRNA comprising at least one nucleotide (e.g., mmRNA molecule), wherein the polynucleotide comprises n number of nucleosides having Formula (Ia-2), as defined herein:



(Ia-2),

the method comprising reacting a compound of Formula (IIIa-2), as defined herein:



(IIIa-2),

with an RNA polymerase, and a cDNA template.

[000343] In a further embodiment, the present invention provides methods of amplifying a modified mRNA comprising at least one nucleotide (e.g., mmRNA molecule), the method comprising:

[000344] reacting a compound of Formula (IIIa-2), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

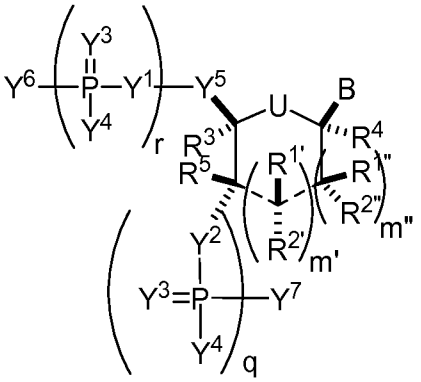
[000345] In some embodiments, the reaction may be repeated from 1 to about 7,000 times. In any of the embodiments herein, B may be a nucleobase of Formula (b1)-(b43).

[000346] The polynucleotides, primary constructs, and mmRNA can optionally include 5′ and/or 3′ flanking regions, which are described herein.

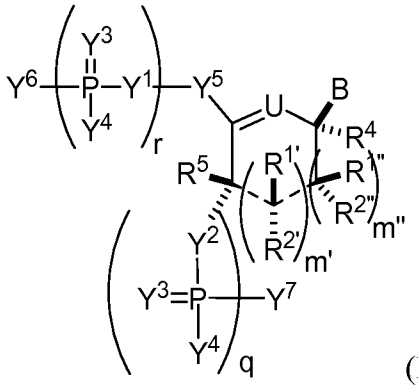
Modified RNA (mmRNA) Molecules

[000347] The present invention also includes building blocks, e.g., modified ribonucleosides, modified ribonucleotides, of modified RNA (mmRNA) molecules. For example, these building blocks can be useful for preparing the polynucleotides, primary constructs, or mmRNA of the invention.

In some embodiments, the building block molecule has Formula (IIIa) or (IIIa-1):

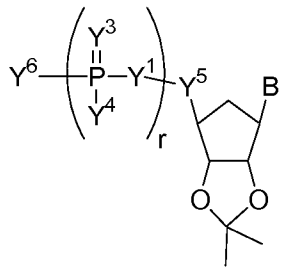


(IIIa),

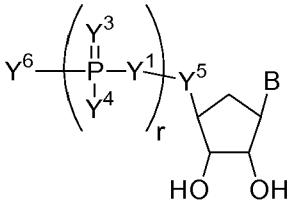


(IIIa-1) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the substituents are as described herein (e.g., for Formula (Ia) and (Ia-1)), and wherein when B is an unmodified nucleobase selected from cytosine, guanine, uracil and adenine, then at least one of Y^1, Y^2, or Y^3 is not O.

[000348] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IVa)-(IVb):



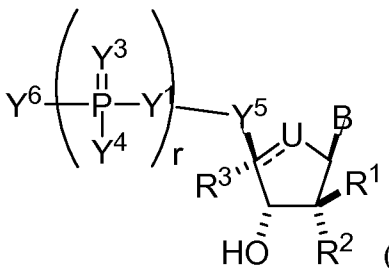
(IVa) or

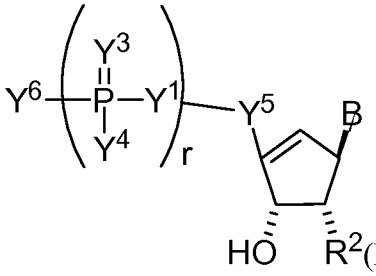


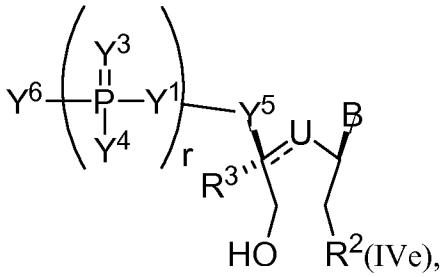
(IVb), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14),

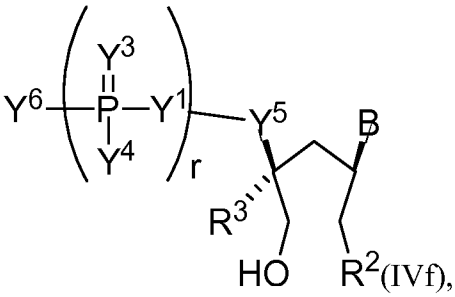
(b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

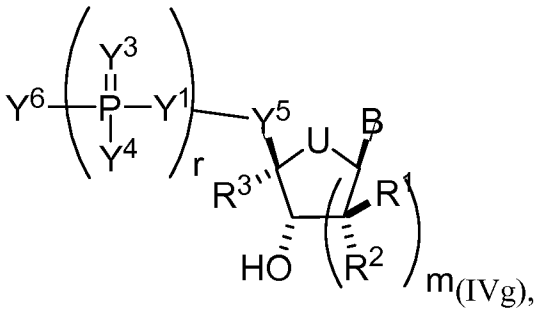
[000349] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IVc)-(IVk):

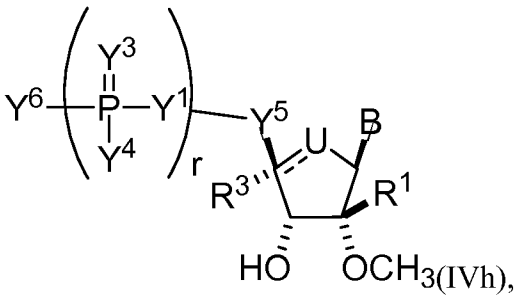

(IVc),

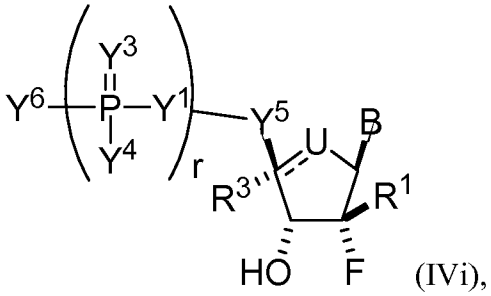

(IVd),

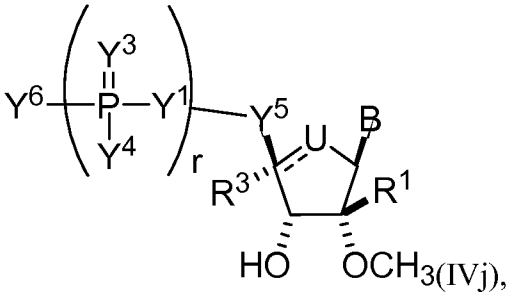

(IVe),

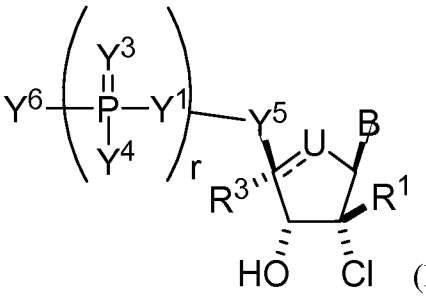

(IVf),


(IVg),

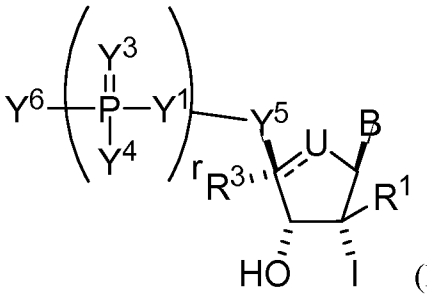

(IVh),


(IVi),


(IVj),

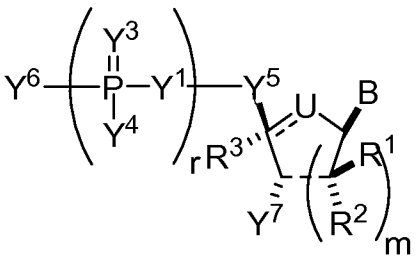


(IVk), or

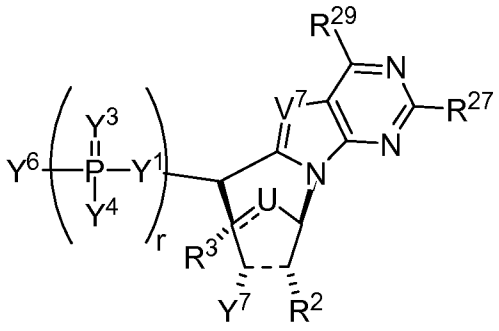


(IVl), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IVc)-(IVk) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, one of Formulas (IVc)-(IVk) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14), (b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, one of Formulas (IVc)-(IVk) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, one of Formulas (IVc)-(IVk) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

[000350] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (Va) or (Vb):

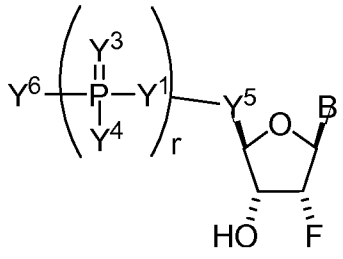


(Va) or

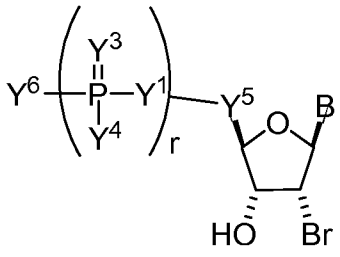


(Vb), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)).

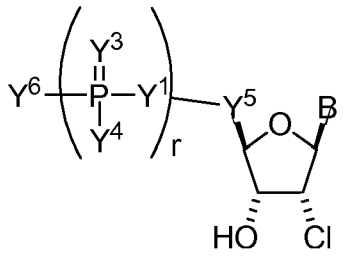
[000351] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXa)-(IXd):



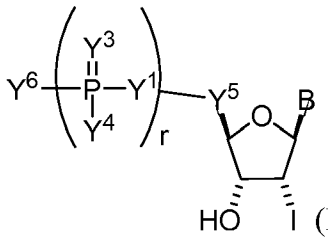
(IXa),



(IXb),

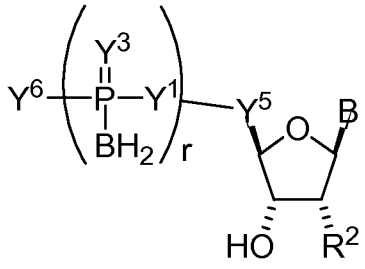


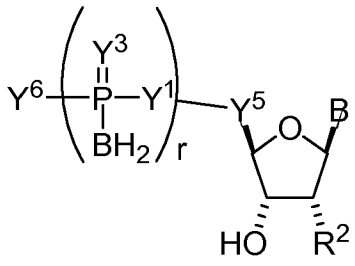
(IXc), or

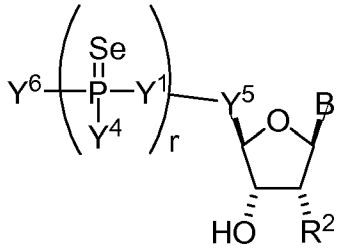


(IXd), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXa)-(IXd) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, one of Formulas (IXa)-(IXd) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14), (b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, one of Formulas (IXa)-(IXd) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, one of Formulas (IXa)-(IXd) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

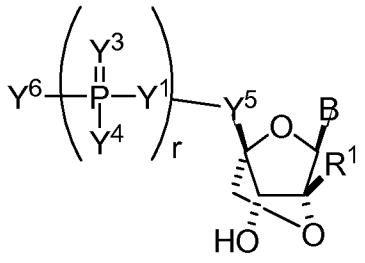
[000352] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXe)-(IXg):

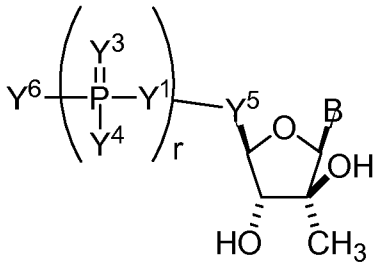

(IXe),

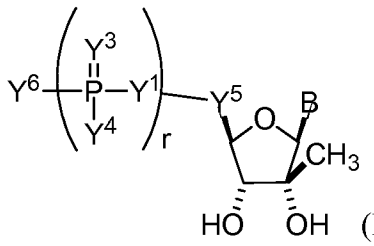

(IXf), or

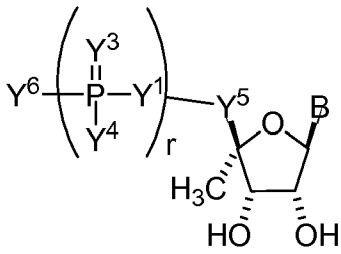

(IXg), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXe)-(IXg) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, one of Formulas (IXe)-(IXg) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14), (b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, one of Formulas (IXe)-(IXg) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, one of Formulas (IXe)-(IXg) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

[000353] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXh)-(IXk):

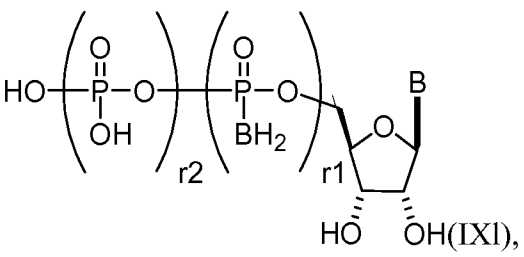

(IXh),


(IXi),

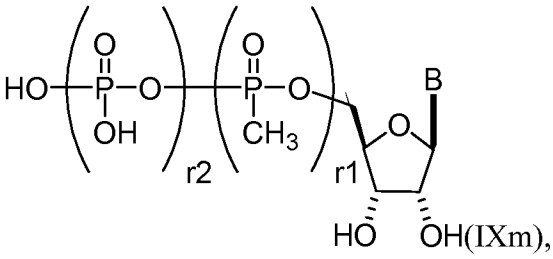

(IXj), or


(IXk), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXh)-(IXk) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, one of Formulas (IXh)-(IXk) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14), (b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, one of Formulas (IXh)-(IXk) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, one of Formulas (IXh)-(IXk) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

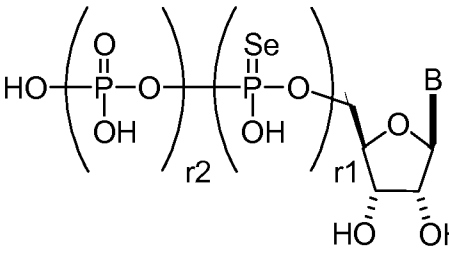
[000354] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXl)-(IXr):



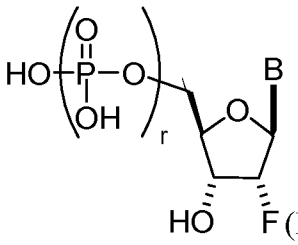
(IXl),



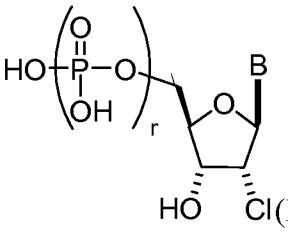
(IXm),



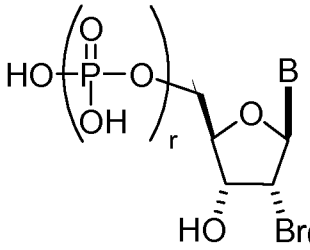
(IXn),



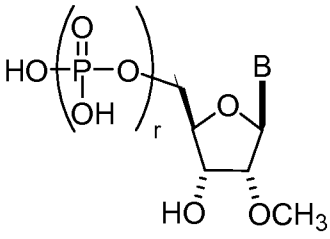
(IXo),



(IXp),

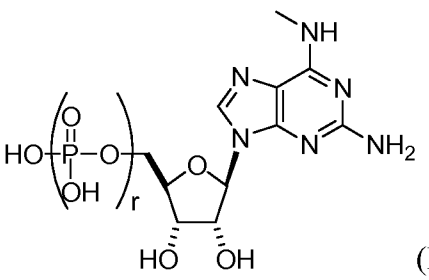


(IXq), or

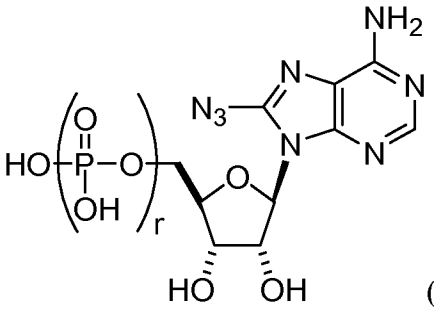


(IXr) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r1 and r2 is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5) and B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXl)-(IXr) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (b8), (b28), (b29), or (b30)). In particular embodiments, one of Formulas (IXl)-(IXr) is combined with a modified cytosine (e.g., any one of formulas (b10)-(b14), (b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, one of Formulas (IXl)-(IXr) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, one of Formulas (IXl)-(IXr) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

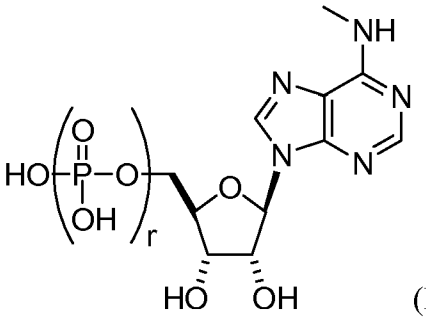
[000355] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be selected from the group consisting of:



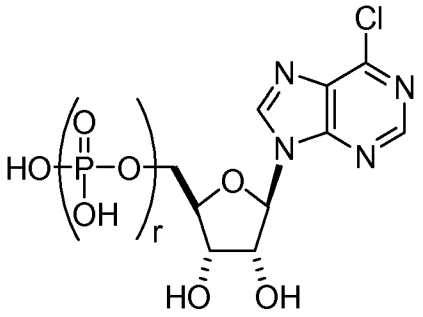
(BB- 1),



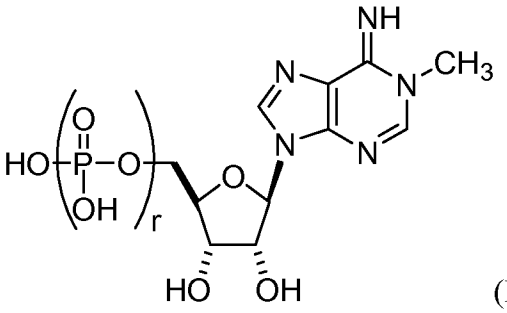
(BB- 2),



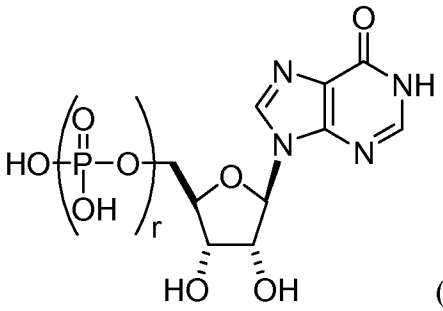
(BB- 3),



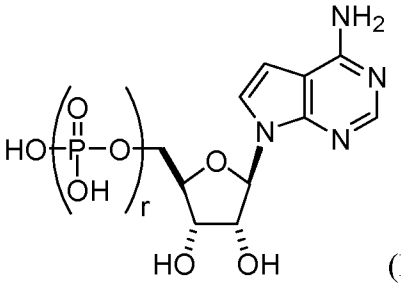
(BB- 4),



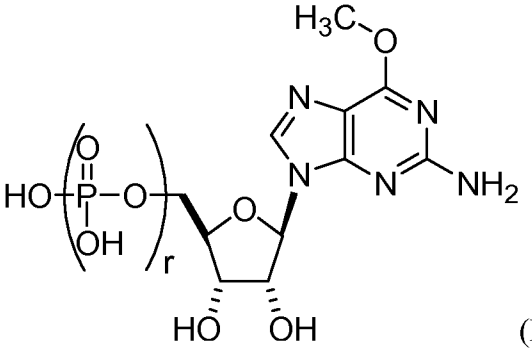
(BB- 5),



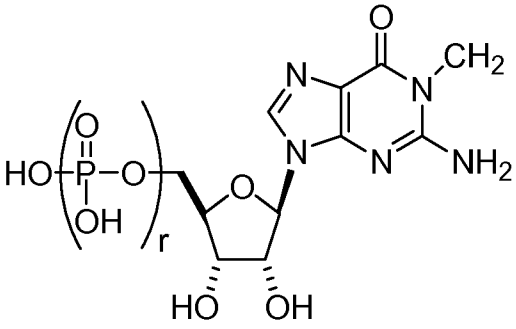
(BB- 6),



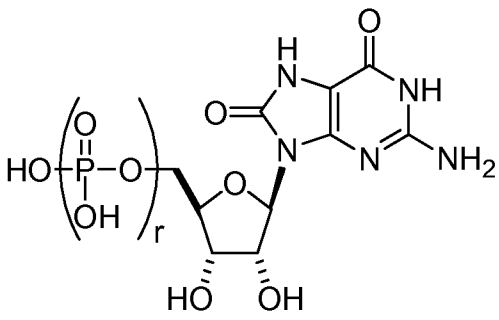
(BB- 7),

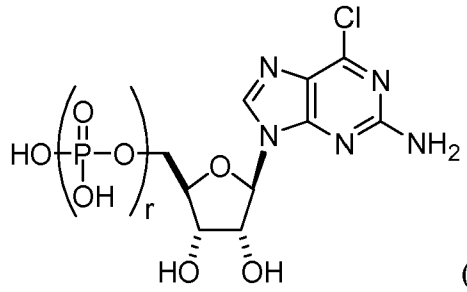


(BB- 8),



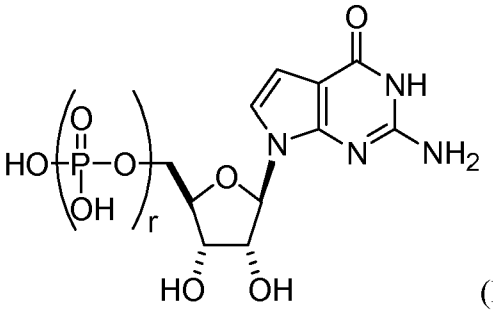
(BB- 9),





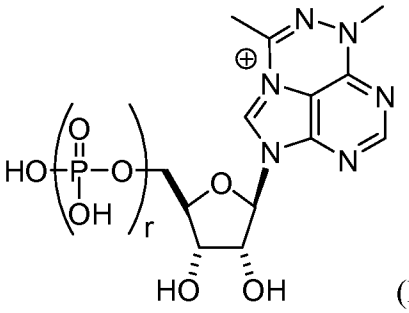
(BB- 10),

(BB- 11), and

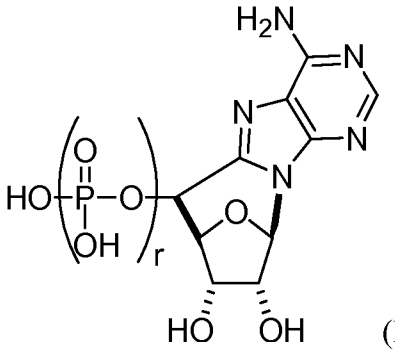


(BB- 12), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

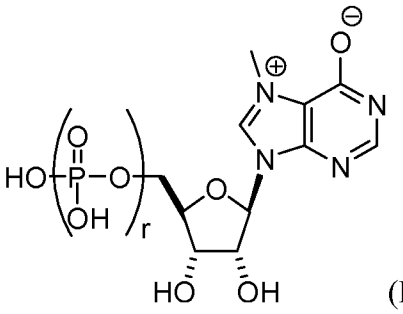
[000356] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be selected from the group consisting of:



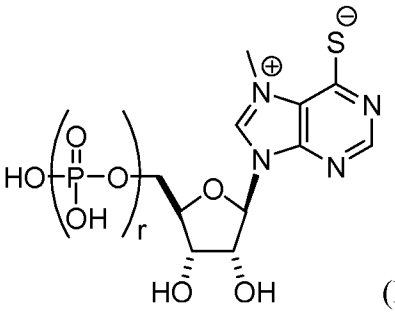
(BB- 13),



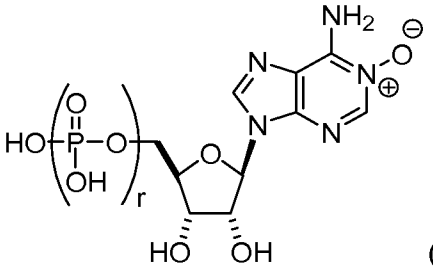
(BB- 14),



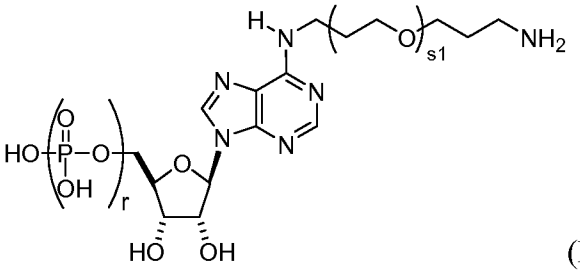
(BB- 15),



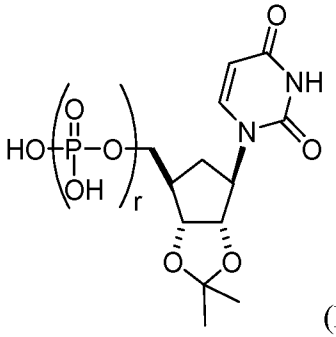
(BB- 16),



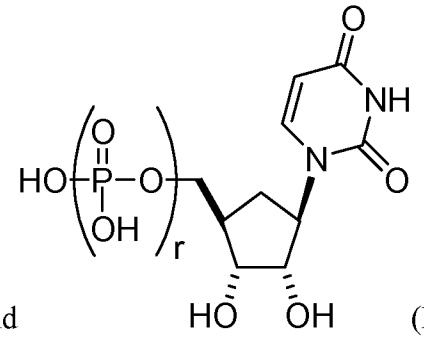
(BB- 17),



(BB- 18),



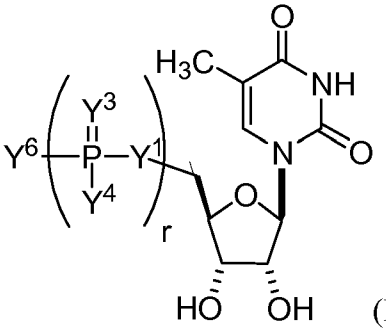
(BB- 19),



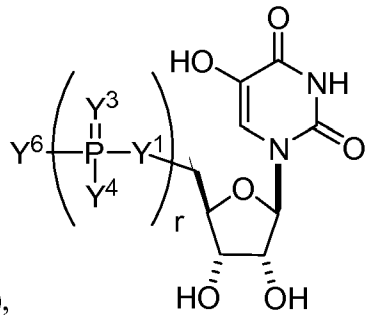
and (BB- 20), or a pharmaceutically acceptable salt or

stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5) and s1 is as described herein.

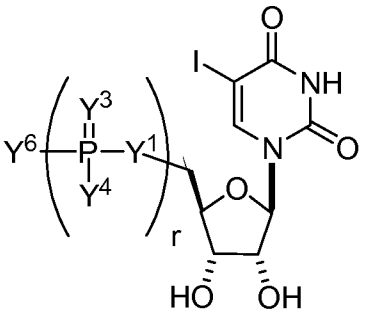
[000357] In some embodiments, the building block molecule, which may be incorporated into a nucleic acid (e.g., RNA, mRNA, polynucleotide, primary construct, or mmRNA), is a modified uridine (e.g., selected from the group consisting of:



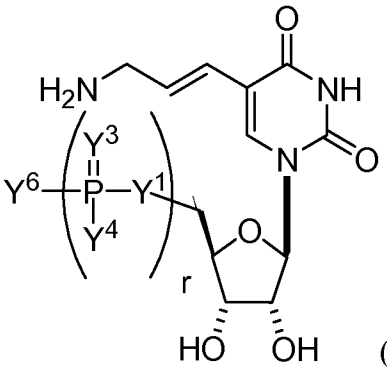
(BB- 21),



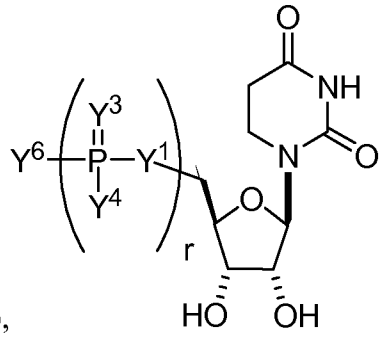
(BB- 22),



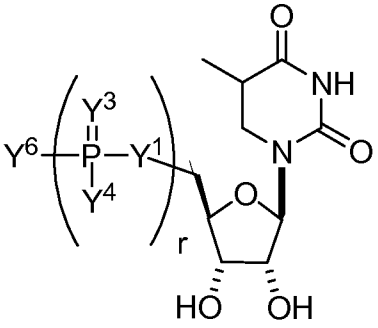
(BB- 23),



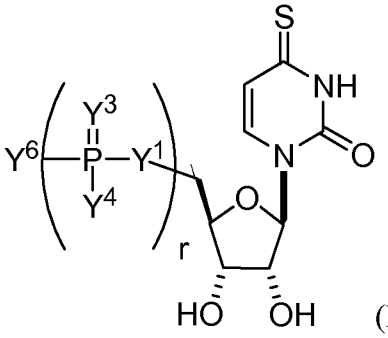
(BB- 24),



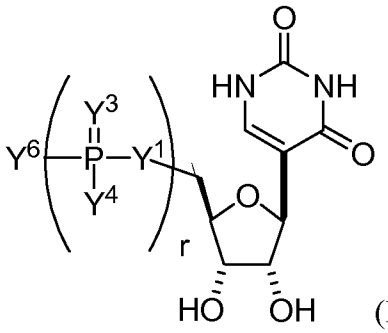
(BB- 25),



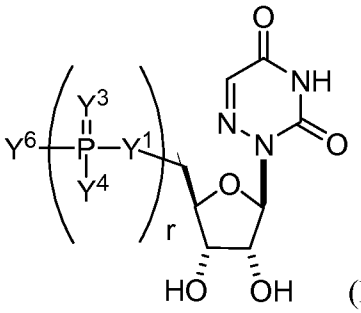
(BB- 26),



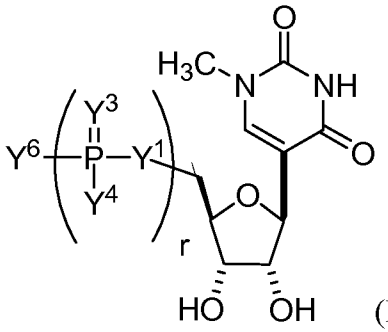
(BB- 27),



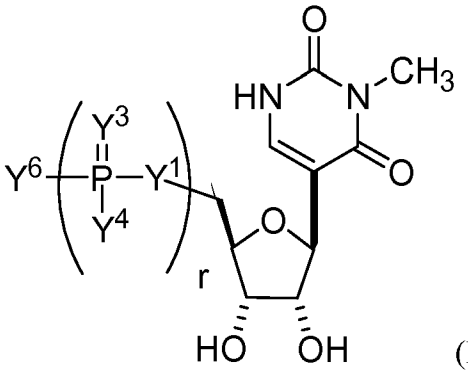
(BB- 28),



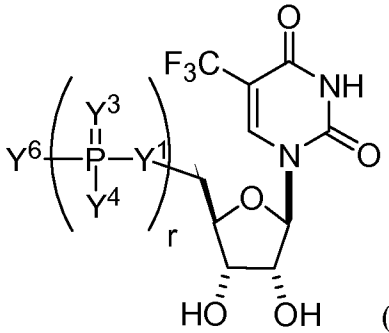
(BB- 29),



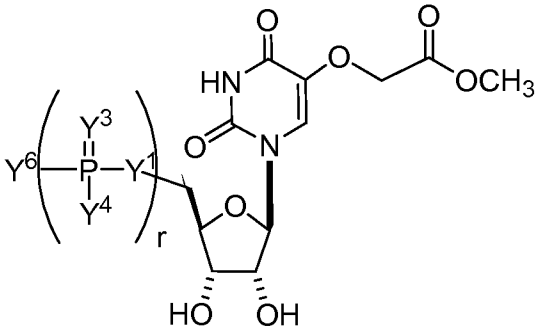
(BB- 30),



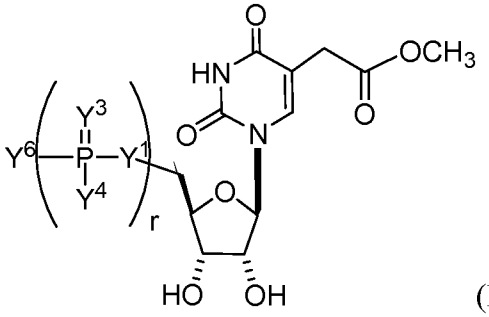
(BB- 31),



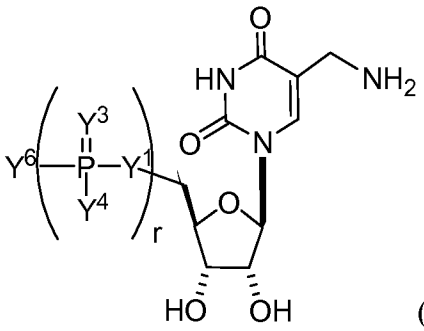
(BB- 32),



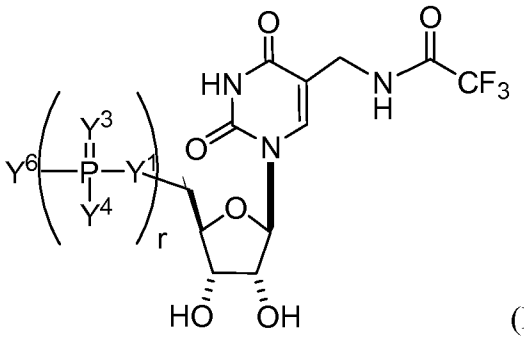
(BB- 33),



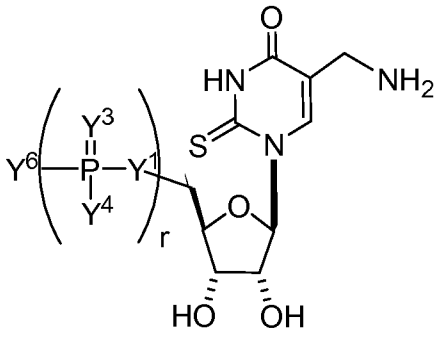
(BB- 34),



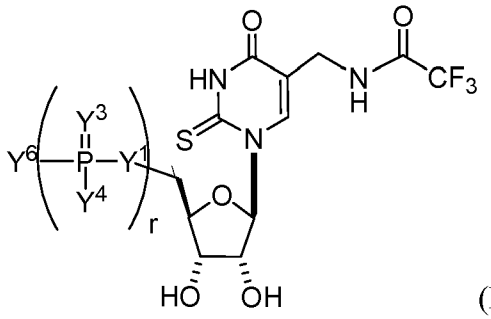
(BB-



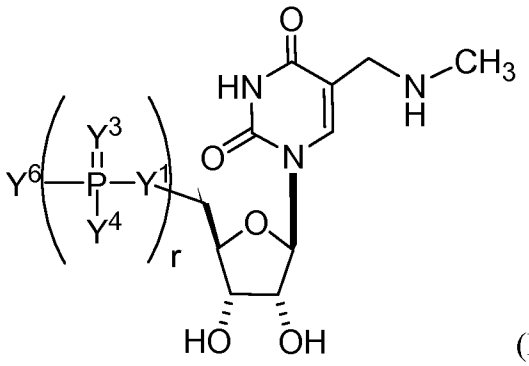
35),



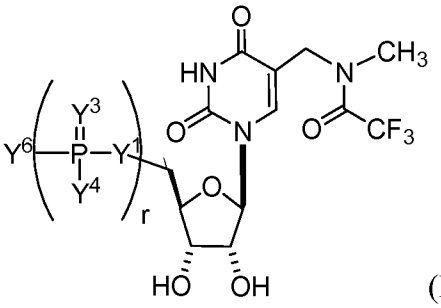
(BB- 36),



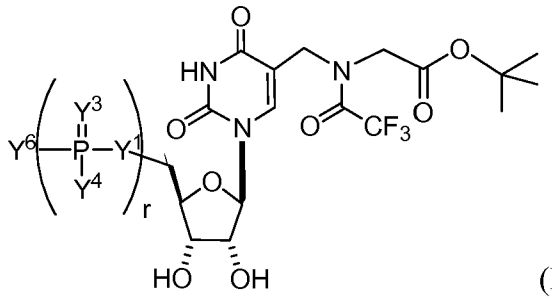
(BB- 37),



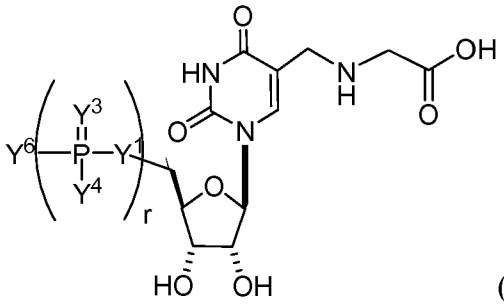
(BB- 38),



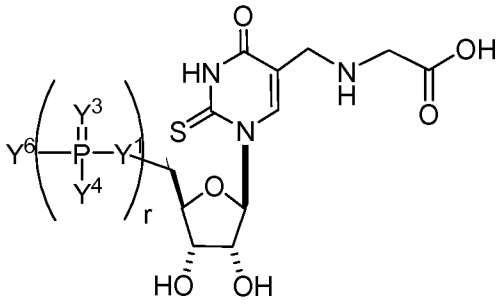
(BB- 39),



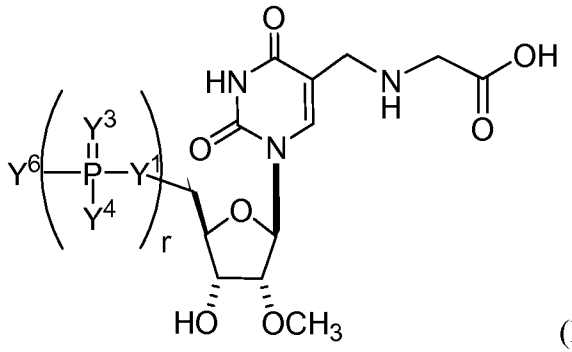
(BB- 40),



(BB- 41),

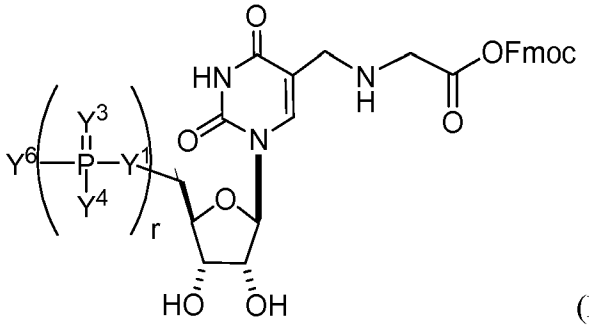


(BB- 42),

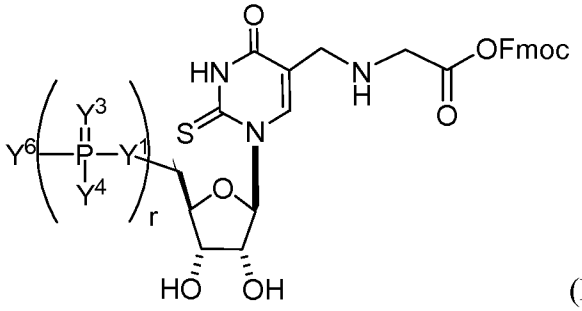


(BB- 43),

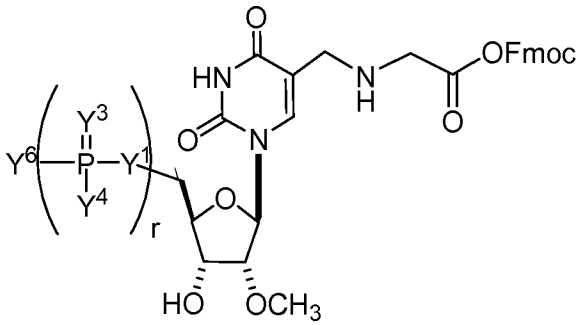
(BB- 44),



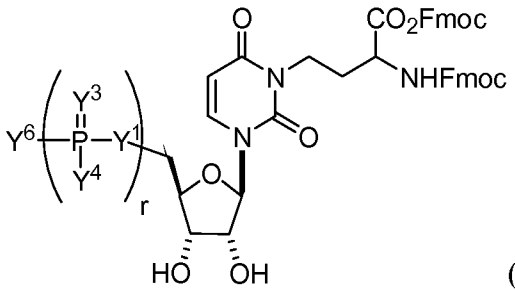
(BB- 45),



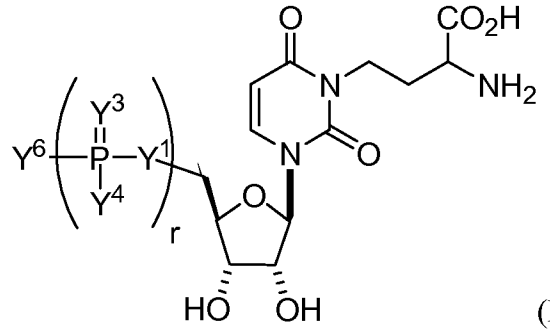
(BB-46),



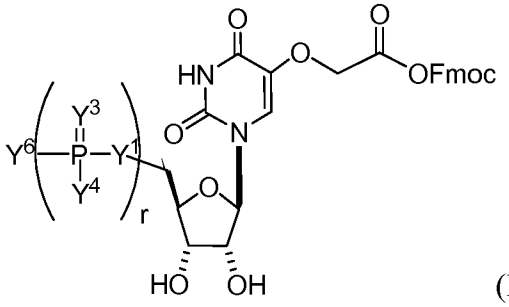
(BB- 47),



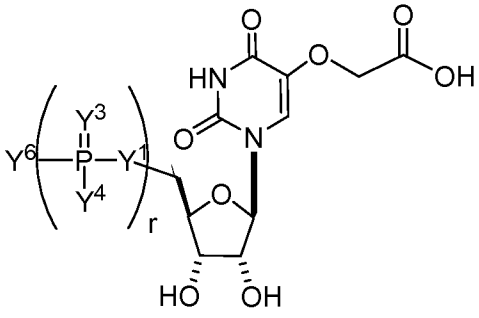
(BB- 48),

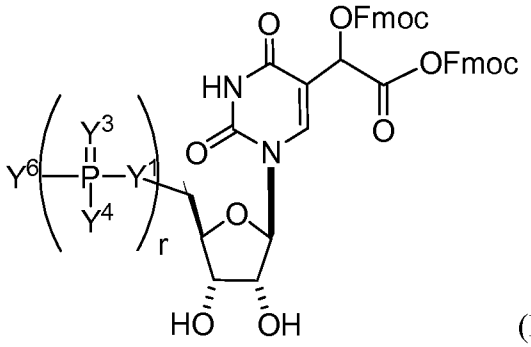


(BB- 49),



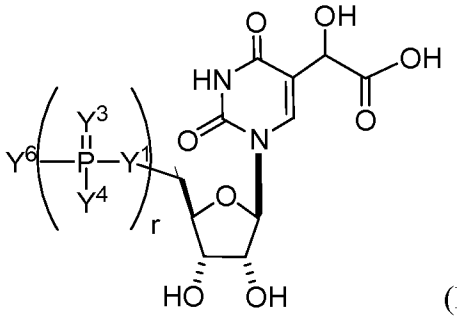
(BB- 50),



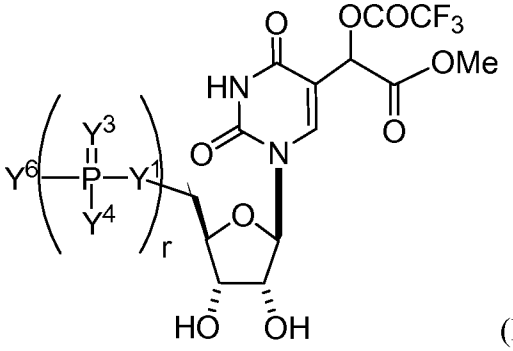


(BB- 51),

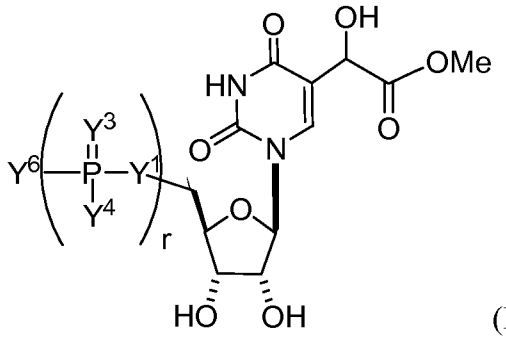
(BB- 52),



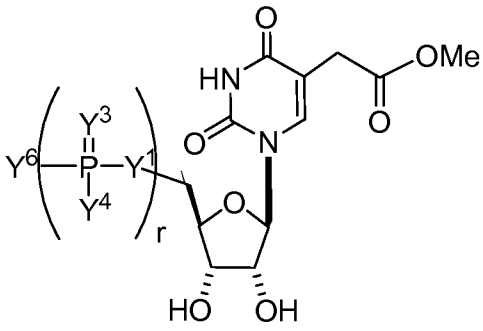
(BB- 53),



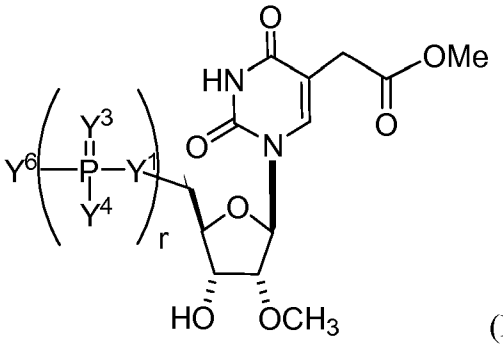
(BB-



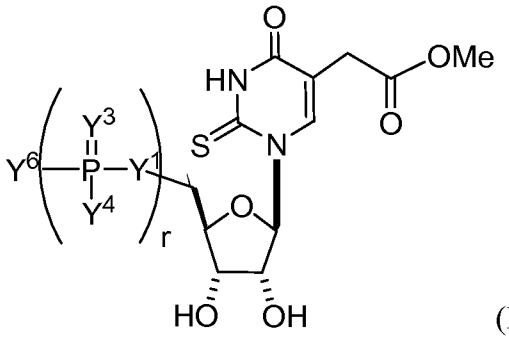
54),



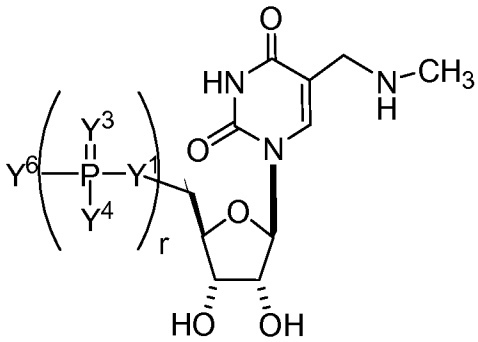
(BB- 55),



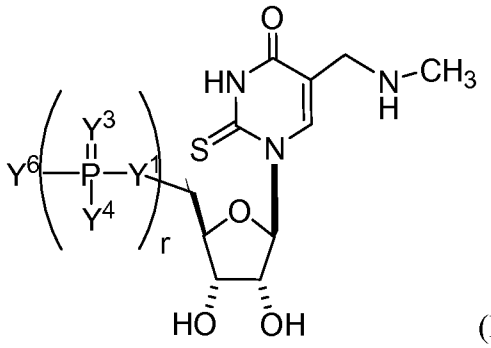
(BB-56),



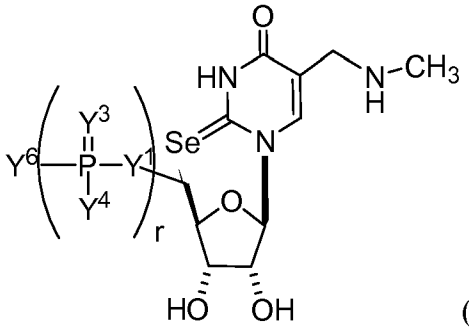
(BB-57),



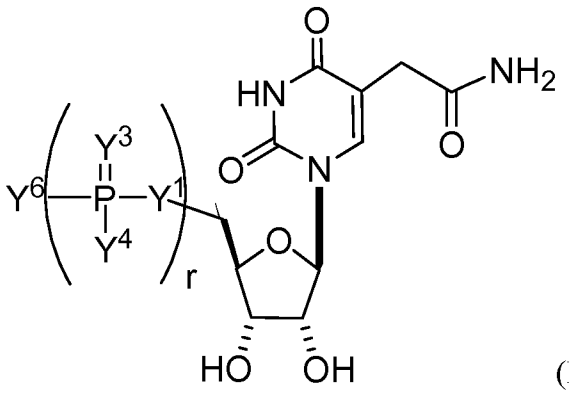
(BB- 58),



(BB- 59),

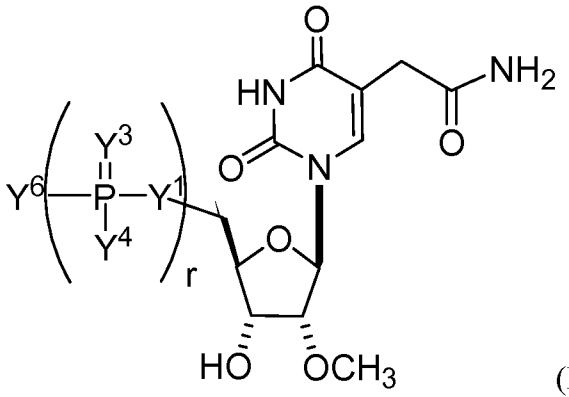


(BB- 60),

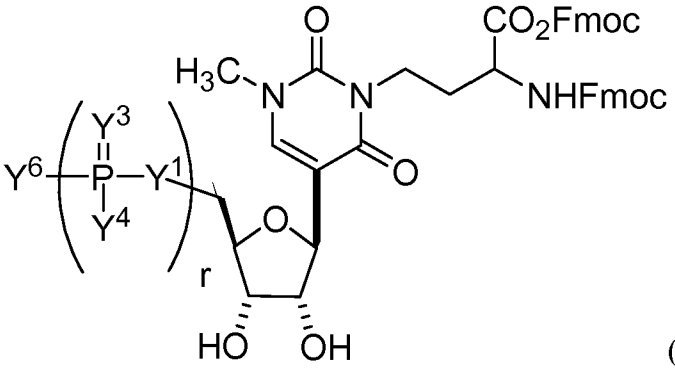


(BB- 61),

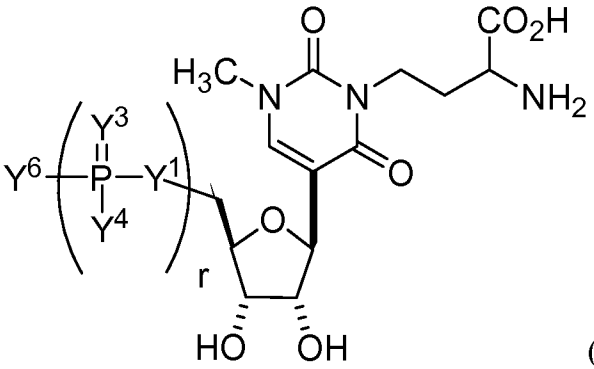
(BB- 62),



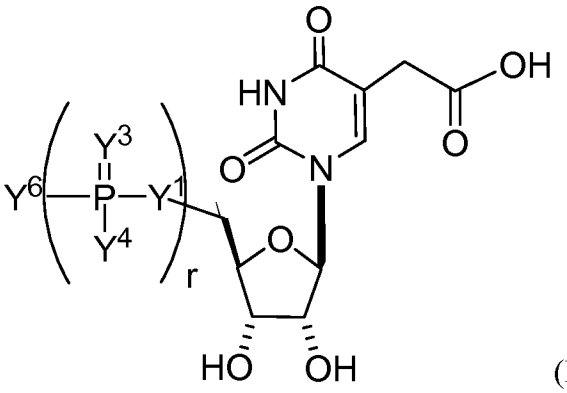
(BB- 63),



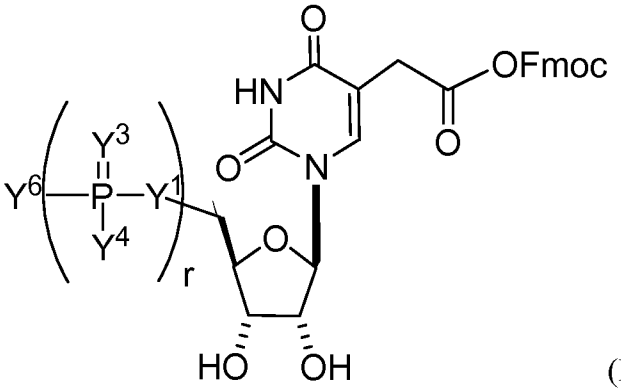
(BB- 64),



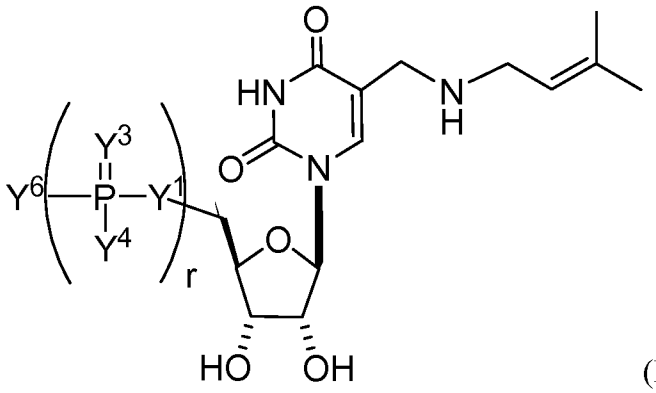
(BB- 65),



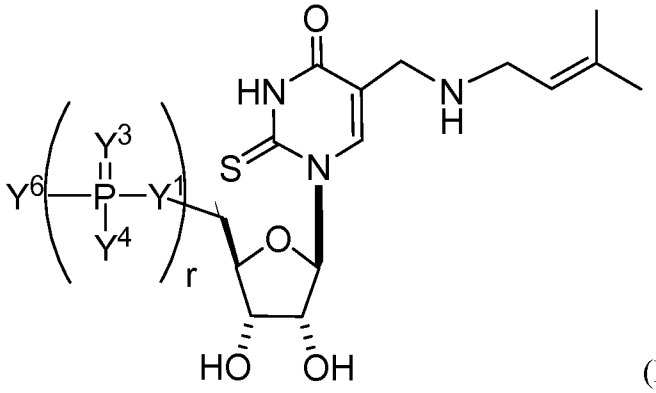
(BB- 66),



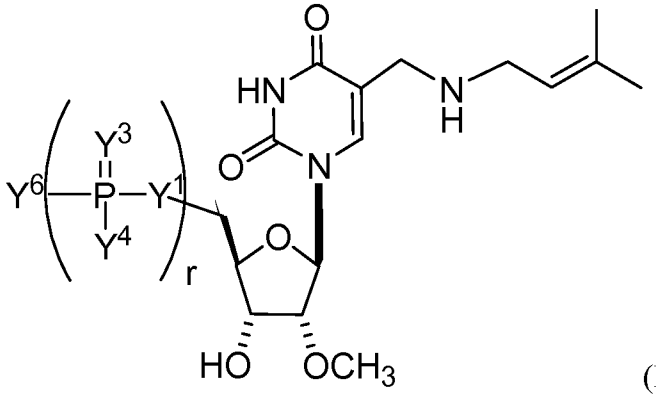
(BB- 67),



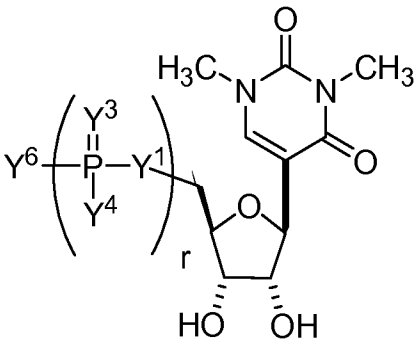
(BB- 68),



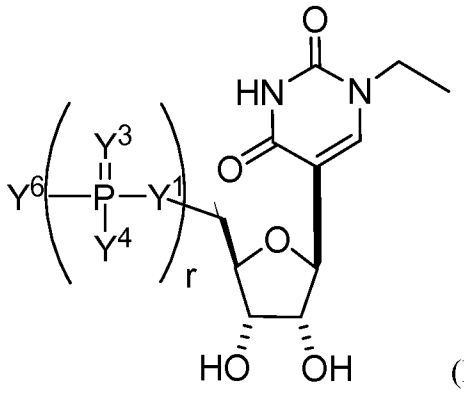
(BB- 69),



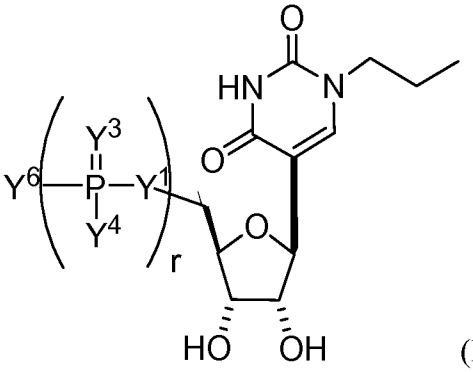
(BB- 70),



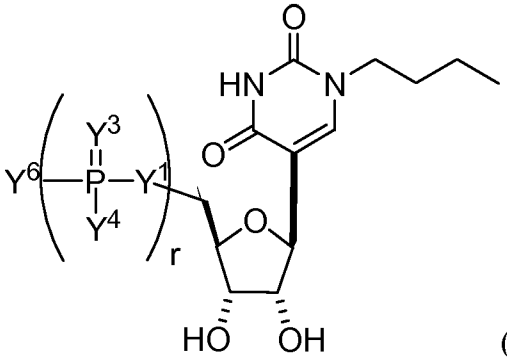
(BB- 71),



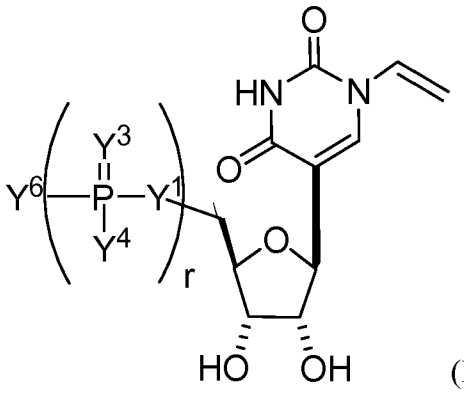
(BB- 72),



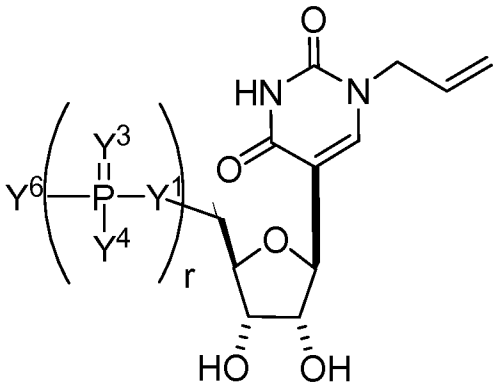
(BB- 73),



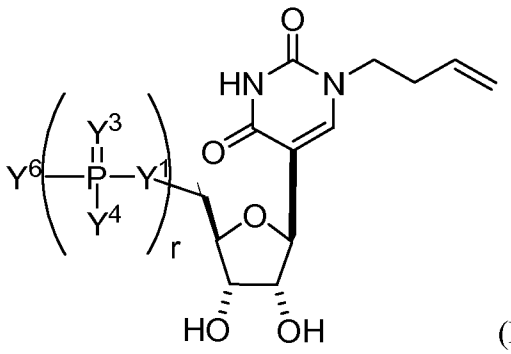
(BB-74),



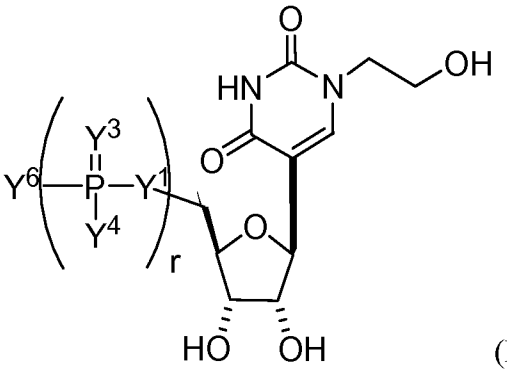
(BB- 75),



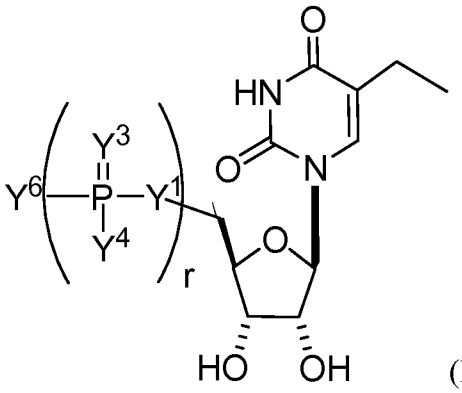
(BB- 76),



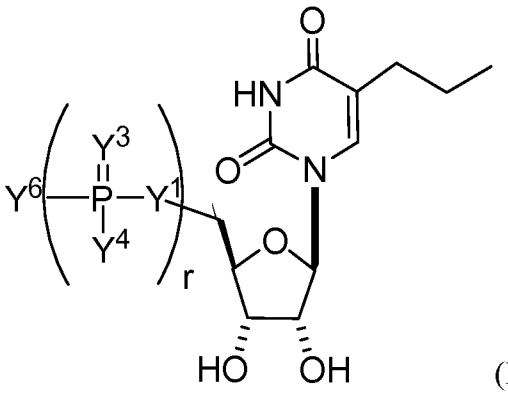
(BB- 77),



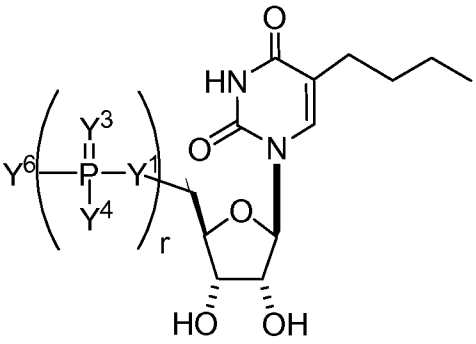
(BB- 78),



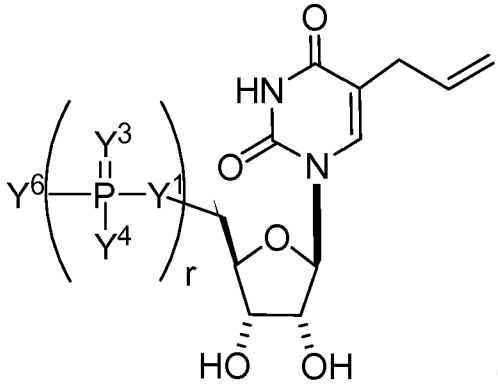
(BB- 79),



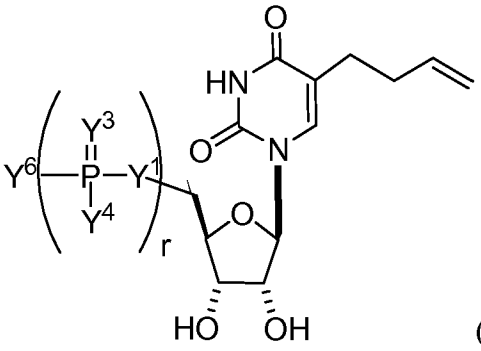
(BB- 80),



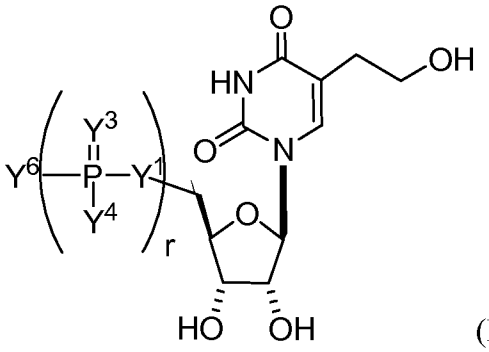
(BB- 81),



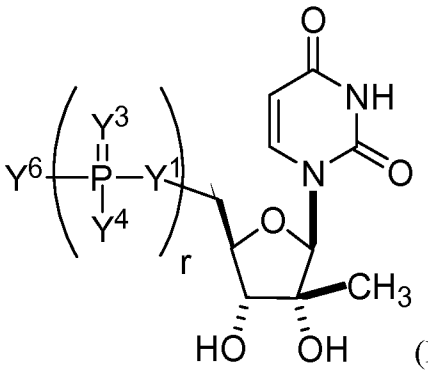
(BB- 82),

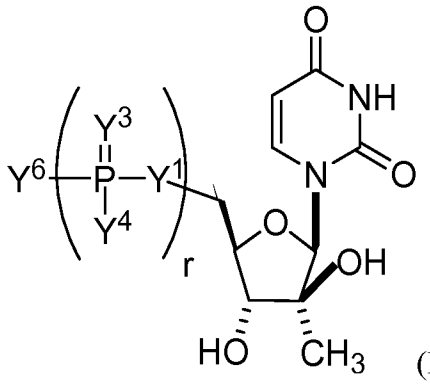
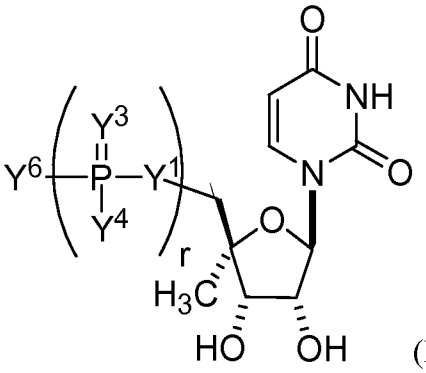


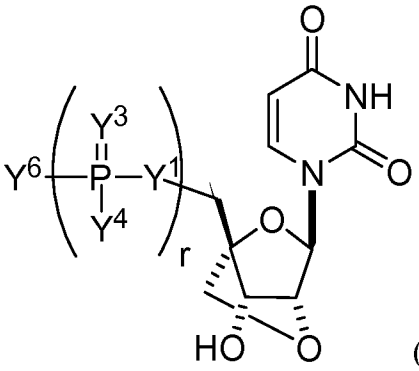
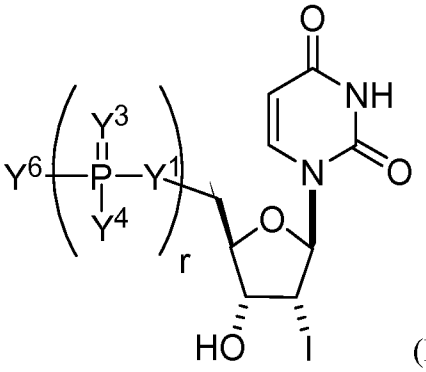
(BB- 83),

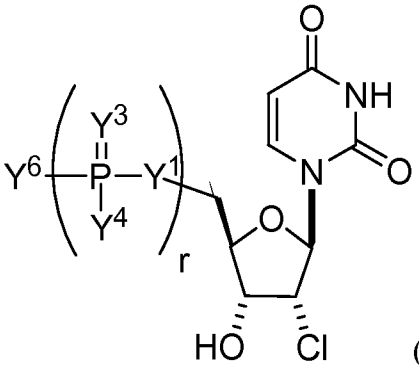
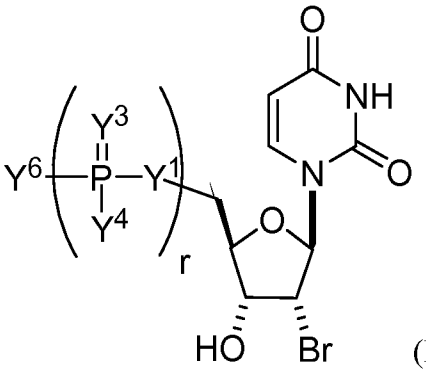


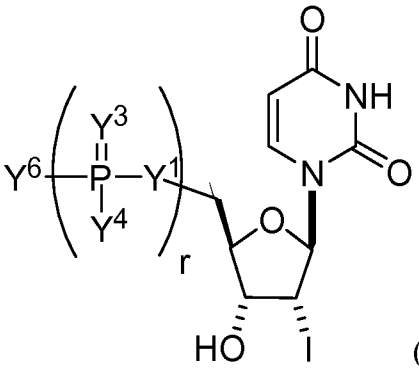
(BB-

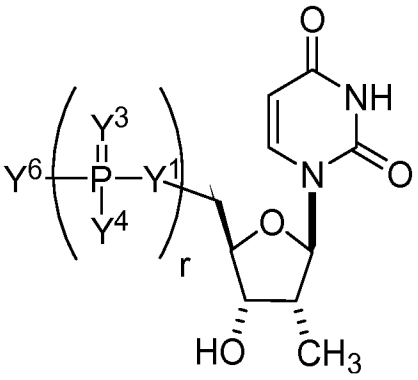


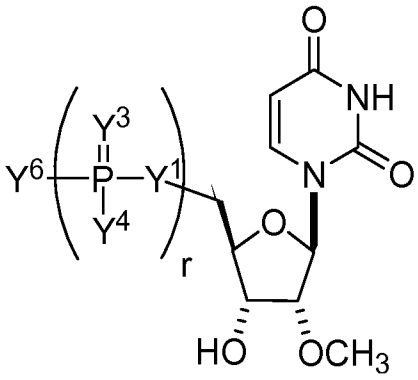
84),  (BB- 85),  (BB- 86),

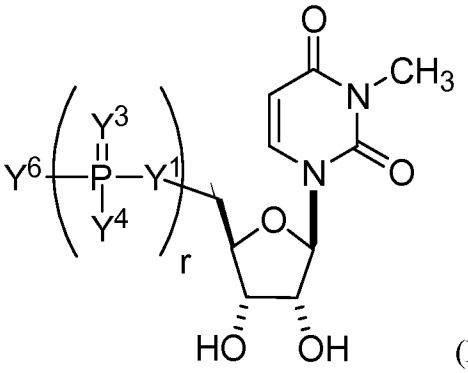
 (BB- 87),  (BB- 88),

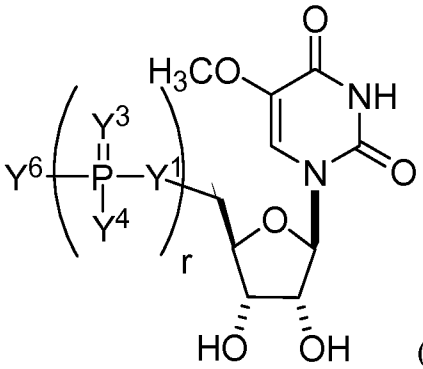
 (BB- 89),  (BB- 90),

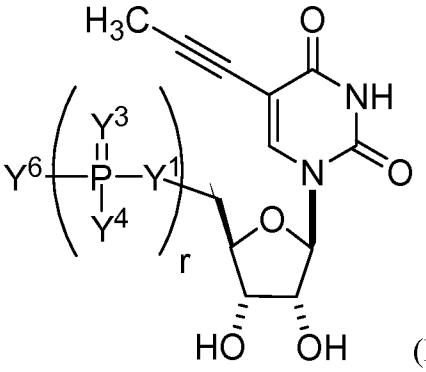
 (BB- 91), (BB- 92),

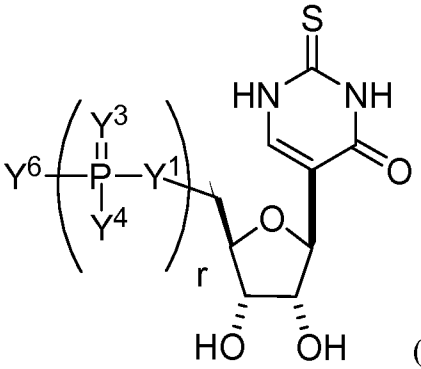

(BB- 93),

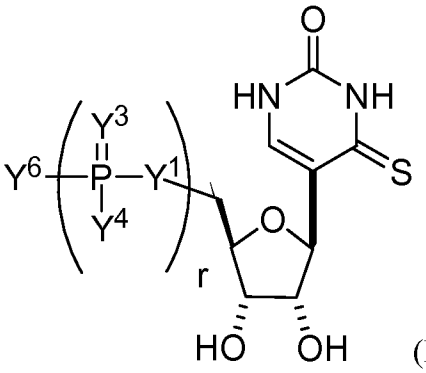

(BB- 94),

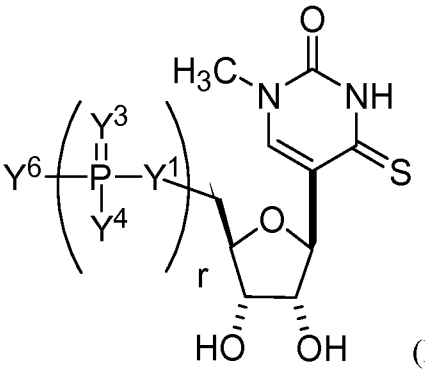

(BB- 95),

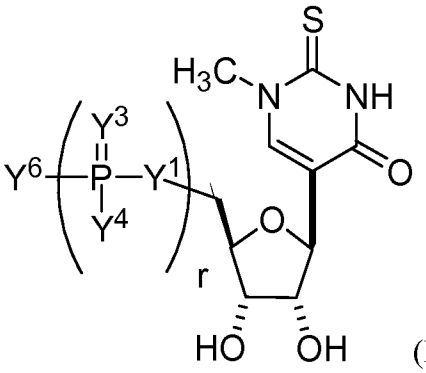

(BB- 96),


(BB- 97),

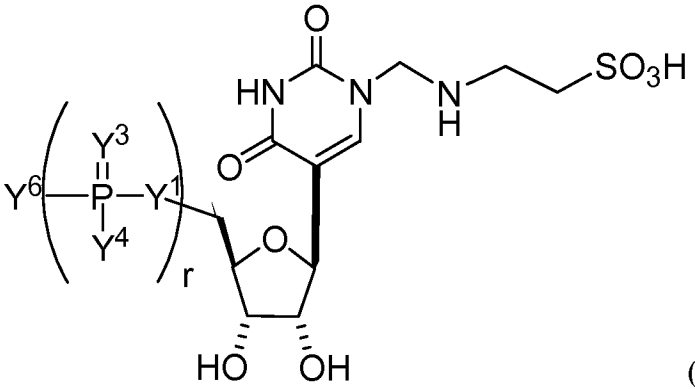

(BB- 98),


(BB- 99),

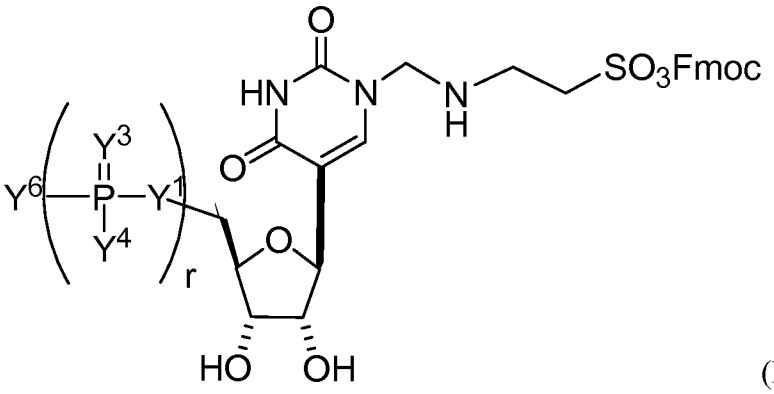

(BB- 100),



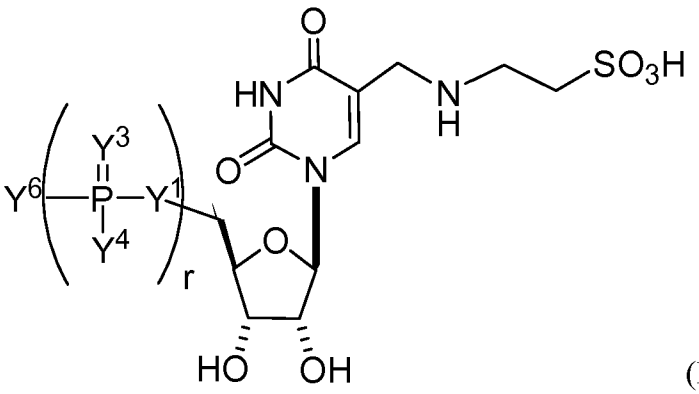
(BB- 101),



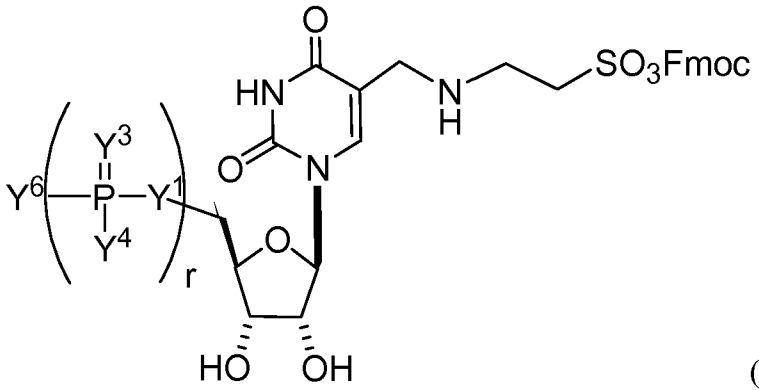
(BB- 102),



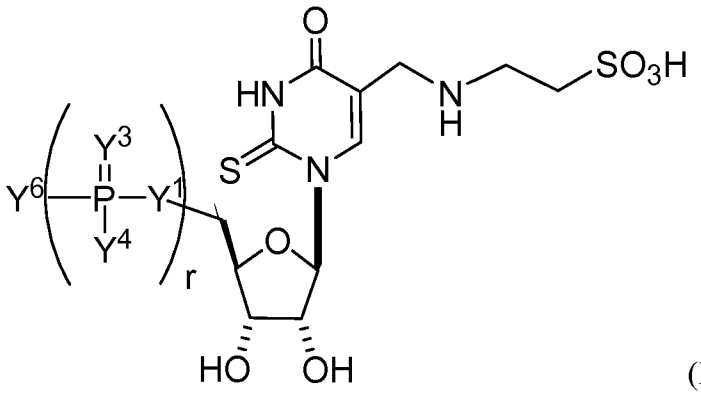
(BB- 103),



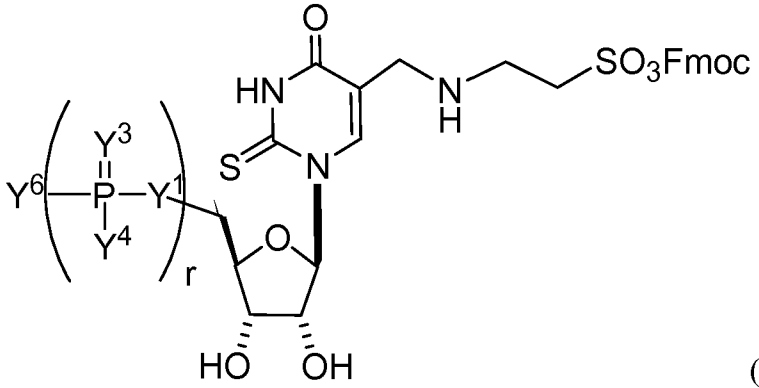
(BB- 104),



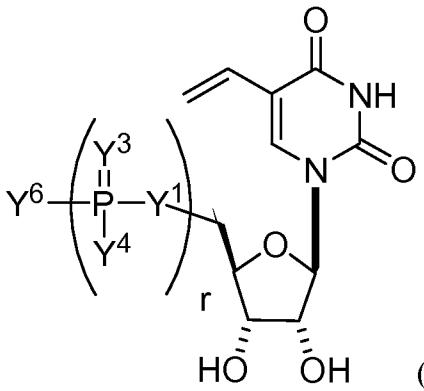
(BB- 105),



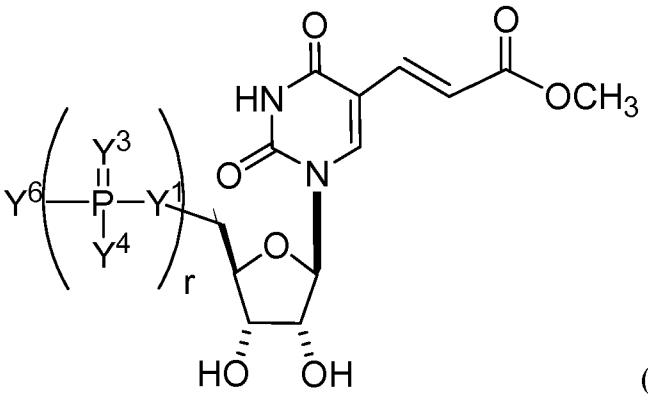
(BB- 106),



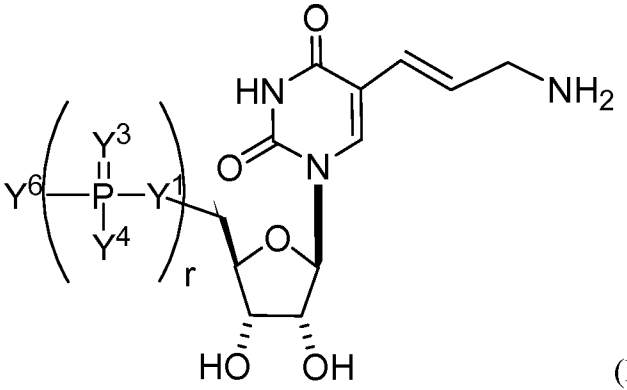
(BB- 107),



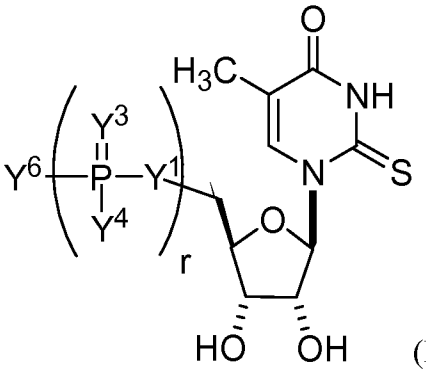
(BB- 108),



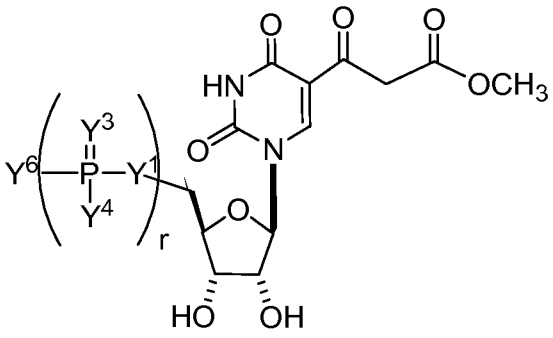
(BB- 109),

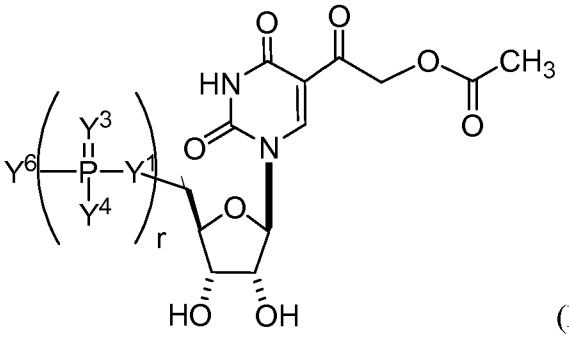


(BB- 110),



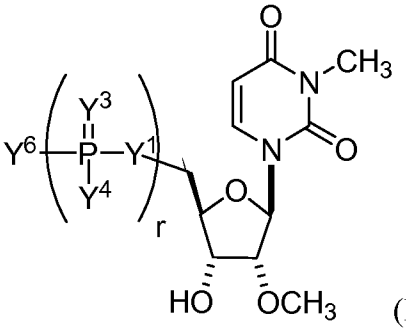
(BB- 111),

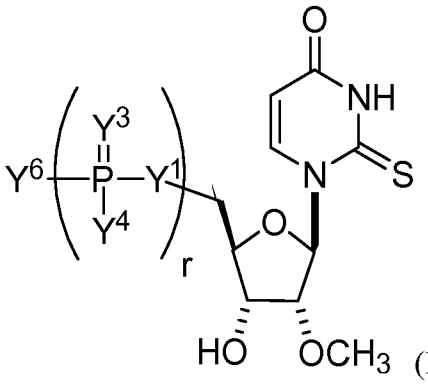


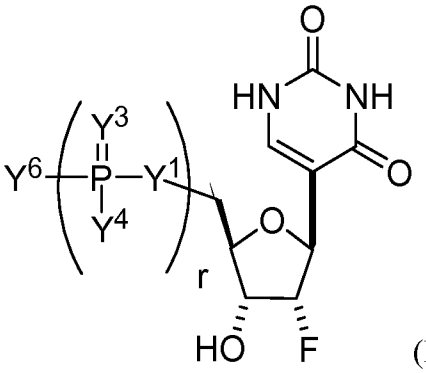


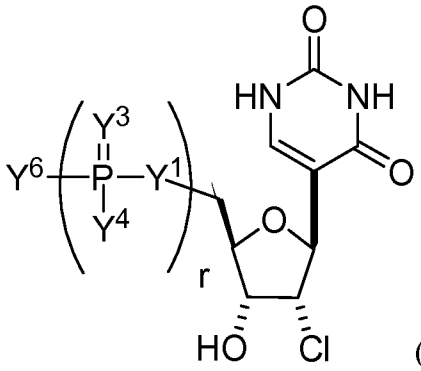
(BB- 112),

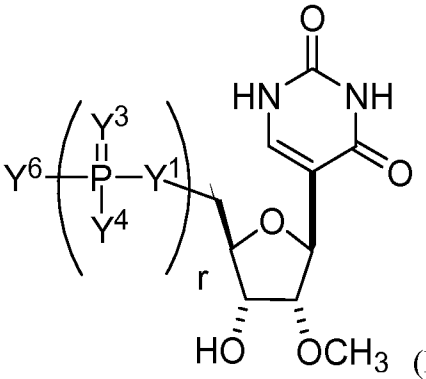
(BB- 113),

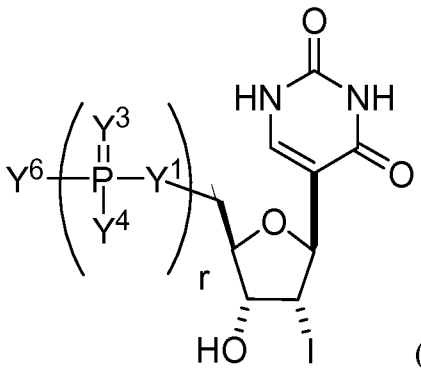

(BB- 114),

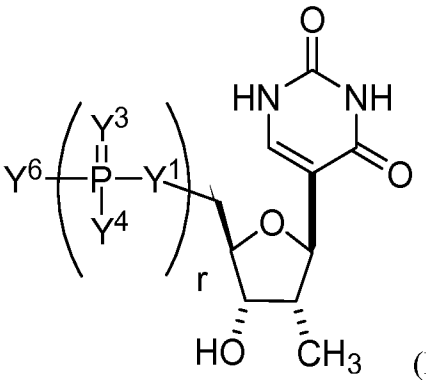

(BB- 115),

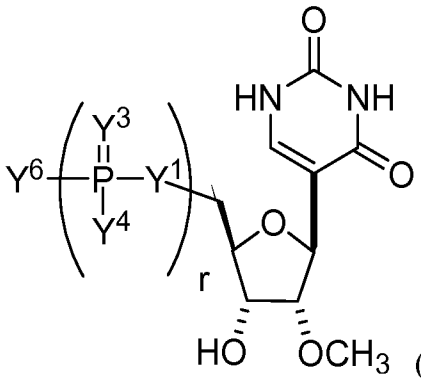

(BB- 116),

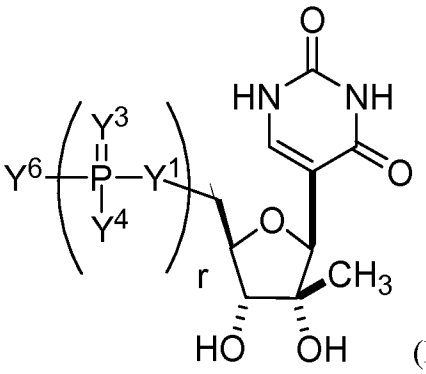

(BB- 117),


(BB- 118),

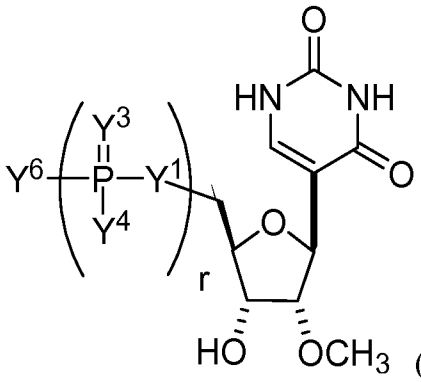

(BB- 119),


(BB- 120),

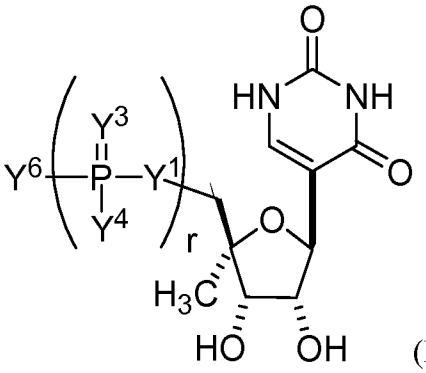

(BB- 121),



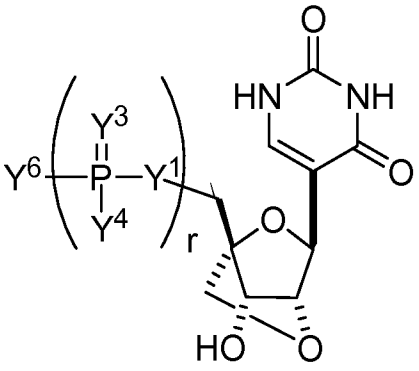
(BB- 122),



(BB- 123),

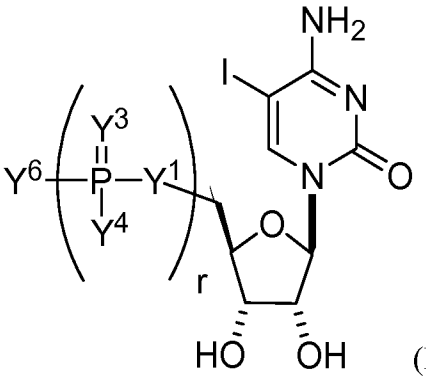


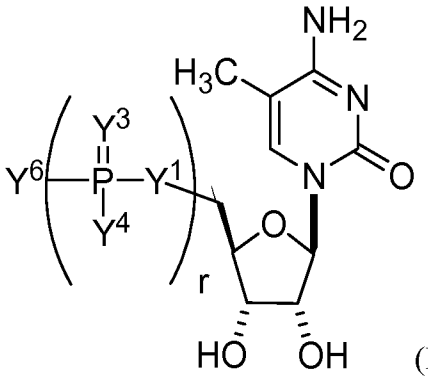
(BB- 124), and

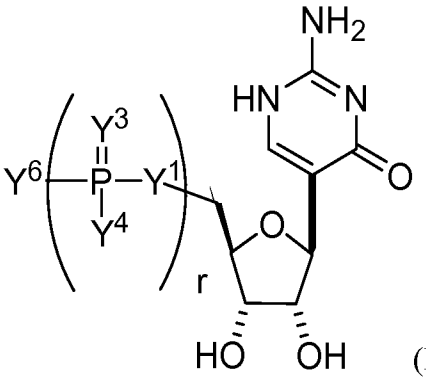


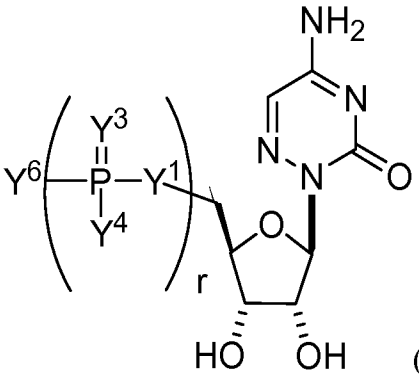
(BB-125), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3, Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)).

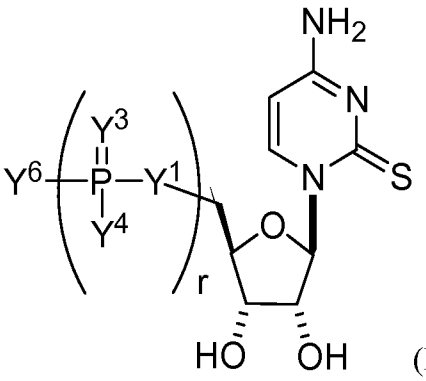
[000358] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, is a modified cytidine (e.g., selected from the group consisting of:

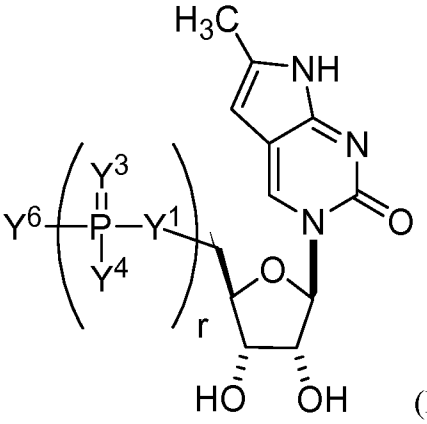

(BB- 126),

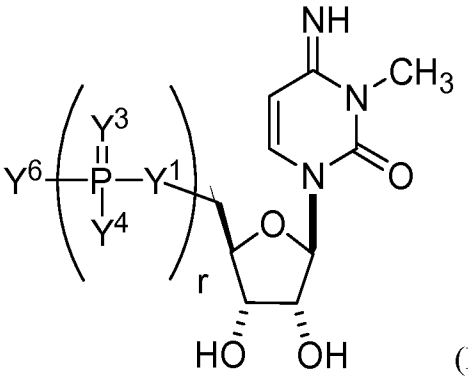

(BB- 127),

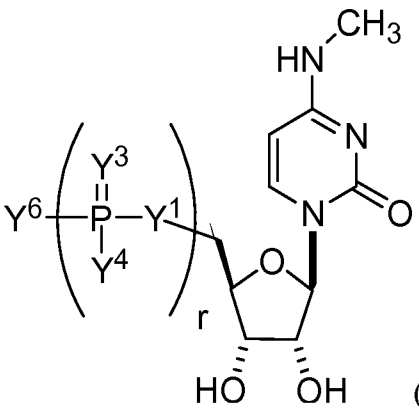

(BB- 128),

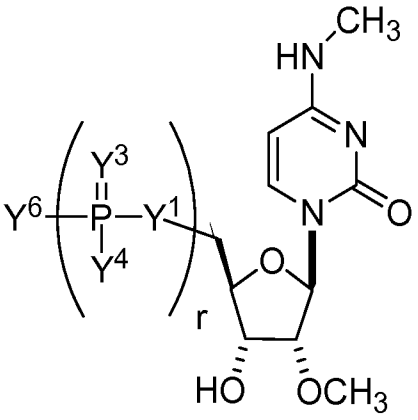

(BB- 129),

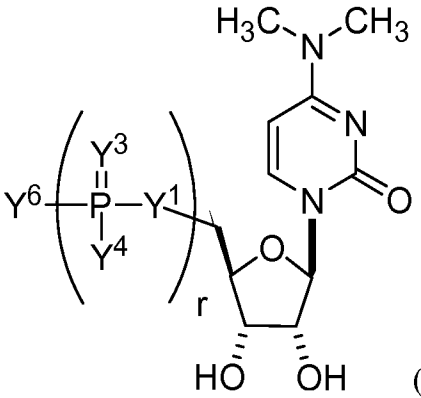

(BB- 130),

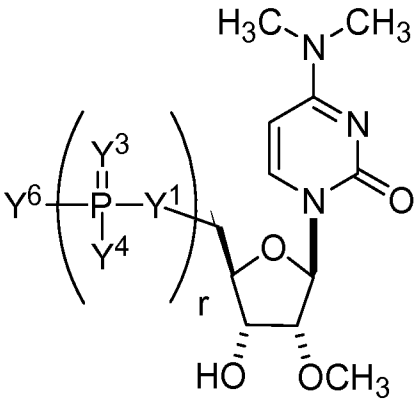

(BB- 131),

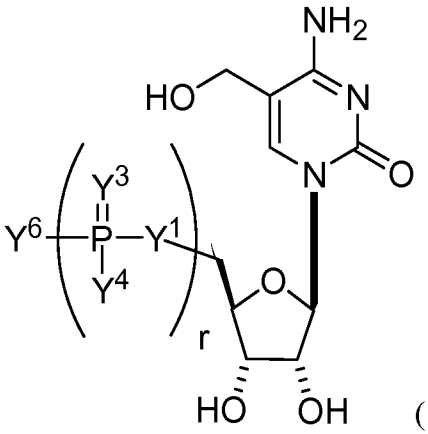

(BB- 132),

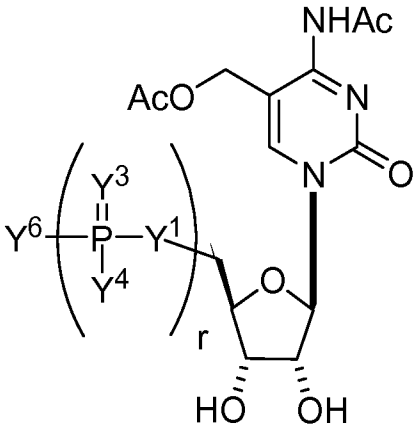

(BB- 133),

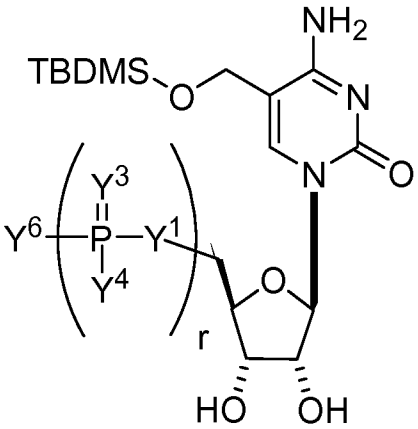

(BB- 134),

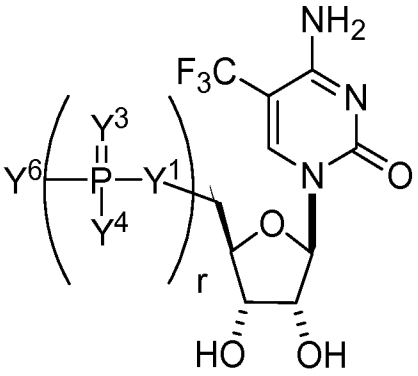

(BB- 135),

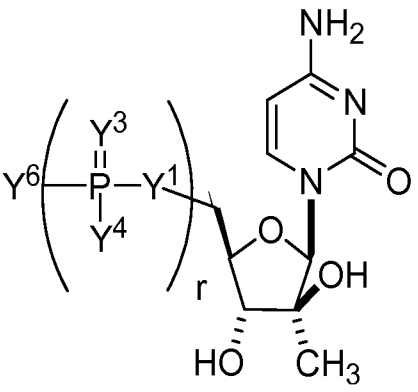

(BB- 136),

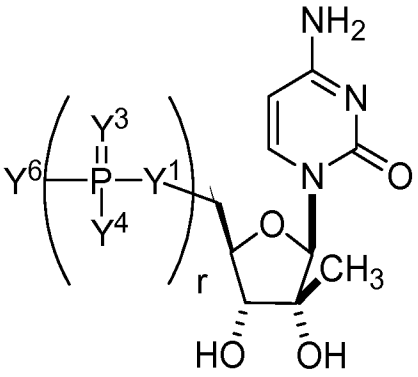

(BB- 137),

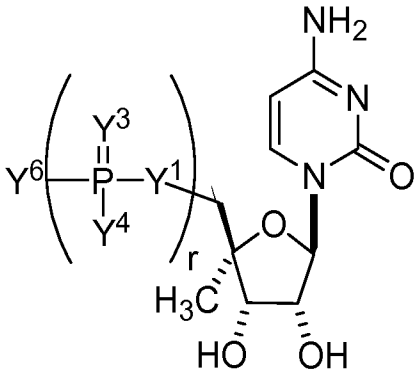

(BB- 138),

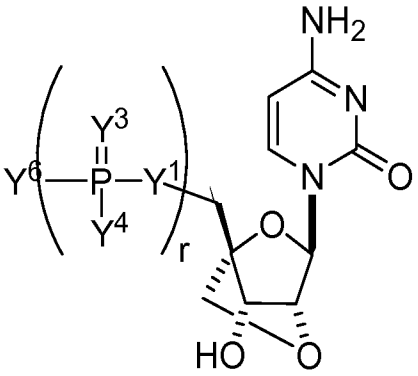

(BB- 139),

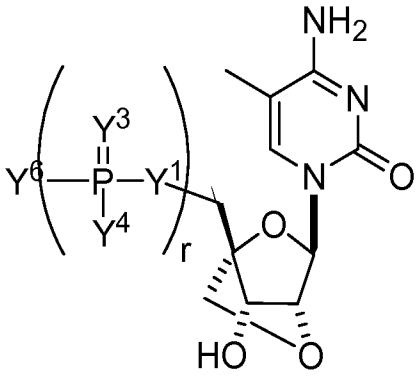

(BB- 140),

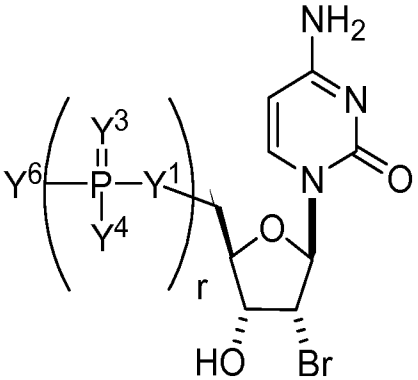

(BB- 141),

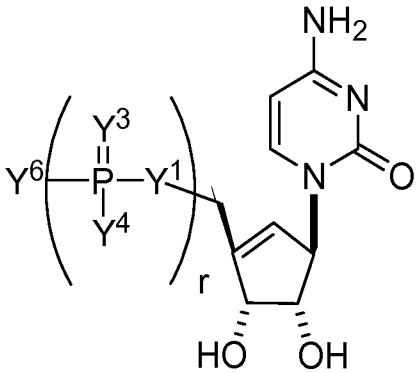

(BB- 142),

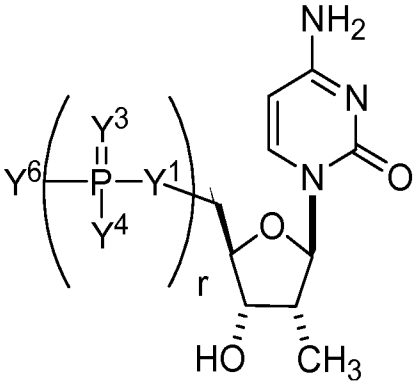

(BB- 143),

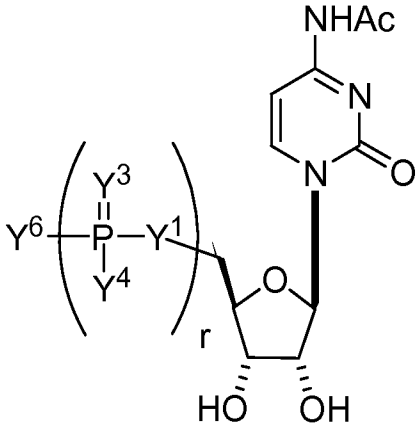

(BB- 144),

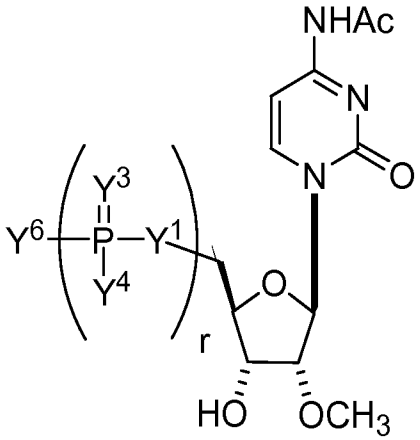

(BB- 145),


(BB- 146),

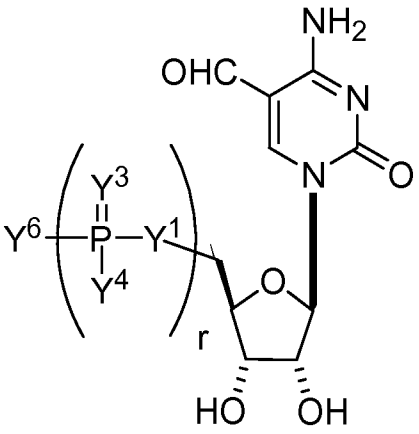

(BB- 147),


(BB- 148),

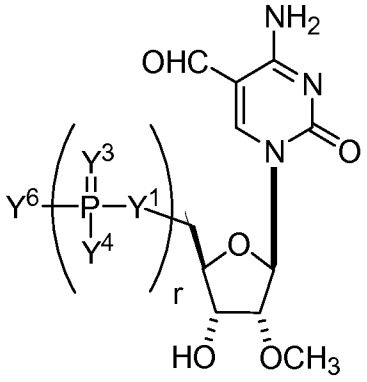

(BB- 149),



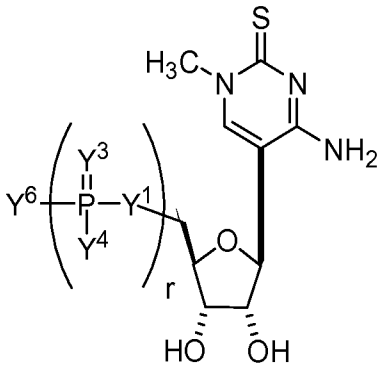
(BB- 150),



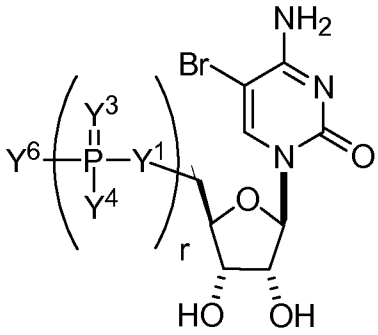
(BB- 151),



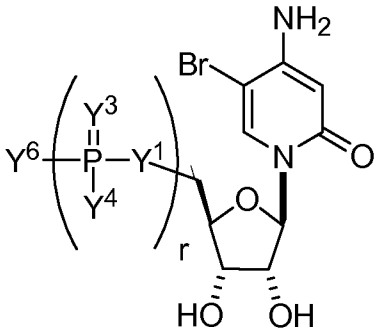
(BB- 152),



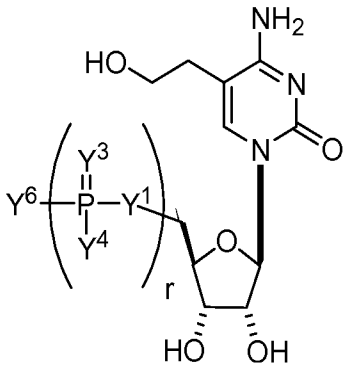
(BB- 153),



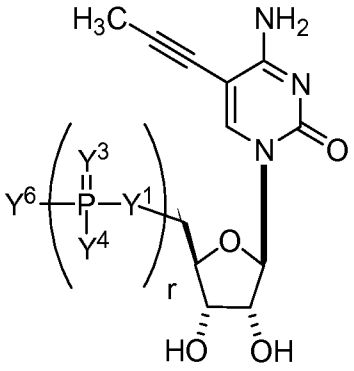
(BB- 154),



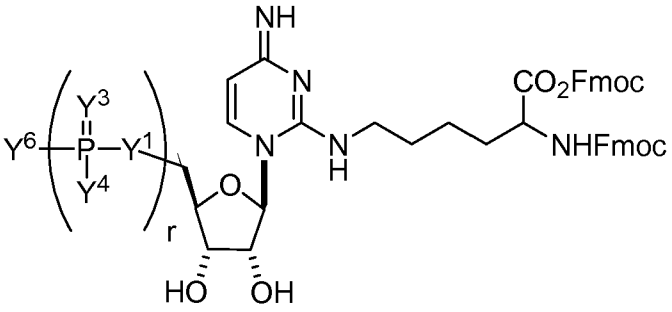
(BB- 155),



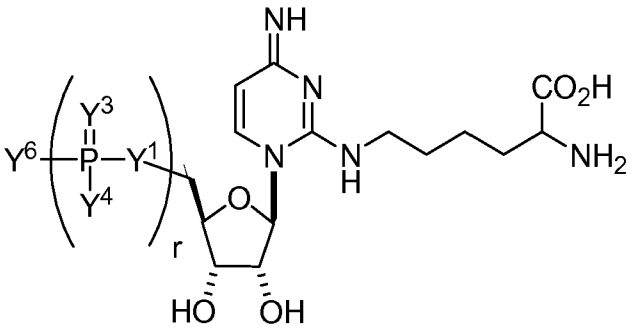
(BB- 156),



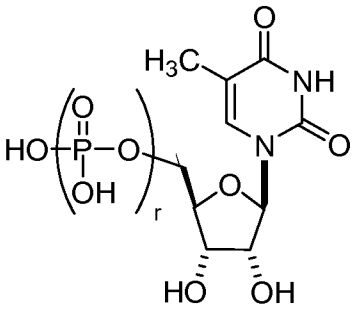
(BB- 157),



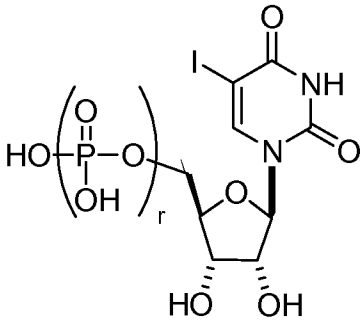
(BB- 158), and



(BB- 159), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3, Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)). For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:

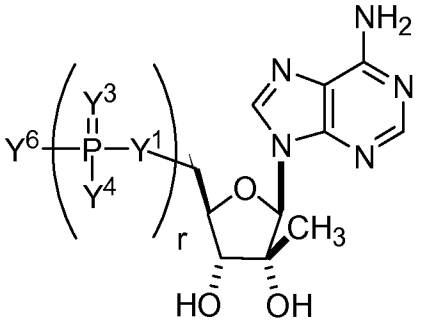


(BB- 160) or

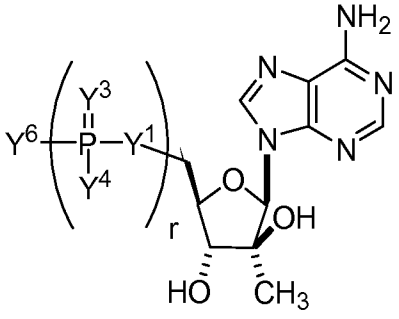


(BB- 161), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

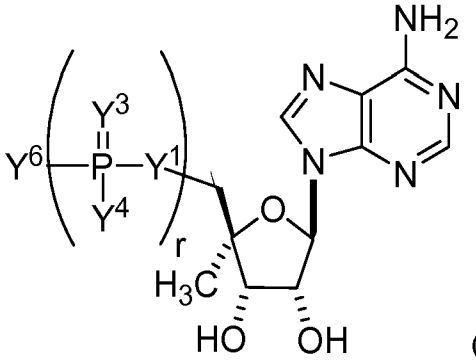
[000359] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, is a modified adenosine (e.g., selected from the group consisting of:



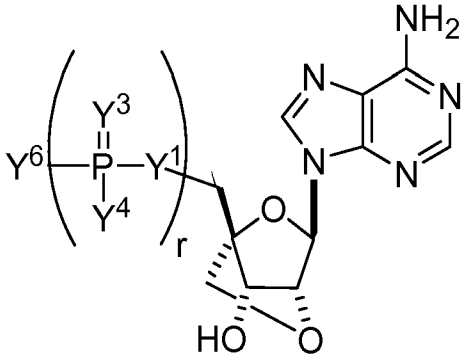
(BB- 162),



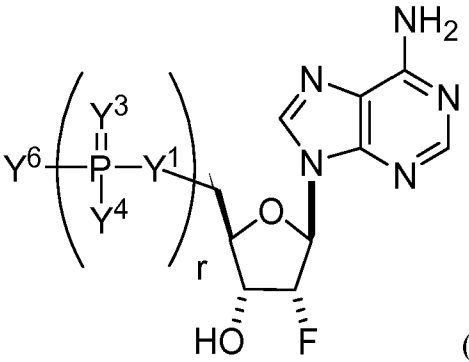
(BB- 163),



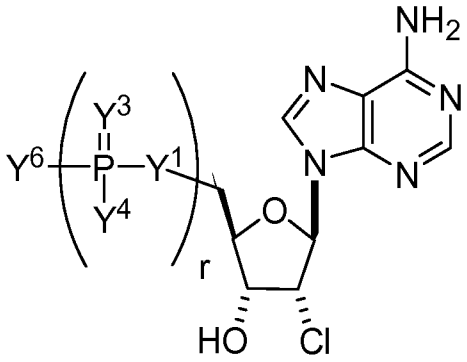
(BB- 164),



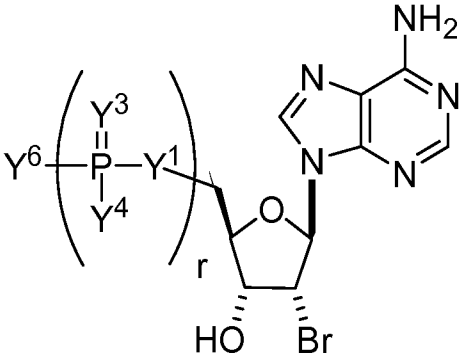
(BB-165),



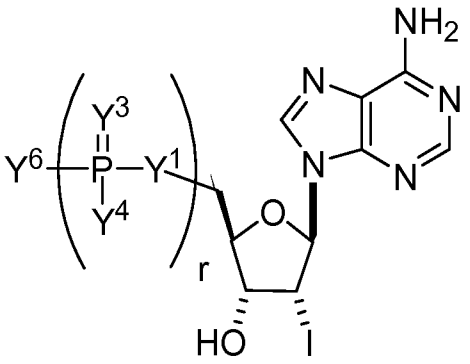
(BB- 166),



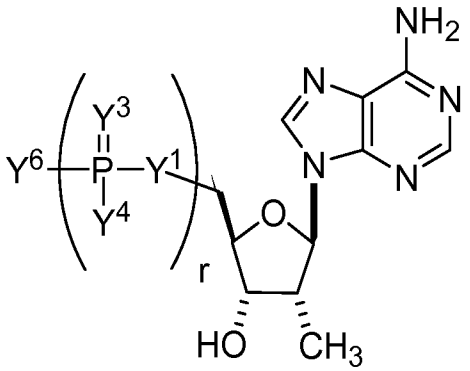
(BB- 167),



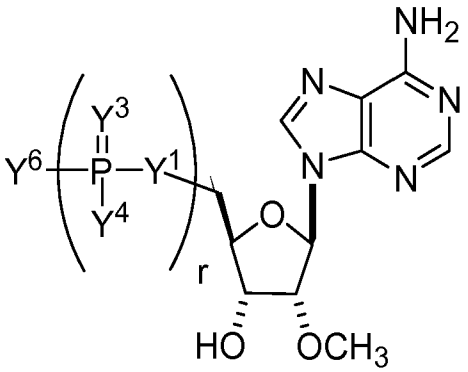
(BB- 168),



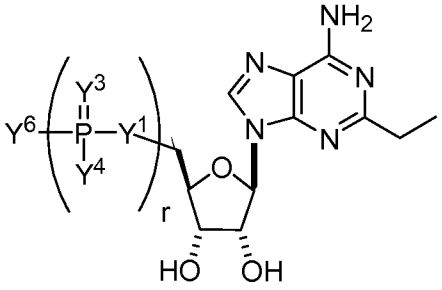
(BB- 169),



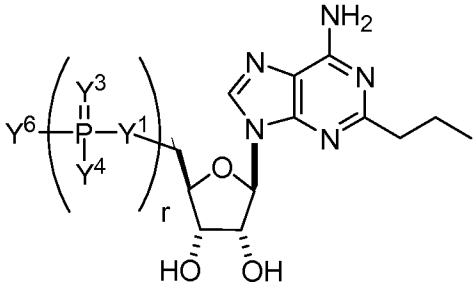
(BB- 170),



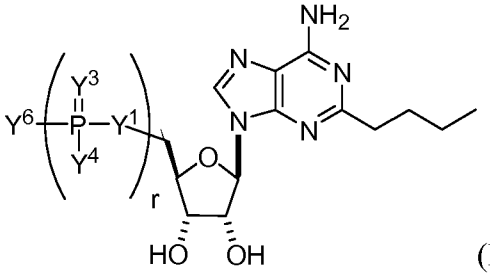
(BB- 171),



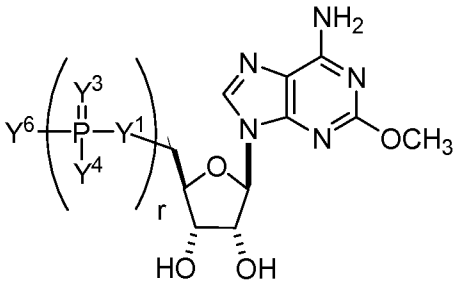
(BB- 172),



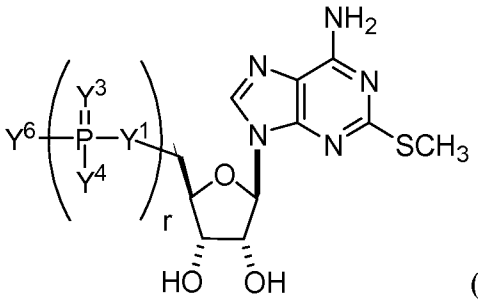
(BB- 173),



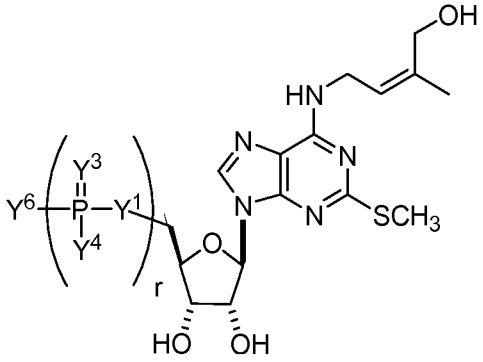
(BB- 174),

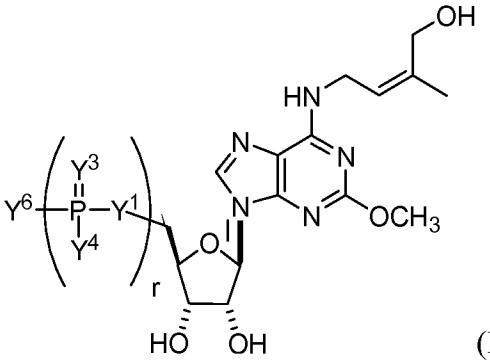


(BB- 175),



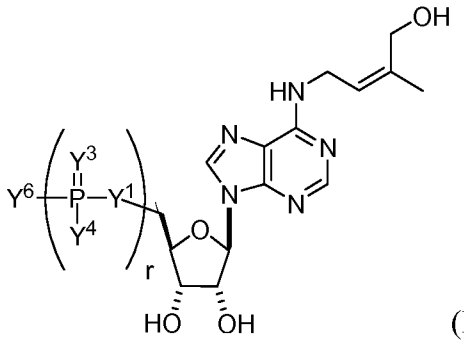
(BB- 176),



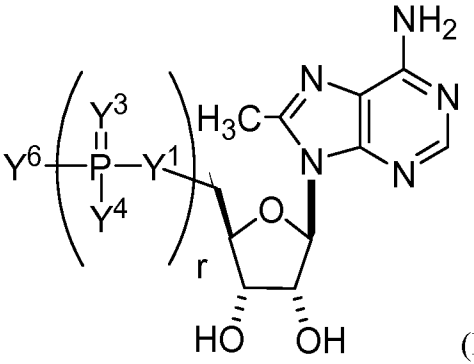


(BB- 177),

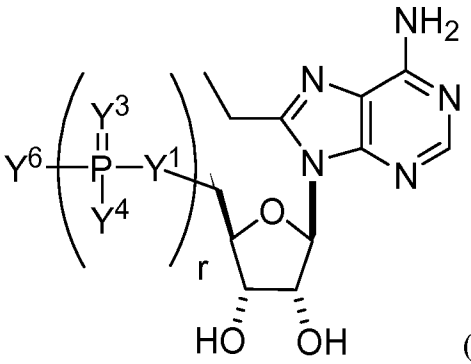
(BB- 178),



(BB- 179),

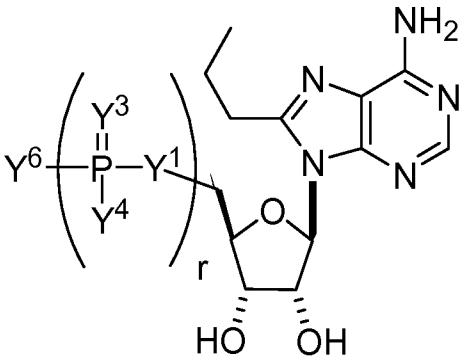


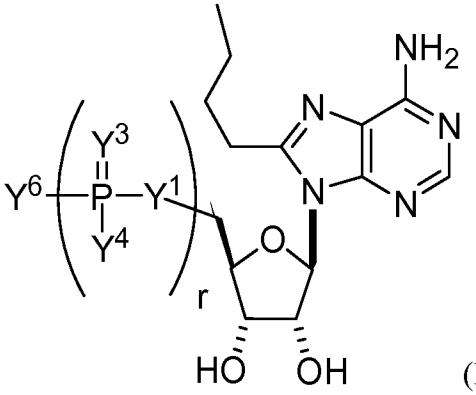
(BB-



180),

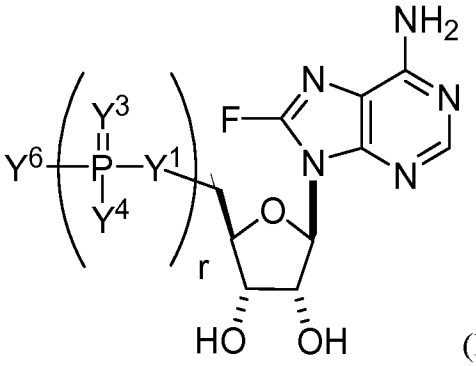
(BB- 181),



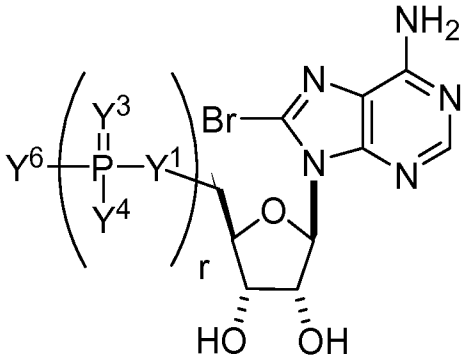


(BB- 182),

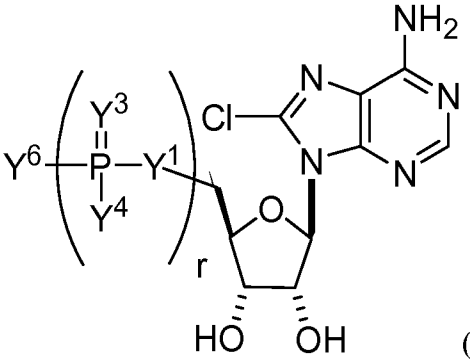
(BB- 183),



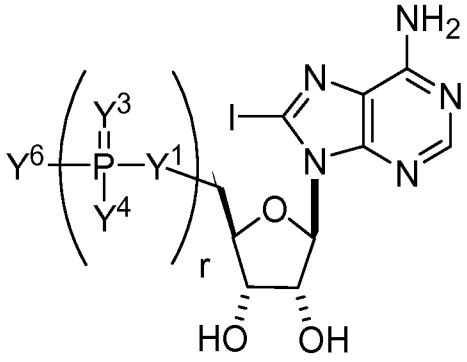
(BB- 184),



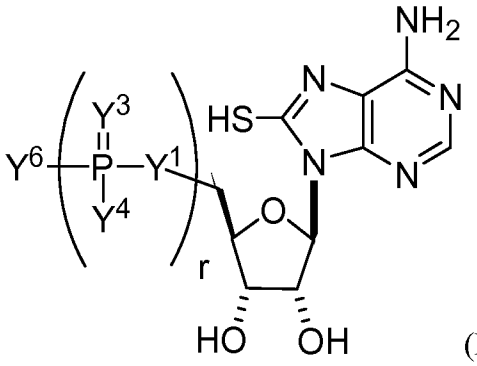
(BB- 185),



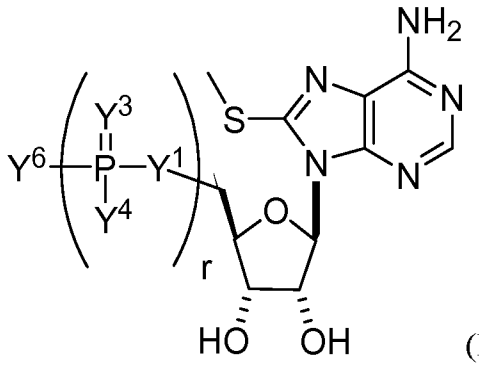
(BB- 186),



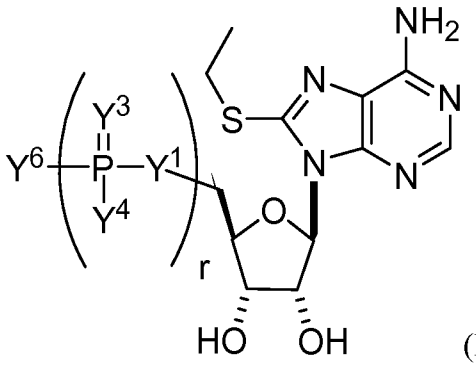
(BB- 187),



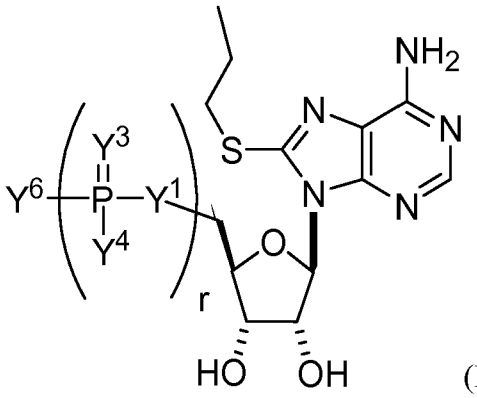
(BB- 188),



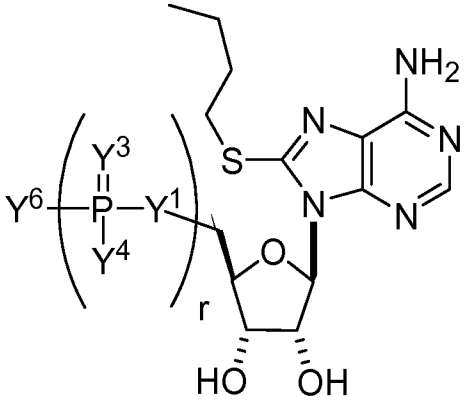
(BB- 189),



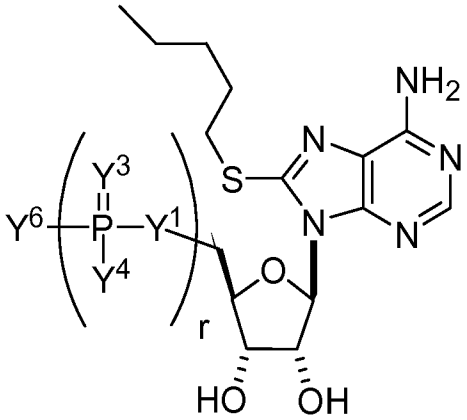
(BB- 190),



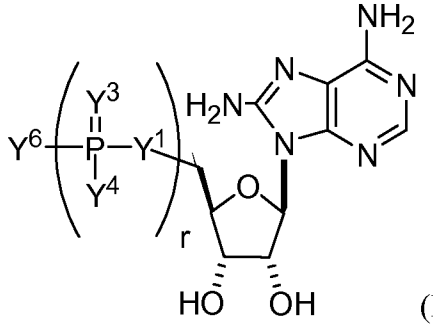
(BB- 191),



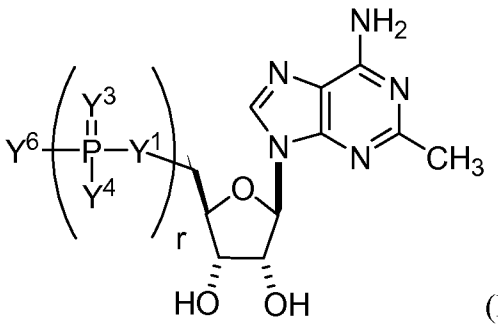
(BB- 192),



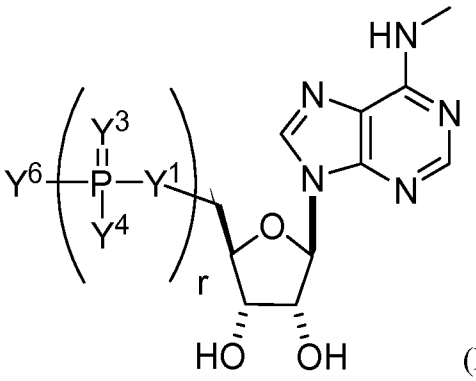
(BB- 193),



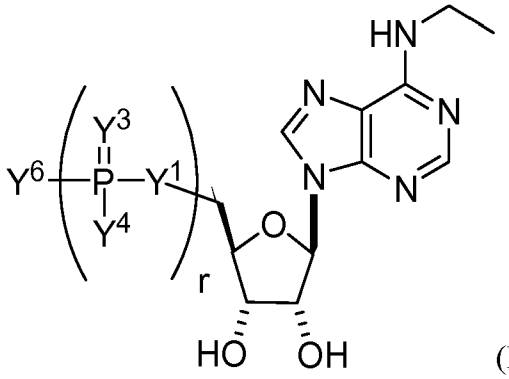
(BB- 194),



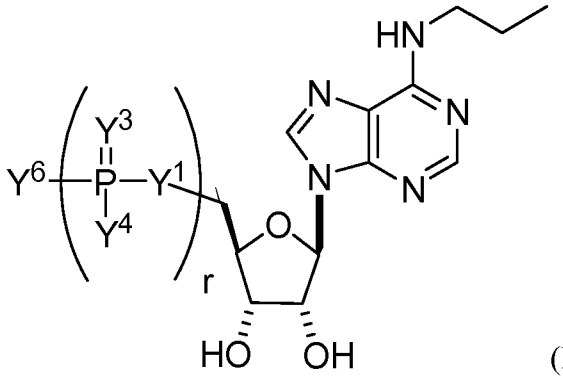
(BB-



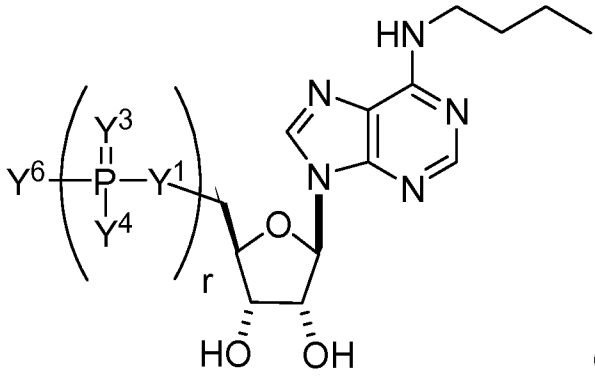
195), (BB- 196),



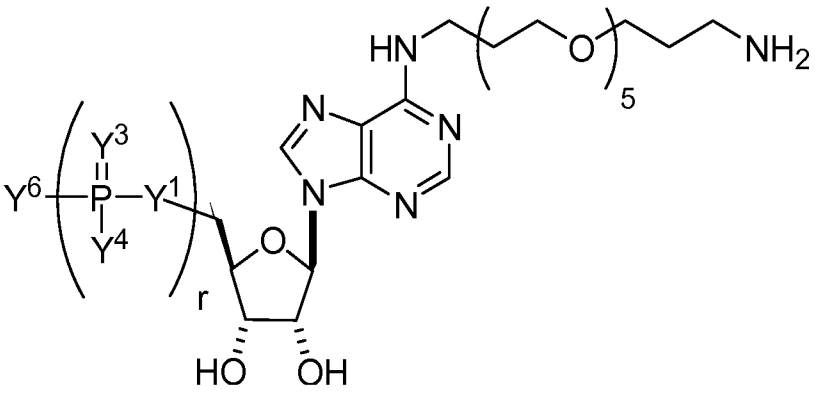
(BB- 197),



(BB- 198),

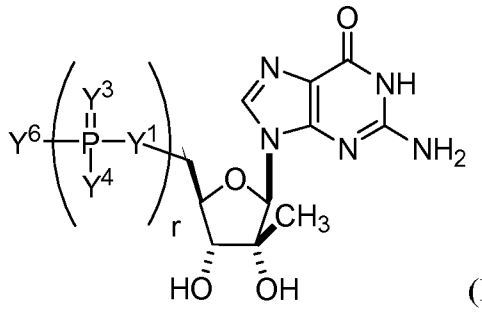


(BB- 199), and

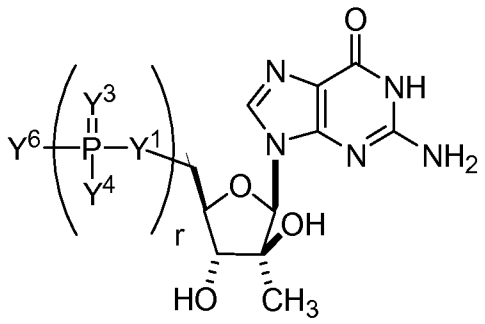


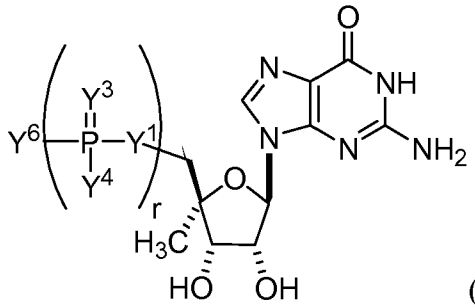
(BB- 200) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3, Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)).

[000360] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, is a modified guanosine (e.g., selected from the group consisting of:



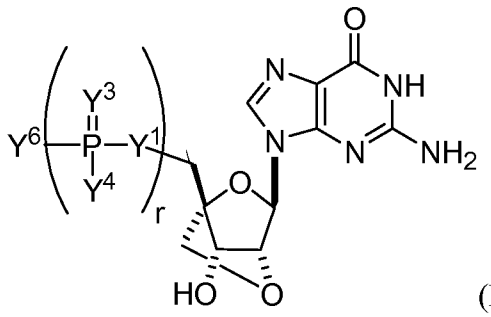
(BB- 201),



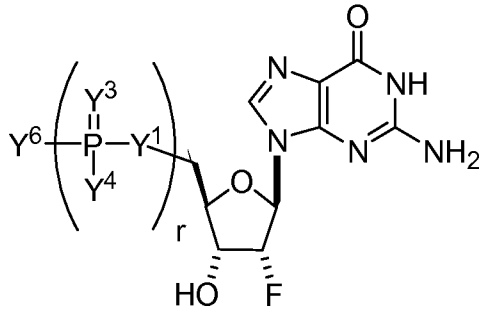


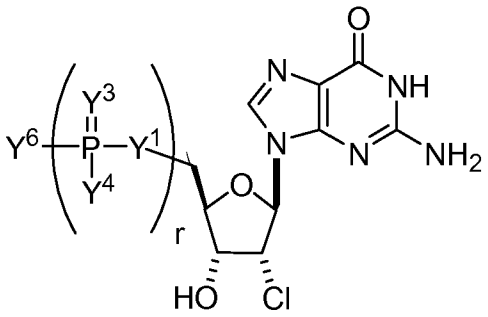
(BB- 202),

(BB- 203),



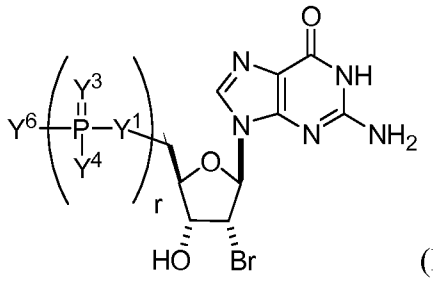
(BB- 204),



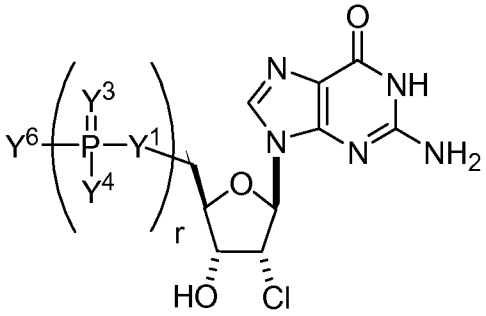


(BB- 205),

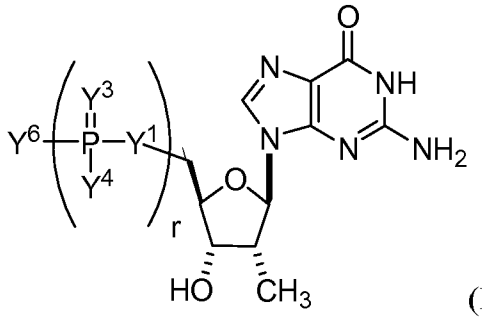
(BB- 206),



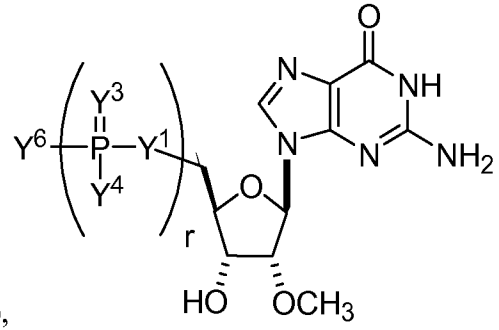
(BB- 207),

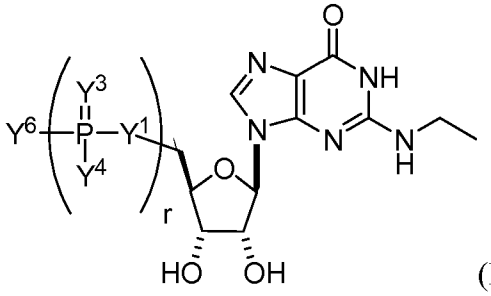


(BB- 208),



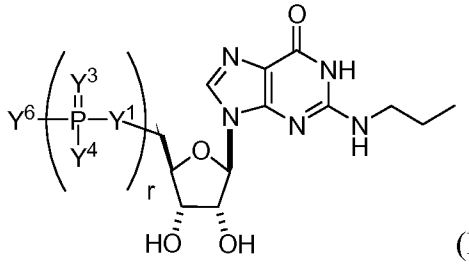
(BB- 209),



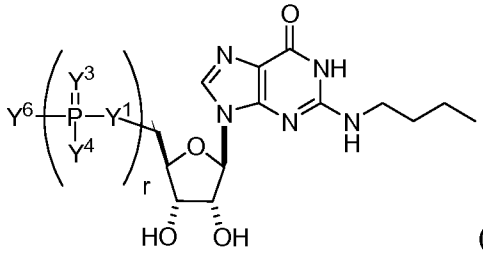


(BB- 210),

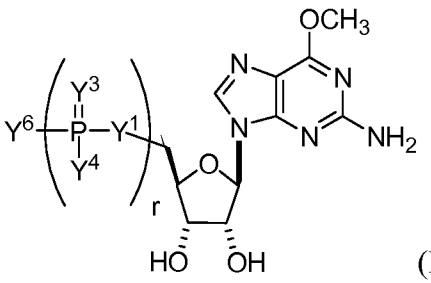
(BB- 211),



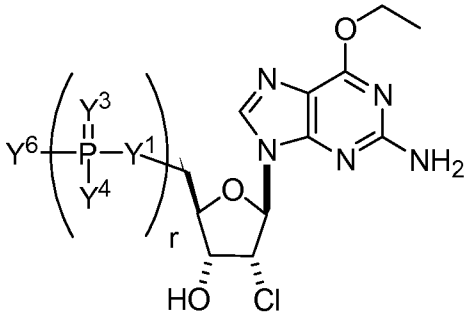
(BB- 212),



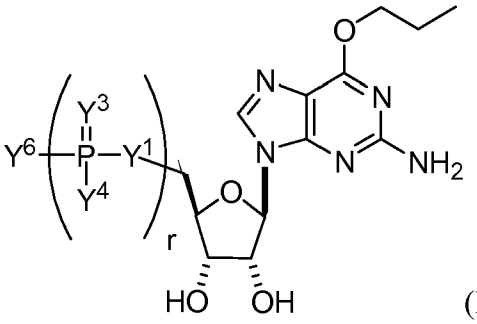
(BB-



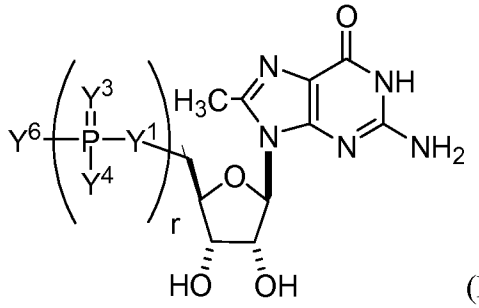
213),



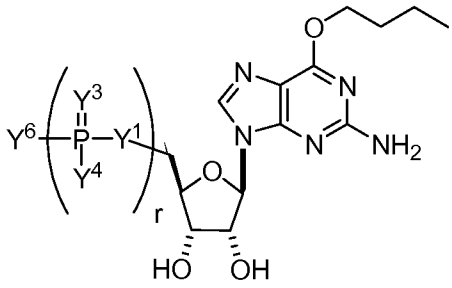
(BB- 214),



(BB- 215),

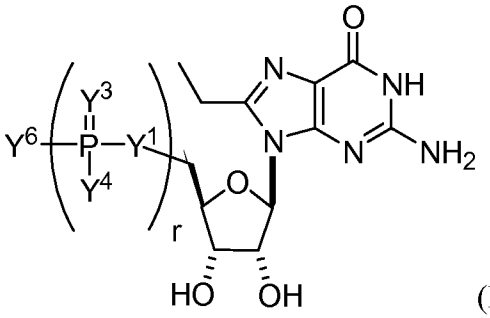


(BB- 216),



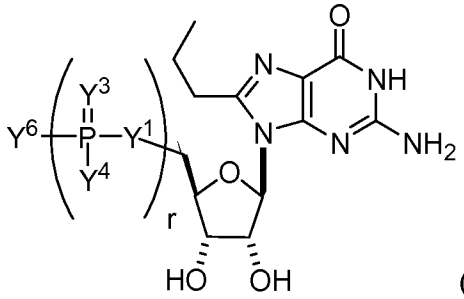
(BB- 217),

(BB-

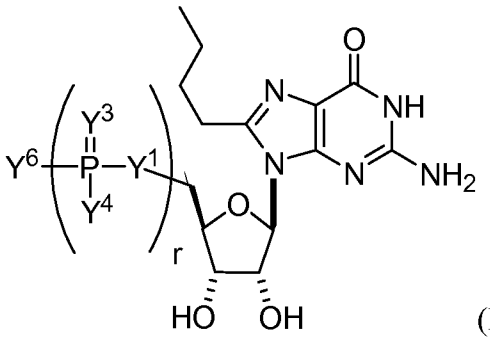


218),

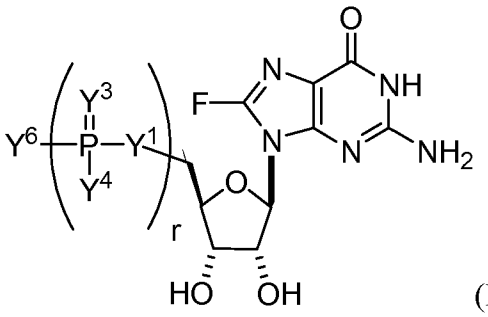
(BB- 219),



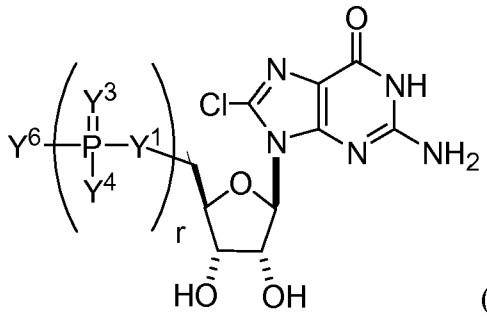
(BB- 220),



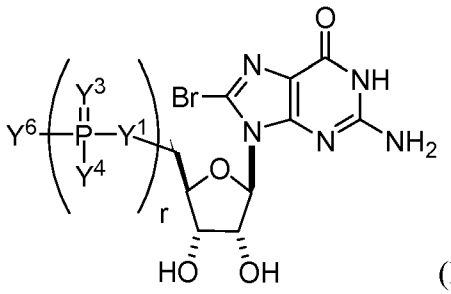
(BB-



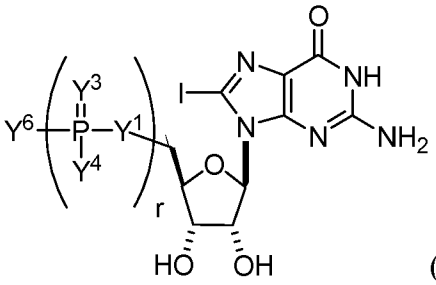
221), (BB- 222),



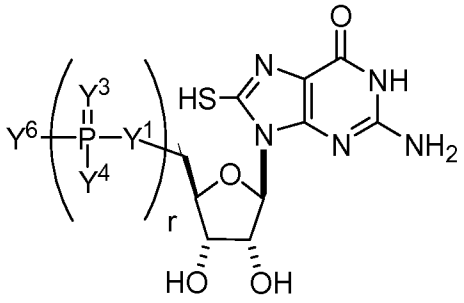
(BB- 223),



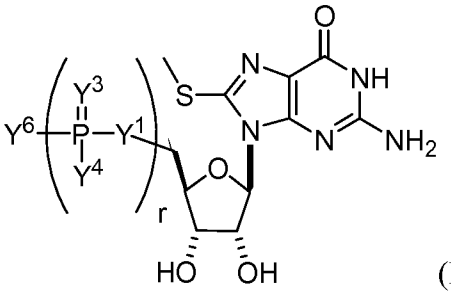
(BB-



224),

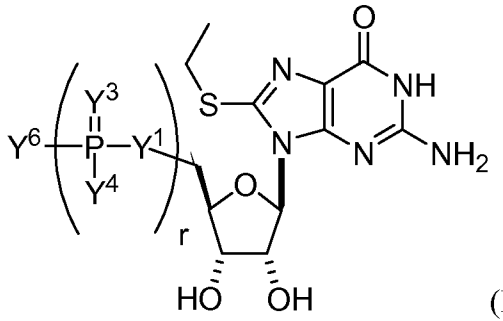


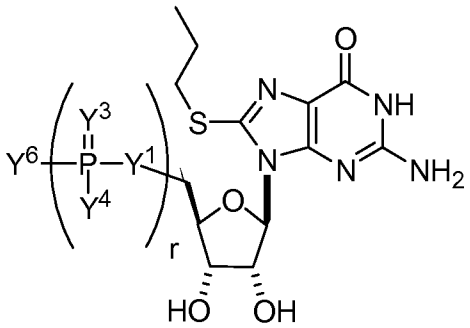
(BB- 225),



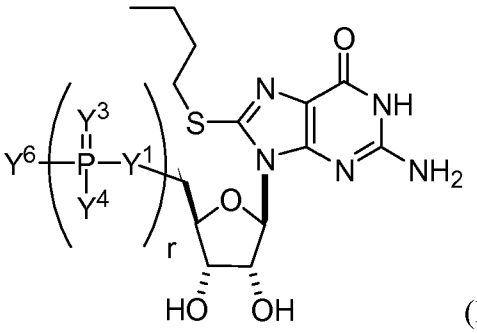
(BB- 226),

(BB- 227),



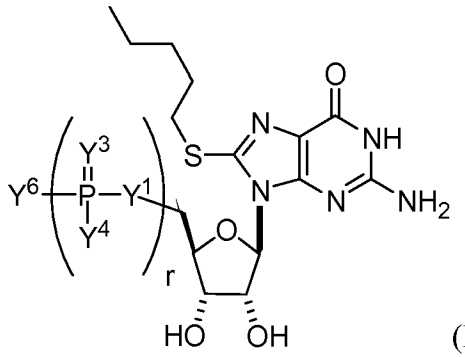


(BB- 228),

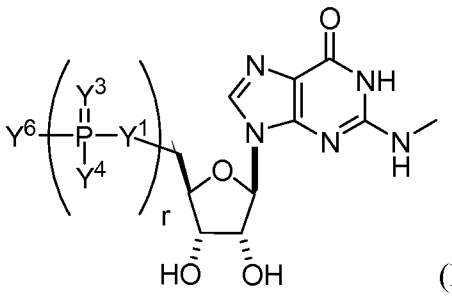


(BB- 229),

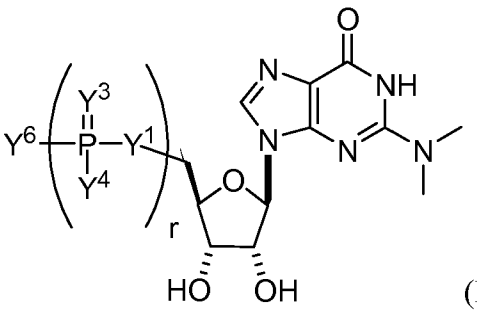
(BB- 230),



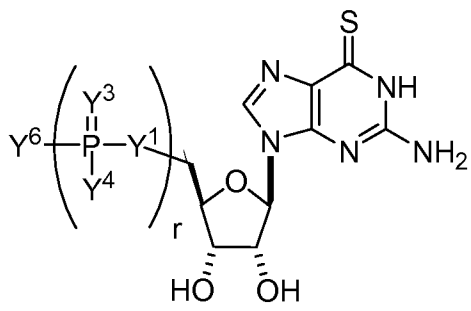
(BB- 231),



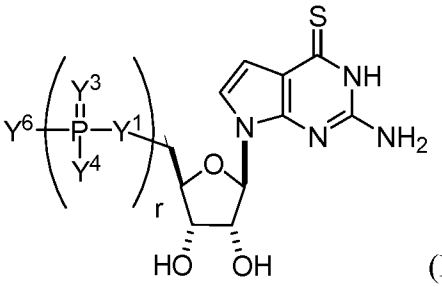
(BB- 232),



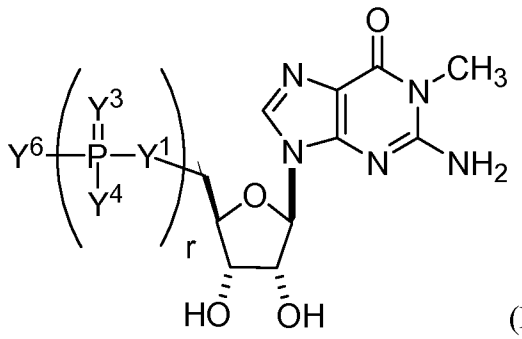
(BB- 233),



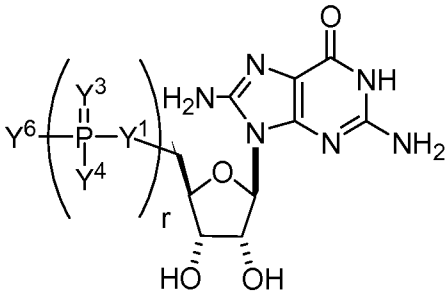
(BB- 234),



(BB- 235),



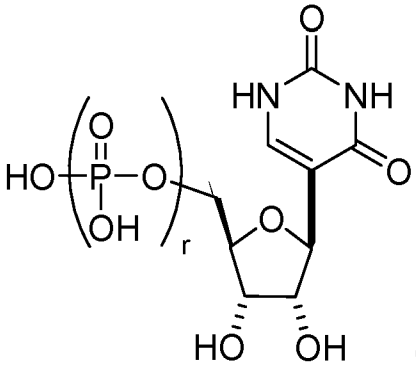
(BB- 236), and



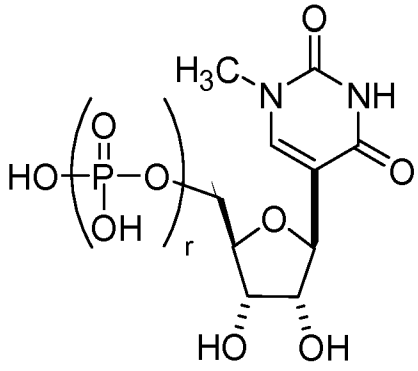
(BB- 237), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3,

Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)).

[000361] In some embodiments, the chemical modification can include replacement of C group at C-5 of the ring (e.g., for a pyrimidine nucleoside, such as cytosine or uracil) with N (e.g., replacement of the >CH group at C-5 with $>NR^{N1}$ group, wherein R^N1 is H or optionally substituted alkyl). For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:

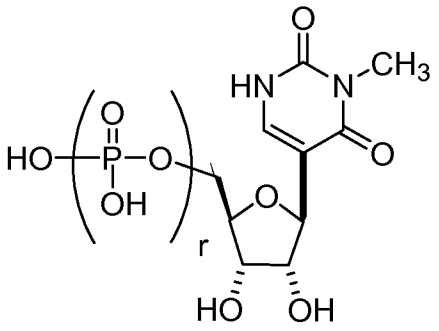


(BB- 238) or

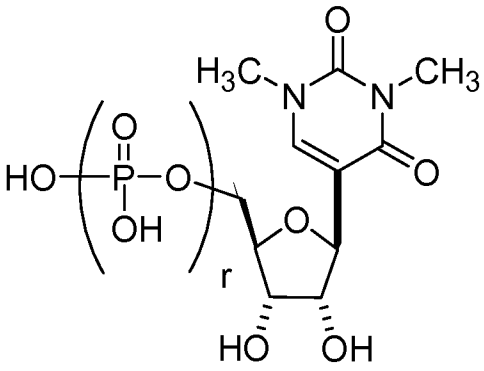


(BB- 239)

or

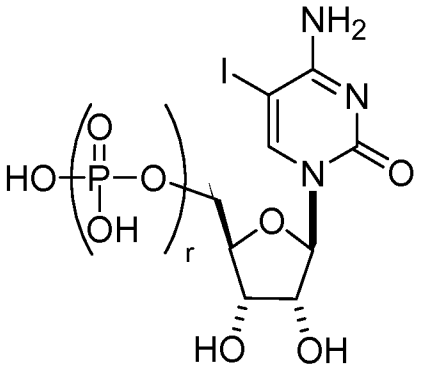


(BB- 240) or

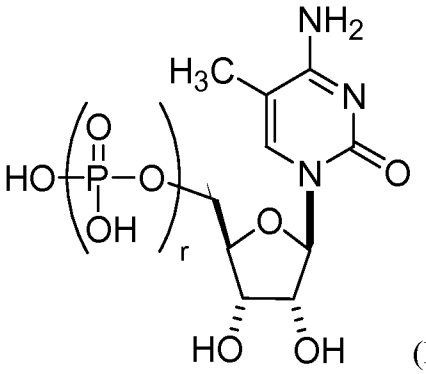


(BB- 241), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

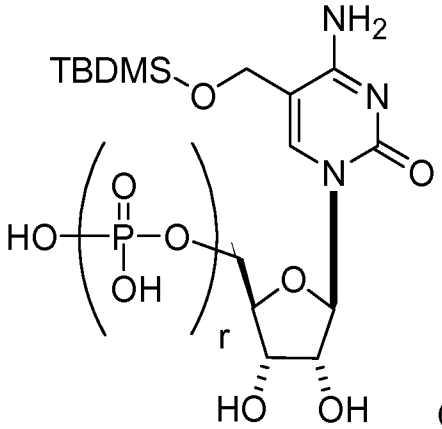
[000362] In another embodiment, the chemical modification can include replacement of the hydrogen at C-5 of cytosine with halo (e.g., Br, Cl, F, or I) or optionally substituted alkyl (e.g., methyl). For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:



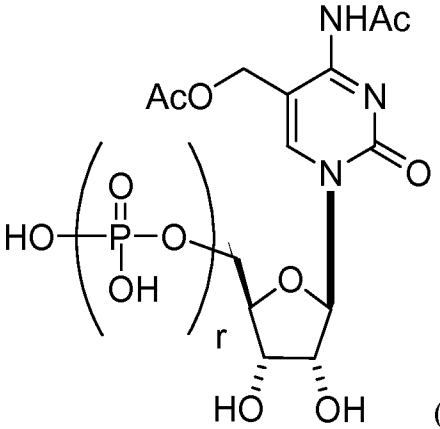
(BB- 242) or



(BB- 243)

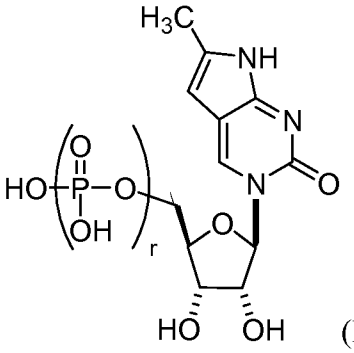


or



(BB- 244) or (BB- 245), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

[000363] In yet a further embodiment, the chemical modification can include a fused ring that is formed by the NH_2 at the C-4 position and the carbon atom at the C-5 position. For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:



(BB- 246), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

Modifications on the Sugar

[000364] The modified nucleosides and nucleotides (e.g., building block molecules), which may be incorporated into a polynucleotide, primary construct, or mmRNA (e.g., RNA or mRNA, as described herein), can be modified on the sugar of the ribonucleic acid. For example, the 2′ hydroxyl group (OH) can be modified or replaced with a number of different substituents. Exemplary substitutions at the 2′-position include, but are not limited to, H, halo, optionally substituted C_{1-6} alkyl; optionally substituted C_{1-6} alkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{3-8} cycloalkyl; optionally substituted C_{3-8} cycloalkoxy; optionally substituted C_{6-10} aryloxy; optionally substituted C_{6-10} aryl-C_{1-6} alkoxy, optionally substituted C_{1-12} (heterocyclyl)oxy; a sugar (e.g., ribose, pentose, or any described herein); a polyethyleneglycol (PEG), -$O(CH_2CH_2O)_nCH_2CH_2OR$, where R is H or optionally substituted alkyl, and n is an integer from 0 to 20 (e.g., from 0 to 4, from 0 to 8, from 0 to 10, from 0 to 16, from 1 to 4, from 1 to 8, from 1 to 10, from 1 to 16, from 1 to 20, from 2 to 4, from 2 to 8, from 2 to 10, from 2 to 16, from 2 to 20, from 4 to 8, from 4 to 10, from 4 to 16, and from 4 to 20); "locked" nucleic acids (LNA) in which the 2′-hydroxyl is connected by a C_{1-6} alkylene or C_{1-6} heteroalkylene bridge to the 4'-carbon of the same ribose sugar, where exemplary bridges included methylene, propylene, ether, or amino bridges; aminoalkyl, as defined herein; aminoalkoxy, as defined herein; amino as defined herein; and amino acid, as defined herein

Generally, RNA includes the sugar group ribose, which is a 5-membered ring having an oxygen. Exemplary, non-limiting modified nucleotides include replacement of the oxygen in ribose (e.g., with S, Se, or alkylene, such as methylene or ethylene); addition of a double bond (e.g., to replace ribose with cyclopentenyl or cyclohexenyl); ring contraction of ribose (e.g., to form a 4-membered ring of cyclobutane or oxetane); ring expansion of ribose (e.g., to form a 6- or 7-membered ring having an additional carbon or heteroatom, such as for anhydrohexitol, altritol, mannitol, cyclohexanyl, cyclohexenyl, and morpholino that also has a phosphoramidate backbone); multicyclic forms (e.g., tricyclo; and "unlocked" forms, such as glycol nucleic acid (GNA) (e.g., R-GNA or S-GNA, where ribose is replaced by glycol units attached to phosphodiester bonds), threose nucleic acid (TNA, where ribose is replace with α-L-threofuranosyl-(3′→2′)) , and peptide nucleic acid (PNA, where 2-amino-ethyl-glycine linkages replace the ribose and

phosphodiester backbone). The sugar group can also contain one or more carbons that possess the opposite stereochemical configuration than that of the corresponding carbon in ribose. Thus, a polynucleotide, primary construct, or mmRNA molecule can include nucleotides containing, e.g., arabinose, as the sugar.

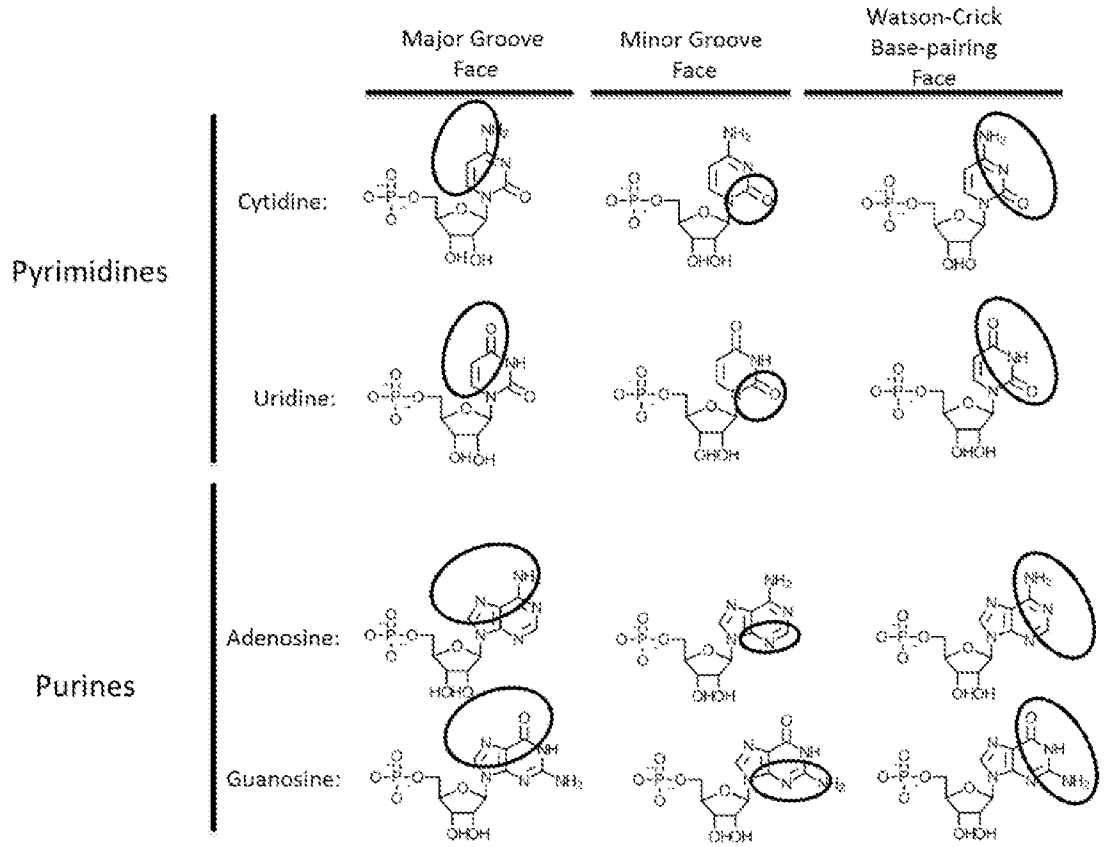
Modifications on the Nucleobase

[000365] The present disclosure provides for modified nucleosides and nucleotides. As described herein "nucleoside" is defined as a compound containing a sugar molecule (e.g., a pentose or ribose) or a derivative thereof in combination with an organic base (e.g., a purine or pyrimidine) or a derivative thereof (also referred to herein as "nucleobase"). As described herein, "nucleotide" is defined as a nucleoside including a phosphate group. The modified nucleotides may by synthesized by any useful method, as described herein (e.g., chemically, enzymatically, or recombinantly to include one or more modified or non-natural nucleosides).

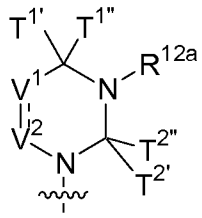
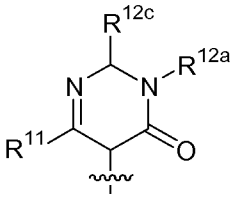
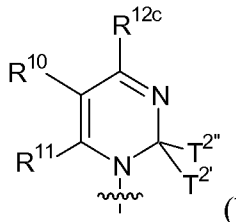
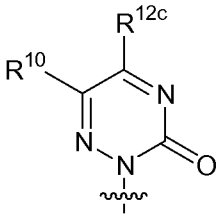
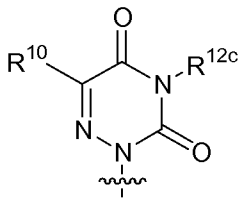
[000366] The modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen bond donors and hydrogen bond acceptors permits hydrogen bonding between a non-standard base and a standard base or between two complementary non-standard base structures. One example of such non-standard base pairing is the base pairing between the modified nucleotide inosine and adenine, cytosine or uracil.

[000367] The modified nucleosides and nucleotides can include a modified nucleobase. Examples of nucleobases found in RNA include, but are not limited to, adenine, guanine, cytosine, and uracil. Examples of nucleobase found in DNA include, but are not limited to, adenine, guanine, cytosine, and thymine. These nucleobases can be modified or wholly replaced to provide polynucleotides, primary constructs, or mmRNA molecules having enhanced properties, e.g., resistance to nucleases through disruption of the binding of a major groove binding partner. Table 8 below identifies the chemical faces of each canonical nucleotide. Circles identify the atoms comprising the respective chemical regions.

Table 8



[000368] In some embodiments, B is a modified uracil. Exemplary modified uracils include those having Formula (b1)-(b5):


(b1),

(b2),

(b3),

(b4),

or (b5), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000369] wherein

[000370] ⎓ is a single or double bond;

[000371] each of $T^{1'}$, $T^{1''}$, $T^{2'}$, and $T^{2''}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of $T^{1'}$ and $T^{1''}$ or the combination of $T^{2'}$ and $T^{2''}$ join together (e.g., as in T^2) to form O (oxo), S (thio), or Se (seleno);

[000372] each of V^1 and V^2 is, independently, O, S, $N(R^{Vb})_{nv}$, or $C(R^{Vb})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vb} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl), optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted acylaminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl), optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, or optionally substituted alkynyloxy (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl);

[000373] R^{10} is H, halo, optionally substituted amino acid, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aminoalkyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl;

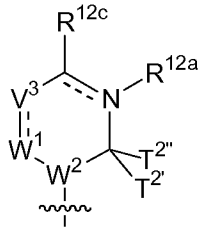
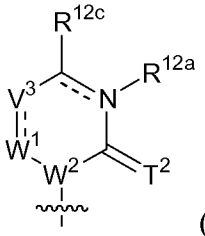
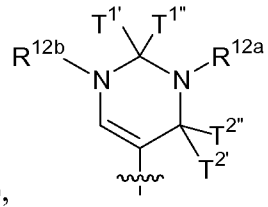
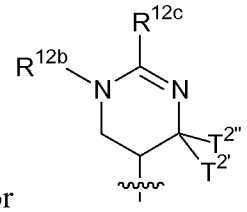
[000374] R^{11} is H or optionally substituted alkyl;

[000375] R^{12a} is H, optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted

aminoalkynyl, optionally substituted carboxyalkyl (e.g., optionally substituted with hydroxy), optionally substituted carboxyalkoxy, optionally substituted carboxyaminoalkyl, or optionally substituted carbamoylalkyl; and

[000376] R^{12c} is H, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted amino, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl.

[000377] Other exemplary modified uracils include those having Formula (b6)-(b9):


(b6),

(b7),

(b8), or


(b9), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000378] wherein

[000379] ≈ is a single or double bond;

[000380] each of $T^{1'}$, $T^{1''}$, $T^{2'}$, and $T^{2''}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of $T^{1'}$ and $T^{1''}$ join together (e.g., as in T^1) or the combination of $T^{2'}$ and $T^{2''}$ join together (e.g., as in T^2) to form O (oxo), S (thio), or Se (seleno), or each T^1 and T^2 is, independently, O (oxo), S (thio), or Se (seleno);

[000381] each of W^1 and W^2 is, independently, $N(R^{Wa})_{nw}$ or $C(R^{Wa})_{nw}$, wherein nw is an integer from 0 to 2 and each R^{Wa} is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy;

[000382] each V^3 is, independently, O, S, $N(R^{Va})_{nv}$, or $C(R^{Va})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Va} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted alkoxy, optionally substituted

alkenyloxy, or optionally substituted alkynyloxy , optionally substituted aminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl), optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted acylaminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl), optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylacyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkyl (e.g., optionally substituted with hydroxy and/or an *O*-protecting group), optionally substituted carboxyalkoxy, optionally substituted carboxyaminoalkyl, or optionally substituted carbamoylalkyl (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl), and wherein R^{Va} and R^{12c} taken together with the carbon atoms to which they are attached can form optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heterocyclyl (e.g., a 5- or 6-membered ring);

[000383] R^{12a} is H, optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted carboxyalkyl (e.g., optionally substituted with hydroxy and/or an *O*-protecting group), optionally substituted carboxyalkoxy, optionally substituted carboxyaminoalkyl, optionally substituted carbamoylalkyl, or absent;

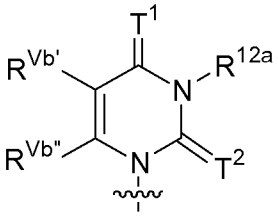
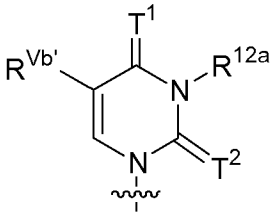
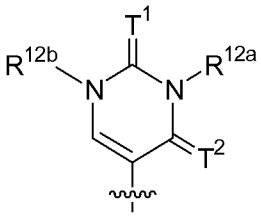
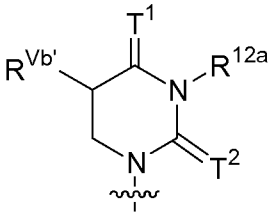
[000384] R^{12b} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted alkaryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted amino acid, optionally substituted alkoxycarbonylacyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkyl (e.g., optionally substituted with hydroxy and/or an *O*-protecting

group), optionally substituted carboxyalkoxy, optionally substituted carboxyaminoalkyl, or optionally substituted carbamoylalkyl,

[000385] wherein the combination of R^{12b} and $T^{1'}$ or the combination of R^{12b} and R^{12c} can join together to form optionally substituted heterocyclyl; and

[000386] R^{12c} is H, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted amino, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl.

[000387] Further exemplary modified uracils include those having Formula (b28)-(b31):


(b28),

(b29),

(b30), or

(b31), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000388] wherein

[000389] each of T^1 and T^2 is, independently, O (oxo), S (thio), or Se (seleno);

[000390] each $R^{Vb'}$ and $R^{Vb''}$ is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl), optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted acylaminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl), optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally

substituted alkoxycarbonylacyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkyl (e.g., optionally substituted with hydroxy and/or an *O*-protecting group), optionally substituted carboxyalkoxy, optionally substituted carboxyaminoalkyl, or optionally substituted carbamoylalkyl (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl) (e.g., $R^{Vb'}$ is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted aminoalkyl, e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl);

[000391] R^{12a} is H, optionally substituted alkyl, optionally substituted carboxyaminoalkyl, optionally substituted aminoalkyl (e.g., e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl), optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl; and

[000392] R^{12b} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl (e.g., e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl),

[000393] optionally substituted alkoxycarbonylacyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl.

[000394] In particular embodiments, T^1 is O (oxo), and T^2 is S (thio) or Se (seleno). In other embodiments, T^1 is S (thio), and T^2 is O (oxo) or Se (seleno). In some embodiments, $R^{Vb'}$ is H, optionally substituted alkyl, or optionally substituted alkoxy.

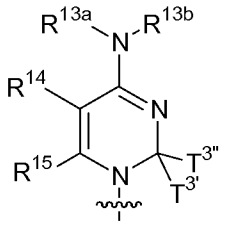
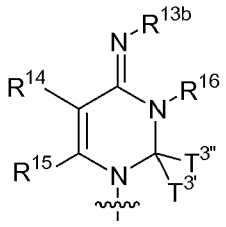
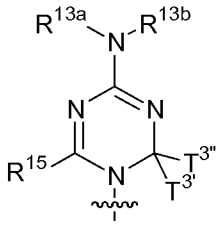
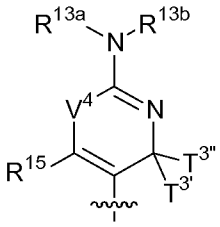
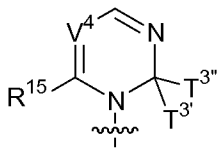
[000395] In other embodiments, each R^{12a} and R^{12b} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted hydroxyalkyl. In particular embodiments, R^{12a} is H. In other embodiments, both R^{12a} and R^{12b} are H.

[000396] In some embodiments, each $R^{Vb'}$ of R^{12b} is, independently, optionally substituted aminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl, or sulfoalkyl), optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, or optionally substituted acylaminoalkyl (e.g., substituted with an N-protecting group, such as any described herein, e.g., trifluoroacetyl). In some embodiments, the amino and/or alkyl of the optionally substituted aminoalkyl is substituted with one or more of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted sulfoalkyl, optionally substituted carboxy (e.g., substituted with an *O*-protecting group), optionally substituted hydroxy (e.g., substituted with an *O*-protecting group), optionally substituted carboxyalkyl (e.g., substituted with an *O*-protecting group), optionally substituted alkoxycarbonylalkyl (e.g., substituted with an *O*-protecting group), or *N*-protecting group. In some embodiments, optionally substituted aminoalkyl is substituted with an optionally substituted sulfoalkyl or optionally substituted alkenyl. In particular embodiments, R^{12a} and $R^{Vb"}$ are both H. In particular embodiments, T^1 is O (oxo), and T^2 is S (thio) or Se (seleno).

[000397] In some embodiments, $R^{Vb'}$ is optionally substituted alkoxycarbonylalkyl or optionally substituted carbamoylalkyl.

[000398] In particular embodiments, the optional substituent for R^{12a}, R^{12b}, R^{12c}, or R^{Va} is a polyethylene glycol group (e.g., $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl); or an amino-polyethylene glycol group (e.g., $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl).

[000399] In some embodiments, B is a modified cytosine. Exemplary modified cytosines include compounds of Formula (b10)-(b14):


(b10),

(b11),

(b12),


(b13), or (b14), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

[000400] each of $T^{3'}$ and $T^{3''}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of $T^{3'}$ and $T^{3''}$ join together (e.g., as in T^3) to form O (oxo), S (thio), or Se (seleno);

[000401] each V^4 is, independently, O, S, $N(R^{Vc})_{nv}$, or $C(R^{Vc})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vc} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted alkynyloxy (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl), wherein the combination of R^{13b} and R^{Vc} can be taken together to form optionally substituted heterocyclyl;

[000402] each V^5 is, independently, $N(R^{Vd})_{nv}$, or $C(R^{Vd})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vd} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted alkynyloxy (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl) (e.g., V^5 is –CH or N);

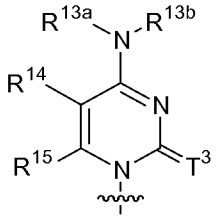
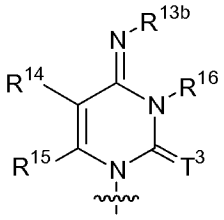
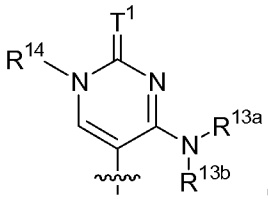
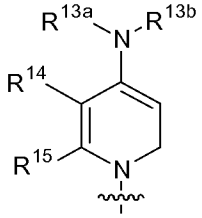
[000403] each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted

alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

[000404] each R^{14} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl (e.g., substituted with an *O*-protecting group), optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted acyloxyalkyl, optionally substituted amino (e.g., -NHR, wherein R is H, alkyl, aryl, or phosphoryl), azido, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkyl; and

[000405] each of R^{15} and R^{16} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[000406] Further exemplary modified cytosines include those having Formula (b32)-(b35):


(b32),

(b33),

(b34), or

(b35), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000407] wherein

[000408] each of T^1 and T^3 is, independently, O (oxo), S (thio), or Se (seleno);

[000409] each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted

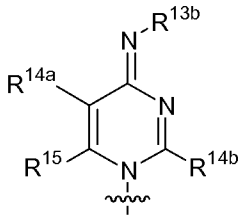
alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

[000410] each R^{14} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl (e.g., substituted with an *O*-protecting group), optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted acyloxyalkyl, optionally substituted amino (e.g., -NHR, wherein R is H, alkyl, aryl, or phosphoryl), azido, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted aminoalkyl (e.g., hydroxyalkyl, alkyl, alkenyl, or alkynyl), optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl; and

[000411] each of R^{15} and R^{16} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl (e.g., R^{15} is H, and R^{16} is H or optionally substituted alkyl).

[000412] In some embodiments, R^{15} is H, and R^{16} is H or optionally substituted alkyl. In particular embodiments, R^{14} is H, acyl, or hydroxyalkyl. In some embodiments, R^{14} is halo. In some embodiments, both R^{14} and R^{15} are H. In some embodiments, both R^{15} and R^{16} are H. In some embodiments, each of R^{14} and R^{15} and R^{16} is H. In further embodiments, each of R^{13a} and R^{13b} is independently, H or optionally substituted alkyl.

[000413] Further non-limiting examples of modified cytosines include compounds of Formula (b36):



(b36) or a pharmaceutically acceptable salt or stereoisomer thereof,

[000414] wherein

[000415] each R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted alkoxy,

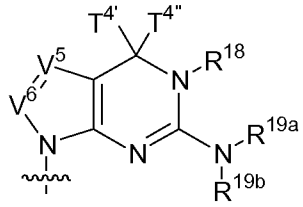
wherein the combination of R^{13b} and R^{14b} can be taken together to form optionally substituted heterocyclyl;

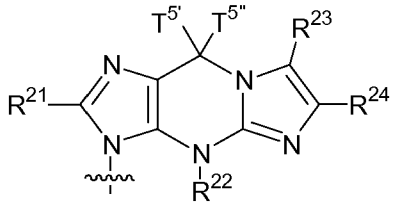
[000416] each R^{14a} and R^{14b} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl (e.g., substituted with an *O*-protecting group), optionally substituted hydroxyalkenyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted acyloxyalkyl, optionally substituted amino (e.g., -NHR, wherein R is H, alkyl, aryl, phosphoryl, optionally substituted aminoalkyl, or optionally substituted carboxyaminoalkyl), azido, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl; and

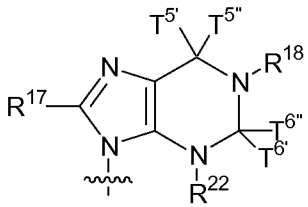
[000417] each of R^{15} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[000418] In particular embodiments, R^{14b} is an optionally substituted amino acid (e.g., optionally substituted lysine). In some embodiments, R^{14a} is H.

[000419] In some embodiments, B is a modified guanine. Exemplary modified guanines include compounds of Formula (b15)-(b17):


(b15),


(b16), or


(b17), or a pharmaceutically acceptable salt or stereoisomer thereof,

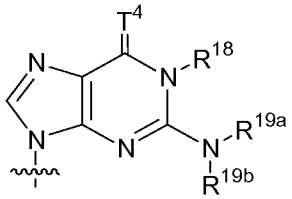
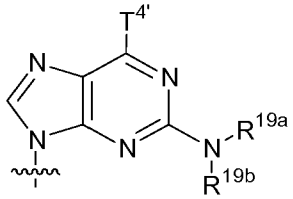
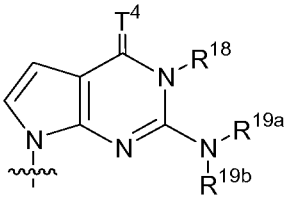
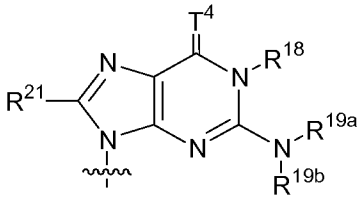
[000420] wherein

[000421] each of $T^{4'}$, $T^{4''}$, $T^{5'}$, $T^{5''}$, $T^{6'}$, and $T^{6''}$ is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy, and wherein the combination of $T^{4'}$ and $T^{4''}$ (e.g., as in T^4) or the combination of $T^{5'}$ and $T^{5''}$ (e.g., as in T^5) or the combination of $T^{6'}$ and $T^{6''}$ (e.g., as in T^6) join together form O (oxo), S (thio), or Se (seleno);

[000422] each of V^5 and V^6 is, independently, O, S, $N(R^{Vd})_{nv}$, or $C(R^{Vd})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vd} is, independently, H, halo, thiol, optionally substituted amino acid, cyano, amidine, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl) , optionally substituted thioalkoxy, or optionally substituted amino; and

[000423] each of R^{17}, R^{18}, R^{19a}, R^{19b}, R^{21}, R^{22}, R^{23}, and R^{24} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, optionally substituted amino, or optionally substituted amino acid.

[000424] Exemplary modified guanosines include compounds of Formula (b37)-(b40):


(b37),

(b38),

(b39),

or (b40), or a pharmaceutically acceptable salt or stereoisomer thereof,

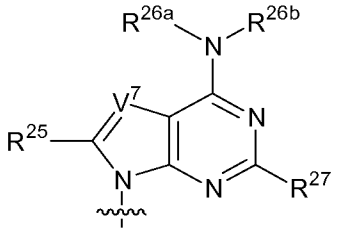
[000425] wherein

[000426] each of $T^{4'}$ is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy, and each T^4 is, independently, O (oxo), S (thio), or Se (seleno);

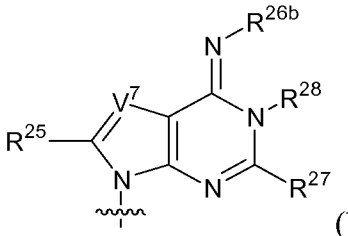
[000427] each of R^{18}, R^{19a}, R^{19b}, and R^{21} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, optionally substituted amino, or optionally substituted amino acid.

[000428] In some embodiments, R^{18} is H or optionally substituted alkyl. In further embodiments, T^4 is oxo. In some embodiments, each of R^{19a} and R^{19b} is, independently, H or optionally substituted alkyl.

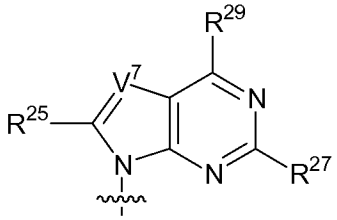
[000429] In some embodiments, B is a modified adenine. Exemplary modified adenines include compounds of Formula (b18)-(b20):



(b18),



(b19), or



(b20), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000430] wherein

[000431] each V^7 is, independently, O, S, $N(R^{Ve})_{nv}$, or $C(R^{Ve})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Ve} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy (e.g., optionally substituted with any substituent described herein, such as those selected from (1)-(21) for alkyl);

[000432] each R^{25} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, or optionally substituted amino;

[000433] each of R^{26a} and R^{26b} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally

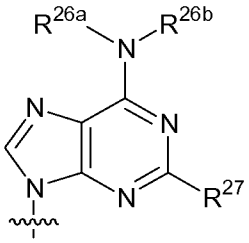
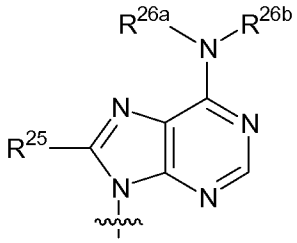
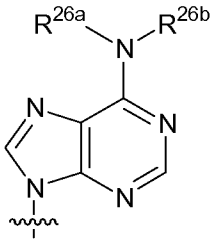
substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkoxy, or polyethylene glycol group (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl); or an amino-polyethylene glycol group (e.g., -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl);

[000434] each R^{27} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted thioalkoxy or optionally substituted amino;

[000435] each R^{28} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

[000436] each R^{29} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted alkoxy, or optionally substituted amino.

[000437] Exemplary modified adenines include compounds of Formula (b41)-(b43):

[000438]  (b41),  (b42), or  (b43), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000439] wherein

[000440] each R^{25} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, or optionally substituted amino;

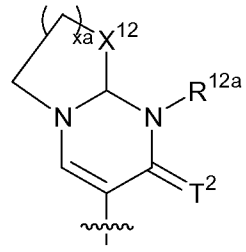
[000441] each of R^{26a} and R^{26b} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkoxy, or polyethylene glycol group (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl); or an amino-polyethylene glycol group (e.g., -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl); and

[000442] each R^{27} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted thioalkoxy, or optionally substituted amino.

[000443] In some embodiments, R^{26a} is H, and R^{26b} is optionally substituted alkyl. In some embodiments, each of R^{26a} and R^{26b} is, independently, optionally substituted alkyl. In particular embodiments, R^{27} is optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy. In other embodiments, R^{25} is optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy.

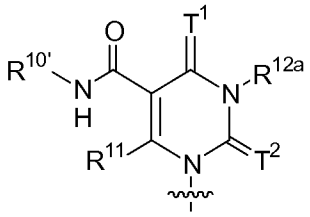
[000444] In particular embodiments, the optional substituent for R^{26a}, R^{26b}, or R^{29} is a polyethylene glycol group (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl); or an amino-polyethylene glycol group (e.g., -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl).

[000445] In some embodiments, B may have Formula (b21):



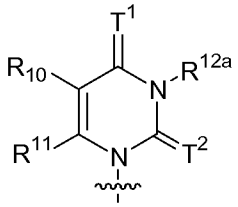
(b21), wherein X^{12} is, independently, O, S, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene, xa is an integer from 0 to 3, and R^{12a} and T^2 are as described herein.

[000446] In some embodiments, B may have Formula (b22):



(b22), wherein $R^{10'}$ is, independently, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl, and R^{11}, R^{12a}, T^1, and T^2 are as described herein.

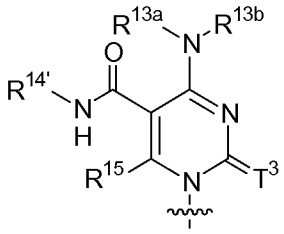
[000447] In some embodiments, B may have Formula (b23):



(b23), wherein R^{10} is optionally substituted heterocyclyl (e.g., optionally substituted furyl, optionally substitued thienyl, or optionally substitued pyrrolyl), optionally substituted aryl (e.g., optionally substituted phenyl or optionally substituted naphthyl), or any substituent described herein (e.g., for R^{10}) ;and wherein R^{11} (e.g., H or any substituent described herein), R^{12a} (e.g., H or any substituent described

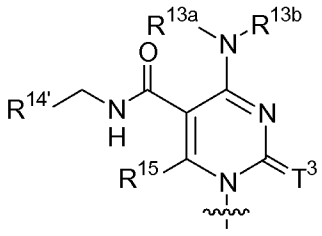
herein), T^1 (e.g., oxo or any substituent described herein), and T^2 (e.g., oxo or any substituent described herein) are as described herein.

In some embodiments, B may have Formula (b24):



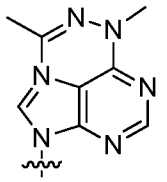
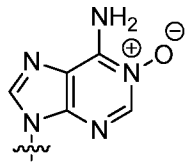
(b24), wherein $R^{14'}$ is, independently, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkaryl, optionally substituted alkheterocyclyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, optionally substituted aminoalkynyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkenyl, optionally substituted alkoxycarbonylalkynyl, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl, and R^{13a}, R^{13b}, R^{15}, and T^3 are as described herein.

[000448] In some embodiments, B may have Formula (b25):



(b25), wherein $R^{14'}$ is optionally substituted heterocyclyl (e.g., optionally substituted furyl, optionally substitued thienyl, or optionally substitued pyrrolyl), optionally substituted aryl (e.g., optionally substituted phenyl or optionally substituted naphthyl), or any substituent described herein (e.g., for R^{14} or $R^{14'}$); and wherein R^{13a} (e.g., H or any substituent described herein), R^{13b} (e.g., H or any substituent described herein), R^{15} (e.g., H or any substituent described herein), and T^3 (e.g., oxo or any substituent described herein) are as described herein.

[000449] In some embodiments, B is a nucleobase selected from the group consisting of cytosine, guanine, adenine, and uracil. In some embodiments, B may be:


(b26) or 
(b27).

[000450] In some embodiments, the modified nucleobase is a modified uracil. Exemplary nucleobases and nucleosides having a modified uracil include pseudouridine (ψ), pyridin-4-one ribonucleoside, 5-aza-uridine, 6-aza-uridine, 2-thio-5-aza-uridine, 2-thio-uridine (s^2U), 4-thio-uridine (s^4U), 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxy-uridine (ho^5U), 5-aminoallyl-uridine, 5-halo-uridine (e.g., 5-iodo-uridine or 5-bromo-uridine), 3-methyl-uridine (m^3U), 5-methoxy-uridine (mo^5U), uridine 5-oxyacetic acid (cmo^5U), uridine 5-oxyacetic acid methyl ester ($mcmo^5U$), 5-carboxymethyl-uridine (cm^5U), 1-carboxymethyl-pseudouridine, 5-carboxyhydroxymethyl-uridine (chm^5U), 5-carboxyhydroxymethyl-uridine methyl ester ($mchm^5U$), 5-methoxycarbonylmethyl-uridine (mcm^5U), 5-methoxycarbonylmethyl-2-thio-uridine (mcm^5s^2U), 5-aminomethyl-2-thio-uridine (nm^5s^2U), 5-methylaminomethyl-uridine (mnm^5U), 5-methylaminomethyl-2-thio-uridine (mnm^5s^2U), 5-methylaminomethyl-2-seleno-uridine (mnm^5se^2U), 5-carbamoylmethyl-uridine (ncm^5U), 5-carboxymethylaminomethyl-uridine ($cmnm^5U$), 5-carboxymethylaminomethyl-2-thio-uridine ($cmnm^5s^2U$), 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyl-uridine (τm^5U), 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine(τm^5s^2U), 1-taurinomethyl-4-thio-pseudouridine, 5-methyl-uridine (m^5U, i.e., having the nucleobase deoxythymine), 1-methylpseudouridine ($m^1\psi$), 5-methyl-2-thio-uridine (m^5s^2U), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine (D), dihydropseudouridine, 5,6-dihydrouridine, 5-methyl-dihydrouridine (m^5D), 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxy-uridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine (also known as 1-methylpseudouridine ($m^1\psi$)), 3-(3-amino-3-carboxypropyl)uridine (acp^3U), 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\psi$), 5-(isopentenylaminomethyl)uridine (inm^5U), 5-(isopentenylaminomethyl)-2-thio-uridine (inm^5s^2U), α-thio-uridine, 2′-O-methyl-uridine (Um), 5,2′-O-dimethyl-

uridine (m^5Um), 2′-O-methyl-pseudouridine (ψm), 2-thio-2′-O-methyl-uridine (s^2Um), 5-methoxycarbonylmethyl-2′-O-methyl-uridine (mcm^5Um), 5-carbamoylmethyl-2′-O-methyl-uridine (ncm^5Um), 5-carboxymethylaminomethyl-2′-O-methyl-uridine ($cmnm^5Um$), 3,2′-O-dimethyl-uridine (m^3Um), 5-(isopentenylaminomethyl)-2′-O-methyl-uridine (inm^5Um), 1-thio-uridine, deoxythymidine, 2'-F-ara-uridine, 2'-F-uridine, 2'-OH-ara-uridine, 5-(2-carbomethoxyvinyl) uridine, and 5-[3-(1-E-propenylamino)uridine.

[000451] In some embodiments, the modified nucleobase is a modified cytosine. Exemplary nucleobases and nucleosides having a modified cytosine include 5-aza-cytidine, 6-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine (m^3C), N4-acetyl-cytidine (ac^4C), 5-formyl-cytidine (f^5C), N4-methyl-cytidine (m^4C), 5-methyl-cytidine (m^5C), 5-halo-cytidine (e.g., 5-iodo-cytidine), 5-hydroxymethyl-cytidine (hm^5C), 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine (s^2C), 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, lysidine (k_2C), α-thio-cytidine, 2′-O-methyl-cytidine (Cm), 5,2′-O-dimethyl-cytidine (m^5Cm), N4-acetyl-2′-O-methyl-cytidine (ac^4Cm), N4,2′-O-dimethyl-cytidine (m^4Cm), 5-formyl-2′-O-methyl-cytidine (f^5Cm), N4,N4,2′-O-trimethyl-cytidine ($m^4{}_2Cm$), 1-thio-cytidine, 2'-F-ara-cytidine, 2'-F-cytidine, and 2'-OH-ara-cytidine.

[000452] In some embodiments, the modified nucleobase is a modified adenine. Exemplary nucleobases and nucleosides having a modified adenine include 2-amino-purine, 2, 6-diaminopurine, 2-amino-6-halo-purine (e.g., 2-amino-6-chloro-purine), 6-halo-purine (e.g., 6-chloro-purine), 2-amino-6-methyl-purine, 8-azido-adenosine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-amino-purine, 7-deaza-8-aza-2-amino-purine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyl-adenosine (m^1A), 2-methyl-adenine (m^2A), N6-methyl-adenosine (m^6A), 2-methylthio-N6-methyl-adenosine (ms^2m^6A), N6-isopentenyl-adenosine (i^6A), 2-methylthio-N6-isopentenyl-adenosine (ms^2i^6A), N6-(cis-hydroxyisopentenyl)adenosine (io^6A), 2-

methylthio-N6-(cis-hydroxyisopentenyl)adenosine (ms^2io^6A), N6-glycinylcarbamoyl-adenosine (g^6A), N6-threonylcarbamoyl-adenosine (t^6A), N6-methyl-N6-threonylcarbamoyl-adenosine (m^6t^6A), 2-methylthio-N6-threonylcarbamoyl-adenosine (ms^2g^6A), N6,N6-dimethyl-adenosine ($m^6{}_2A$), N6-hydroxynorvalylcarbamoyl-adenosine (hn^6A), 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine (ms^2hn^6A), N6-acetyl-adenosine (ac^6A), 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, α-thio-adenosine, 2′-O-methyl-adenosine (Am), N6,2′-O-dimethyl-adenosine (m^6Am), N6,N6,2′-O-trimethyl-adenosine ($m^6{}_2Am$), 1,2′-O-dimethyl-adenosine (m^1Am), 2′-O-ribosyladenosine (phosphate) (Ar(p)), 2-amino-N6-methyl-purine, 1-thio-adenosine, 8-azido-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino-pentaoxanonadecyl)-adenosine.

[000453] In some embodiments, the modified nucleobase is a modified guanine. Exemplary nucleobases and nucleosides having a modified guanine include inosine (I), 1-methyl-inosine (m^1I), wyosine (imG), methylwyosine (mimG), 4-demethyl-wyosine (imG-14), isowyosine (imG2), wybutosine (yW), peroxywybutosine (o_2yW), hydroxywybutosine (OHyW), undermodified hydroxywybutosine (OHyW*), 7-deaza-guanosine, queuosine (Q), epoxyqueuosine (oQ), galactosyl-queuosine (galQ), mannosyl-queuosine (manQ), 7-cyano-7-deaza-guanosine ($preQ_0$), 7-aminomethyl-7-deaza-guanosine ($preQ_1$), archaeosine (G^+), 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine (m^7G), 6-thio-7-methyl-guanosine, 7-methyl-inosine, 6-methoxy-guanosine, 1-methyl-guanosine (m^1G), N2-methyl-guanosine (m^2G), N2,N2-dimethyl-guanosine ($m^2{}_2G$), N2,7-dimethyl-guanosine ($m^{2,7}G$), N2, N2,7-dimethyl-guanosine ($m^{2,2,7}G$), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, N2,N2-dimethyl-6-thio-guanosine, α-thio-guanosine, 2′-O-methyl-guanosine (Gm), N2-methyl-2′-O-methyl-guanosine (m^2Gm), N2,N2-dimethyl-2′-O-methyl-guanosine ($m^2{}_2Gm$), 1-methyl-2′-O-methyl-guanosine (m^1Gm), N2,7-dimethyl-2′-O-methyl-guanosine ($m^{2,7}Gm$), 2′-O-methyl-inosine (Im), 1,2′-O-dimethyl-inosine (m^1Im), and 2′-O-ribosylguanosine (phosphate) (Gr(p)).

[000454] The nucleobase of the nucleotide can be independently selected from a purine, a pyrimidine, a purine or pyrimidine analog. For example, the nucleobase can each be

independently selected from adenine, cytosine, guanine, uracil, or hypoxanthine. In another embodiment, the nucleobase can also include, for example, naturally-occurring and synthetic derivatives of a base, including pyrazolo[3,4-d]pyrimidines, 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo (*e.g.,* 8-bromo), 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, deazaguanine, 7-deazaguanine, 3-deazaguanine, deazaadenine, 7-deazaadenine, 3-deazaadenine, pyrazolo[3,4-d]pyrimidine, imidazo[1,5-a]1,3,5 triazinones, 9-deazapurines, imidazo[4,5-d]pyrazines, thiazolo[4,5-d]pyrimidines, pyrazin-2-ones, 1,2,4-triazine, pyridazine; and 1,3,5 triazine. When the nucleotides are depicted using the shorthand A, G, C, T or U, each letter refers to the representative base and/or derivatives thereof, *e.g.*, A includes adenine or adenine analogs, *e.g.,* 7-deaza adenine).

Modifications on the Internucleoside Linkage

[000455] The modified nucleotides, which may be incorporated into a polynucleotide, primary construct, or mmRNA molecule, can be modified on the internucleoside linkage (e.g., phosphate backbone). Herein, in the context of the polynucleotide backbone, the phrases "phosphate" and "phosphodiester" are used interchangeably. Backbone phosphate groups can be modified by replacing one or more of the oxygen atoms with a different substituent. Further, the modified nucleosides and nucleotides can include the wholesale replacement of an unmodified phosphate moiety with another internucleoside linkage as described herein. Examples of modified phosphate groups include, but are not limited to, phosphorothioate, phosphoroselenates, boranophosphates,boranophosphate esters, hydrogen phosphonates, phosphoramidates, phosphorodiamidates, alkyl or aryl phosphonates, and phosphotriesters. Phosphorodithioates have both non-linking oxygens replaced by sulfur. The phosphate linker can also be modified by the replacement of a

linking oxygen with nitrogen (bridged phosphoramidates), sulfur (bridged phosphorothioates), and carbon (bridged methylene-phosphonates).

[000456] The α-thio substituted phosphate moiety is provided to confer stability to RNA and DNA polymers through the unnatural phosphorothioate backbone linkages. Phosphorothioate DNA and RNA have increased nuclease resistance and subsequently a longer half-life in a cellular environment. Phosphorothioate linked polynucleotides, primary constructs, or mmRNA molecules are expected to also reduce the innate immune response through weaker binding/activation of cellular innate immune molecules.

[000457] In specific embodiments, a modified nucleoside includes an alpha-thio-nucleoside (e.g., 5′-O-(1-thiophosphate)-adenosine, 5′-O-(1-thiophosphate)-cytidine (α-thio-cytidine), 5′-O-(1-thiophosphate)-guanosine, 5′-O-(1-thiophosphate)-uridine, or 5′-O-(1-thiophosphate)-pseudouridine).

[000458] Other internucleoside linkages that may be employed according to the present invention, including internucleoside linkages which do not contain a phosphorous atom, are described herein below.

Combinations of Modified Sugars, Nucleobases, and Internucleoside Linkages

[000459] The polynucleotides, primary constructs, and mmRNA of the invention can include a combination of modifications to the sugar, the nucleobase, and/or the internucleoside linkage. These combinations can include any one or more modifications described herein. For examples, any of the nucleotides described herein in Formulas (Ia), (Ia-1)-(Ia-3), (Ib)-(If), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr) can be combined with any of the nucleobases described herein (e.g., in Formulas (b1)-(b43) or any other described herein).

Synthesis of Polypeptides, Primary Constructs, and mmRNA Molecules

[000460] The polypeptides, primary constructs, and mmRNA molecules for use in accordance with the invention may be prepared according to any useful technique, as described herein. The modified nucleosides and nucleotides used in the synthesis of polynucleotides, primary constructs, and mmRNA molecules disclosed herein can be prepared from readily available starting materials using the following general methods and procedures. Where typical or preferred process conditions (e.g., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are provided, a

skilled artisan would be able to optimize and develop additional process conditions. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[000461] The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C) infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry, or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography.

[000462] Preparation of polypeptides, primary constructs, and mmRNA molecules of the present invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Greene, et al., *Protective Groups in Organic Synthesis*, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

[000463] The reactions of the processes described herein can be carried out in suitable solvents, which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially nonreactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected.

[000464] Resolution of racemic mixtures of modified nucleosides and nucleotides can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallization using a "chiral resolving acid" which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or

the various optically active camphorsulfonic acids. Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Modified nucleosides and nucleotides (e.g., building block molecules) can be prepared according to the synthetic methods described in Ogata et al., J. Org. Chem. 74:2585-2588 (2009); Purmal et al., Nucl. Acids Res. 22(1): 72-78, (1994); Fukuhara et al., Biochemistry, 1(4): 563-568 (1962); and Xu et al., Tetrahedron, 48(9): 1729-1740 (1992), each of which are incorporated by reference in their entirety.

[000465] The polypeptides, primary constructs, and mmRNA of the invention may or may not be uniformly modified along the entire length of the molecule. For example, one or more or all types of nucleotide (*e.g.*, purine or pyrimidine, or any one or more or all of A, G, U, C) may or may not be uniformly modified in a polynucleotide of the invention, or in a given predetermined sequence region thereof (*e.g.* one or more of the sequence regions represented in Figure 1). In some embodiments, all nucleotides X in a polynucleotide of the invention (or in a given sequence region thereof) are modified, wherein X may any one of nucleotides A, G, U, C, or any one of the combinations A+G, A+U, A+C, G+U, G+C, U+C, A+G+U, A+G+C, G+U+C or A+G+C.

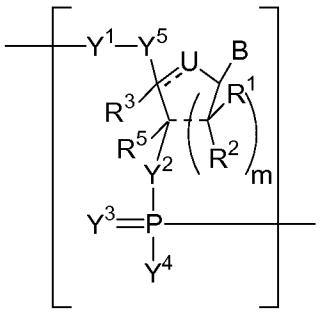
[000466] Different sugar modifications, nucleotide modifications, and/or internucleoside linkages (e.g., backbone structures) may exist at various positions in the polynucleotide, primary construct, or mmRNA. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a polynucleotide, primary construct, or mmRNA such that the function of the polynucleotide, primary construct, or mmRNA is not substantially decreased. A modification may also be a 5′ or 3′ terminal modification. The polynucleotide, primary construct, or mmRNA may contain from about 1% to about 100% modified nucleotides (either in relation to overall nucleotide content, or in relation to one or more types of nucleotide, i.e. any one or more of A, G, U or C) or any intervening percentage (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from

10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100%).

[000467] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a modified pyrimidine (e.g., a modified uracil/uridine/U or modified cytosine/cytidine/C). In some embodiments, the uracil or uridine (generally: U) in the polynucleotide, primary construct, or mmRNA molecule may be replaced with from about 1% to about 100% of a modified uracil or modified uridine (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from 20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100% of a modified uracil or modified uridine). The modified uracil or uridine can be replaced by a compound having a single unique structure or by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures, as described herein). In some embodiments, the cytosine or cytidine (generally: C) in the polynucleotide, primary construct, or mmRNA molecule may be replaced with from about 1% to about 100% of a modified cytosine or modified cytidine (e.g., from 1% to 20%, from 1% to 25%, from 1% to 50%, from 1% to 60%, from 1% to 70%, from 1% to 80%, from 1% to 90%, from 1% to 95%, from 10% to 20%, from 10% to 25%, from 10% to 50%, from 10% to 60%, from 10% to 70%, from 10% to 80%, from 10% to 90%, from 10% to 95%, from 10% to 100%, from 20% to 25%, from 20% to 50%, from 20% to 60%, from 20% to 70%, from

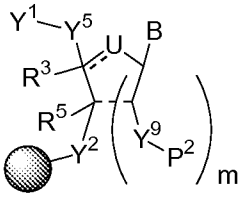
20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, from 90% to 100%, and from 95% to 100% of a modified cytosine or modified cytidine). The modified cytosine or cytidine can be replaced by a compound having a single unique structure or by a plurality of compounds having different structures (e.g., 2, 3, 4 or more unique structures, as described herein).

In some embodiments, the present disclosure provides methods of synthesizing a polynucleotide, primary construct, or mmRNA (e.g., the first region, first flanking region, or second flanking region) including n number of linked nucleosides having Formula (Ia-1):



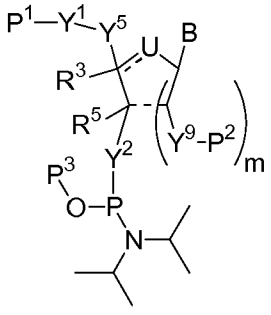
(Ia-1), comprising:

a) reacting a nucleotide of Formula (IV-1):



(IV-1),

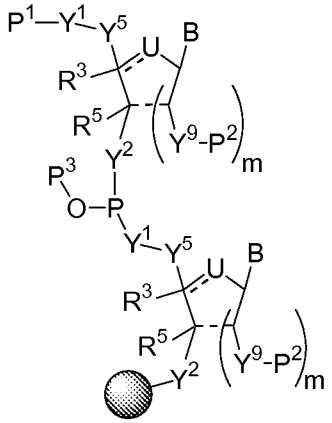
with a phosphoramidite compound of Formula (V-1):



(V-1),

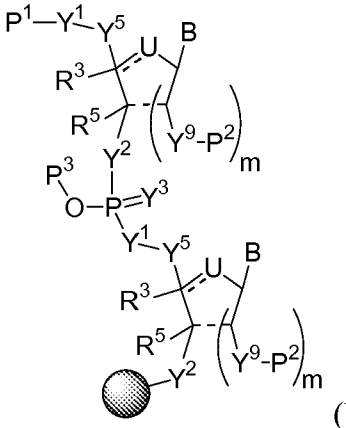
wherein Y^9 is H, hydroxy, phosphoryl, pyrophosphate, sulfate, amino, thiol, optionally substituted amino acid, or a peptide (e.g., including from 2 to 12 amino acids); and each P^1, P^2, and P^3 is, independently, a suitable protecting group; and  denotes a solid support;

to provide a polynucleotide, primary construct, or mmRNA of Formula (VI-1):



(VI-1), and

b) oxidizing or sulfurizing the polynucleotide, primary construct, or mmRNA of Formula (V) to yield a polynucleotide, primary construct, or mmRNA of Formula (VII-1):



(VII-1), and

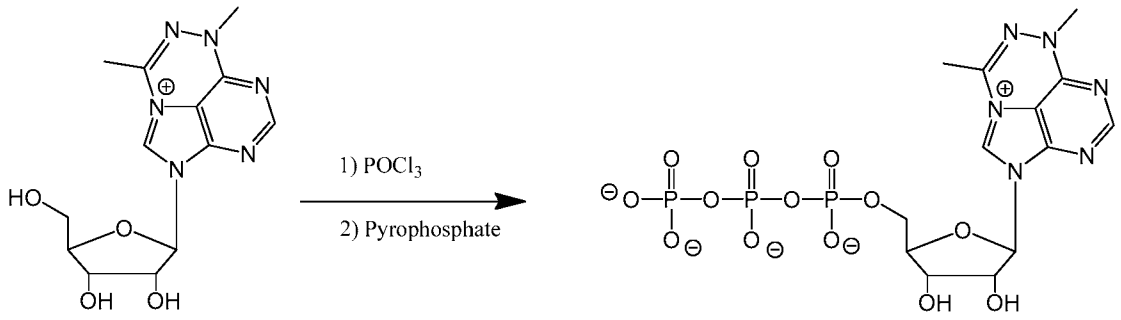
c) removing the protecting groups to yield the polynucleotide, primary construct, or mmRNA of Formula (Ia).

[000468] In some embodiments, steps a) and b) are repeated from 1 to about 10,000 times. In some embodiments, the methods further comprise a nucleotide (e.g., mmRNA molecule) selected from the group consisting of A, C, G and U adenosine, cytosine, guanosine, and uracil. In some embodiments, the nucleobase may be a pyrimidine or derivative thereof. In some embodiments, the polynucleotide, primary construct, or mmRNA is translatable.

[000469] Other components of polynucleotides, primary constructs, and mmRNA are optional, and are beneficial in some embodiments. For example, a 5′ untranslated region (UTR) and/or a 3′UTR are provided, wherein either or both may independently contain one or more different nucleotide modifications. In such embodiments, nucleotide modifications may also be present in the translatable region. Also provided are polynucleotides, primary constructs, and mmRNA containing a Kozak sequence.

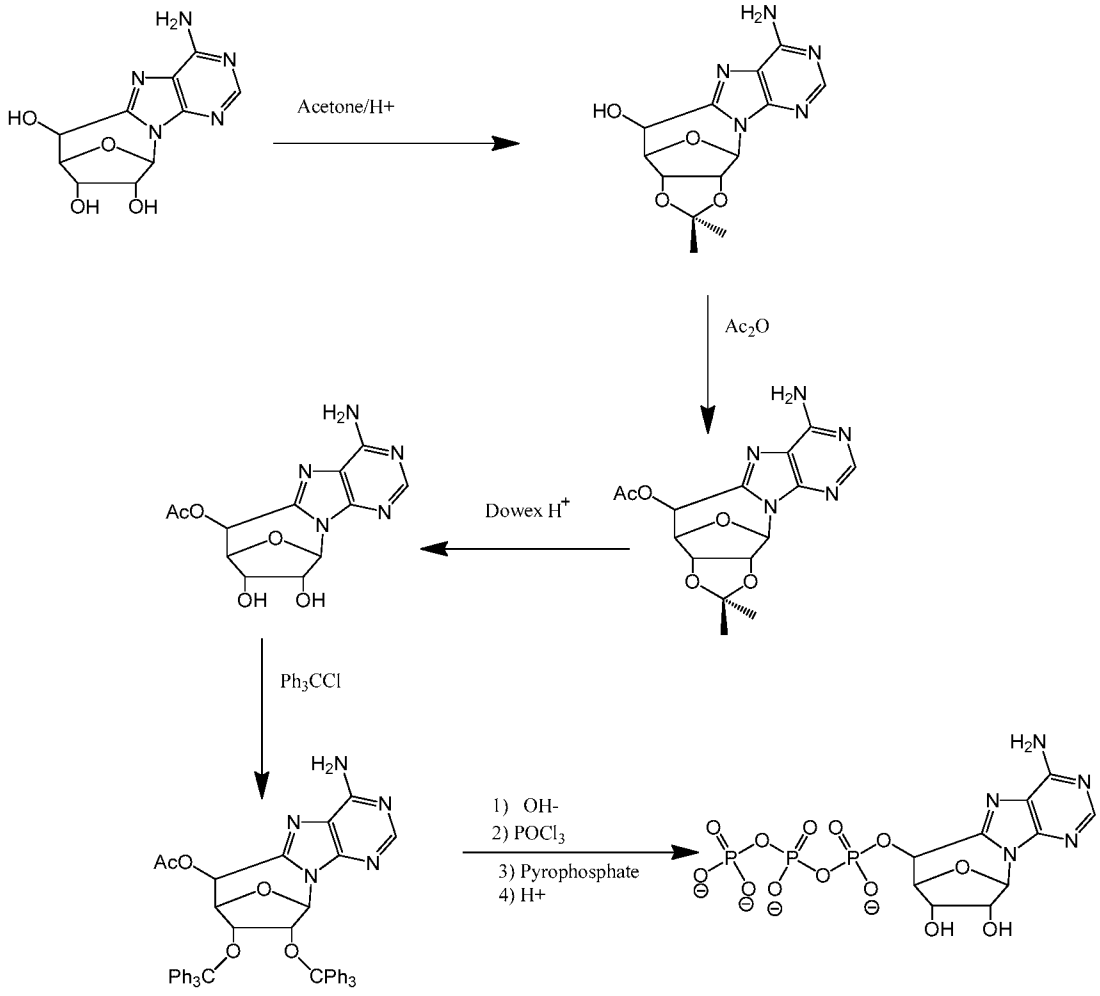
[000470] Exemplary syntheses of modified nucleotides, which are incorporated into a modified nucleic acid or mmRNA, e.g., RNA or mRNA, are provided below in Scheme 1 through Scheme 11. Scheme 1 provides a general method for phosphorylation of nucleosides, including modified nucleosides.

Scheme 1



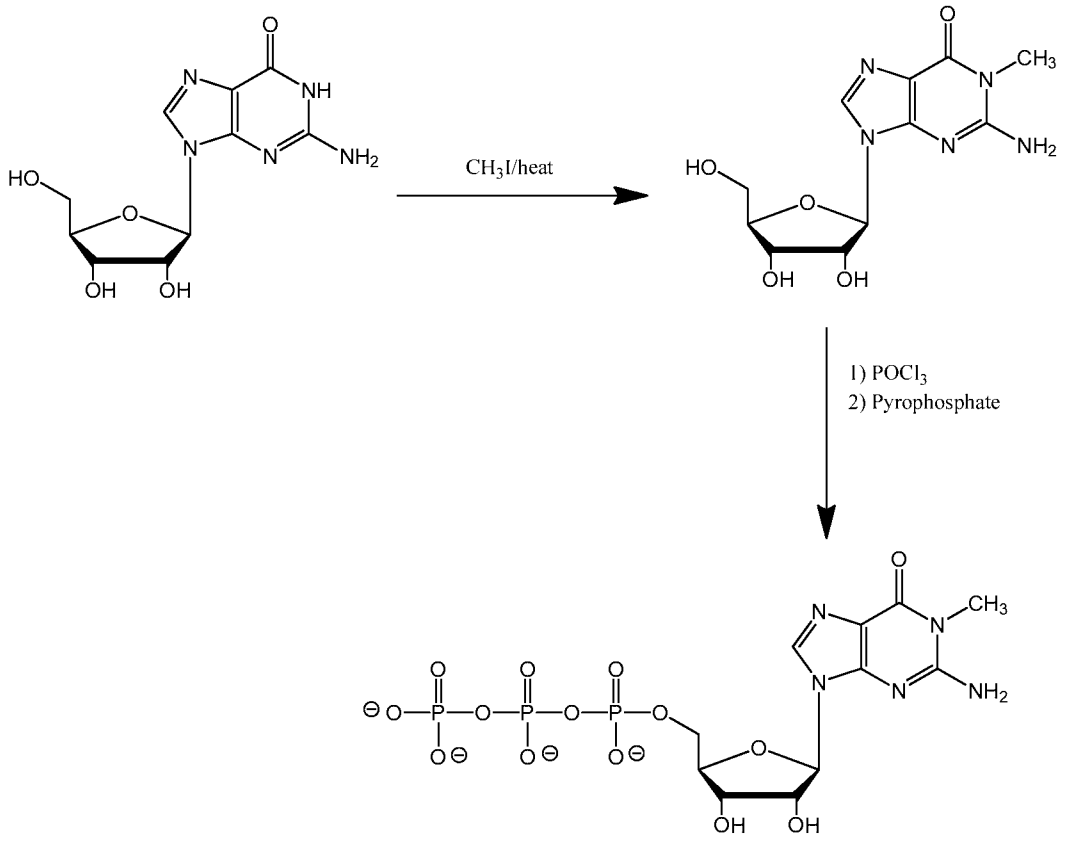
[000471] Various protecting groups may be used to control the reaction. For example, Scheme 2 provides the use of multiple protecting and deprotecting steps to promote phosphorylation at the 5′ position of the sugar, rather than the 2′ and 3′ hydroxyl groups.

Scheme 2

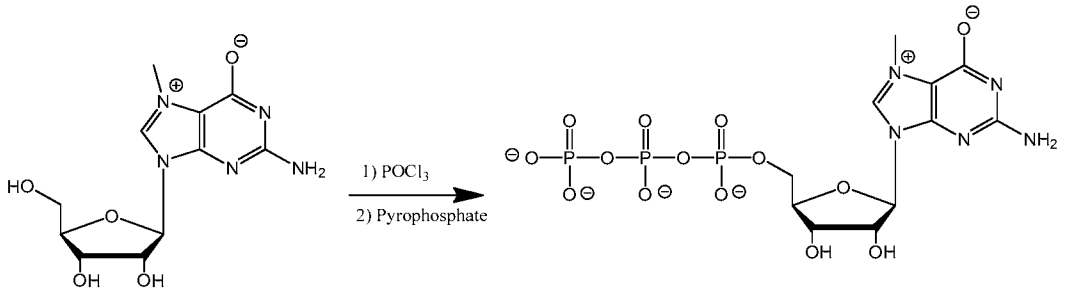


[000472] Modified nucleotides can be synthesized in any useful manner. Schemes 3, 4, and 7 provide exemplary methods for synthesizing modified nucleotides having a modified purine nucleobase; and Schemes 5 and 6 provide exemplary methods for synthesizing modified nucleotides having a modified pseudouridine or pseudoisocytidine, respectively.

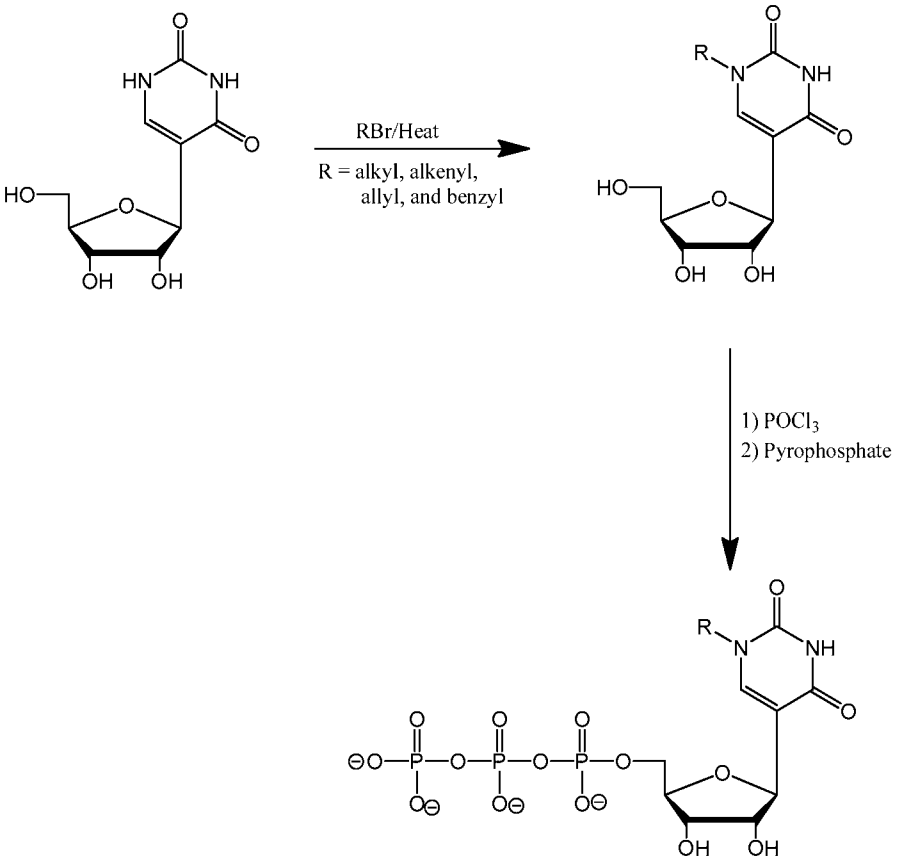
Scheme 3



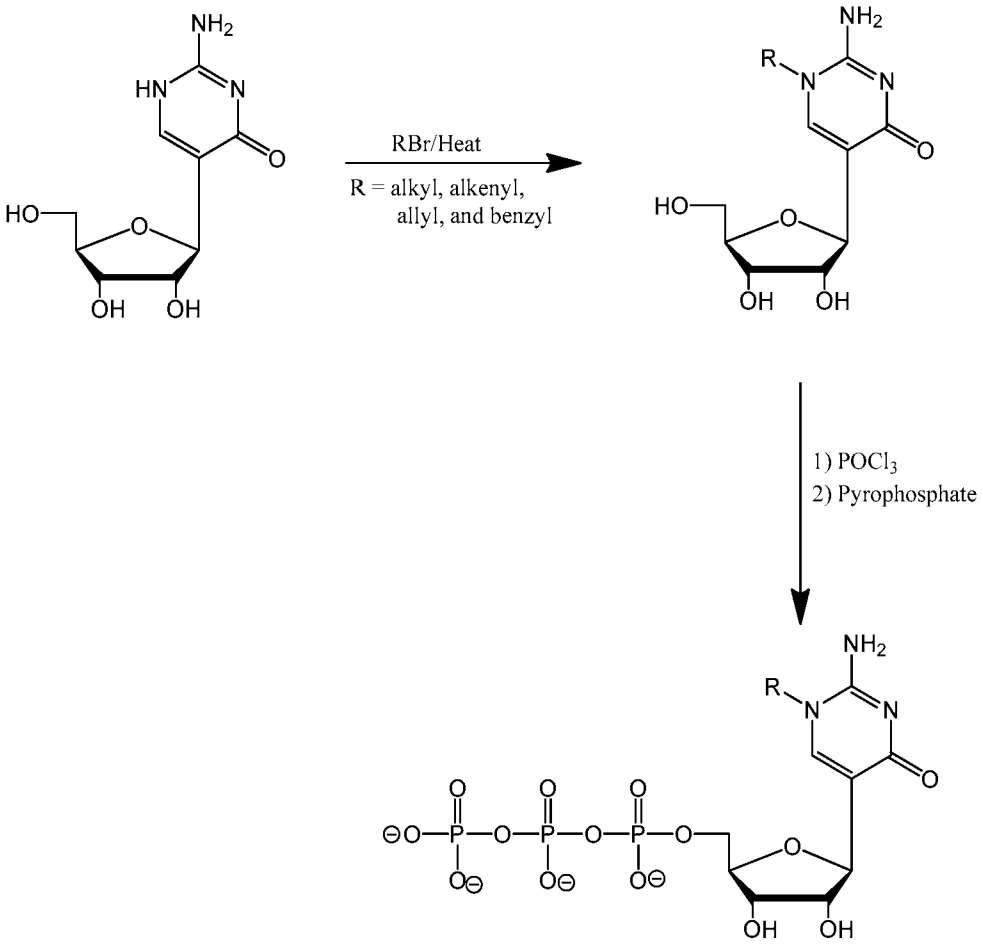
Scheme 4



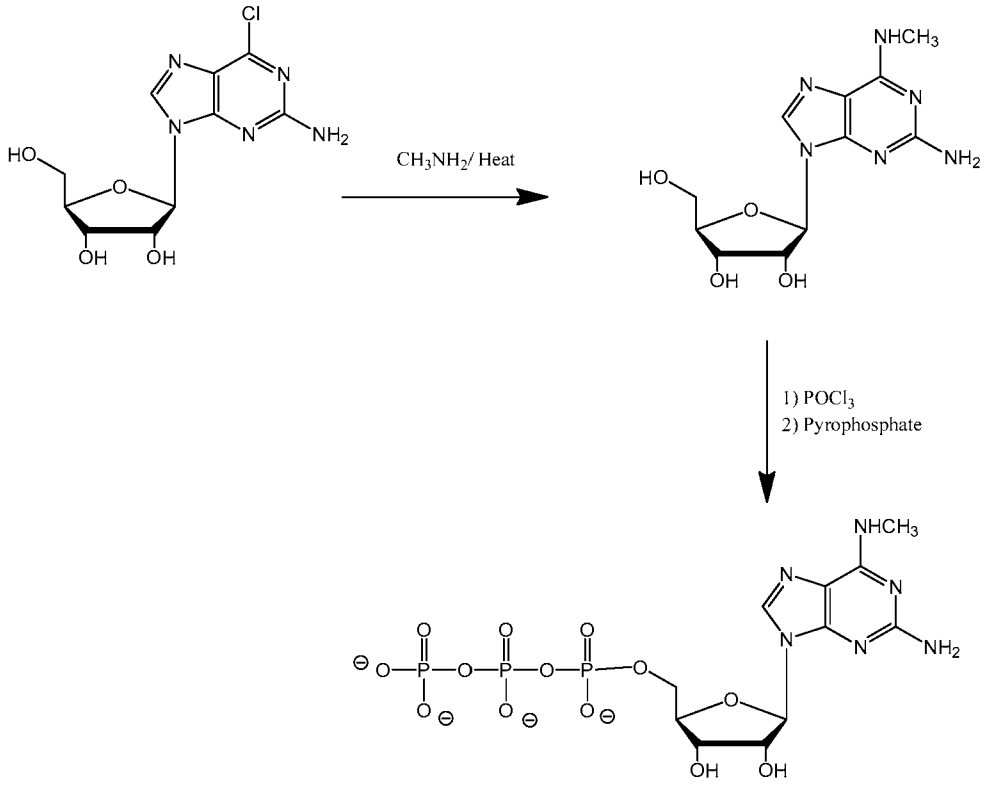
Scheme 5


RBr/Heat
R = alkyl, alkenyl,
allyl, and benzyl
1) POCl3
2) Pyrophosphate

Scheme 6

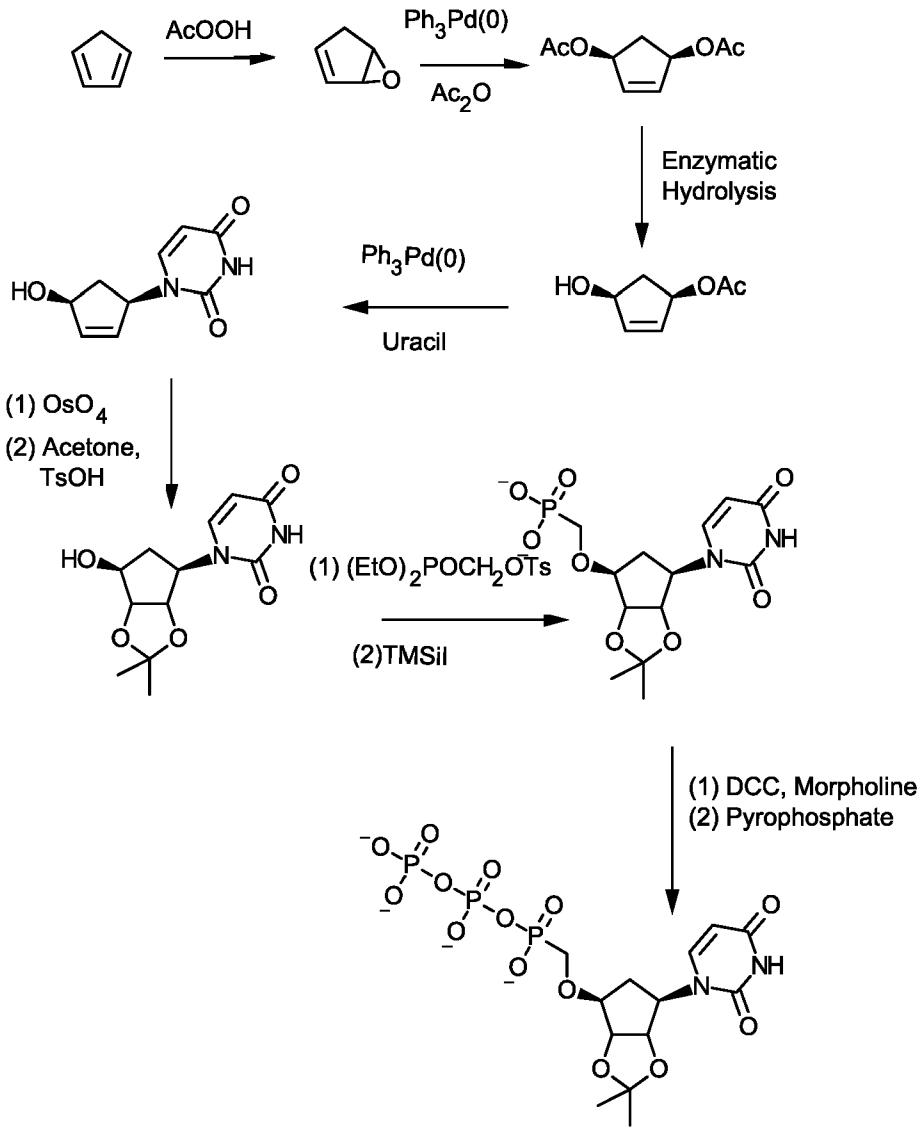

NH2
HN
N
O
HO
O
OH
OH
RBr/Heat
R = alkyl, alkenyl,
allyl, and benzyl
R
1) POCl3
2) Pyrophosphate
⊖O
P
O⊖

Scheme 7

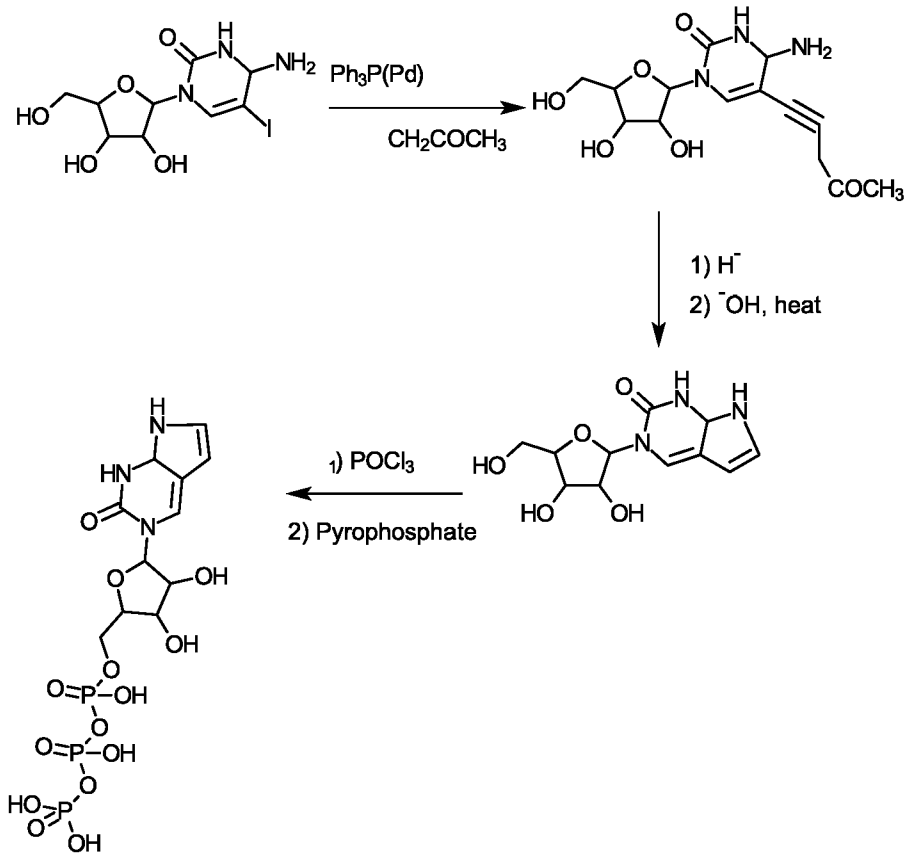


[000473] Schemes 8 and 9 provide exemplary syntheses of modified nucleotides. Scheme 10 provides a non-limiting biocatalytic method for producing nucleotides.

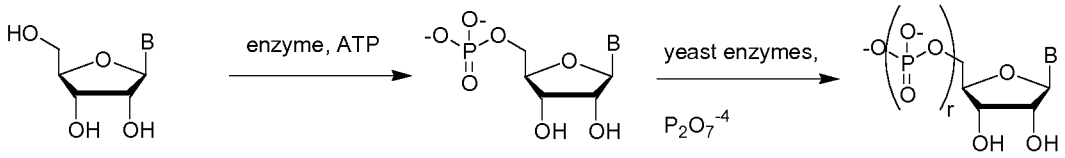
Scheme 8


AcOOH
Ph3Pd(0)
Ac2O
AcO
OAc
Enzymatic
Hydrolysis
HO
OAc
Ph3Pd(0)
Uracil
HO
NH
(1) OsO4
(2) Acetone,
TsOH
(1) (EtO)2POCH2OTs
(2)TMSiI
(1) DCC, Morpholine
(2) Pyrophosphate

Scheme 9



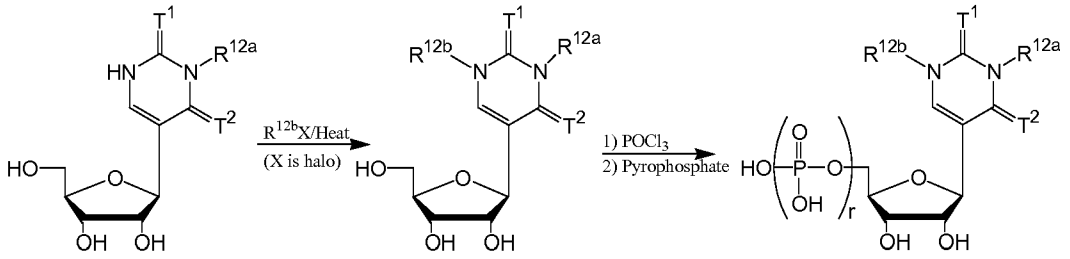
Scheme 10



[000474] Scheme 11 provides an exemplary synthesis of a modified uracil, where the N1 position is modified with R^{12b}, as provided elsewhere, and the 5′-position of ribose is phosphorylated. T^1, T^2, R^{12a}, R^{12b}, and r are as provided herein. This synthesis, as well as optimized versions thereof, can be used to modify other pyrimidine nucleobases and purine nucleobases (see e.g., Formulas (b1)-(b43)) and/or to install one or more phosphate groups (e.g., at the 5′ position of the sugar). This alkylating reaction can also be used to include one or more optionally substituted alkyl group at any reactive group

(e.g., amino group) in any nucleobase described herein (e.g., the amino groups in the Watson-Crick base-pairing face for cytosine, uracil, adenine, and guanine).

Scheme 11



Combinations of Nucleotides in mmRNA

[000475] Further examples of modified nucleotides and modified nucleotide combinations are provided below in Table 9. These combinations of modified nucleotides can be used to form the polypeptides, primary constructs, or mmRNA of the invention. Unless otherwise noted, the modified nucleotides may be completely substituted for the natural nucleotides of the modified nucleic acids or mmRNA of the invention. As a non-limiting example, the natural nucleotide uridine may be substituted with a modified nucleoside described herein. In another non-limiting example, the natural nucleotide uridine may be partially substituted (e.g., about 0.1%, 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99.9%) with at least one of the modified nucleoside disclosed herein.

Table 9

Modified Nucleotide	Modified Nucleotide Combination
α-thio-cytidine	α-thio-cytidine/5-iodo-uridine
	α-thio-cytidine/N1-methyl-pseudouridine
	α-thio-cytidine/α-thio-uridine
	α-thio-cytidine/5-methyl-uridine
	α-thio-cytidine/pseudo-uridine
	about 50% of the cytosines are α-thio-cytidine
pseudoisocytidine	pseudoisocytidine/5-iodo-uridine
	pseudoisocytidine/N1-methyl-pseudouridine
	pseudoisocytidine/α-thio-uridine
	pseudoisocytidine/5-methyl-uridine
	pseudoisocytidine/pseudouridine
	about 25% of cytosines are pseudoisocytidine
	pseudoisocytidine/about 50% of uridines are N1-methyl-pseudouridine and about 50% of uridines are pseudouridine

	pseudoisocytidine/about 25% of uridines are N1-methyl-pseudouridine and about 25% of uridines are pseudouridine
pyrrolo-cytidine	pyrrolo-cytidine/5-iodo-uridine
	pyrrolo-cytidine/N1-methyl-pseudouridine
	pyrrolo-cytidine/α-thio-uridine
	pyrrolo-cytidine/5-methyl-uridine
	pyrrolo-cytidine/pseudouridine
	about 50% of the cytosines are pyrrolo-cytidine
5-methyl-cytidine	5-methyl-cytidine/5-iodo-uridine
	5-methyl-cytidine/N1-methyl-pseudouridine
	5-methyl-cytidine/α-thio-uridine
	5-methyl-cytidine/5-methyl-uridine
	5-methyl-cytidine/pseudouridine
	about 25% of cytosines are 5-methyl-cytidine
	about 50% of cytosines are 5-methyl-cytidine
	5-methyl-cytidine/5-methoxy-uridine
	5-methyl-cytidine/5-bromo-uridine
	5-methyl-cytidine/2-thio-uridine
	5-methyl-cytidine/about 50% of uridines are 2-thio-uridine
	about 50% of uridines are 5-methyl-cytidine/ about 50% of uridines are 2-thio-uridine
N4-acetyl-cytidine	N4-acetyl-cytidine /5-iodo-uridine
	N4-acetyl-cytidine /N1-methyl-pseudouridine
	N4-acetyl-cytidine /α-thio-uridine
	N4-acetyl-cytidine /5-methyl-uridine
	N4-acetyl-cytidine /pseudouridine
	about 50% of cytosines are N4-acetyl-cytidine
	about 25% of cytosines are N4-acetyl-cytidine
	N4-acetyl-cytidine /5-methoxy-uridine
	N4-acetyl-cytidine /5-bromo-uridine
	N4-acetyl-cytidine /2-thio-uridine
	about 50% of cytosines are N4-acetyl-cytidine/ about 50% of uridines are 2-thio-uridine

[000476] Further examples of modified nucleotide combinations are provided below in Table 10. These combinations of modified nucleotides can be used to form the polypeptides, primary constructs, or mmRNA of the invention.

Table 10

Modified Nucleotide	**Modified Nucleotide Combination**
modified cytidine having one or more nucleobases of Formula (b10)	modified cytidine with (b10)/pseudouridine
	modified cytidine with (b10)/N1-methyl-pseudouridine
	modified cytidine with (b10)/5-methoxy-uridine
	modified cytidine with (b10)/5-methyl-uridine

	modified cytidine with (b10)/5-bromo-uridine
	modified cytidine with (b10)/2-thio-uridine
	about 50% of cytidine substituted with modified cytidine (b10)/ about 50% of uridines are 2-thio-uridine
modified cytidine having one or more nucleobases of Formula (b32)	modified cytidine with (b32)/pseudouridine
	modified cytidine with (b32)/N1-methyl-pseudouridine
	modified cytidine with (b32)/5-methoxy-uridine
	modified cytidine with (b32)/5-methyl-uridine
	modified cytidine with (b32)/5-bromo-uridine
	modified cytidine with (b32)/2-thio-uridine
	about 50% of cytidine substituted with modified cytidine (b32)/ about 50% of uridines are 2-thio-uridine
modified uridine having one or more nucleobases of Formula (b1)	modified uridine with (b1)/ N4-acetyl-cytidine
	modified uridine with (b1)/ 5-methyl-cytidine
modified uridine having one or more nucleobases of Formula (b8)	modified uridine with (b8)/ N4-acetyl-cytidine
	modified uridine with (b8)/ 5-methyl-cytidine
modified uridine having one or more nucleobases of Formula (b28)	modified uridine with (b28)/ N4-acetyl-cytidine
	modified uridine with (b28)/ 5-methyl-cytidine
modified uridine having one or more nucleobases of Formula (b29)	modified uridine with (b29)/ N4-acetyl-cytidine
	modified uridine with (b29)/ 5-methyl-cytidine
modified uridine having one or more nucleobases of Formula (b30)	modified uridine with (b30)/ N4-acetyl-cytidine
	modified uridine with (b30)/ 5-methyl-cytidine

[000477] In some embodiments, at least 25% of the cytosines are replaced by a compound of Formula (b10)-(b14) (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

[000478] In some embodiments, at least 25% of the uracils are replaced by a compound of Formula (b1)-(b9) (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

[000479] In some embodiments, at least 25% of the cytosines are replaced by a compound of Formula (b10)-(b14), and at least 25% of the uracils are replaced by a compound of Formula (b1)-(b9) (e.g., at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%).

IV. Pharmaceutical Compositions

Formulation, Administration, Delivery and Dosing

[000480] The present invention provides polynucleotides, primary constructs and mmRNA compositions and complexes in combination with one or more pharmaceutically acceptable excipients. Pharmaceutical compositions may optionally comprise one or more additional active substances, e.g. therapeutically and/or prophylactically active substances. General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in *Remington: The Science and Practice of Pharmacy* 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference).

[000481] In some embodiments, compositions are administered to humans, human patients or subjects. For the purposes of the present disclosure, the phrase "active ingredient" generally refers to polynucleotides, primary constructs and mmRNA to be delivered as described herein.

[000482] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, *e.g.,* to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs,

horses, sheep, cats, dogs, mice, and/or rats; and/or birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[000483] Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with an excipient and/or one or more other accessory ingredients, and then, if necessary and/or desirable, dividing, shaping and/or packaging the product into a desired single- or multi-dose unit.

[000484] A pharmaceutical composition in accordance with the invention may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[000485] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the invention will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

Formulations

[000486] The polynucleotide, primary construct, and mmRNA of the invention can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit the sustained or delayed release (e.g., from a depot formulation of the polynucleotide, primary construct, or mmRNA); (4) alter the biodistribution (e.g., target the polynucleotide, primary construct, or mmRNA to specific tissues or cell types); (5) increase the translation of encoded protein *in vivo*; and/or (6) alter the release profile of encoded protein in vivo. In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension

aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, excipients of the present invention can include, without limitation, lipidoids, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, cells transfected with polynucleotide, primary construct, or mmRNA (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof. Accordingly, the formulations of the invention can include one or more excipients, each in an amount that together increases the stability of the polynucleotide, primary construct, or mmRNA, increases cell transfection by the polynucleotide, primary construct, or mmRNA, increases the expression of polynucleotide, primary construct, or mmRNA encoded protein, and/or alters the release profile of polynucleotide, primary construct, or mmRNA encoded proteins. Further, the primary construct and mmRNA of the present invention may be formulated using self-assembled nucleic acid nanoparticles.

[000487] Formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[000488] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" refers to a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient may generally be equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage including, but not limited to, one-half or one-third of such a dosage.

[000489] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may comprise between 0.1% and 99% (w/w) of the active ingredient.

[000490] In some embodiments, the formulations described herein may contain at least one mmRNA. As a non-limiting example, the formulations may contain 1, 2, 3, 4 or 5 mmRNA. In one embodiment the formulation may contain modified mRNA encoding proteins selected from categories such as, but not limited to, human proteins, veterinary proteins, bacterial proteins, biological proteins, antibodies, immunogenic proteins, therapeutic peptides and proteins, secreted proteins, plasma membrane proteins, cytoplasmic and cytoskeletal proteins, intrancellular membrane bound proteins, nuclear proteins, proteins associated with human disease and/or proteins associated with non-human diseases. In one embodiment, the formulation contains at least three modified mRNA encoding proteins. In one embodiment, the formulation contains at least five modified mRNA encoding proteins.

[000491] Pharmaceutical formulations may additionally comprise a pharmaceutically acceptable excipient, which, as used herein, includes, but is not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparing the composition are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of a conventional excipient medium may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient medium may be incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition.

[000492] In some embodiments, the particle size of the lipid nanoparticle may be increased and/or decreased. The change in particle size may be able to help counter biological reaction such as, but not limited to, inflammation or may increase the biological effect of the modified mRNA delivered to mammals.

[000493] Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, surface active

agents and/or emulsifiers, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in the pharmaceutical formulations of the invention.

Lipidoids

[000494] The synthesis of lipidoids has been extensively described and formulations containing these compounds are particularly suited for delivery of polynucleotides, primary constructs or mmRNA (see Mahon et al., Bioconjug Chem. 2010 21:1448-1454; Schroeder et al., J Intern Med. 2010 267:9-21; Akinc et al., Nat Biotechnol. 2008 26:561-569; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-3001; all of which are incorporated herein in their entireties).

[000495] While these lipidoids have been used to effectively deliver double stranded small interfering RNA molecules in rodents and non-human primates (see Akinc et al., Nat Biotechnol. 2008 26:561-569; Frank-Kamenetsky et al., Proc Natl Acad Sci U S A. 2008 105:11915-11920; Akinc et al., Mol Ther. 2009 17:872-879; Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869; Leuschner et al., Nat Biotechnol. 2011 29:1005-1010; all of which is incorporated herein in their entirety), the present disclosure describes their formulation and use in delivering single stranded polynucleotides, primary constructs, or mmRNA. Complexes, micelles, liposomes or particles can be prepared containing these lipidoids and therefore, can result in an effective delivery of the polynucleotide, primary construct, or mmRNA, as judged by the production of an encoded protein, following the injection of a lipidoid formulation via localized and/or systemic routes of administration. Lipidoid complexes of polynucleotides, primary constructs, or mmRNA can be administered by various means including, but not limited to, intravenous, intramuscular, or subcutaneous routes.

[000496] *In vivo* delivery of nucleic acids may be affected by many parameters, including, but not limited to, the formulation composition, nature of particle PEGylation, degree of loading, oligonucleotide to lipid ratio, and biophysical parameters such as, but not limited to, particle size (Akinc et al., Mol Ther. 2009 17:872-879; herein incorporated by reference in its entirety). As an example, small changes in the anchor chain length of poly(ethylene glycol) (PEG) lipids may result in significant effects on in vivo efficacy.

Formulations with the different lipidoids, including, but not limited to penta[3-(1-laurylaminopropionyl)]-triethylenetetramine hydrochloride (TETA–5LAP; aka 98N12-5, see Murugaiah et al., Analytical Biochemistry, 401:61 (2010); herein incorporated by reference in its entirety), C12-200 (including derivatives and variants), and MD1, can be tested for *in vivo* activity.

[000497] The lipidoid referred to herein as "98N12-5" is disclosed by Akinc et al., Mol Ther. 2009 17:872-879 and is incorporated by reference in its entirety. (See Figure 2)

[000498] The lipidoid referred to herein as "C12-200" is disclosed by Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869 (see Figure 2) and Liu and Huang, Molecular Therapy. 2010 669-670 (see Figure 2); both of which are herein incorporated by reference in their entirety. The lipidoid formulations can include particles comprising either 3 or 4 or more components in addition to polynucleotide, primary construct, or mmRNA. As an example, formulations with certain lipidoids, include, but are not limited to, 98N12-5 and may contain 42% lipidoid, 48% cholesterol and 10% PEG (C14 alkyl chain length). As another example, formulations with certain lipidoids, include, but are not limited to, C12-200 and may contain 50% lipidoid, 10% disteroylphosphatidyl choline, 38.5% cholesterol, and 1.5% PEG-DMG.

[000499] In one embodiment, a polynucleotide, primary construct, or mmRNA formulated with a lipidoid for systemic intravenous administration can target the liver. For example, a final optimized intravenous formulation using polynucleotide, primary construct, or mmRNA, and comprising a lipid molar composition of 42% 98N12-5, 48% cholesterol, and 10% PEG-lipid with a final weight ratio of about 7.5 to 1 total lipid to polynucleotide, primary construct, or mmRNA, and a C14 alkyl chain length on the PEG lipid, with a mean particle size of roughly 50–60 nm, can result in the distribution of the formulation to be greater than 90% to the liver.(see, Akinc et al., Mol Ther. 2009 17:872-879; herein incorporated by reference in its entirety). In another example, an intravenous formulation using a C12-200 (see US provisional application 61/175,770 and published international application WO2010129709, each of which is herein incorporated by reference in their entirety) lipidoid may have a molar ratio of 50/10/38.5/1.5 of C12-200/disteroylphosphatidyl choline/cholesterol/PEG-DMG, with a weight ratio of 7 to 1 total lipid to polynucleotide, primary construct, or mmRNA, and a mean particle size of

80 nm may be effective to deliver polynucleotide, primary construct, or mmRNA to hepatocytes (see, Love et al., Proc Natl Acad Sci U S A. 2010 107:1864-1869 herein incorporated by reference in its entirety). In another embodiment, an MD1 lipidoid-containing formulation may be used to effectively deliver polynucleotide, primary construct, or mmRNA to hepatocytes *in vivo*. The characteristics of optimized lipidoid formulations for intramuscular or subcutaneous routes may vary significantly depending on the target cell type and the ability of formulations to diffuse through the extracellular matrix into the blood stream. While a particle size of less than 150 nm may be desired for effective hepatocyte delivery due to the size of the endothelial fenestrae (see, Akinc et al., Mol Ther. 2009 17:872-879 herein incorporated by reference in its entirety), use of a lipidoid-formulated polynucleotide, primary construct, or mmRNA to deliver the formulation to other cells types including, but not limited to, endothelial cells, myeloid cells, and muscle cells may not be similarly size-limited. Use of lipidoid formulations to deliver siRNA in vivo to other non-hepatocyte cells such as myeloid cells and endothelium has been reported (see Akinc et al., Nat Biotechnol. 2008 26:561-569; Leuschner et al., Nat Biotechnol. 2011 29:1005-1010; Cho et al. Adv. Funct. Mater. 2009 19:3112-3118; 8th International Judah Folkman Conference, Cambridge, MA October 8-9, 2010; each of which is herein incorporated by reference in its entirety). Effective delivery to myeloid cells, such as monocytes, lipidoid formulations may have a similar component molar ratio. Different ratios of lipidoids and other components including, but not limited to, disteroylphosphatidyl choline, cholesterol and PEG-DMG, may be used to optimize the formulation of the polynucleotide, primary construct, or mmRNA for delivery to different cell types including, but not limited to, hepatocytes, myeloid cells, muscle cells, etc. For example, the component molar ratio may include, but is not limited to, 50% C12-200, 10% disteroylphosphatidyl choline, 38.5% cholesterol, and %1.5 PEG-DMG (see Leuschner et al., Nat Biotechnol 2011 29:1005-1010; herein incorporated by reference in its entirety). The use of lipidoid formulations for the localized delivery of nucleic acids to cells (such as, but not limited to, adipose cells and muscle cells) via either subcutaneous or intramuscular delivery, may not require all of the formulation components desired for systemic delivery, and as such may comprise only the lipidoid and the polynucleotide, primary construct, or mmRNA.

[000500] Combinations of different lipidoids may be used to improve the efficacy of polynucleotide, primary construct, or mmRNA directed protein production as the lipidoids may be able to increase cell transfection by the polynucleotide, primary construct, or mmRNA; and/or increase the translation of encoded protein (see Whitehead et al., Mol. Ther. 2011, 19:1688-1694, herein incorporated by reference in its entirety).

Liposomes, Lipoplexes, and Lipid Nanoparticles

[000501] The polynucleotide, primary construct, and mmRNA of the invention can be formulated using one or more liposomes, lipoplexes, or lipid nanoparticles. In one embodiment, pharmaceutical compositions of polynucleotide, primary construct, or mmRNA include liposomes. Liposomes are artificially-prepared vesicles which may primarily be composed of a lipid bilayer and may be used as a delivery vehicle for the administration of nutrients and pharmaceutical formulations. Liposomes can be of different sizes such as, but not limited to, a multilamellar vesicle (MLV) which may be hundreds of nanometers in diameter and may contain a series of concentric bilayers separated by narrow aqueous compartments, a small unicellular vesicle (SUV) which may be smaller than 50 nm in diameter, and a large unilamellar vesicle (LUV) which may be between 50 and 500 nm in diameter. Liposome design may include, but is not limited to, opsonins or ligands in order to improve the attachment of liposomes to unhealthy tissue or to activate events such as, but not limited to, endocytosis. Liposomes may contain a low or a high pH in order to improve the delivery of the pharmaceutical formulations.

[000502] The formation of liposomes may depend on the physicochemical characteristics such as, but not limited to, the pharmaceutical formulation entrapped and the liposomal ingredients , the nature of the medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, any additional processes involved during the application and/or delivery of the vesicles, the optimization size, polydispersity and the shelf-life of the vesicles for the intended application, and the batch-to-batch reproducibility and possibility of large-scale production of safe and efficient liposomal products.

[000503] In one embodiment, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from 1,2-dioleyloxy-*N,N*-

dimethylaminopropane (DODMA) liposomes, DiLa2 liposomes from Marina Biotech (Bothell, WA), 1,2-dilinoleyloxy-3-dimethylaminopropane (DLin-DMA), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-KC2-DMA), and MC3 (US20100324120; herein incorporated by reference in its entirety) and liposomes which may deliver small molecule drugs such as, but not limited to, DOXIL® from Janssen Biotech, Inc. (Horsham, PA).

[000504] In one embodiment, pharmaceutical compositions described herein may include, without limitation, liposomes such as those formed from the synthesis of stabilized plasmid-lipid particles (SPLP) or stabilized nucleic acid lipid particle (SNALP) that have been previously described and shown to be suitable for oligonucleotide delivery in vitro and in vivo (see Wheeler et al. Gene Therapy. 1999 6:271-281; Zhang et al. Gene Therapy. 1999 6:1438-1447; Jeffs et al. Pharm Res. 2005 22:362-372; Morrissey et al., Nat Biotechnol. 2005 2:1002-1007; Zimmermann et al., Nature. 2006 441:111-114; Heyes et al. J Contr Rel. 2005 107:276-287; Semple et al. Nature Biotech. 2010 28:172-176; Judge et al. J Clin Invest. 2009 119:661-673; deFougerolles *Hum Gene Ther.* 2008 19:125-132; all of which are incorporated herein in their entireties). The original manufacture method by Wheeler et al. was a detergent dialysis method, which was later improved by Jeffs et al. and is referred to as the spontaneous vesicle formation method. The liposome formulations are composed of 3 to 4 lipid components in addition to the polynucleotide, primary construct, or mmRNA. As an example a liposome can contain, but is not limited to, 55% cholesterol, 20% disteroylphosphatidyl choline (DSPC), 10% PEG-S-DSG, and 15% 1,2-dioleyloxy-*N,N*-dimethylaminopropane (DODMA), as described by Jeffs et al. As another example, certain liposome formulations may contain, but are not limited to, 48% cholesterol, 20% DSPC, 2% PEG-c-DMA, and 30% cationic lipid, where the cationic lipid can be 1,2-distearloxy-*N,N*-dimethylaminopropane (DSDMA), DODMA, DLin-DMA, or 1,2-dilinolenyloxy-3-dimethylaminopropane (DLenDMA), as described by Heyes et al.

[000505] In one embodiment, pharmaceutical compositions may include liposomes which may be formed to deliver mmRNA which may encode at least one immunogen. The mmRNA may be encapsulated by the liposome and/or it may be contained in an aqueous core which may then be encapsulated by the liposome (see International Pub.

Nos. WO2012031046, WO2012031043, WO2012030901 and WO2012006378; each of which is herein incorporated by reference in their entirety). In another embodiment, the mmRNA which may encode an immunogen may be formulated in a cationic oil-in-water emulsion where the emulsion particle comprises an oil core and a cationic lipid which can interact with the mmRNA anchoring the molecule to the emulsion particle (see International Pub. No. WO2012006380; herein incorporated by reference in its entirety). In yet another embodiment, the lipid formulation may include at least cationic lipid, a lipid which may enhance transfection and a least one lipid which contains a hydrophilic head group linked to a lipid moiety (International Pub. No. WO2011076807 and U.S. Pub. No. 20110200582; each of which is herein incorporated by reference in their entirety). In another embodiment, the polynucleotides, primary constructs and/or mmRNA encoding an immunogen may be formulated in a lipid vesicle which may have crosslinks between functionalized lipid bilayers (see U.S. Pub. No. 20120177724, herein incorporated by reference in its entirety).

[000506] In one embodiment, the polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid vesicle which may have crosslinks between functionalized lipid bilayers.

[000507] In one embodiment, the polynucleotides, primary constructs and/or mmRNA may be formulated in a liposome comprising a cationic lipid. The liposome may have a molar ratio of nitrogen atoms in the cationic lipid to the phophates in the RNA (N:P ratio) of between 1:1 and 20:1 as described in International Publication No. WO2013006825, herein incorporated by reference in its entirety. In another embodiment, the liposome may have a N:P ratio of greater than 20:1 or less than 1:1.

[000508] In one embodiment, the polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid-polycation complex. The formation of the lipid-polycation complex may be accomplished by methods known in the art and/or as described in U.S. Pub. No. 20120178702, herein incorporated by reference in its entirety. As a non-limiting example, the polycation may include a cationic peptide or a polypeptide such as, but not limited to, polylysine, polyornithine and/or polyarginine and the cationic peptides described in International Pub. No. WO2012013326; herein incorporated by reference in its entirety. In another embodiment, the polynucleotides, primary constructs and/or

mmRNA may be formulated in a lipid-polycation complex which may further include a neutral lipid such as, but not limited to, cholesterol or dioleoyl phosphatidylethanolamine (DOPE).

[000509] The liposome formulation may be influenced by, but not limited to, the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. In one example by Semple et al. (Semple et al. Nature Biotech. 2010 28:172-176; herein incorporated by reference in its entirety), the liposome formulation was composed of 57.1 % cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3 % cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid could more effectively deliver siRNA to various antigen presenting cells (Basha et al. Mol Ther. 2011 19:2186-2200; herein incorporated by reference in its entirety).

[000510] In some embodiments, the ratio of PEG in the lipid nanoparticle (LNP) formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the LNP formulations. As a non-limiting example, LNP formulations may contain 1-5% of the lipid molar ratio of PEG-c-DOMG as compared to the cationic lipid, DSPC and cholesterol. In another embodiment the PEG-c-DOMG may be replaced with a PEG lipid such as, but not limited to, PEG- DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol) or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art such as, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

[000511] In one embodiment, the polynucleotides, primary constructs or mmRNA may be formulated in a lipid nanoparticle such as those described in International Publication No. WO2012170930, herein incorporated by reference in its entirety.

[000512] In one embodiment, the cationic lipid may be selected from, but not limited to, a cationic lipid described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259, WO2012054365, WO2012044638, WO2010080724, WO201021865 and WO2008103276, US Patent Nos. 7,893,302, 7,404,969 and 8,283,333 and US Patent

Publication No. US20100036115 and US20120202871; each of which is herein incorporated by reference in their entirety. In another embodiment, the cationic lipid may be selected from, but not limited to, formula A described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259, WO2012054365 and WO2012044638; each of which is herein incorporated by reference in their entirety. In yet another embodiment, the cationic lipid may be selected from, but not limited to, formula CLI-CLXXIX of International Publication No. WO2008103276, formula CLI-CLXXIX of US Patent No. 7,893,302, formula CLI-CLXXXXII of US Patent No. 7,404,969 and formula I-VI of US Patent Publication No. US20100036115; each of which is herein incorporated by reference in their entirety. As a non-limiting example, the cationic lipid may be selected from (20Z,23Z)-N,N-dimethylnonacosa-20,23-dien-10-amine, (17Z,20Z)-N,N-dimemylhexacosa-17,20-dien-9-amine, (1Z,19Z)-N5N-dimethylpentacosa-l 6, 19-dien-8-amine, (13Z,16Z)-N,N-dimethyldocosa-13,16-dien-5-amine, (12Z,15Z)-N,N-dimethylhenicosa-12,15-dien-4-amine, (14Z,17Z)-N,N-dimethyltricosa-14,17-dien-6-amine, (15Z,18Z)-N,N-dimethyltetracosa-15,18-dien-7-amine, (18Z,21Z)-N,N-dimethylheptacosa-18,21-dien-10-amine, (15Z,18Z)-N,N-dimethyltetracosa-15,18-dien-5-amine, (14Z,17Z)-N,N-dimethyltricosa-14,17-dien-4-amine, (19Z,22Z)-N,N-dimeihyloctacosa-19,22-dien-9-amine, (18Z,21 Z)-N,N-dimethylheptacosa- 18 ,21 -dien-8 –amine, (17Z,20Z)-N,N-dimethylhexacosa- 17,20-dien-7-amine, (16Z,19Z)-N,N-dimethylpentacosa-16,19-dien-6-amine, (22Z,25Z)-N,N-dimethylhentriaconta-22,25-dien-10-amine, (21 Z ,24Z)-N,N-dimethyltriaconta-21,24-dien-9-amine, (18Z)-N,N-dimetylheptacos-18-en-10-amine, (17Z)-N,N-dimethylhexacos-17-en-9-amine, (19Z,22Z)-N,N-dimethyloctacosa-19,22-dien-7-amine, N,N-dimethylheptacosan-10-amine, (20Z,23Z)-N-ethyl-N-methylnonacosa-20,23-dien-l0-amine, 1-[(11Z,14Z)-l-nonylicosa-11,14-dien-l-yl] pyrrolidine, (20Z)-N,N-dimethylheptacos-20-en-l 0-amine, (15Z)-N,N-dimethyl eptacos-15-en-l 0-amine, (14Z)-N,N-dimethylnonacos-14-en-l0-amine, (17Z)-N,N-dimethylnonacos-17-en-l0-amine, (24Z)-N,N-dimethyltritriacont-24-en-l0-amine, (20Z)-N,N-dimethylnonacos-20-en-l 0-amine, (22Z)-N,N-dimethylhentriacont-22-en-l0-amine, (16Z)-N,N-dimethylpentacos-16-en-8-amine, (12Z,15Z)-N,N-dimethyl-2-nonylhenicosa-12,15-dien-1–amine, (13Z,16Z)-

N,N-dimethyl-3-nonyldocosa-l3,16-dien-l–amine, N,N-dimethyl-l-[(lS,2R)-2-octylcyclopropyl] eptadecan-8-amine, 1-[(1S,2R)-2-hexylcyclopropyl]-N,N-dimethylnonadecan-10-amine, N,N-dimethyl-1-[(1S ,2R)-2-octylcyclopropyl]nonadecan-10-amine, N,N-dimethyl-21-[(lS,2R)-2-octylcyclopropyl]henicosan-l0-amine,N,N-dimethyl-1-[(1S,2S)-2-{[(lR,2R)-2-pentylcycIopropyl]methyl}cyclopropyl]nonadecan-10-amine,N,N-dimethyl-1-[(1S,2R)-2-octylcyclopropyl]hexadecan-8-amine, N,N-dimethyl-[(lR,2S)-2-undecyIcyclopropyl]tetradecan-5-amine, N,N-dimethyl-3-{7-[(1S,2R)-2-octylcyclopropyl]heptyl} dodecan-1–amine, 1-[(1R,2S)-2-hepty lcyclopropyl]-N,N-dimethyloctadecan-9–amine, 1-[(1S,2R)-2-decylcyclopropyl]-N,N-dimethylpentadecan-6-amine, N,N-dimethyl-l-[(lS,2R)-2-octylcyclopropyl]pentadecan-8-amine, R-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, S-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-(octyloxy)propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}pyrrolidine, (2S)-N,N-dimethyl-1-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-3-[(5Z)-oct-5-en-1-yloxy]propan-2-amine, 1-{2-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-1-[(octyloxy)methyl]ethyl}azetidine, (2S)-1-(hexyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2S)-1-(heptyloxy)-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-(nonyloxy)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, N,N-dimethyl-1-[(9Z)-octadec-9-en-1-yloxy]-3-(octyloxy)propan-2-amine; (2S)-N,N-dimethyl-1-[(6Z,9Z,12Z)-octadeca-6,9,12-trien-1-yloxy]-3-(octyloxy)propan-2-amine, (2S)-1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethyl-3-(pentyloxy)propan-2-amine, (2S)-1-(hexyloxy)-3-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethylpropan-2-amine, 1-[(11Z,14Z)-icosa-11,14-dien-1-yloxy]-N,N-dimethy1-3-(octyloxy)propan-2-amine, 1-[(13Z,16Z)-docosa-l3,16-dien-l-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2S)-1-[(13Z,16Z)-docosa-13,16-dien-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, (2S)-1-[(13Z)-docos-13-en-1-yloxy]-3-(hexyloxy)-N,N-dimethylpropan-2-amine, 1-[(13Z)-docos-13-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, 1-[(9Z)-hexadec-9-en-1-yloxy]-N,N-dimethyl-3-(octyloxy)propan-2-amine, (2R)-N,N-dimethyl-H(1-metoylo ctyl)oxy]-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-2-amine, (2R)-1-[(3,7-dimethyloctyl)oxy]-N,N-dimethyl-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]propan-

2-amine, N,N-dimethyl-1-(octyloxy)-3-({8-[(1S,2S)-2-{[(1R,2R)-2-pentylcyclopropyl]methyl}cyclopropyl]octyl}oxy)propan-2-amine, N,N-dimethyl-1-{[8-(2-oc1ylcyclopropyl)octyl]oxy}-3-(octyloxy)propan-2-amine and (11E,20Z,23Z)-N,N-dimethylnonacosa-11,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

[000513] In one embodiment, the lipid may be a cleavable lipid such as those described in International Publication No. WO2012170889, herein incorporated by reference in its entirety.

[000514] In one embodiment, the cationic lipid may be synthesized by methods known in the art and/or as described in International Publication Nos. WO2012040184, WO2011153120, WO2011149733, WO2011090965, WO2011043913, WO2011022460, WO2012061259, WO2012054365, WO2012044638, WO2010080724 and WO201021865; each of which is herein incorporated by reference in their entirety.

[000515] In one embodiment, the LNP formulations of the polynucleotides, primary constructs and/or mmRNA may contain PEG-c-DOMG at 3% lipid molar ratio. In another embodiment, the LNP formulations polynucleotides, primary constructs and/or mmRNA may contain PEG-c-DOMG at 1.5% lipid molar ratio.

[000516] In one embodiment, the pharmaceutical compositions of the polynucleotides, primary constructs and/or mmRNA may include at least one of the PEGylated lipids described in International Publication No. 2012099755, herein incorporated by reference.

[000517] In one embodiment, the LNP formulation may contain PEG-DMG 2000 (1,2-dimyristoyl-sn-glycero-3-phophoethanolamine-N-[methoxy(polyethylene glycol)-2000). In one embodiment, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art and at least one other component. In another embodiment, the LNP formulation may contain PEG-DMG 2000, a cationic lipid known in the art, DSPC and cholesterol. As a non-limiting example, the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol. As another non-limiting example the LNP formulation may contain PEG-DMG 2000, DLin-DMA, DSPC and cholesterol in a molar ratio of 2:40:10:48 (see e.g., Geall et al., Nonviral delivery of self-amplifying RNA vaccines, PNAS 2012; PMID: 22908294; herein incorporated by reference in its entirety). . As another non-limiting example, modified RNA described herein may be formulated

in a nanoparticle to be delivered by a parenteral route as described in U.S. Pub. No. 20120207845; herein incorporated by reference in its entirety.

In one embodiment, the LNP formulation may be formulated by the methods described in International Publication Nos. WO2011127255 or WO2008103276, each of which is herein incorporated by reference in their entirety. As a non-limiting example, modified RNA described herein may be encapsulated in LNP formulations as described in WO2011127255 and/or WO2008103276; each of which is herein incorporated by reference in their entirety.

In one embodiment, LNP formulations described herein may comprise a polycationic composition. As a non-limiting example, the polycationic composition may be selected from formula 1-60 of US Patent Publication No. US20050222064; herein incorporated by reference in its entirety. In another embodiment, the LNP formulations comprising a polycationic composition may be used for the delivery of the modified RNA described herein *in vivo* and/or *in vitro*.

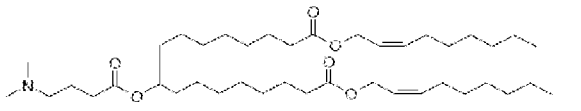
[000518] In one embodiment, the LNP formulations described herein may additionally comprise a permeability enhancer molecule. Non-limiting permeability enhancer molecules are described in US Patent Publication No. US20050222064; herein incorporated by reference in its entirety.

[000519] In one embodiment, the pharmaceutical compositions may be formulated in liposomes such as, but not limited to, DiLa2 liposomes (Marina Biotech, Bothell, WA), SMARTICLES® (Marina Biotech, Bothell, WA), neutral DOPC (1,2-dioleoyl-sn-glycero-3-phosphocholine) based liposomes (e.g., siRNA delivery for ovarian cancer (Landen et al. Cancer Biology & Therapy 2006 5(12)1708-1713); herein incorporated by reference in its entirety) and hyaluronan-coated liposomes (Quiet Therapeutics, Israel).

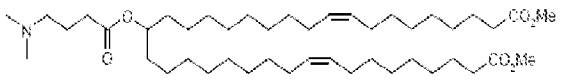
[000520] The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a modified nucleic acid molecule (e.g., mmRNA). As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type material, phtoglycogen octenyl succinate, phytoglycogen beta-dextrin, anhydride-modified phytoglycogen beta-dextrin. (See e.g., International Publication No. WO2012109121; herein incorporated by reference in its entirety).

[000521] Lipid nanoparticle formulations may be improved by replacing the cationic lipid with a biodegradable cationic lipid which is known as a rapidly eliminated lipid nanoparticle (reLNP). Ionizable cationic lipids, such as, but not limited to, DLinDMA, DLin-KC2-DMA, and DLin-MC3-DMA, have been shown to accumulate in plasma and tissues over time and may be a potential source of toxicity. The rapid metabolism of the rapidly eliminated lipids can improve the tolerability and therapeutic index of the lipid nanoparticles by an order of magnitude from a 1 mg/kg dose to a 10 mg/kg dose in rat. Inclusion of an enzymatically degraded ester linkage can improve the degradation and metabolism profile of the cationic component, while still maintaining the activity of the reLNP formulation. The ester linkage can be internally located within the lipid chain or it may be terminally located at the terminal end of the lipid chain. The internal ester linkage may replace any carbon in the lipid chain.

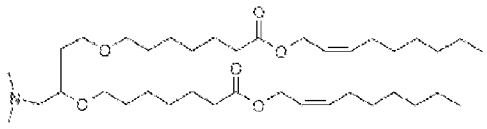
[000522] In one embodiment, the internal ester linkage may be located on either side of the saturated carbon. Non-limiting examples of reLNPs include,



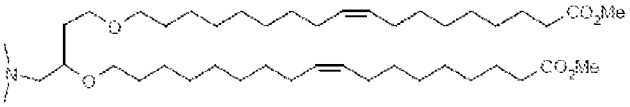
,



,



and



.

[000523] In one embodiment, an immune response may be elicited by delivering a lipid nanoparticle which may include a nanospecies, a polymer and an immunogen. (U.S. Publication No. 20120189700 and International Publication No. WO2012099805; each of which is herein incorporated by reference in their entirety). The polymer may encapsulate the nanospecies or partially encapsulate the nanospecies. The immunogen may be a recombinant protein, a modified RNA and/or a primary construct described

herein. In one embodiment, the lipid nanoparticle may be formulated for use in a vaccine such as, but not limited to, against a pathogen.

[000524] Lipid nanoparticles may be engineered to alter the surface properties of particles so the lipid nanoparticles may penetrate the mucosal barrier. Mucus is located on mucosal tissue such as, but not limted to, oral (e.g., the buccal and esophageal membranes and tonsil tissue), ophthalmic, gastrointestinal (e.g., stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (e.g., nasal, pharyngeal, tracheal and bronchial membranes), genital (e.g., vaginal, cervical and urethral membranes). Nanoparticles larger than 10-200 nm which are preferred for higher drug encapsulation efficiency and the ability to provide the sustained delivery of a wide array of drugs have been thought to be too large to rapidly diffuse through mucosal barriers. Mucus is continuously secreted, shed, discarded or digested and recycled so most of the trapped particles may be removed from the mucosla tissue within seconds or within a few hours. Large polymeric nanoparticles (200nm -500nm in diameter) which have been coated densely with a low molecular weight polyethylene glycol (PEG) diffused through mucus only 4 to 6-fold lower than the same particles diffusing in water (Lai et al. PNAS 2007 104(5):1482-487; Lai et al. Adv Drug Deliv Rev. 2009 61(2): 158-171; each of which is herein incorporated by reference in their entirety). The transport of nanoparticles may be determined using rates of permeation and/or fluorescent microscopy techniques including, but not limited to, fluorescence recovery after photobleaching (FRAP) and high resolution multiple particle tracking (MPT). As a non-limiting example, compositions which can penetrate a mucosal barrier may be made as described in U.S. Pat. No. 8,241,670, herein incorporated by reference in its entirety.

[000525] The lipid nanoparticle engineered to penetrate mucus may comprise a polymeric material (i.e. a polymeric core) and/or a polymer-vitamin conjugate and/or a tri-block co-polymer. The polymeric material may include, but is not limited to, polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, poly(styrenes), polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. The polymeric material may be biodegradable and/or biocompatible. The polymeric material may additionally be irradiated. As a non-limiting

example, the polymeric material may be gamma irradiated (See e.g., International App. No. WO201282165, herein incorporated by reference in its entirety). Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L-lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacralate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), polyethyleneglycol, poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate, polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.The lipid nanoparticle may be coated or associated with a co-polymer such as, but not limited to, a block co-polymer (such as a branched polyether-polyamide block copolymer described in International Publication No. WO2013012476, herein incorporated by reference in its entirety), and (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (see e.g., US Publication 20120121718 and

US Publication 20100003337 and U.S. Pat. No. 8,263,665; each of which is herein incorporated by reference in their entirety). The co-polymer may be a polymer that is generally regarded as safe (GRAS) and the formation of the lipid nanoparticle may be in such a way that no new chemical entities are created. For example, the lipid nanoparticle may comprise poloxamers coating PLGA nanoparticles without forming new chemical entities which are still able to rapidly penetrate human mucus (Yang et al. Angew. Chem. Int. Ed. 2011 50:2597-2600; herein incorporated by reference in its entirety).

[000526] The vitamin of the polymer-vitamin conjugate may be vitamin E. The vitamin portion of the conjugate may be substituted with other suitable components such as, but not limited to, vitamin A, vitamin E, other vitamins, cholesterol, a hydrophobic moiety, or a hydrophobic component of other surfactants (e.g., sterol chains, fatty acids, hydrocarbon chains and alkylene oxide chains).

[000527] The lipid nanoparticle engineered to penetrate mucus may include surface altering agents such as, but not limited to, mmRNA, anionic proteins (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin, polyethylene glycol and poloxamer), mucolytic agents (e.g., N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4 dornase alfa, neltenexine, erdosteine) and various DNases including rhDNase.. The surface altering agent may be embedded or enmeshed in the particle's surface or disposed (e.g., by coating, adsorption, covalent linkage, or other process) on the surface of the lipid nanoparticle. (see e.g., US Publication 20100215580 and US Publication 20080166414; each of which is herein incorporated by reference in their entirety).

[000528] The mucus penetrating lipid nanoparticles may comprise at least one mmRNA described herein. The mmRNA may be encapsulated in the lipid nanoparticle and/or disposed on the surface of the paricle. The mmRNA may be covalently coupled to the lipid nanoparticle. Formulations of mucus penetrating lipid nanoparticles may comprise a plurality of nanoparticles. Further, the formulations may contain particles which may interact with the mucus and alter the structural and/or adhesive properties of the

surrounding mucus to decrease mucoadhesion which may increase the delivery of the mucus penetrating lipid nanoparticles to the mucosal tissue.

[000529] In one embodiment, the polynucleotide, primary construct, or mmRNA is formulated as a lipoplex, such as, without limitation, the ATUPLEX™ system, the DACC system, the DBTC system and other siRNA-lipoplex technology from Silence Therapeutics (London, United Kingdom), STEMFECT™ from STEMGENT® (Cambridge, MA), and polyethylenimine (PEI) or protamine-based targeted and non-targeted delivery of nucleic acids acids (Aleku et al. Cancer Res. 2008 68:9788-9798; Strumberg et al. Int J Clin Pharmacol Ther 2012 50:76-78; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Kaufmann et al. Microvasc Res 2010 80:286-293Weide et al. J Immunother. 2009 32:498-507; Weide et al. J Immunother. 2008 31:180-188; Pascolo Expert Opin. Biol. Ther. 4:1285-1294; Fotin-Mleczek et al., 2011 J. Immunother. 34:1-15; Song et al., Nature Biotechnol. 2005, 23:709-717; Peer et al., Proc Natl Acad Sci U S A. 2007 6;104:4095-4100; deFougerolles *Hum Gene Ther.* 2008 19:125-132; all of which are incorporated herein by reference in its entirety).

[000530] In one embodiment such formulations may also be constructed or compositions altered such that they passively or actively are directed to different cell types *in vivo*, including but not limited to hepatocytes, immune cells, tumor cells, endothelial cells, antigen presenting cells, and leukocytes (Akinc et al. Mol Ther. 2010 18:1357-1364; Song et al., Nat Biotechnol. 2005 23:709-717; Judge et al., J Clin Invest. 2009 119:661-673; Kaufmann et al., Microvasc Res 2010 80:286-293; Santel et al., Gene Ther 2006 13:1222-1234; Santel et al., Gene Ther 2006 13:1360-1370; Gutbier et al., Pulm Pharmacol. Ther. 2010 23:334-344; Basha et al., Mol. Ther. 2011 19:2186-2200; Fenske and Cullis, Expert Opin Drug Deliv. 2008 5:25-44; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety). One example of passive targeting of formulations to liver cells includes the DLin-DMA, DLin-KC2-DMA and DLin-MC3-DMA-based lipid nanoparticle formulations which have been shown to bind to apolipoprotein E and promote binding and uptake of these formulations into hepatocytes in vivo (Akinc et al. Mol Ther. 2010 18:1357-1364; herein incorporated by reference in

its entirety). Formulations can also be selectively targeted through expression of different ligands on their surface as exemplified by, but not limited by, folate, transferrin, N-acetylgalactosamine (GalNAc), and antibody targeted approaches (Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, *Front Biosci.* 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; Peer and Lieberman, Gene Ther. 2011 18:1127-1133; all of which are incorporated herein by reference in its entirety)..

[000531] In one embodiment, the polynucleotide, primary construct, or mmRNA is formulated as a solid lipid nanoparticle. A solid lipid nanoparticle (SLN) may be spherical with an average diameter between 10 to 1000 nm. SLN possess a solid lipid core matrix that can solubilize lipophilic molecules and may be stabilized with surfactants and/or emulsifiers. In a further embodiment, the lipid nanoparticle may be a self-assembly lipid-polymer nanoparticle (see Zhang et al., ACS Nano, 2008, 2 (8), pp 1696–1702; herein incorporated by reference in its entirety).

[000532] Liposomes, lipoplexes, or lipid nanoparticles may be used to improve the efficacy of polynucleotide, primary construct, or mmRNA directed protein production as these formulations may be able to increase cell transfection by the polynucleotide, primary construct, or mmRNA; and/or increase the translation of encoded protein. One such example involves the use of lipid encapsulation to enable the effective systemic delivery of polyplex plasmid DNA (Heyes et al., Mol Ther. 2007 15:713-720; herein incorporated by reference in its entirety). The liposomes, lipoplexes, or lipid nanoparticles may also be used to increase the stability of the polynucleotide, primary construct, or mmRNA.

[000533] In one embodiment, the the polynucleotides, primary constructs, and/or the mmRNA of the present invention can be formulated for controlled release and/or targeted delivery. As used herein, "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome. In one embodiment, the polynucleotides, primary constructs or the mmRNA may be encapsulated into a delivery agent described herein and/or known in the art for controlled release and/or targeted delivery. As used herein, the term "encapsulate" means to enclose, surround or encase. As it relates to the formulation of the compounds of the invention, encapsulation may be substantial, complete or partial. The term "substitantially encapsulated" means that at least greater than 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.9 or greater than 99.999% of the pharmaceutical composition or compound of the invention may be enclosed, surrounded or encased within the delivery agent. "Partially encapsulation" means that less than 10, 10, 20, 30, 40 50 or less of the pharmaceutical composition or compound of the invention may be enclosed, surrounded or encased within the delivery agent. Advantageously, encapsulation may be determined by measuring the escape or the activity of the pharmaceutical composition or compound of the invention using fluorescence and/or electron micrograph. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the pharmaceutical composition or compound of the invention are encapsulated in the delivery agent.

[000534] In one embodiment, the controlled release formulation may include, but is not limited to, tri-block co-polymers. As a non-limiting example, the formulation may include two different types of tri-block co-polymers (International Pub. No. WO2012131104 and WO2012131106; each of which is herein incorporated by reference in its entirety).

[000535] In another embodiment, the the polynucleotides, primary constructs, or the mmRNA may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE®

(Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, IL).

[000536] In another embodiment, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

[000537] In one embodiment, the the polynucleotide, primary construct, or mmRNA formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

[000538] In one embodiment, the controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

[000539] In one embodiment, the the polynucleotides, primary constructs, and/or the mmRNA of the present invention may be encapsulated in a therapeutic nanoparticle. Therapeutic nanoparticles may be formulated by methods described herein and known in the art such as, but not limited to, International Pub Nos. WO2010005740, WO2010030763, WO2010005721, WO2010005723, WO2012054923, US Pub. Nos. US20110262491, US20100104645, US20100087337, US20100068285, US20110274759, US20100068286 and US20120288541 and US Pat No. 8,206,747, 8,293,276, 8,318,208 and 8,318,211 each of which is herein incorporated by reference in their entirety. In another embodiment, therapeutic polymer nanoparticles may be

identified by the methods described in US Pub No. US20120140790, herein incorporated by reference in its entirety.

[000540] In one embodiment, the therapeutic nanoparticle may be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or compound that conforms to a release rate over a specific period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the the polynucleotides, primary constructs, and mmRNA of the present invention (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, each of which is herein incorporated by reference in their entirety).

[000541] In one embodiment, the therapeutic nanoparticles may be formulated to be target specific. As a non-limiting example, the thereapeutic nanoparticles may include a corticosteroid (see International Pub. No. WO2011084518; herein incorporated by reference in its entirety). In one embodiment, the therapeutic nanoparticles may be formulated to be cancer specific. As a non-limiting example, the therapeutic nanoparticles may be formulated in nanoparticles described in International Pub No. WO2008121949, WO2010005726, WO2010005725, WO2011084521 and US Pub No. US20100069426, US20120004293 and US20100104655, each of which is herein incorporated by reference in their entirety.

[000542] In one embodiment, the nanoparticles of the present invention may comprise a polymeric matrix. As a non-limiting example, the nanoparticle may comprise two or more polymers such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

[000543] In one embodiment, the therapeutic nanoparticle comprises a diblock copolymer. In one embodiment, the diblock copolymer may include PEG in combination

with a polymer such as, but not limited to, polyethylenes, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester) or combinations thereof.

[000544] As a non-limiting example the therapeutic nanoparticle comprises a PLGA-PEG block copolymer (see US Pub. No. US20120004293 and US Pat No. 8,236,330, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the therapeutic nanoparticle is a stealth nanoparticle comprising a diblock copolymer of PEG and PLA or PEG and PLGA (see US Pat No 8,246,968 and International Publication No. WO2012166923, each of which is herein incorporated by reference in its entirety).

[000545] In one embodiment, the therapeutic nanoparticle may comprise a multiblock copolymer (See e.g., U.S. Pat. No. 8,263,665 and 8,287,910; each of which is herein incorporated by reference in its entirety).

[000546] In one embodiment, the block copolymers described herein may be included in a polyion complex comprising a non-polymeric micelle and the block copolymer. (See e.g., U.S. Pub. No. 20120076836; herein incorporated by reference in its entirety).

[000547] In one embodiment, the therapeutic nanoparticle may comprise at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

[000548] In one embodiment, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

[000549] In one embodiment, the therapeutic nanoparticles may comprise at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine,

poly(amidoamine) dendrimers, poly(beta-amino esters) (See e.g., U.S. Pat. No. 8,287,849; herein incorporated by reference in its entirety) and combinations thereof.

[000550] In one embodiment, the therapeutic nanoparticles may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

[000551] In another embodiment, the therapeutic nanoparticle may include a conjugation of at least one targeting ligand. The targeting ligand may be any ligand known in the art such as, but not limited to, a monoclonal antibody. (Kirpotin et al, Cancer Res. 2006 66:6732-6740; herein incorporated by reference in its entirety).

[000552] In one embodiment, the therapeutic nanoparticle may be formulated in an aqueous solution which may be used to target cancer (see International Pub No. WO2011084513 and US Pub No. US20110294717, each of which is herein incorporated by reference in their entirety).

[000553] In one embodiment, the polynucleotides, primary constructs, or mmRNA may be encapsulated in, linked to and/or associated with synthetic nanocarriers. . Synthetic nanocarriers include, but are not limited to, those described in International Pub. Nos. WO2010005740, WO2010030763, WO201213501, WO2012149252, WO2012149255, WO2012149259, WO2012149265, WO2012149268, WO2012149282, WO2012149301, WO2012149393, WO2012149405, WO2012149411, WO2012149454 and WO2013019669, and US Pub. Nos. US20110262491, US20100104645, US20100087337 and US20120244222, each of which is herein incorporated by reference in their entirety. The synthetic nanocarriers may be formulated using methods known in the art and/or described herein. As a non-limiting example, the synthetic nanocarriers may be formulated by the methods described in International Pub Nos. WO2010005740, WO2010030763 and WO201213501and US Pub. Nos. US20110262491, US20100104645, US20100087337 and US2012024422, each of which is herein incorporated by reference in their entirety. In another embodiment, the synthetic nanocarrier formulations may be lyophilized by methods described in International Pub.

No. WO2011072218 and US Pat No. 8,211,473; each of which is herein incorporated by reference in their entirety.

[000554] In one embodiment, the synthetic nanocarriers may contain reactive groups to release the polynucleotides, primary constructs and/or mmRNA described herein (see International Pub. No. WO20120952552 and US Pub No. US20120171229, each of which is herein incorporated by reference in their entirety).

[000555] In one embodiment, the synthetic nanocarriers may contain an immunostimulatory agent to enhance the immune response from delivery of the synthetic nanocarrier. As a non-limiting example, the synthetic nanocarrier may comprise a Th1 immunostimulatory agent which may enhance a Th1-based response of the immune system (see International Pub No. WO2010123569 and US Pub. No. US20110223201, each of which is herein incorporated by reference in its entirety).

[000556] In one embodiment, the synthetic nanocarriers may be formulated for targeted release. In one embodiment, the synthetic nanocarrier is formulated to release the polynucleotides, primary constructs and/or mmRNA at a specified pH and/or after a desired time interval. As a non-limiting example, the synthetic nanoparticle may be formulated to release the polynucleotides, primary constructs and/or mmRNA after 24 hours and/or at a pH of 4.5 (see International Pub. Nos. WO2010138193 and WO2010138194 and US Pub Nos. US20110020388 and US20110027217, each of which is herein incorporated by reference in their entireties).

[000557] In one embodiment, the synthetic nanocarriers may be formulated for controlled and/or sustained release of the polynucleotides, primary constructs and/or mmRNA described herein. As a non-limiting example, the synthetic nanocarriers for sustained release may be formulated by methods known in the art, described herein and/or as described in International Pub No. WO2010138192 and US Pub No. 20100303850, each of which is herein incorporated by reference in their entirety.

[000558] In one embodiment, the synthetic nanocarrier may be formulated for use as a vaccine. In one embodiment, the synthetic nanocarrier may encapsulate at least one polynucleotide, primary construct and/or mmRNA which encode at least one antigen. As a non-limiting example, the synthetic nanocarrier may include at least one antigen and an excipient for a vaccine dosage form (see International Pub No. WO2011150264 and US

Pub No. US20110293723, each of which is herein incorporated by reference in their entirety). As another non-limiting example, a vaccine dosage form may include at least two synthetic nanocarriers with the same or different antigens and an excipient (see International Pub No. WO2011150249 and US Pub No. US20110293701, each of which is herein incorporated by reference in their entirety). The vaccine dosage form may be selected by methods described herein, known in the art and/or described in International Pub No. WO2011150258 and US Pub No. US20120027806, each of which is herein incorporated by reference in their entirety).

[000559] In one embodiment, the synthetic nanocarrier may comprise at least one polynucleotide, primary construct and/or mmRNA which encodes at least one adjuvant. As non-limiting example, the adjuvant may comprise dimethyldioctadecylammonium-bromide, dimethyldioctadecylammonium-chloride, dimethyldioctadecylammonium-phosphate or dimethyldioctadecylammonium-acetate (DDA) and an apolar fraction or part of said apolar fraction of a total lipid extract of a mycobacterium (See e.g, U.S. Pat. No. 8,241,610; herein incorporated by reference in its entirety). In another embodiment, the synthetic nanocarrier may comprise at least one polynucleotide, primary construct and/or mmRNA and an adjuvant. As a non-limiting example, the synthetic nanocarrier comprising and adjuvant may be formulated by the methods described in International Pub No. WO2011150240 and US Pub No. US20110293700, each of which is herein incorporated by reference in its entirety.

[000560] In one embodiment, the synthetic nanocarrier may encapsulate at least one polynucleotide, primary construct and/or mmRNA which encodes a peptide, fragment or region from a virus. As a non-limiting example, the synthetic nanocarrier may include, but is not limited to, the nanocarriers described in International Pub No. WO2012024621, WO201202629, WO2012024632 and US Pub No. US20120064110, US20120058153 and US20120058154, each of which is herein incorporated by reference in their entirety.

[000561] In one embodiment, the synthetic nanocarrier may be coupled to a polynucleotide, primary construct or mmRNA which may be able to trigger a humoral and/or cytotoxic T lymphocyte (CTL) response (See e.g., International Publication No. WO2013019669, herein incorporated by reference in its entirety).

[000562] In one embodiment, the nanoparticle may be optimized for oral administration. The nanoparticle may comprise at least one cationic biopolymer such as, but not limited to, chitosan or a derivative thereof. As a non-limiting example, the nanoparticle may be formulated by the methods described in U.S. Pub. No. 20120282343; herein incorporated by reference in its entirety.

Polymers, Biodegradable Nanoparticles, and Core-Shell Nanoparticles

[000563] The polynucleotide, primary construct, and mmRNA of the invention can be formulated using natural and/or synthetic polymers. Non-limiting examples of polymers which may be used for delivery include, but are not limited to, DYNAMIC POLYCONJUGATE® (Arrowhead Reasearch Corp., Pasadena, CA) formulations from MIRUS® Bio (Madison, WI) and Roche Madison (Madison, WI), PHASERX™ polymer formulations such as, without limitation, SMARTT POLYMER TECHNOLOGY™ (PHASERX®, Seattle, WA), DMRI/DOPE, poloxamer, VAXFECTIN® adjuvant from Vical (San Diego, CA), chitosan, cyclodextrin from Calando Pharmaceuticals (Pasadena, CA), dendrimers and poly(lactic-co-glycolic acid) (PLGA) polymers. RONDEL™ (RNAi/Oligonucleotide Nanoparticle Delivery) polymers (Arrowhead Research Corporation, Pasadena, CA) and pH responsive co-block polymers such as, but not limited to, PHASERX® (Seattle, WA).

[000564] A non-limiting example of chitosan formulation includes a core of positively charged chitosan and an outer portion of negatively charged substrate (U.S. Pub. No. 20120258176; herein incorporated by reference in its entirety). Chitosan includes, but is not limited to N-trimethyl chitosan, mono-N-carboxymethyl chitosan (MCC), N-palmitoyl chitosan (NPCS), EDTA-chitosan, low molecular weight chitosan, chitosan derivatives, or combinations thereof.

[000565] In one embodiment, the polymers used in the present invention have undergone processing to reduce and/or inhibit the attachement of unwanted substances such as, but not limited to, bacteria, to the surface of the polymer. The polymer may be processed by methods known and/or described in the art and/or described in International Pub. No. WO2012150467, herein incorporated by reference in its entirety.

[000566] A non-limiting example of PLGA formulations include, but are not limited to, PLGA injectable depots (e.g., ELIGARD® which is formed by dissolving PLGA in 66%

N-methyl-2-pyrrolidone (NMP) and the remainder being aqueous solvent and leuprolide. Once injected, the PLGA and leuprolide peptide precipitates into the subcutaneous space).

[000567] Many of these polymer approaches have demonstrated efficacy in delivering oligonucleotides *in vivo* into the cell cytoplasm (reviewed in deFougerolles *Hum Gene Ther.* 2008 19:125-132; herein incorporated by reference in its entirety). Two polymer approaches that have yielded robust *in vivo* delivery of nucleic acids, in this case with small interfering RNA (siRNA), are dynamic polyconjugates and cyclodextrin-based nanoparticles. The first of these delivery approaches uses dynamic polyconjugates and has been shown *in vivo* in mice to effectively deliver siRNA and silence endogenous target mRNA in hepatocytes (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; herein incorporated by reference in its entirety). This particular approach is a multicomponent polymer system whose key features include a membrane-active polymer to which nucleic acid, in this case siRNA, is covalently coupled via a disulfide bond and where both PEG (for charge masking) and *N*-acetylgalactosamine (for hepatocyte targeting) groups are linked via pH-sensitive bonds (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; herein incorporated by reference in its entirety). On binding to the hepatocyte and entry into the endosome, the polymer complex disassembles in the low-pH environment, with the polymer exposing its positive charge, leading to endosomal escape and cytoplasmic release of the siRNA from the polymer. Through replacement of the *N*-acetylgalactosamine group with a mannose group, it was shown one could alter targeting from asialoglycoprotein receptor-expressing hepatocytes to sinusoidal endothelium and Kupffer cells. Another polymer approach involves using transferrin-targeted cyclodextrin-containing polycation nanoparticles. These nanoparticles have demonstrated targeted silencing of the *EWS-FLI1* gene product in transferrin receptor-expressing Ewing's sarcoma tumor cells (Hu-Lieskovan *et al.*, Cancer Res.2005 65: 8984-8982; herein incorporated by reference in its entirety) and siRNA formulated in these nanoparticles was well tolerated in non-human primates (Heidel *et al.*, Proc Natl Acad Sci USA 2007 104:5715-21; herein incorporated by reference in its entirety). Both of these delivery strategies incorporate rational approaches using both targeted delivery and endosomal escape mechanisms.

[000568] The polymer formulation can permit the sustained or delayed release of polynucleotide, primary construct, or mmRNA (e.g., following intramuscular or subcutaneous injection). The altered release profile for the polynucleotide, primary construct, or mmRNA can result in, for example, translation of an encoded protein over an extended period of time. The polymer formulation may also be used to increase the stability of the polynucleotide, primary construct, or mmRNA. Biodegradable polymers have been previously used to protect nucleic acids other than mmRNA from degradation and been shown to result in sustained release of payloads in vivo (Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Sullivan et al., Expert Opin Drug Deliv. 2010 7:1433-1446; Convertine et al., Biomacromolecules. 2010 Oct 1; Chu et al., Acc Chem Res. 2012 Jan 13; Manganiello et al., Biomaterials. 2012 33:2301-2309; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Singha et al., Nucleic Acid Ther. 2011 2:133-147; deFougerolles Hum Gene Ther. 2008 19:125-132; Schaffert and Wagner, Gene Ther. 2008 16:1131-1138; Chaturvedi et al., Expert Opin Drug Deliv. 2011 8:1455-1468; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; each of which is herein incorporated by reference in its entirety).

[000569] In one embodiment, the pharmaceutical compositions may be sustained release formulations. In a further embodiment, the sustained release formulations may be for subcutaneous delivery. Sustained release formulations may include, but are not limited to, PLGA microspheres, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, FL), HYLENEX® (Halozyme Therapeutics, San Diego CA), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, GA), TISSELL® (Baxter International, Inc Deerfield, IL), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, IL).

[000570] As a non-limiting example modified mRNA may be formulated in PLGA microspheres by preparing the PLGA microspheres with tunable release rates (e.g., days and weeks) and encapsulating the modified mRNA in the PLGA microspheres while maintaining the integrity of the modified mRNA during the encapsulation process. EVAc are non-biodegradeable, biocompatible polymers which are used extensively in pre-clinical sustained release implant applications (e.g., extended release products Ocusert a pilocarpine ophthalmic insert for glaucoma or progestasert a sustained release

progesterone intrauterine deivce; transdermal delivery systems Testoderm, Duragesic and Selegiline; catheters). Poloxamer F-407 NF is a hydrophilic, non-ionic surfactant triblock copolymer of polyoxyethylene-polyoxypropylene-polyoxyethylene having a low viscosity at temperatures less than 5°C and forms a solid gel at temperatures greater than 15°C. PEG-based surgical sealants comprise two synthetic PEG components mixed in a delivery device which can be prepared in one minute, seals in 3 minutes and is reabsorbed within 30 days. GELSITE® and natural polymers are capable of in-situ gelation at the site of administration. They have been shown to interact with protein and peptide therapeutic candidates through ionic ineraction to provide a stabilizing effect.

[000571] Polymer formulations can also be selectively targeted through expression of different ligands as exemplified by, but not limited by, folate, transferrin, and N-acetylgalactosamine (GalNAc) (Benoit et al., Biomacromolecules. 2011 12:2708-2714; Rozema et al., Proc Natl Acad Sci U S A. 2007 104:12982-12887; Davis, Mol Pharm. 2009 6:659-668; Davis, Nature 2010 464:1067-1070; each of which is herein incorporated by reference in its entirety).

[000572] The modified nucleic acid, and mmRNA of the invention may be formulated with or in a polymeric compound. The polymer may include at least one polymer such as, but not limited to, polyethenes, polyethylene glycol (PEG), poly(l-lysine)(PLL), PEG grafted to PLL, cationic lipopolymer, biodegradable cationic lipopolymer, polyethyleneimine (PEI), cross-linked branched poly(alkylene imines), a polyamine derivative, a modified poloxamer, a biodegradable polymer, elastic biodegradable polymer, biodegradable block copolymer, biodegradable random copolymer, biodegradable polyester copolymer, biodegradable polyester block copolymer, biodegradable polyester block random copolymer, multiblock copolymers, linear biodegradable copolymer, poly[α-(4-aminobutyl)-L-glycolic acid) (PAGA), biodegradable cross-linked cationic multi-block copolymers, polycarbonates, polyanhydrides, polyhydroxyacids, polypropylfumerates, polycaprolactones, polyamides, polyacetals, polyethers, polyesters, poly(orthoesters), polycyanoacrylates, polyvinyl alcohols, polyurethanes, polyphosphazenes, polyacrylates, polymethacrylates, polycyanoacrylates, polyureas, polystyrenes, polyamines, polylysine, poly(ethylene imine), poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester),

acrylic polymers, amine-containing polymers, dextran polymers, dextran polymer derivatives or or combinations thereof .

[000573] As a non-limiting example, the modified nucleic acid or mmRNA of the invention may be formulated with the polymeric compound of PEG grafted with PLL as described in U.S. Pat. No. 6,177,274; herein incorporated by reference in its entirety. The formulation may be used for transfecting cells *in vitro* or for *in vivo* delivery of the modified nucleic acid and mmRNA. In another example, the modified nucleic acid and mmRNA may be suspended in a solution or medium with a cationic polymer, in a dry pharmaceutical composition or in a solution that is capable of being dried as described in U.S. Pub. Nos. 20090042829 and 20090042825; each of which are herein incorporated by reference in their entireties.

[000574] As another non-limiting example the polynucleotides, primary constructs or mmRNA of the invention may be formulated with a PLGA-PEG block copolymer (see US Pub. No. US20120004293 and US Pat No. 8,236,330, herein incorporated by reference in their entireties) or PLGA-PEG-PLGA block copolymers (See U.S. Pat. No. 6,004,573, herein incorporated by reference in its entirety). As a non-limiting example, the polynucleotides, primary constructs or mmRNA of the invention may be formulated with a diblock copolymer of PEG and PLA or PEG and PLGA (see US Pat No 8,246,968, herein incorporated by reference in its entirety).

[000575] A polyamine derivative may be used to deliver nucleic acids or to treat and/or prevent a disease or to be included in an implantable or injectable device (U.S. Pub. No. 20100260817 herein incorporated by reference in its entirety). As a non-limiting example, a pharmaceutical composition may include the modified nucleic acids and mmRNA and the polyamine derivative described in U.S. Pub. No. 20100260817 (the contents of which are incorporated herein by reference in its entirety. As a non-limiting example the polynucleotides, primary constructs and mmRNA of the present invention may be delivered using a polyaminde polymer such as, but not limited to, a polymer comprising a 1,3-dipolar addition polymer prepared by combining a carbohydrate diazide monomer with a dilkyne unite comprising oligoamines (U.S. Pat. No. 8,236,280; herein incorporated by reference in its entirety).

[000576] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may be formulated with at least one polymer and/or derivatives thereof described in International Publication Nos. WO2011115862, WO2012082574 and WO2012068187 and U.S. Pub. No. 20120283427, each of which are herein incorporated by reference in their entireties. In another embodiment, the modified nucleic acid or mmRNA of the present invention may be formulated with a polymer of formula Z as described in WO2011115862, herein incorporated by reference in its entirety. In yet another embodiment, the modified nucleic acid or mmRNA may be formulated with a polymer of formula Z, Z' or Z'' as described in International Pub. Nos. WO2012082574 or WO2012068187 and U.S. Pub. No. 2012028342, each of which are herein incorporated by reference in their entireties. The polymers formulated with the modified RNA of the present invention may be synthesized by the methods described in International Pub. Nos. WO2012082574 or WO2012068187, each of which are herein incorporated by reference in their entireties.

[000577] The polynucleotides, primary constructs or mmRNA of the invention may be formulated with at least one acrylic polymer. Acrylic polymers include but are not limited to, acrylic acid, methacrylic acid, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, amino alkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), polycyanoacrylates and combinations thereof.

[000578] Formulations of polynucleotides, primary constructs or mmRNA of the invention may include at least one amine-containing polymer such as, but not limited to polylysine, polyethylene imine, poly(amidoamine) dendrimers or combinations thereof.

[000579] For example, the modified nucleic acid or mmRNA of the invention may be formulated in a pharmaceutical compound including a poly(alkylene imine), a biodegradable cationic lipopolymer, a biodegradable block copolymer, a biodegradable polymer, or a biodegradable random copolymer, a biodegradable polyester block copolymer, a biodegradable polyester polymer, a biodegradable polyester random copolymer, a linear biodegradable copolymer, PAGA, a biodegradable cross-linked cationic multi-block copolymer or combinations thereof. The biodegradable cationic lipopolymer may be made by methods known in the art and/or described in U.S. Pat. No.

6,696,038, U.S. App. Nos. 20030073619 and 20040142474 each of which is herein incorporated by reference in their entireties. The poly(alkylene imine) may be made using methods known in the art and/or as described in U.S. Pub. No. 20100004315, herein incorporated by reference in its entirety. The biodegradabale polymer, biodegradable block copolymer, the biodegradable random copolymer, biodegradable polyester block copolymer, biodegradable polyester polymer, or biodegradable polyester random copolymer may be made using methods known in the art and/or as described in U.S. Pat. Nos. 6,517,869 and 6,267,987, the contents of which are each incorporated herein by reference in their entirety. The linear biodegradable copolymer may be made using methods known in the art and/or as described in U.S. Pat. No. 6,652,886. The PAGA polymer may be made using methods known in the art and/or as described in U.S. Pat. No. 6,217,912 herein incorporated by reference in its entirety. The PAGA polymer may be copolymerized to form a copolymer or block copolymer with polymers such as but not limited to, poly-L-lysine, polyargine, polyornithine, histones, avidin, protamines, polylactides and poly(lactide-co-glycolides). The biodegradable cross-linked cationic multi-block copolymers may be made my methods known in the art and/or as described in U.S. Pat. No. 8,057,821 or U.S. Pub. No. 2012009145 each of which are herein incorporated by reference in their entireties. For example, the multi-block copolymers may be synthesized using linear polyethyleneimine (LPEI) blocks which have distinct patterns as compared to branched polyethyleneimines. Further, the composition or pharmaceutical composition may be made by the methods known in the art, described herein, or as described in U.S. Pub. No. 20100004315 or U.S. Pat. Nos. 6,267,987 and 6,217,912 each of which are herein incorporated by reference in their entireties.

[000580] The polynucleotides, primary constructs, and mmRNA of the invention may be formulated with at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

[000581] The polynucleotides, primary construct, mmRNA of the invention may be formulated with at least one crosslinkable polyester. Crosslinkable polyesters include

those known in the art and described in US Pub. No. 20120269761, herein incorporated by reference in its entirety.

[000582] In one embodiment, the polymers described herein may be conjugated to a lipid-terminating PEG. As a non-limiting example, PLGA may be conjugated to a lipid-terminating PEG forming PLGA-DSPE-PEG. As another non-limiting example, PEG conjugates for use with the present invention are described in International Publication No. WO2008103276, herein incorporated by reference in its entirety. The polymers may be conjugated using a ligand conjugate such as, but not limited to, the conjugates described in U.S. Pat. No. 8,273,363, herein incorporated by reference in its entirety.

[000583] In one embodiment, the modified RNA described herein may be conjugated with another compound. Non-limiting examples of conjugates are described in US Patent Nos. 7,964,578 and 7,833,992, each of which are herein incorporated by reference in their entireties. In another embodiment, modified RNA of the present invention may be conjugated with conjugates of formula 1-122 as described in US Patent Nos. 7,964,578 and 7,833,992, each of which are herein incorporated by reference in their entireties. The polynucleotides, primary constructs and/or mmRNA described herein may be conjugated with a metal such as, but not limited to, gold. (See e.g., Giljohann et al. Journ. Amer. Chem. Soc. 2009 131(6): 2072-2073; herein incorporated by reference in its entirety). In another embodiment, the polynucleotides, primary constructs and/or mmRNA described herein may be conjugated and/or encapsulated in gold-nanoparticles. (Interantional Pub. No. WO201216269 and U.S. Pub. No. 20120302940; each of which is herein incorporated by reference in its entirety).

[000584] As described in U.S. Pub. No. 20100004313, herein incorporated by reference in its entirety, a gene delivery composition may include a nucleotide sequence and a poloxamer. For example, the modified nucleic acid and mmRNA of the present inveition may be used in a gene delivery composition with the poloxamer described in U.S. Pub. No. 20100004313.

[000585] In one embodiment, the polymer formulation of the present invention may be stabilized by contacting the polymer formulation, which may include a cationic carrier, with a cationic lipopolymer which may be covalently linked to cholesterol and polyethylene glycol groups. The polymer formulation may be contacted with a cationic

lipopolymer using the methods described in U.S. Pub. No. 20090042829 herein incorporated by reference in its entirety. The cationic carrier may include, but is not limited to, polyethylenimine, poly(trimethylenimine), poly(tetramethylenimine), polypropylenimine, aminoglycoside-polyamine, dideoxy-diamino-b-cyclodextrin, spermine, spermidine, poly(2-dimethylamino)ethyl methacrylate, poly(lysine), poly(histidine), poly(arginine), cationized gelatin, dendrimers, chitosan, 1,2-Dioleoyl-3-Trimethylammonium-Propane(DOTAP), N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), 1-[2-(oleoyloxy)ethyl]-2-oleyl-3-(2-hydroxyethyl)imidazolinium chloride (DOTIM), 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 3B-[N—(N′,N′-Dimethylaminoethane)-carbamoyl]Cholesterol Hydrochloride (DC-Cholesterol HCl) diheptadecylamidoglycyl spermidine (DOGS), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), N,N-dioleyl-N,N-dimethylammonium chloride DODAC) and combinations thereof.

[000586] The polynucleotides, primary constructs and/or mmRNA of the invention may be formulated in a polyplex of one or more polymers (U.S. Pub. No. 20120237565 and 20120270927; each of which is herein incorporated by reference in its entirety). In one embodiment, the polyplex comprises two or more cationic polymers. The catioinic polymer may comprise a poly(ethylene imine) (PEI) such as linear PEI.

[000587] The polynucleotide, primary construct, and mmRNA of the invention can also be formulated as a nanoparticle using a combination of polymers, lipids, and/or other biodegradable agents, such as, but not limited to, calcium phosphate. Components may be combined in a core-shell, hybrid, and/or layer-by-layer architecture, to allow for fine-tuning of the nanoparticle so to delivery of the polynucleotide, primary construct and mmRNA may be enhanced (Wang et al., Nat Mater. 2006 5:791-796; Fuller et al., Biomaterials. 2008 29:1526-1532; DeKoker et al., Adv Drug Deliv Rev. 2011 63:748-761; Endres et al., Biomaterials. 2011 32:7721-7731; Su et al., Mol Pharm. 2011 Jun 6;8(3):774-87; herein incorporated by reference in its entirety). As a non-limiting example, the nanoparticle may comprise a plurality of polymers such as, but not limited to hydrophilic-hydrophobic polymers (e.g., PEG-PLGA), hydrophobic polymers (e.g.,

PEG) and/or hydrophilic polymers (International Pub. No. WO20120225129; herein incorporated by reference in its entirety).

[000588] Biodegradable calcium phosphate nanoparticles in combination with lipids and/or polymers have been shown to deliver polynucleotides, primary constructs and mmRNA *in vivo*. In one embodiment, a lipid coated calcium phosphate nanoparticle, which may also contain a targeting ligand such as anisamide, may be used to deliver the polynucleotide, primary construct and mmRNA of the present invention. For example, to effectively deliver siRNA in a mouse metastatic lung model a lipid coated calcium phosphate nanoparticle was used (Li et al., J Contr Rel. 2010 142: 416-421; Li et al., J Contr Rel. 2012 158:108-114; Yang et al., Mol Ther. 2012 20:609-615; herein incorporated by reference in its entirety). This delivery system combines both a targeted nanoparticle and a component to enhance the endosomal escape, calcium phosphate, in order to improve delivery of the siRNA.

[000589] In one embodiment, calcium phosphate with a PEG-polyanion block copolymer may be used to delivery polynucleotides, primary constructs and mmRNA (Kazikawa et al., J Contr Rel. 2004 97:345-356; Kazikawa et al., J Contr Rel. 2006 111:368-370; herein incorporated by reference in its entirety).

[000590] In one embodiment, a PEG-charge-conversional polymer (Pitella et al., Biomaterials. 2011 32:3106-3114) may be used to form a nanoparticle to deliver the polynucleotides, primary constructs and mmRNA of the present invention. The PEG-charge-conversional polymer may improve upon the PEG-polyanion block copolymers by being cleaved into a polycation at acidic pH, thus enhancing endosomal escape.

[000591] The use of core-shell nanoparticles has additionally focused on a high-throughput approach to synthesize cationic cross-linked nanogel cores and various shells (Siegwart et al., Proc Natl Acad Sci U S A. 2011 108:12996-13001). The complexation, delivery, and internalization of the polymeric nanoparticles can be precisely controlled by altering the chemical composition in both the core and shell components of the nanoparticle. For example, the core-shell nanoparticles may efficiently deliver siRNA to mouse hepatocytes after they covalently attach cholesterol to the nanoparticle.

[000592] In one embodiment, a hollow lipid core comprising a middle PLGA layer and an outer neutral lipid layer containg PEG may be used to delivery of the polynucleotide,

primary construct and mmRNA of the present invention. As a non-limiting example, in mice bearing a luciferease-expressing tumor, it was determined that the lipid-polymer-lipid hybrid nanoparticle significantly suppressed luciferase expression, as compared to a conventional lipoplex (Shi et al, Angew Chem Int Ed. 2011 50:7027-7031; herein incorporated by reference in its entirety).

[000593] In one embodiment, the lipid nanoparticles may comprise a core of the modified nucleic acid molecules disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the modified nucleic acids in the core.

[000594] Core–shell nanoparticles for use with the modified nucleic acid molecules of the present invention are described and may be formed by the methods described in U.S. Pat. No. 8,313,777 herein incorporated by reference in its entirety.

[000595] In one embodiment, the core-shell nanoparticles may comprise a core of the modified nucleic acid molecules disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the modified nucleic acid molecules in the core. As a non-limiting example, the core-shell nanoparticle may be used to treat an eye disease or disorder (See e.g. US Publication No. 20120321719, herein incorporated by reference in its entirety).

[000596] In one embodiment, the polymer used with the formulations described herein may be a modified polymer (such as, but not limited to, a modified polyacetal) as described in International Publication No. WO2011120053, herein incorporated by reference in its entirety.

Peptides and Proteins

[000597] The polynucleotide, primary construct, and mmRNA of the invention can be formulated with peptides and/or proteins in order to increase transfection of cells by the polynucleotide, primary construct, or mmRNA. In one embodiment, peptides such as, but not limited to, cell penetrating peptides and proteins and peptides that enable intracellular delivery may be used to deliver pharmaceutical formulations. A non-limiting example of a cell penetrating peptide which may be used with the pharmaceutical formulations of the

present invention includes a cell-penetrating peptide sequence attached to polycations that facilitates delivery to the intracellular space, e.g., HIV-derived TAT peptide, penetratins, transportans, or hCT derived cell-penetrating peptides (see, e.g., Caron et al., Mol. Ther. 3(3):310-8 (2001); Langel, Cell-Penetrating Peptides: Processes and Applications (CRC Press, Boca Raton FL, 2002); El-Andaloussi et al., Curr. Pharm. Des. 11(28):3597-611 (2003); and Deshayes et al., Cell. Mol. Life Sci. 62(16):1839-49 (2005), all of which are incorporated herein by reference in their entirety). The compositions can also be formulated to include a cell penetrating agent, e.g., liposomes, which enhance delivery of the compositions to the intracellular space. Polynucleotides, primary constructs, and mmRNA of the invention may be complexed to peptides and/or proteins such as, but not limited to, peptides and/or proteins from Aileron Therapeutics (Cambridge, MA) and Permeon Biologics (Cambridge, MA) in order to enable intracellular delivery (Cronican et al., ACS Chem. Biol. 2010 5:747-752; McNaughton et al., Proc. Natl. Acad. Sci. USA 2009 106:6111-6116; Sawyer, Chem Biol Drug Des. 2009 73:3-6; Verdine and Hilinski, Methods Enzymol. 2012;503:3-33; all of which are herein incorporated by reference in its entirety).

[000598] In one embodiment, the cell-penetrating polypeptide may comprise a first domain and a second domain. The first domain may comprise a supercharged polypeptide. The second domain may comprise a protein-binding partner. As used herein, "protein-binding partner" includes, but are not limited to, antibodies and functional fragments thereof, scaffold proteins, or peptides. The cell-penetrating polypeptide may further comprise an intracellular binding partner for the protein-binding partner. The cell-penetrating polypeptide may be capable of being secreted from a cell where the polynucleotide, primary construct, or mmRNA may be introduced.

[000599] Formulations of the including peptides or proteins may be used to increase cell transfection by the polynucleotide, primary construct, or mmRNA, alter the biodistribution of the polynucleotide, primary construct, or mmRNA (e.g., by targeting specific tissues or cell types), and/or increase the translation of encoded protein. (See e.g., International Pub. No. WO2012110636; herein incorporated by reference in its entirety).

Cells

[000600] The polynucleotide, primary construct, and mmRNA of the invention can be transfected *ex vivo* into cells, which are subsequently transplanted into a subject. As non-limiting examples, the pharmaceutical compositions may include red blood cells to deliver modified RNA to liver and myeloid cells, virosomes to deliver modified RNA in virus-like particles (VLPs), and electroporated cells such as, but not limited to, from MAXCYTE® (Gaithersburg, MD) and from ERYTECH® (Lyon, France) to deliver modified RNA. Examples of use of red blood cells, viral particles and electroporated cells to deliver payloads other than mmRNA have been documented (Godfrin et al., Expert Opin Biol Ther. 2012 12:127-133; Fang et al., Expert Opin Biol Ther. 2012 12:385-389; Hu et al., Proc Natl Acad Sci U S A. 2011 108:10980-10985; Lund et al., Pharm Res. 2010 27:400-420; Huckriede et al., J Liposome Res. 2007;17:39-47; Cusi, Hum Vaccin. 2006 2:1-7; de Jonge et al., Gene Ther. 2006 13:400-411; all of which are herein incorporated by reference in its entirety).

[000601] The polynucleotides, primary constructs and mmRNA may be delivered in synthetic VLPs synthesized by the methods described in International Pub No. WO2011085231 and US Pub No. 20110171248, each of which are herein incorporated by reference in their entireties.

[000602] Cell-based formulations of the polynucleotide, primary construct, and mmRNA of the invention may be used to ensure cell transfection (e.g., in the cellular carrier), alter the biodistribution of the polynucleotide, primary construct, or mmRNA (e.g., by targeting the cell carrier to specific tissues or cell types), and/or increase the translation of encoded protein.

[000603] A variety of methods are known in the art and suitable for introduction of nucleic acid into a cell, including viral and non-viral mediated techniques. Examples of typical non-viral mediated techniques include, but are not limited to, electroporation, calcium phosphate mediated transfer, nucleofection, sonoporation, heat shock, magnetofection, liposome mediated transfer, microinjection, microprojectile mediated transfer (nanoparticles), cationic polymer mediated transfer (DEAE-dextran, polyethylenimine, polyethylene glycol (PEG) and the like) or cell fusion.

[000604] The technique of sonoporation, or cellular sonication, is the use of sound (e.g., ultrasonic frequencies) for modifying the permeability of the cell plasma membrane. Sonoporation methods are known to those in the art and are used to deliver nucleic acids *in vivo* (Yoon and Park, Expert Opin Drug Deliv. 2010 7:321-330; Postema and Gilja, Curr Pharm Biotechnol. 2007 8:355-361; Newman and Bettinger, Gene Ther. 2007 14:465-475; all herein incorporated by reference in their entirety). Sonoporation methods are known in the art and are also taught for example as it relates to bacteria in US Patent Publication 20100196983 and as it relates to other cell types in, for example, US Patent Publication 20100009424, each of which are incorporated herein by reference in their entirety.

[000605] Electroporation techniques are also well known in the art and are used to deliver nucleic acids *in vivo* and clinically (Andre et al., Curr Gene Ther. 2010 10:267-280; Chiarella et al., Curr Gene Ther. 2010 10:281-286; Hojman, Curr Gene Ther. 2010 10:128-138; all herein incorporated by reference in their entirety). In one embodiment, polynucleotides, primary constructs or mmRNA may be delivered by electroporation as described in Example 8.

Hyaluronidase

[000606] The intramuscular or subcutaneous localized injection of polynucleotide, primary construct, or mmRNA of the invention can include hyaluronidase, which catalyzes the hydrolysis of hyaluronan. By catalyzing the hydrolysis of hyaluronan, a constituent of the interstitial barrier, hyaluronidase lowers the viscosity of hyaluronan, thereby increasing tissue permeability (Frost, Expert Opin. Drug Deliv. (2007) 4:427-440; herein incorporated by reference in its entirety). It is useful to speed their dispersion and systemic distribution of encoded proteins produced by transfected cells. Alternatively, the hyaluronidase can be used to increase the number of cells exposed to a polynucleotide, primary construct, or mmRNA of the invention administered intramuscularly or subcutaneously.

Nanoparticle Mimics

[000607] The polynucleotide, primary construct or mmRNA of the invention may be encapsulated within and/or absorbed to a nanoparticle mimic. A nanoparticle mimic can mimic the delivery function organisms or particles such as, but not limited to, pathogens,

viruses, bacteria, fungus, parasites, prions and cells. As a non-limiting example the polynucleotide, primary construct or mmRNA of the invention may be encapsulated in a non-viron particle which can mimic the delivery function of a virus (see International Pub. No. WO2012006376 herein incorporated by reference in its entirety).

Nanotubes

[000608] The polynucleotides, primary constructs or mmRNA of the invention can be attached or otherwise bound to at least one nanotube such as, but not limited to, rosette nanotubes, rosette nanotubes having twin bases with a linker, carbon nanotubes and/or single-walled carbon nanotubes, The polynucleotides, primary constructs or mmRNA may be bound to the nanotubes through forces such as, but not limited to, steric, ionic, covalent and/or other forces.

[000609] In one embodiment, the nanotube can release one or more polynucleotides, primary constructs or mmRNA into cells. The size and/or the surface structure of at least one nanotube may be altered so as to govern the interaction of the nanotubes within the body and/or to attach or bind to the polynucleotides, primary constructs or mmRNA disclosed herein. In one embodiment, the building block and/or the functional groups attached to the building block of the at least one nanotube may be altered to adjust the dimensions and/or properties of the nanotube. As a non-limiting example, the length of the nanotubes may be altered to hinder the nanotubes from passing through the holes in the walls of normal blood vessels but still small enough to pass through the larger holes in the blood vessels of tumor tissue.

[000610] In one embodiment, at least one nanotube may also be coated with delivery enhancing compounds including polymers, such as, but not limited to, polyethylene glycol. In another embodiment, at least one nanotube and/or the polynucleotides, primary constructs or mmRNA may be mixed with pharmaceutically acceptable excipients and/or delivery vehicles.

[000611] In one embodiment, the polynucleotides, primary constructs or mmRNA are attached and/or otherwise bound to at least one rosette nanotube. The rosette nanotubes may be formed by a process known in the art and/or by the process described in International Publication No. WO2012094304, herein incorporated by reference in its entirety. At least one polynucleotide, primary construct and/or mmRNA may be attached

and/or otherwise bound to at least one rosette nanotube by a process as described in International Publication No. WO2012094304, herein incorporated by reference in its entirety, where rosette nanotubes or modules forming rosette nanotubes are mixed in aqueous media with at least one polynucleotide, primary construct and/or mmRNA under conditions which may cause at least one polynucleotide, primary construct or mmRNA to attach or otherwise bind to the rosette nanotubes.

[000612] In one embodiment, the polynucleotides, primary constructs or mmRNA may be attached to and/or otherwise bound to at least one carbon nanotube. As a non-limiting example, the polynucleotides, primary constructs or mmRNA may be bound to a linking agent and the linked agent may be bound to the carbon nanotube (See e.g., U.S. Pat No. 8,246,995; herein incorporated by reference in its entirety). The carbon nanotube may be a single-walled nanotube (See e.g., U.S. Pat No. 8,246,995; herein incorporated by reference in its entirety).

Conjugates

[000613] The polynucleotides, primary constructs, and mmRNA of the invention include conjugates, such as a polynucleotide, primary construct, or mmRNA covalently linked to a carrier or targeting group, or including two encoding regions that together produce a fusion protein (e.g., bearing a targeting group and therapeutic protein or peptide).

[000614] The conjugates of the invention include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), high-density lipoprotein (HDL), or globulin); an carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand may also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid, an oligonucleotide (e.g. an aptamer). Examples of polyamino acids include polyamino acid is a polylysine (PLL), poly L-aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine,

spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or an alpha helical peptide.

[000615] Representative U.S. patents that teach the preparation of polynucleotide conjugates, particularly to RNA, include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941; 6,294,664; 6,320,017; 6,576,752; 6,783,931; 6,900,297; 7,037,646; each of which is herein incorporated by reference in their entireties.

[000616] In one embodiment, the conjugate of the present invention may function as a carrier for the modified nucleic acids and mmRNA of the present invention. The conjugate may comprise a cationic polymer such as, but not limited to, polyamine, polylysine, polyalkylenimine, and polyethylenimine which may be grafted to with poly(ethylene glycol). As a non-limiting example, the conjugate may be similar to the polymeric conjugate and the method of synthesizing the polymeric conjugate described in U.S. Pat. No. 6,586,524 herein incorporated by reference in its entirety.

[000617] The conjugates can also include targeting groups, e.g., a cell or tissue targeting agent, e.g., a lectin, glycoprotein, lipid or protein, e.g., an antibody, that binds to a specified cell type such as a kidney cell. A targeting group can be a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, an RGD peptide, an RGD peptide mimetic or an aptamer.

[000618] Targeting groups can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a cancer cell, endothelial cell, or bone cell. Targeting groups may also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, or aptamers. The ligand can be, for example, a lipopolysaccharide, or an activator of p38 MAP kinase.

[000619] The targeting group can be any ligand that is capable of targeting a specific receptor. Examples include, without limitation, folate, GalNAc, galactose, mannose, mannose-6P, apatamers, integrin receptor ligands, chemokine receptor ligands, transferrin, biotin, serotonin receptor ligands, PSMA, endothelin, GCPII, somatostatin, LDL, and HDL ligands. In particular embodiments, the targeting group is an aptamer. The aptamer can be unmodified or have any combination of modifications disclosed herein.

[000620] In one embodiment, pharmaceutical compositions of the present invention may include chemical modifications such as, but not limited to, modifications similar to locked nucleic acids.

[000621] Representative U.S. Patents that teach the preparation of locked nucleic acid (LNA) such as those from Santaris, include, but are not limited to, the following: U.S. Pat. Nos. 6,268,490; 6,670,461; 6,794,499; 6,998,484; 7,053,207; 7,084,125; and 7,399,845, each of which is herein incorporated by reference in its entirety.

[000622] Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found, for example, in Nielsen *et al.*, Science, 1991, 254, 1497-1500.

[000623] Some embodiments featured in the invention include polynucleotides, primary constructs or mmRNA with phosphorothioate backbones and oligonucleosides with other modified backbones, and in particular --CH_2--NH--CH_2--, --CH_2--N(CH_3)--O--CH_2-- [known as a methylene (methylimino) or MMI backbone], --CH_2--O--N(CH_3)--CH_2--, --CH_2--N(CH_3)--N(CH_3)--CH_2-- and --N(CH_3)--CH_2--CH_2--[wherein the native

phosphodiester backbone is represented as --O—$P(O)_2$--O--CH_2--] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240. In some embodiments, the polynucletotides featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

[000624] Modifications at the 2′ position may also aid in delivery. Preferably, modifications at the 2′ position are not located in a polypeptide-coding sequence, i.e., not in a translatable region. Modifications at the 2′ position may be located in a 5′UTR, a 3′UTR and/or a tailing region. Modifications at the 2′ position can include one of the following at the 2' position: H (i.e., 2′-deoxy); F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Exemplary suitable modifications include $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. In other embodiments, the polynucleotides, primary constructs or mmRNA include one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties, or a group for improving the pharmacodynamic properties, and other substituents having similar properties. In some embodiments, the modification includes a 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin *et al.*, *Helv. Chim. Acta*, 1995, 78:486-504) *i.e.*, an alkoxy-alkoxy group. Another exemplary modification is 2'-dimethylaminooxyethoxy, *i.e.*, a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), *i.e.*, 2'-O--CH_2--O--CH_2--$N(CH_2)_2$, also described in examples herein below. Other modifications include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked dsRNAs and the 5' position of 5' terminal nucleotide. Polynucleotides of the

invention may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920 and each of which is herein incorporated by reference.

[000625] In still other embodiments, the polynucleotide, primary construct, or mmRNA is covalently conjugated to a cell penetrating polypeptide. The cell-penetrating peptide may also include a signal sequence. The conjugates of the invention can be designed to have increased stability; increased cell transfection; and/or altered the biodistribution (e.g., targeted to specific tissues or cell types).

[000626] In one embodiment, the polynucleotides, primary constructs or mmRNA may be conjugated to an agent to enhance delivery. As a non-limiting example, the agent may be a monomer or polymer such as a targeting monomer or a polymer having targeting blocks as described in International Publication No. WO2011062965, herein incorporated by reference in its entirety. In another non-limiting example, the agent may be a transport agent covalently coupled to the polynucleotides, primary constructs or mmRNA of the present invention (See e.g., U.S. Pat. Nos. 6,835.393 and 7,374,778, each of which is herein incorporated by reference in its entirety). In yet another non-limiting example, the agent may be a membrane barrier transport enhancing agent such as those described in U.S. Pat. Nos. 7,737,108 and 8,003,129, each of which is herein incorporated by reference in its entirety.

[000627] In another embodiment, polynucleotides, primary constructs or mmRNA may be conjugated to SMARTT POLYMER TECHNOLOGY® (PHASERX®, Inc. Seattle, WA).

Self-Assembled Nanoparticles

Nucleic Acid Self-Assembled Nanoparticles

[000628] Self-assembled nanoparticles have a well-defined size which may be precisely controlled as the nucleic acid strands may be easily reprogrammable. For example, the optimal particle size for a cancer-targeting nanodelivery carrier is 20-100 nm as a

diameter greater than 20 nm avoids renal clearance and enhances delivery to certain tumors through enhanced permeability and retention effect. Using self-assembled nucleic acid nanoparticles a single uniform population in size and shape having a precisely controlled spatial orientation and density of cancer-targeting ligands for enhanced delivery. As a non-limiting example, oligonucleotide nanoparticles were prepared using programmable self-assembly of short DNA fragments and therapeutic siRNAs. These nanoparticles are molecularly identical with controllable particle size and target ligand location and density. The DNA fragments and siRNAs self-assembled into a one-step reaction to generate DNA/siRNA tetrahedral nanoparticles for targeted *in vivo* delivery. (Lee et al., Nature Nanotechnology 2012 7:389-393; herein incorporated by reference in its entirety).

[000629] In one embodiment, the polynucleotides, primary constructs and/or mmRNA disclosed herein may be formulated as self-assembled nanoparticles. As a non-limiting example, nucleic acids may be used to make nanoparticles which may be used in a delivery system for the polynucleotides, primary constructs and/or mmRNA of the present invention (See e.g., International Pub. No. WO2012125987; herein incorporated by reference in its entirety).

[000630] In one embodiment, the nucleic acid self-assembled nanoparticles may comprise a core of the polynucleotides, primary constructs or mmRNA disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the polynucleotides, primary contructs and mmRNA in the core.

Polymer-Based Self-Assembled Nanoparticles

[000631] Polymers may be used to form sheets which self-assembled into nanoparticles. These nanoparticles may be used to deliver the polynucleotides, primary constructs and mmRNA of the present invention. In one embodiment, these self-assembled nanoparticles may be microsponges formed of long polymers of RNA hairpins which form into crystalline 'pleated' sheets before self-assembling into microsponges. These microsponges are densely-packed sponge like microparticles which may function as an efficient carrier and may be able to deliver cargo to a cell. The microsponges may be from 1um to 300 nm in diameter. The microsponges may be complexed with other

agents known in the art to form larger microsponges. As a non-limiting example, the microsponge may be complexed with an agent to form an outer layer to promote cellular uptake such as polycation polyethyleneime (PEI). This complex can form a 250-nm diameter particle that can remain stable at high temperatures (150°C) (Grabow and Jaegar, Nature Materials 2012, 11:269-269; herein incorporated by reference in its entirety). Additionally these microsponges may be able to exhibit an extraordinary degree of protection from degradation by ribonucleases.

[000632] In another embodiment, the polymer-based self-assembled nanoparticles such as, but not limited to, microsponges, may be fully programmable nanoparticles. The geometry, size and stoichiometry of the nanoparticle may be precisely controlled to create the optimal nanoparticle for delivery of cargo such as, but not limited to, polynucleotides, primary constructs and/or mmRNA.

[000633] In one embodiment, the polymer based nanoparticles may comprise a core of the polynucleotides, primary constructs and/or mmRNA disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the polynucleotides, primary construct and/or mmRNA in the core.

[000634] In yet another embodiment, the polymer based nanoparticle may comprise a non-nucleic acid polymer comprising a plurality of heterogenous monomers such as those described in Interantional Publication No. WO2013009736, herein incorporated by reference in its entirety.

Inorganic Nanoparticles

[000635] The polynucleotides, primary constructs and/or mmRNAs of the present invention may be formulated in inorganic nanoparticles (U.S. Pat. No. 8,257,745, herein incorporated by reference in its entirety). The inorganic nanoparticles may include, but are not limited to, clay substances that are water swellable. As a non-limiting example, the inorganic nanoparticle may include synthetic smectite clays which are made from simple silicates (See e.g., U.S. Pat. No. 5,585,108 and 8,257,745 each of which are herein incorporated by reference in their entirety).

[000636] In one embodiment, the inorganic nanoparticles may comprise a core of the modified nucleic acids disclosed herein and a polymer shell. The polymer shell may be

any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the modified nucleic acids in the core.

Semi-conductive and Metallic Nanoparticles

[000637] The polynucleotides, primary constructs and/or mmRNAs of the present invention may be formulated in water-dispersible nanoparticle comprising a semiconductive or metallic material (U.S. Pub. No. 20120228565; herein incorporated by reference in its entirety) or formed in a magnetic nanoparticle (U.S. Pub. No. 20120265001 and 20120283503; each of which is herein incorporated by reference in its entirety). The water-dispersible nanoparticles may be hydrophobic nanoparticles or hydrophilic nanoparticles.

[000638] In one embodiment, the semi-conductive and/or metallic nanoparticles may comprise a core of the polynucleotides, primary constructs and/or mmRNA disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the polynucleotides, primary constructs and/or mmRNA in the core.

Gels and Hydrogels

[000639] In one embodiment, the polynucleotides, primary constructs and/or mmRNA disclosed herein may be encapsulated into any hydrogel known in the art which may form a gel when injected into a subject. Hydrogels are a network of polymer chains that are hydrophilic, and are sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 99% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content. The hydrogel described herein may used to encapsulate lipid nanoparticles which are biocompatible, biodegradable and/or porous.

[000640] As a non-limiting example, the hydrogel may be an aptamer-functionalized hydrogel. The aptamer-functionalized hydrogel may be programmed to release one or more polynucleotides, primary constructs and/or mmRNA using nucleic acid hybridization. (Battig et al., J. Am. Chem. Society. 2012 134:12410-12413; herein incorporated by reference in its entirety).

[000641] As another non-limiting example, the hydrogel may be a shaped as an inverted opal.

The opal hydrogels exhibit higher swelling ratios and the swelling kinetics is an order of magnitude faster as well. Methods of producing opal hydrogels and description of opal hydrogels are described in International Pub. No. WO2012148684, herein incorporated by reference in its entirety.

[000642] In yet another non-limiting example, the hydrogel may be an antibacterial hydrogel. The antibacterial hydrogel may comprise a pharmaceutical acceptable salt or organic material such as, but not limited to pharmaceutical grade and/or medical grade silver salt and aloe vera gel or extract. (International Pub. No. WO2012151438, herein incorporated by reference in its entirety).

[000643] In one embodiment, the modified mRNA may be encapsulated in a lipid nanoparticle and then the lipid nanoparticle may be encapsulated into a hyrdogel.

[000644] In one embodiment, the polynucleotides, primary constructs and/or mmRNA disclosed herein may be encapsulated into any gel known in the art. As a non-limiting example the gel may be a fluorouracil injectable gel or a fluorouracil injectable gel containing a chemical compound and/or drug known in the art. As another example, the polynucleotides, primary constructs and/or mmRNA may be encapsulated in a fluorouracil gel containing epinephrine (See e.g., Smith et al. Cancer Chemotherapty and Pharmacology, 1999 44(4):267-274; herein incorporated by reference in its entirety).

[000645] In one embodiment, the polynucleotides, primary constructs and/or mmRNA disclosed herein may be encapsulated into a fibrin gel, fibrin hydrogel or fibrin glue. In another embodiment, the polynucleotides, primary constructs and/or mmRNA may be formulated in a lipid nanoparticle or a rapidly eliminated lipid nanoparticle prior to being encapsulated into a fibrin gel, fibrin hydrogel or a fibrin glue. In yet another embodiment, the polynucleotides, primary constructs and/or mmRNA may be formulated as a lipoplex prior to being encapsulated into a fibrin gel, hydrogel or a fibrin glue. Fibrin gels, hydrogels and glues comprise two components, a fibrinogen solution and a thrombin solution which is rich in calcium (See e.g., Spicer and Mikos, Journal of Controlled Release 2010. 148: 49-55; Kidd et al. Journal of Controlled Release 2012. 157:80-85; each of which is herein incorporated by reference in its entirety). The

concentration of the components of the fibrin gel, hydrogel and/or glue can be altered to change the characteristics, the network mesh size, and/or the degradation characteristics of the gel, hydrogel and/or glue such as, but not limited to changing the release characteristics of the fibrin gel, hydrogel and/or glue. (See e.g., Spicer and Mikos, Journal of Controlled Release 2010. 148: 49-55; Kidd et al. Journal of Controlled Release 2012. 157:80-85; Catelas et al. Tissue Engineering 2008. 14:119-128; each of which is herein incorporated by reference in its entirety). This feature may be advantageous when used to deliver the modified mRNA disclosed herein. (See e.g., Kidd et al. Journal of Controlled Release 2012. 157:80-85; Catelas et al. Tissue Engineering 2008. 14:119-128; each of which is herein incorporated by reference in its entirety).

Cations and Anions

[000646] Formulations of polynucleotides, primary constructs and/or mmRNA disclosed herein may include cations or anions. In one embodiment, the formulations include metal cations such as, but not limited to, Zn2+, Ca2+, Cu2+, Mg+ and combinations thereof. As a non-limiting example, formulations may include polymers and a polynucleotides, primary constructs and/or mmRNA complexed with a metal cation (See e.g., U.S. Pat. Nos. 6,265,389 and 6,555,525, each of which is herein incorporated by reference in its entirety).

Molded Nanoparticles and Microparticles

[000647] The polynucleotides, primary constructs and/or mmRNA disclosed herein may be formulated in nanoparticles and/or microparticles. These nanoparticles and/or microparticles may be molded into any size shape and chemistry. As an example, the nanoparticles and/or microparticles may be made using the PRINT® technology by LIQUIDA TECHNOLOGIES® (Morrisville, NC) (See e.g., International Pub. No. WO2007024323; herein incorporated by reference in its entirety).

[000648] In one embodiment, the molded nanoparticles may comprise a core of the polynucleotides, primary constructs and/or mmRNA disclosed herein and a polymer shell. The polymer shell may be any of the polymers described herein and are known in the art. In an additional embodiment, the polymer shell may be used to protect the polynucleotides, primary construct and/or mmRNA in the core.

NanoJackets and NanoLiposomes

[000649] The polynucleotides, primary constructs and/or mmRNA disclosed herein may be formulated in NanoJackets and NanoLiposomes by Keystone Nano (State College, PA). NanoJackets are made of compounds that are naturally found in the body including calcium, phosphate and may also include a small amount of silicates. Nanojackets may range in size from 5 to 50 nm and may be used to deliver hydrophilic and hydrophobic compounds such as, but not limited to, polynucleotides, primary constructs and/or mmRNA.

[000650] NanoLiposomes are made of lipids such as, but not limited to, lipids which naturally occur in the body. NanoLiposomes may range in size from 60-80 nm and may be used to deliver hydrophilic and hydrophobic compounds such as, but not limited to, polynucleotides, primary constructs and/or mmRNA. In one aspect, the polynucleotides, primary constructs and/or mmRNA disclosed herein are formulated in a NanoLiposome such as, but not limited to, Ceramide NanoLiposomes.

Excipients

[000651] Pharmaceutical formulations may additionally comprise a pharmaceutically acceptable excipient, which, as used herein, includes any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's *The Science and Practice of Pharmacy*, 21st Edition, A. R. Gennaro (Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety) discloses various excipients used in formulating pharmaceutical compositions and known techniques for the preparation thereof. Except insofar as any conventional excipient medium is incompatible with a substance or its derivatives, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutical composition, its use is contemplated to be within the scope of this invention.

[000652] In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use in humans and for veterinary use. In some embodiments, an excipient is approved by United States Food and Drug Administration.

In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[000653] Pharmaceutically acceptable excipients used in the manufacture of pharmaceutical compositions include, but are not limited to, inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Such excipients may optionally be included in pharmaceutical compositions.

[000654] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

[000655] Exemplary granulating and/or dispersing agents include, but are not limited to, potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation-exchange resins, calcium carbonate, silicates, sodium carbonate, cross-linked poly(vinyl-pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross-linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (VEEGUM®), sodium lauryl sulfate, quaternary ammonium compounds, *etc.*, and/or combinations thereof.

[000656] Exemplary surface active agents and/or emulsifiers include, but are not limited to, natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (e.g. bentonite [aluminum silicate] and VEEGUM® [magnesium aluminum silicate]), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid

polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (e.g. polyoxyethylene sorbitan monolaurate [TWEEN®20], polyoxyethylene sorbitan [TWEENn®60], polyoxyethylene sorbitan monooleate [TWEEN®80], sorbitan monopalmitate [SPAN®40], sorbitan monostearate [SPAN®60], sorbitan tristearate [SPAN®65], glyceryl monooleate, sorbitan monooleate [SPAN®80]), polyoxyethylene esters (e.g. polyoxyethylene monostearate [MYRJ®45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and SOLUTOL®), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. CREMOPHOR®), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [BRIJ®30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, PLUORINC®F 68, POLOXAMER®188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, etc. and/or combinations thereof.

[000657] Exemplary binding agents include, but are not limited to, starch (*e.g.* cornstarch and starch paste); gelatin; sugars (*e.g.* sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol,); natural and synthetic gums (*e.g.* acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum®), and larch arabogalactan); alginates; polyethylene oxide; polyethylene glycol; inorganic calcium salts; silicic acid; polymethacrylates; waxes; water; alcohol; *etc.*; and combinations thereof.

[000658] Exemplary preservatives may include, but are not limited to, antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and/or other preservatives. Exemplary antioxidants include, but are not limited to, alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium

metabisulfite, and/or sodium sulfite. Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA), citric acid monohydrate, disodium edetate, dipotassium edetate, edetic acid, fumaric acid, malic acid, phosphoric acid, sodium edetate, tartaric acid, and/or trisodium edetate. Exemplary antimicrobial preservatives include, but are not limited to, benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and/or thimerosal. Exemplary antifungal preservatives include, but are not limited to, butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and/or sorbic acid. Exemplary alcohol preservatives include, but are not limited to, ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and/or phenylethyl alcohol. Exemplary acidic preservatives include, but are not limited to, vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and/or phytic acid. Other preservatives include, but are not limited to, tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluened (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, GLYDANT PLUS®, PHENONIP®, methylparaben, GERMALL®115, GERMABEN®II, NEOLONE™, KATHON™, and/or EUXYL®.

[000659] Exemplary buffering agents include, but are not limited to, citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic

sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, *etc.*, and/or combinations thereof.

[000660] Exemplary lubricating agents include, but are not limited to, magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behanate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, *etc.*, and combinations thereof.

[000661] Exemplary oils include, but are not limited to, almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut, mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils. Exemplary oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and/or combinations thereof.

[000662] Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and/or perfuming agents can be present in the composition, according to the judgment of the formulator.

Delivery

[000663] The present disclosure encompasses the delivery of polynucleotides, primary constructs or mmRNA for any of therapeutic, pharmaceutical, diagnostic or imaging by any appropriate route taking into consideration likely advances in the sciences of drug delivery. Delivery may be naked or formulated.

Naked Delivery

[000664] The polynucleotides, primary constructs or mmRNA of the present invention may be delivered to a cell naked. As used herein in, "naked" refers to delivering

polynucleotides, primary constructs or mmRNA free from agents which promote transfection. For example, the polynucleotides, primary constructs or mmRNA delivered to the cell may contain no modifications. The naked polynucleotides, primary constructs or mmRNA may be delivered to the cell using routes of administration known in the art and described herein.

Formulated Delivery

[000665] The polynucleotides, primary constructs or mmRNA of the present invention may be formulated, using the methods described herein. The formulations may contain polynucleotides, primary constructs or mmRNA which may be modified and/or unmodified. The formulations may further include, but are not limited to, cell penetration agents, a pharmaceutically acceptable carrier, a delivery agent, a bioerodible or biocompatible polymer, a solvent, and a sustained-release delivery depot. The formulated polynucleotides, primary constructs or mmRNA may be delivered to the cell using routes of administration known in the art and described herein.

[000666] The compositions may also be formulated for direct delivery to an organ or tissue in any of several ways in the art including, but not limited to, direct soaking or bathing, via a catheter, by gels, powder, ointments, creams, gels, lotions, and/or drops, by using substrates such as fabric or biodegradable materials coated or impregnated with the compositions, and the like.

Administration

[000667] The polynucleotides, primary constructs or mmRNA of the present invention may be administered by any route which results in a therapeutically effective outcome. These include, but are not limited to enteral, gastroenteral, epidural, oral, transdermal, epidural (peridural), intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal, (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intraarterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraperitoneal, (infusion or injection into the peritoneum), intravesical infusion, intravitreal, (through the eye), intracavernous injection, (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic

administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), or in ear drops. In specific embodiments, compositions may be administered in a way which allows them cross the blood-brain barrier, vascular barrier, or other epithelial barrier.Non-limiting routes of administration for the polynucleotides, primary constructs or mmRNA of the present invention are described below.

Parenteral and Injectible Administration

[000668] Liquid dosage forms for parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

[000669] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can

be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

[000670] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000671] In order to prolong the effect of an active ingredient, it is often desirable to slow the absorption of the active ingredient from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

Rectal and Vaginal Administration

[000672] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing compositions with suitable non-irritating excipients such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

Oral Administration

[000673] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl

carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and/or perfuming agents. In certain embodiments for parenteral administration, compositions are mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

[000674] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, an active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient such as sodium citrate or dicalcium phosphate and/or fillers or extenders (*e.g.* starches, lactose, sucrose, glucose, mannitol, and silicic acid), binders (*e.g.* carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia), humectants (*e.g.* glycerol), disintegrating agents (*e.g.* agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate), solution retarding agents (*e.g.* paraffin), absorption accelerators (*e.g.* quaternary ammonium compounds), wetting agents (*e.g.* cetyl alcohol and glycerol monostearate), absorbents (*e.g.* kaolin and bentonite clay), and lubricants (*e.g.* talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate), and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

Topical or Transdermal Administration

[000675] As described herein, compositions containing the polynucleotides, primary constructs or mmRNA of the invention may be formulated for administration topically. The skin may be an ideal target site for delivery as it is readily accessible. Gene expression may be restricted not only to the skin, potentially avoiding nonspecific toxicity, but also to specific layers and cell types within the skin.

[000676] The site of cutaneous expression of the delivered compositions will depend on the route of nucleic acid delivery. Three routes are commonly considered to deliver polynucleotides, primary constructs or mmRNA to the skin: (i) topical application (e.g.

for local/regional treatment and/or cosmetic applications); (ii) intradermal injection (e.g. for local/regional treatment and/or cosmetic applications); and (iii) systemic delivery (e.g. for treatment of dermatologic diseases that affect both cutaneous and extracutaneous regions). Polynucleotides, primary constructs or mmRNA can be delivered to the skin by several different approaches known in the art. Most topical delivery approaches have been shown to work for delivery of DNA, such as but not limited to, topical application of non-cationic liposome–DNA complex, cationic liposome–DNA complex, particle-mediated (gene gun), puncture-mediated gene transfections, and viral delivery approaches. After delivery of the nucleic acid, gene products have been detected in a number of different skin cell types, including, but not limited to, basal keratinocytes, sebaceous gland cells, dermal fibroblasts and dermal macrophages.

[000677] In one embodiment, the invention provides for a variety of dressings (e.g., wound dressings) or bandages (e.g., adhesive bandages) for conveniently and/or effectively carrying out methods of the present invention. Typically dressing or bandages may comprise sufficient amounts of pharmaceutical compositions and/or polynucleotides, primary constructs or mmRNA described herein to allow a user to perform multiple treatments of a subject(s).

[000678] In one embodiment, the invention provides for the polynucleotides, primary constructs or mmRNA compositions to be delivered in more than one injection.

[000679] In one embodiment, before topical and/or transdermal administration at least one area of tissue, such as skin, may be subjected to a device and/or solution which may increase permeability. In one embodiment, the tissue may be subjected to an abrasion device to increase the permeability of the skin (see U.S. Patent Publication No. 20080275468, herein incorporated by reference in its entirety). In another embodiment, the tissue may be subjected to an ultrasound enhancement device. An ultrasound enhancement device may include, but is not limited to, the devices described in U.S. Publication No. 20040236268 and U.S. Patent Nos. 6,491,657 and 6,234,990; each of which are herein incorporated by reference in their entireties. Methods of enhancing the permeability of tissue are described in U.S. Publication Nos. 20040171980 and 20040236268 and U.S. Pat. No. 6,190,315; each of which are herein incorporated by reference in their entireties.

[000680] In one embodiment, a device may be used to increase permeability of tissue before delivering formulations of modified mRNA described herein. The permeability of skin may be measured by methods known in the art and/or described in U.S. Patent No. 6,190,315, herein incorporated by reference in its entirety. As a non-limiting example, a modified mRNA formulation may be delivered by the drug delivery methods described in U.S. Patent No. 6,190,315, herein incorporated by reference in its entirety.

[000681] In another non-limiting example tissue may be treated with a eutectic mixture of local anesthetics (EMLA) cream before, during and/or after the tissue may be subjected to a device which may increase permeability. Katz et al. (Anesth Analg (2004); 98:371-76; herein incorporated by reference in its entirety) showed that using the EMLA cream in combination with a low energy, an onset of superficial cutaneous analgesia was seen as fast as 5 minutes after a pretreatment with a low energy ultrasound.

[000682] In one embodiment, enhancers may be applied to the tissue before, during, and/or after the tissue has been treated to increase permeability. Enhancers include, but are not limited to, transport enhancers, physical enhancers, and cavitation enhancers. Non-limiting examples of enhancers are described in U.S. Patent No. 6,190,315, herein incorporated by reference in its entirety.

[000683] In one embodiment, a device may be used to increase permeability of tissue before delivering formulations of modified mRNA described herein, which may further contain a substance that invokes an immune response. In another non-limiting example, a formulation containing a substance to invoke an immune response may be delivered by the methods described in U.S. Publication Nos. 20040171980 and 20040236268; each of which are herein incorporated by reference in their entireties.

[000684] Dosage forms for topical and/or transdermal administration of a composition may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, an active ingredient is admixed under sterile conditions with a pharmaceutically acceptable excipient and/or any needed preservatives and/or buffers as may be required.

[000685] Additionally, the present invention contemplates the use of transdermal patches, which often have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms may be prepared, for example, by dissolving

and/or dispensing the compound in the proper medium. Alternatively or additionally, rate may be controlled by either providing a rate controlling membrane and/or by dispersing the compound in a polymer matrix and/or gel.

[000686] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions.

[000687] Topically-administrable formulations may, for example, comprise from about 0.1% to about 10% (w/w) active ingredient, although the concentration of active ingredient may be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

Depot Administration

[000688] As described herein, in some embodiments, the composition is formulated in depots for extended release. Generally, a specific organ or tissue (a "target tissue") is targeted for administration.

[000689] In some aspects of the invention, the polynucleotides, primary constructs or mmRNA are spatially retained within or proximal to a target tissue. Provided are method of providing a composition to a target tissue of a mammalian subject by contacting the target tissue (which contains one or more target cells) with the composition under conditions such that the composition, in particular the nucleic acid component(s) of the composition, is substantially retained in the target tissue, meaning that at least 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the composition is retained in the target tissue. Advantageously, retention is determined by measuring the amount of the nucleic acid present in the composition that enters one or more target cells. For example, at least 1, 5, 10, 20, 30, 40, 50, 60, 70, 80, 85, 90, 95, 96, 97, 98, 99, 99.9, 99.99 or greater than 99.99% of the nucleic acids administered to the subject are present intracellularly at a period of time following administration. For example, intramuscular injection to a mammalian subject is performed using an aqueous composition containing a ribonucleic acid and a transfection reagent, and retention of the

composition is determined by measuring the amount of the ribonucleic acid present in the muscle cells.

[000690] Aspects of the invention are directed to methods of providing a composition to a target tissue of a mammalian subject, by contacting the target tissue (containing one or more target cells) with the composition under conditions such that the composition is substantially retained in the target tissue. The composition contains an effective amount of a polynucleotides, primary constructs or mmRNA such that the polypeptide of interest is produced in at least one target cell. The compositions generally contain a cell penetration agent, although "naked" nucleic acid (such as nucleic acids without a cell penetration agent or other agent) is also contemplated, and a pharmaceutically acceptable carrier.

[000691] In some circumstances, the amount of a protein produced by cells in a tissue is desirably increased. Preferably, this increase in protein production is spatially restricted to cells within the target tissue. Thus, provided are methods of increasing production of a protein of interest in a tissue of a mammalian subject. A composition is provided that contains polynucleotides, primary constructs or mmRNA characterized in that a unit quantity of composition has been determined to produce the polypeptide of interest in a substantial percentage of cells contained within a predetermined volume of the target tissue.

[000692] In some embodiments, the composition includes a plurality of different polynucleotides, primary constructs or mmRNA, where one or more than one of the polynucleotides, primary constructs or mmRNA encodes a polypeptide of interest. Optionally, the composition also contains a cell penetration agent to assist in the intracellular delivery of the composition. A determination is made of the dose of the composition required to produce the polypeptide of interest in a substantial percentage of cells contained within the predetermined volume of the target tissue (generally, without inducing significant production of the polypeptide of interest in tissue adjacent to the predetermined volume, or distally to the target tissue). Subsequent to this determination, the determined dose is introduced directly into the tissue of the mammalian subject.

[000693] In one embodiment, the invention provides for the polynucleotides, primary constructs or mmRNA to be delivered in more than one injection or by split dose injections.

[000694] In one embodiment, the invention may be retained near target tissue using a small disposable drug reservoir, patch pump or osmotic pump. Non-limiting examples of patch pumps include those manufactured and/or sold by BD® (Franklin Lakes, NJ), Insulet Corporation (Bedford, MA), SteadyMed Therapeutics (San Francisco, CA), Medtronic (Minneapolis, MN) (e.g., MiniMed), UniLife (York, PA), Valeritas (Bridgewater, NJ), and SpringLeaf Therapeutics (Boston, MA). A non-limiting example of an osmotic pump include those manufactured by DURECT® (Cupertino, CA) (e.g., DUROS® and ALZET ®).

Pulmonary Administration

[000695] A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. Such compositions are suitably in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant may be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nm and at least 95% of the particles by number have a diameter less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[000696] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50% to 99.9% (w/w) of the composition, and active ingredient may constitute 0.1% to 20% (w/w) of the composition. A propellant may further comprise additional ingredients

such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[000697] As a non-limiting example, the polynucleotides, primary constructs and/or mmRNA described herein may be formulated for pulmonary delivery by the methods described in U.S. Pat. No. 8,257,685; herein incorporated by reference in its entirety.

[000698] Pharmaceutical compositions formulated for pulmonary delivery may provide an active ingredient in the form of droplets of a solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. Droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

Intranasal, nasal and buccal Administration

[000699] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such a formulation is administered in the manner in which snuff is taken, *i.e.* by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

[000700] Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, 0.1% to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may

comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 nm to about 200 nm, and may further comprise one or more of any additional ingredients described herein.

Ophthalmic Administration

[000701] A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the active ingredient in an aqueous or oily liquid excipient. Such drops may further comprise buffering agents, salts, and/or one or more other of any additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this invention. A multilayer thin film device may be prepared to contain a pharmaceutical composition for delivery to the eye and/or surrounding tissue.

Payload Administration: Detectable Agents and Therapeutic Agents

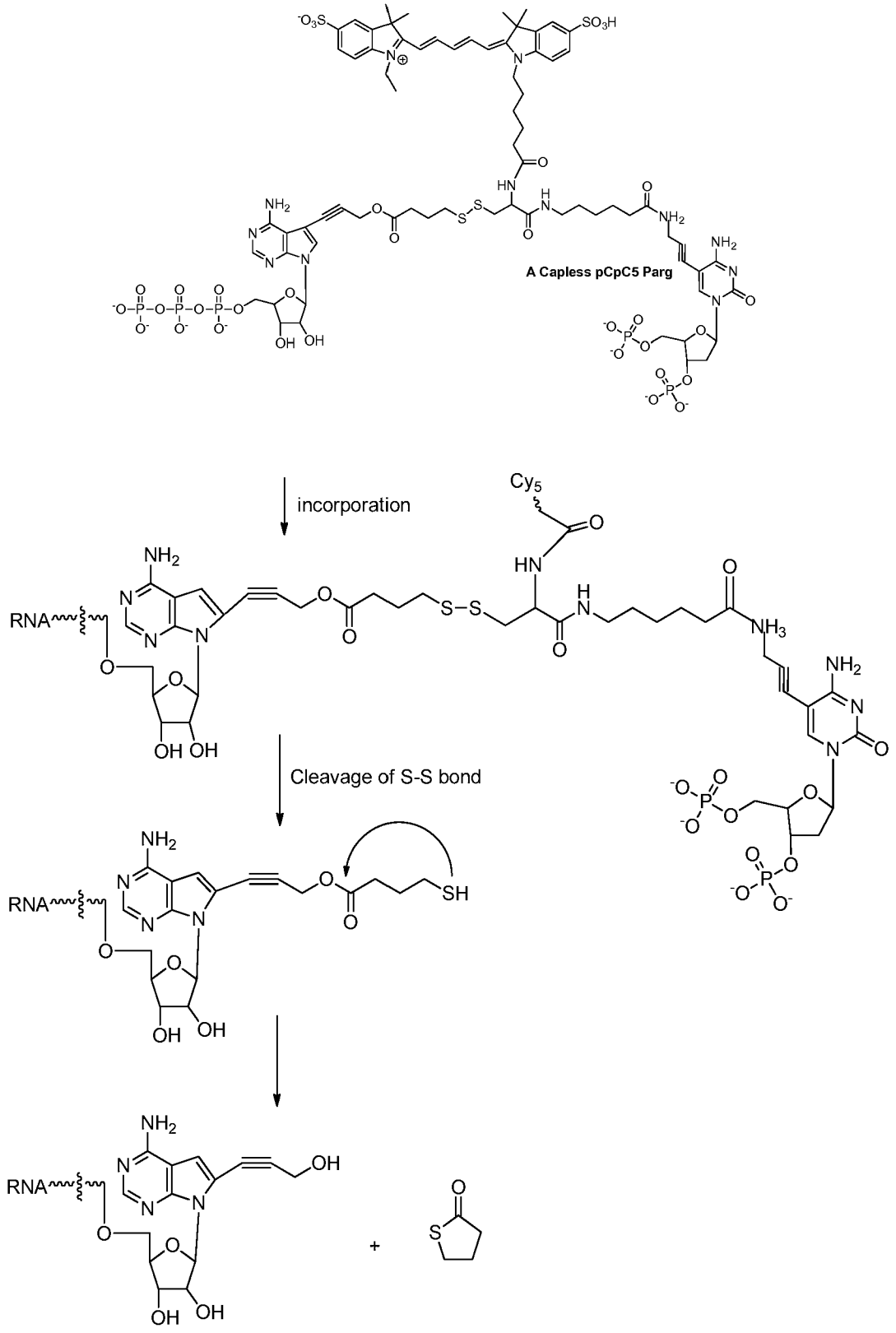
[000702] The polynucleotides, primary constructs or mmRNA described herein can be used in a number of different scenarios in which delivery of a substance (the "payload") to a biological target is desired, for example delivery of detectable substances for detection of the target, or delivery of a therapeutic agent. Detection methods can include, but are not limited to, both imaging *in vitro* and *in vivo* imaging methods, *e.g.*, immunohistochemistry, bioluminescence imaging (BLI), Magnetic Resonance Imaging (MRI), positron emission tomography (PET), electron microscopy, X-ray computed tomography, Raman imaging, optical coherence tomography, absorption imaging, thermal imaging, fluorescence reflectance imaging, fluorescence microscopy, fluorescence molecular tomographic imaging, nuclear magnetic resonance imaging, X-ray imaging, ultrasound imaging, photoacoustic imaging, lab assays, or in any situation where tagging/staining/imaging is required.

[000703] The polynucleotides, primary constructs or mmRNA can be designed to include both a linker and a payload in any useful orientation. For example, a linker

having two ends is used to attach one end to the payload and the other end to the nucleobase, such as at the C-7 or C-8 positions of the deaza-adenosine or deaza-guanosine or to the N-3 or C-5 positions of cytosine or uracil. The polynucleotide of the invention can include more than one payload (e.g., a label and a transcription inhibitor), as well as a cleavable linker. In one embodiment, the modified nucleotide is a modified 7-deaza-adenosine triphosphate, where one end of a cleavable linker is attached to the C7 position of 7-deaza-adenine, the other end of the linker is attached to an inhibitor (e.g., to the C5 position of the nucleobase on a cytidine), and a label (e.g., Cy5) is attached to the center of the linker (see, e.g., compound 1 of A*pCp C5 Parg Capless in Fig. 5 and columns 9 and 10 of U.S. Pat. No. 7,994,304, incorporated herein by reference). Upon incorporation of the modified 7-deaza-adenosine triphosphate to an encoding region, the resulting polynucleotide having a cleavable linker attached to a label and an inhibitor (e.g., a polymerase inhibitor). Upon cleavage of the linker (e.g., with reductive conditions to reduce a linker having a cleavable disulfide moiety), the label and inhibitor are released. Additional linkers and payloads (e.g., therapeutic agents, detectable labels, and cell penetrating payloads) are described herein.

[000704] Scheme 12 below depicts an exemplary modified nucleotide wherein the nucleobase, adenine, is attached to a linker at the C-7 carbon of 7-deaza adenine. In addition, Scheme 12 depicts the modified nucleotide with the linker and payload, e.g., a detectable agent, incorporated onto the 3' end of the mRNA. Disulfide cleavage and 1,2-addition of the thiol group onto the propargyl ester releases the detectable agent. The remaining structure (depicted, for example, as pApC5Parg in Scheme 12) is the inhibitor. The rationale for the structure of the modified nucleotides is that the tethered inhibitor sterically interferes with the ability of the polymerase to incorporate a second base. Thus, it is critical that the tether be long enough to affect this function and that the inhibiter be in a stereochemical orientation that inhibits or prohibits second and follow on nucleotides into the growing polynucleotide strand.

Scheme 12



[000705] For example, the polynucleotides, primary constructs or mmRNA described herein can be used in reprogramming induced pluripotent stem cells (iPS cells), which

can directly track cells that are transfected compared to total cells in the cluster. In another example, a drug that may be attached to the polynucleotides, primary constructs or mmRNA via a linker and may be fluorescently labeled can be used to track the drug *in vivo*, *e.g.* intracellularly. Other examples include, but are not limited to, the use of a polynucleotides, primary constructs or mmRNA in reversible drug delivery into cells.

[000706] The polynucleotides, primary constructs or mmRNA described herein can be used in intracellular targeting of a payload, *e.g.*, detectable or therapeutic agent, to specific organelle. Exemplary intracellular targets can include, but are not limited to, the nuclear localization for advanced mRNA processing, or a nuclear localization sequence (NLS) linked to the mRNA containing an inhibitor.

[000707] In addition, the polynucleotides, primary constructs or mmRNA described herein can be used to deliver therapeutic agents to cells or tissues, *e.g.*, in living animals. For example, the polynucleotides, primary constructs or mmRNA described herein can be used to deliver highly polar chemotherapeutics agents to kill cancer cells. The polynucleotides, primary constructs or mmRNA attached to the therapeutic agent through a linker can facilitate member permeation allowing the therapeutic agent to travel into a cell to reach an intracellular target.

[000708] In one example, the linker is attached at the 2'-position of the ribose ring and/or at the 3' and/or 5' positionof the polynucleotides, primary constructs mmRNA (See e.g., International Pub. No. WO2012030683, herein incorporated by reference in its entirety). The linker may be any linker disclosed herein, known in the art and/or disclosed in International Pub. No. WO2012030683, herein incorporated by reference in its entirety.

[000709] In another example, the polynucleotides, primary constructs or mmRNA can be attached to the polynucleotides, primary constructs or mmRNA a viral inhibitory peptide (VIP) through a cleavable linker. The cleavable linker can release the VIP and dye into the cell. In another example, the polynucleotides, primary constructs or mmRNA can be attached through the linker to an ADP-ribosylate, which is responsible for the actions of some bacterial toxins, such as cholera toxin, diphtheria toxin, and pertussis toxin. These toxin proteins are ADP-ribosyltransferases that modify target proteins in human cells. For example, cholera toxin ADP-ribosylates G proteins modifies

human cells by causing massive fluid secretion from the lining of the small intestine, which results in life-threatening diarrhea.

[000710] In some embodiments, the payload may be a therapeutic agent such as a cytotoxin, radioactive ion, chemotherapeutic, or other therapeutic agent. A cytotoxin or cytotoxic agent includes any agent that may be detrimental to cells. Examples include, but are not limited to, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, doxorubicin, daunorubicin, dihydroxyanthracinedione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, maytansinoids, *e.g.*, maytansinol (see U.S. Pat. No. 5,208,020 incorporated herein in its entirety), rachelmycin (CC-1065, see U.S. Pat. Nos. 5,475,092, 5,585,499, and 5,846,545, all of which are incorporated herein by reference), and analogs or homologs thereof. Radioactive ions include, but are not limited to iodine (*e.g.*, iodine 125 or iodine 131), strontium 89, phosphorous, palladium, cesium, iridium, phosphate, cobalt, yttrium 90, samarium 153, and praseodymium. Other therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thiotepa chlorambucil, rachelmycin (CC-1065), melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine, vinblastine, taxol and maytansinoids).

[000711] In some embodiments, the payload may be a detectable agent, such as various organic small molecules, inorganic compounds, nanoparticles, enzymes or enzyme substrates, fluorescent materials, luminescent materials (e.g., luminol), bioluminescent materials (e.g., luciferase, luciferin, and aequorin), chemiluminescent materials, radioactive materials (e.g., ^{18}F, ^{67}Ga, ^{81m}Kr, ^{82}Rb, ^{111}In, ^{123}I, ^{133}Xe, ^{201}Tl, ^{125}I, ^{35}S, ^{14}C, ^{3}H, or ^{99m}Tc (e.g., as pertechnetate (technetate(VII), TcO_4^-)), and contrast agents (e.g., gold (*e.g.*, gold nanoparticles), gadolinium (e.g., chelated Gd), iron oxides (e.g., superparamagnetic iron oxide (SPIO), monocrystalline iron oxide nanoparticles

(MIONs), and ultrasmall superparamagnetic iron oxide (USPIO)), manganese chelates (e.g., Mn-DPDP), barium sulfate, iodinated contrast media (iohexol), microbubbles, or perfluorocarbons). Such optically-detectable labels include for example, without limitation, 4-acetamido-4'-isothiocyanatostilbene-2,2′disulfonic acid; acridine and derivatives (e.g., acridine and acridine isothiocyanate); 5-(2′-aminoethyl)aminonaphthalene-1-sulfonic acid (EDANS); 4-amino-N-[3-vinylsulfonyl)phenyl]naphthalimide-3,5 disulfonate; N-(4-anilino-l-naphthyl)maleimide; anthranilamide; BODIPY; Brilliant Yellow; coumarin and derivatives (e.g., coumarin, 7-amino-4-methylcoumarin (AMC, Coumarin 120), and 7-amino-4-trifluoromethylcoumarin (Coumarin 151)); cyanine dyes; cyanosine; 4',6-diaminidino-2-phenylindole (DAPI); 5′ 5"-dibromopyrogallol-sulfonaphthalein (Bromopyrogallol Red); 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin; diethylenetriamine pentaacetate; 4,4'-diisothiocyanatodihydro-stilbene-2,2′-disulfonic acid; 4,4'-diisothiocyanatostilbene-2,2′-disulfonic acid; 5-[dimethylamino]-naphthalene-1-sulfonyl chloride (DNS, dansylchloride); 4-dimethylaminophenylazophenyl-4'-isothiocyanate (DABITC); eosin and derivatives (e.g., eosin and eosin isothiocyanate); erythrosin and derivatives (e.g., erythrosin B and erythrosin isothiocyanate); ethidium; fluorescein and derivatives (e.g., 5-carboxyfluorescein (FAM), 5-(4,6-dichlorotriazin-2-yl)aminofluorescein (DTAF), 2′,7'-dimethoxy-4'5′-dichloro-6-carboxyfluorescein, fluorescein, fluorescein isothiocyanate, X-rhodamine-5-(and-6)-isothiocyanate (QFITC or XRITC), and fluorescamine); 2-[2-[3-[[1,3-dihydro-1,1-dimethyl-3-(3-sulfopropyl)-2H-benz[e]indol-2-ylidene]ethylidene]-2-[4-(ethoxycarbonyl)-1-piperazinyl]-1-cyclopenten-1-yl]ethenyl]-1,1-dimethyl-3-(3-sulforpropyl)-1H-benz[e]indolium hydroxide, inner salt, compound with n,n-diethylethanamine(1:1) (IR144); 5-chloro-2-[2-[3-[(5-chloro-3-ethyl-2(3H)-benzothiazol- ylidene)ethylidene]-2-(diphenylamino)-1-cyclopenten-1-yl]ethenyl]-3-ethyl benzothiazolium perchlorate (IR140); Malachite Green isothiocyanate; 4-methylumbelliferone orthocresolphthalein; nitrotyrosine; pararosaniline; Phenol Red; B-phycoerythrin; o-phthaldialdehyde; pyrene and derivatives(e.g., pyrene, pyrene butyrate, and succinimidyl 1-pyrene); butyrate quantum dots; Reactive Red 4 (CIBACRON^{TM} Brilliant Red 3B-A); rhodamine and derivatives (e.g., 6-carboxy-X-rhodamine (ROX), 6-carboxyrhodamine (R6G), lissamine rhodamine

B sulfonyl chloride rhodarnine (Rhod), rhodamine B, rhodamine 123, rhodamine X isothiocyanate, sulforhodamine B, sulforhodamine 101, sulfonyl chloride derivative of sulforhodamine 101 (Texas Red), N,N,N',N'tetramethyl-6-carboxyrhodamine (TAMRA) tetramethyl rhodamine, and tetramethyl rhodamine isothiocyanate (TRITC)); riboflavin; rosolic acid; terbium chelate derivatives; Cyanine-3 (Cy3); Cyanine-5 (Cy5); cyanine-5.5 (Cy5.5), Cyanine-7 (Cy7); IRD 700; IRD 800; Alexa 647; La Jolta Blue; phthalo cyanine; and naphthalo cyanine.

[000712] In some embodiments, the detectable agent may be a non-detectable pre-cursor that becomes detectable upon activation (e.g., fluorogenic tetrazine-fluorophore constructs (e.g., tetrazine-BODIPY FL, tetrazine-Oregon Green 488, or tetrazine-BODIPY TMR-X) or enzyme activatable fluorogenic agents (e.g., PROSENSE® (VisEn Medical))). In vitro assays in which the enzyme labeled compositions can be used include, but are not limited to, enzyme linked immunosorbent assays (ELISAs), immunoprecipitation assays, immunofluorescence, enzyme immunoassays (EIA), radioimmunoassays (RIA), and Western blot analysis.

Combinations

[000713] The polynucleotides, primary constructs or mmRNA may be used in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body. As a non-limiting example, the nucleic acids or mmRNA may be used in combination with a pharmaceutical agent for the treatment of cancer or to control hyperproliferative cells. In U.S. Pat. No. 7,964,571, herein incorporated by reference in its entirety, a combination therapy for the treatment of solid primary or

metastasized tumor is described using a pharmaceutical composition including a DNA plasmid encoding for interleukin-12 with a lipopolymer and also administering at least one anticancer agent or chemotherapeutic. Further, the nucleic acids and mmRNA of the present invention that encodes anti-proliferative molecules may be in a pharmaceutical composition with a lipopolymer (see e.g., U.S. Pub. No. 20110218231, herein incorporated by reference in its entirety, claiming a pharmaceutical composition comprising a DNA plasmid encoding an anti-proliferative molecule and a lipopolymer) which may be administered with at least one chemotherapeutic or anticancer agent.

[000714] It will further be appreciated that therapeutically, prophylactically, diagnostically, or imaging active agents utilized in combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that agents utilized in combination with be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually. In one embodiment, the combinations, each or together may be administered according to the split dosing regimens described herein.

Dosing

[000715] The present invention provides methods comprising administering modified mRNAs and their encoded proteins or complexes in accordance with the invention to a subject in need thereof. Nucleic acids, proteins or complexes, or pharmaceutical, imaging, diagnostic, or prophylactic compositions thereof, may be administered to a subject using any amount and any route of administration effective for preventing, treating, diagnosing, or imaging a disease, disorder, and/or condition (*e.g.*, a disease, disorder, and/or condition relating to working memory deficits). The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Compositions in accordance with the invention are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present invention may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective,

prophylactically effective, or appropriate imaging dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

[000716] In certain embodiments, compositions in accordance with the present invention may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, prophylactic, or imaging effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used.

[000717] According to the present invention, it has been discovered that administration of mmRNA in split-dose regimens produce higher levels of proteins in mammalian subjects. As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses, e.g, two or more administrations of the single unit dose. As used herein, a "single unit dose" is a dose of any therapeutic administed in one dose/at one time/single route/single point of contact, i.e., single administration event. As used herein, a "total daily dose" is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose. In one embodiment, the mmRNA of the present

invention are administed to a subject in split doses. The mmRNA may be formulated in buffer only or in a formulation described herein.

Dosage Forms

[000718] A pharmaceutical composition described herein can be formulated into a dosage form described herein, such as a topical, intranasal, intratracheal, or injectable (e.g., intravenous, intraocular, intravitreal, intramuscular, intracardiac, intraperitoneal, subcutaneous).

Liquid dosage forms

[000719] Liquid dosage forms for parenteral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and/or elixirs. In addition to active ingredients, liquid dosage forms may comprise inert diluents commonly used in the art including, but not limited to, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. In certain embodiments for parenteral administration, compositions may be mixed with solubilizing agents such as CREMOPHOR®, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and/or combinations thereof.

Injectable

[000720] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art and may include suitable dispersing agents, wetting agents, and/or suspending agents. Sterile injectable preparations may be sterile injectable solutions, suspensions, and/or emulsions in nontoxic parenterally acceptable diluents and/or solvents, for example, a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed include, but are not limited to, water, Ringer's solution, U.S.P., and isotonic sodium chloride solution. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono-

or diglycerides. Fatty acids such as oleic acid can be used in the preparation of injectables.

Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, and/or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

In order to prolong the effect of an active ingredient, it may be desirable to slow the absorption of the active ingredient from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the polynucleotide, primary construct or mmRNA then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered polynucleotide, primary construct or mmRNA may be accomplished by dissolving or suspending the polynucleotide, primary construct or mmRNA in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the polynucleotide, primary construct or mmRNA in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of polynucleotide, primary construct or mmRNA to polymer and the nature of the particular polymer employed, the rate of polynucleotide, primary construct or mmRNA release can be controlled. Examples of other biodegradable polymers include, but are not limited to, poly(orthoesters) and poly(anhydrides). Depot injectable formulations may be prepared by entrapping the polynucleotide, primary construct or mmRNA in liposomes or microemulsions which are compatible with body tissues.

Pulmonary

[000721] Formulations described herein as being useful for pulmonary delivery may also be used for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration may be a coarse powder comprising the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such a formulation may be administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

[000722] Formulations suitable for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may comprise one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may, for example, contain about 0.1% to 20% (w/w) active ingredient, where the balance may comprise an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations suitable for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 nm to about 200 nm, and may further comprise one or more of any additional ingredients described herein.

[000723] General considerations in the formulation and/or manufacture of pharmaceutical agents may be found, for example, in Remington: The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005 (incorporated herein by reference in its entirety).

Coatings or Shells

[000724] Solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type may be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

Properties of Pharmaceutical Compositions

[000725] The pharmaceutical compositions described herein can be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

Bioavailability

[000726] The polynucleotides, primary constructs or mmRNA, when formulated into a composition with a delivery agent as described herein, can exhibit an increase in bioavailability as compared to a composition lacking a delivery agent as described herein. As used herein, the term "bioavailability" refers to the systemic availability of a given amount of polynucleotides, primary constructs or mmRNA administered to a mammal. Bioavailability can be assessed by measuring the area under the curve (AUC) or the maximum serum or plasma concentration (C_{max}) of the unchanged form of a compound following administration of the compound to a mammal. AUC is a determination of the area under the curve plotting the serum or plasma concentration of a compound along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the AUC for a particular compound can be calculated using methods known to those of ordinary skill in the art and as described in G. S. Banker, Modern Pharmaceutics, Drugs and the Pharmaceutical Sciences, v. 72, Marcel Dekker, New York, Inc., 1996, herein incorporated by reference in its entirety.

[000727] The C_{max} value is the maximum concentration of the compound achieved in the serum or plasma of a mammal following administration of the compound to the mammal. The C_{max} value of a particular compound can be measured using methods known to those of ordinary skill in the art. The phrases "increasing bioavailability" or "improving the pharmacokinetics," as used herein mean that the systemic availability of a first polynucleotide, primary construct or mmRNA, measured as AUC, C_{max}, or C_{min} in a mammal is greater, when co-administered with a delivery agent as described herein, than when such co-administration does not take place. In some embodiments, the bioavailability of the polynucleotide, primary construct or mmRNA can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Therapeutic Window

[000728] The polynucleotides, primary constructs or mmRNA, when formulated into a composition with a delivery agent as described herein, can exhibit an increase in the therapeutic window of the administered polynucleotide, primary construct or mmRNA composition as compared to the therapeutic window of the administered polynucleotide, primary construct or mmRNA composition lacking a delivery agent as described herein. As used herein "therapeutic window" refers to the range of plasma concentrations, or the range of levels of therapeutically active substance at the site of action, with a high probability of eliciting a therapeutic effect. In some embodiments, the therapeutic window of the polynucleotide, primary construct or mmRNA when co-administered with a delivery agent as described herein can increase by at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or about 100%.

Volume of Distribution

[000729] The polynucleotides, primary constructs or mmRNA, when formulated into a composition with a delivery agent as described herein, can exhibit an improved volume of distribution (V_{dist}), e.g., reduced or targeted, relative to a composition lacking a delivery agent as described herein. The volume of distribution (Vdist) relates the amount of the drug in the body to the concentration of the drug in the blood or plasma. As used herein, the term "volume of distribution" refers to the fluid volume that would be required to contain the total amount of the drug in the body at the same concentration as in the blood or plasma: Vdist equals the amount of drug in the body/concentration of drug in blood or plasma. For example, for a 10 mg dose and a plasma concentration of 10 mg/L, the volume of distribution would be 1 liter. The volume of distribution reflects the extent to which the drug is present in the extravascular tissue. A large volume of distribution reflects the tendency of a compound to bind to the tissue components compared with plasma protein binding. In a clinical setting, Vdist can be used to determine a loading dose to achieve a steady state concentration. In some embodiments, the volume of distribution of the polynucleotide, primary construct or mmRNA when co-

administered with a delivery agent as described herein can decrease at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%.

Biological Effect

[000730] In one embodiment, the biological effect of the modified mRNA delivered to the animals may be categorized by analyzing the protein expression in the animals. The protein expression may be determined from analyzing a biological sample collected from a mammal administered the modified mRNA of the present invention. In one embodiment, the expression protein encoded by the modified mRNA administered to the mammal of at least 50 pg/ml may be preferred. For example, a protein expression of 50-200 pg/ml for the protein encoded by the modified mRNA delivered to the mammal may be seen as a therapeutically effective amount of protein in the mammal.

Detection of Modified Nucleic Acids by Mass Spectrometry

[000731] Mass spectrometry (MS) is an analytical technique that can provide structural and molecular mass/concentration information on molecules after their conversion to ions. The molecules are first ionized to acquire positive or negative charges and then they travel through the mass analyzer to arrive at different areas of the detector according to their mass/charge (m/z) ratio.

[000732] Mass spectrometry is performed using a mass spectrometer which includes an ion source for ionizing the fractionated sample and creating charged molecules for further analysis. For example ionization of the sample may be performed by electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), photoionization, electron ionization, fast atom bombardment (FAB)/liquid secondary ionization (LSIMS), matrix assisted laser desorption/ionization (MALDI), field ionization, field desorption, thermospray/plasmaspray ionization, and particle beam ionization. The skilled artisan will understand that the choice of ionization method can be determined based on the analyte to be measured, type of sample, the type of detector, the choice of positive versus negative mode, etc.

[000733] After the sample has been ionized, the positively charged or negatively charged ions thereby created may be analyzed to determine a mass-to-charge ratio (i.e., m/z). Suitable analyzers for determining mass-to-charge ratios include quadropole analyzers, ion traps analyzers, and time-of-flight analyzers. The ions may be detected using several detection modes. For example, selected ions may be detected (i.e., using a selective ion monitoring mode (SIM)), or alternatively, ions may be detected using a scanning mode, e.g., multiple reaction monitoring (MRM) or selected reaction monitoring (SRM).

[000734] Liquid chromatography-multiple reaction monitoring (LC-MS/MRM) coupled with stable isotope labeled dilution of peptide standards has been shown to be an effective method for protein verification (e.g., Keshishian et al., Mol Cell Proteomics 2009 8: 2339-2349; Kuhn et al., Clin Chem 2009 55:1108-1117; Lopez et al., Clin Chem 2010 56:281-290; each of which are herein incorporated by reference in its entirety). Unlike untargeted mass spectrometry frequently used in biomarker discovery studies, targeted MS methods are peptide sequence–based modes of MS that focus the full analytical capacity of the instrument on tens to hundreds of selected peptides in a complex mixture. By restricting detection and fragmentation to only those peptides derived from proteins of interest, sensitivity and reproducibility are improved dramatically compared to discovery-mode MS methods. This method of mass spectrometry-based multiple reaction monitoring (MRM) quantitation of proteins can dramatically impact the discovery and quantitation of biomarkers via rapid, targeted, multiplexed protein expression profiling of clinical samples.

[000735] In one embodiment, a biological sample which may contain at least one protein encoded by at least one modified mRNA of the present invention may be analyzed by the method of MRM-MS. The quantification of the biological sample may further include, but is not limited to, isotopically labeled peptides or proteins as internal standards.

[000736] According to the present invention, the biological sample, once obtained from the subject, may be subjected to enzyme digestion. As used herein, the term "digest" means to break apart into shorter peptides. As used herein, the phrase "treating a sample to digest proteins" means manipulating a sample in such a way as to break down proteins

in a sample. These enzymes include, but are not limited to, trypsin, endoproteinase Glu-C and chymotrypsin. In one embodiment, a biological sample which may contain at least one protein encoded by at least one modified mRNA of the present invention may be digested using enzymes.

[000737] In one embodiment, a biological sample which may contain protein encoded by modified mRNA of the present invention may be analyzed for protein using electrospray ionization. Electrospray ionization (ESI) mass spectrometry (ESIMS) uses electrical energy to aid in the transfer of ions from the solution to the gaseous phase before they are analyzed by mass spectrometry. Samples may be analyzed using methods known in the art (e.g., Ho et al., Clin Biochem Rev. 2003 24(1):3-12; herein incorporated by reference in its entirety). The ionic species contained in solution may be transferred into the gas phase by dispersing a fine spray of charge droplets, evaporating the solvent and ejecting the ions from the charged droplets to generate a mist of highly charged droplets. The mist of highly charged droplets may be analyzed using at least 1, at least 2, at least 3 or at least 4 mass analyzers such as, but not limited to, a quadropole mass analyzer. Further, the mass spectrometry method may include a purification step. As a non-limiting example, the first quadrapole may be set to select a single m/z ratio so it may filter out other molecular ions having a different m/z ratio which may eliminate complicated and time-consuming sample purification procedures prior to MS analysis.

[000738] In one embodiment, a biological sample which may contain protein encoded by modified mRNA of the present invention may be analyzed for protein in a tandem ESIMS system (e.g., MS/MS). As non-limiting examples, the droplets may be analyzed using a product scan (or daughter scan) a precursor scan (parent scan) a neutral loss or a multiple reaction monitoring.

[000739] In one embodiment, a biological sample which may contain protein encoded by modified mRNA of the present invention may be analyzed using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MALDIMS). MALDI provides for the nondestructive vaporization and ionization of both large and small molecules, such as proteins. In MALDI analysis, the analyte is first co-crystallized with a large molar excess of a matrix compound, which may also include, but is not limited to, an ultraviolet absorbing weak organic acid. Non-limiting examples of matrices used in MALDI are α-

cyano-4-hydroxycinnamic acid, 3,5-dimethoxy-4-hydroxycinnamic acid and 2,5-dihydroxybenzoic acid. Laser radiation of the analyte-matrix mixture may result in the vaporization of the matrix and the analyte. The laser induced desorption provides high ion yields of the intact analyte and allows for measurement of compounds with high accuracy. Samples may be analyzed using methods known in the art (e.g., Lewis, Wei and Siuzdak, Encyclopedia of Analytical Chemistry 2000:5880-5894; herein incorporated by reference in its entirety). As non-limiting examples, mass analyzers used in the MALDI analysis may include a linear time-of-flight (TOF), a TOF reflectron or a Fourier transform mass analyzer.

[000740] In one embodiment, the analyte-matrix mixture may be formed using the dried-droplet method. A biologic sample is mixed with a matrix to create a saturated matrix solution where the matrix-to-sample ratio is approximately 5000:1. An aliquot (approximately 0.5-2.0 uL) of the saturated matrix solution is then allowed to dry to form the analyte-matrix mixture.

[000741] In one embodiment, the analyte-matrix mixture may be formed using the thin-layer method. A matrix homogeneous film is first formed and then the sample is then applied and may be absorbed by the matrix to form the analyte-matrix mixture.

[000742] In one embodiment, the analyte-matrix mixture may be formed using the thick-layer method. A matrix homogeneous film is formed with a nitro-cellulose matrix additive. Once the uniform nitro-cellulose matrix layer is obtained the sample is applied and absorbed into the matrix to form the analyte-matrix mixture.

[000743] In one embodiment, the analyte-matrix mixture may be formed using the sandwich method. A thin layer of matrix crystals is prepared as in the thin-layer method followed by the addition of droplets of aqueous trifluoroacetic acid, the sample and matrix. The sample is then absorbed into the matrix to form the analyte-matrix mixture.

V. Uses of Polynucleotides, primary constructs and mmRNA of the Invention

[000744] The polynucleotides, primary constructs and mmRNA of the present invention are designed, in preferred embodiments, to provide for avoidance or evasion of deleterious bio-responses such as the immune response and/or degradation pathways, overcoming the threshold of expression and/or improving protein production capacity, improved expression rates or translation efficiency, improved drug or protein half life

and/or protein concentrations, optimized protein localization, to improve one or more of the stability and/or clearance in tissues, receptor uptake and/or kinetics, cellular access by the compositions, engagement with translational machinery, secretion efficiency (when applicable), accessibility to circulation, and/or modulation of a cell's status, function and/or activity.

Therapeutics

Therapeutic Agents

[000745] The polynucleotides, primary constructs or mmRNA of the present invention, such as modified nucleic acids and modified RNAs, and the proteins translated from them described herein can be used as therapeutic or prophylactic agents. They are provided for use in medicine. For example, a polynucleotide, primary construct or mmRNA described herein can be administered to a subject, wherein the polynucleotide, primary construct or mmRNA is translated *in vivo* to produce a therapeutic or prophylactic polypeptide in the subject. Provided are compositions, methods, kits, and reagents for diagnosis, treatment or prevention of a disease or condition in humans and other mammals. The active therapeutic agents of the invention include polynucleotides, primary constructs or mmRNA, cells containing polynucleotides, primary constructs or mmRNA or polypeptides translated from the polynucleotides, primary constructs or mmRNA.

[000746] In certain embodiments, provided herein are combination therapeutics containing one or more polynucleotide, primary construct or mmRNA containing translatable regions that encode for a protein or proteins that boost a mammalian subject's immunity along with a protein that induces antibody-dependent cellular toxicity. For example, provided herein are therapeutics containing one or more nucleic acids that encode trastuzumab and granulocyte-colony stimulating factor (G-CSF). In particular, such combination therapeutics are useful in Her2+ breast cancer patients who develop induced resistance to trastuzumab. (See, e.g., Albrecht, Immunotherapy. 2(6):795-8 (2010)).

[000747] Provided herein are methods of inducing translation of a recombinant polypeptide in a cell population using the polynucleotide, primary construct or mmRNA described herein. Such translation can be *in vivo*, *ex vivo*, *in culture*, or *in vitro*. The cell population is contacted with an effective amount of a composition containing a nucleic

acid that has at least one nucleoside modification, and a translatable region encoding the recombinant polypeptide. The population is contacted under conditions such that the nucleic acid is localized into one or more cells of the cell population and the recombinant polypeptide is translated in the cell from the nucleic acid.

[000748] An "effective amount" of the composition is provided based, at least in part, on the target tissue, target cell type, means of administration, physical characteristics of the nucleic acid (e.g., size, and extent of modified nucleosides), and other determinants. In general, an effective amount of the composition provides efficient protein production in the cell, preferably more efficient than a composition containing a corresponding unmodified nucleic acid. Increased efficiency may be demonstrated by increased cell transfection (i.e., the percentage of cells transfected with the nucleic acid), increased protein translation from the nucleic acid, decreased nucleic acid degradation (as demonstrated, e.g., by increased duration of protein translation from a modified nucleic acid), or reduced innate immune response of the host cell.

[000749] Aspects of the invention are directed to methods of inducing *in vivo* translation of a recombinant polypeptide in a mammalian subject in need thereof. Therein, an effective amount of a composition containing a nucleic acid that has at least one structural or chemical modification and a translatable region encoding the recombinant polypeptide is administered to the subject using the delivery methods described herein. The nucleic acid is provided in an amount and under other conditions such that the nucleic acid is localized into a cell of the subject and the recombinant polypeptide is translated in the cell from the nucleic acid. The cell in which the nucleic acid is localized, or the tissue in which the cell is present, may be targeted with one or more than one rounds of nucleic acid administration.

[000750] In certain embodiments, the administered polynucleotide, primary construct or mmRNA directs production of one or more recombinant polypeptides that provide a functional activity which is substantially absent in the cell, tissue or organism in which the recombinant polypeptide is translated. For example, the missing functional activity may be enzymatic, structural, or gene regulatory in nature. In related embodiments, the administered polynucleotide, primary construct or mmRNA directs production of one or more recombinant polypeptides that increases (e.g., synergistically) a functional activity

which is present but substantially deficient in the cell in which the recombinant polypeptide is translated.

[000751] In other embodiments, the administered polynucleotide, primary construct or mmRNA directs production of one or more recombinant polypeptides that replace a polypeptide (or multiple polypeptides) that is substantially absent in the cell in which the recombinant polypeptide is translated. Such absence may be due to genetic mutation of the encoding gene or regulatory pathway thereof. In some embodiments, the recombinant polypeptide increases the level of an endogenous protein in the cell to a desirable level; such an increase may bring the level of the endogenous protein from a subnormal level to a normal level or from a normal level to a super-normal level.

[000752] Alternatively, the recombinant polypeptide functions to antagonize the activity of an endogenous protein present in, on the surface of, or secreted from the cell. Usually, the activity of the endogenous protein is deleterious to the subject; for example, due to mutation of the endogenous protein resulting in altered activity or localization. Additionally, the recombinant polypeptide antagonizes, directly or indirectly, the activity of a biological moiety present in, on the surface of, or secreted from the cell. Examples of antagonized biological moieties include lipids (e.g., cholesterol), a lipoprotein (e.g., low density lipoprotein), a nucleic acid, a carbohydrate, a protein toxin such as shiga and tetanus toxins, or a small molecule toxin such as botulinum, cholera, and diphtheria toxins. Additionally, the antagonized biological molecule may be an endogenous protein that exhibits an undesirable activity, such as a cytotoxic or cytostatic activity.

[000753] The recombinant proteins described herein may be engineered for localization within the cell, potentially within a specific compartment such as the nucleus, or are engineered for secretion from the cell or translocation to the plasma membrane of the cell.

[000754] In some embodiments, modified mRNAs and their encoded polypeptides in accordance with the present invention may be used for treatment of any of a variety of diseases, disorders, and/or conditions, including but not limited to one or more of the following: autoimmune disorders (*e.g.* diabetes, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis); inflammatory disorders (*e.g.* arthritis, pelvic inflammatory disease); infectious diseases (*e.g.* viral infections (*e.g.*, HIV, HCV, RSV), bacterial infections,

fungal infections, sepsis); neurological disorders (*e.g.* Alzheimer's disease, Huntington's disease; autism; Duchenne muscular dystrophy); cardiovascular disorders (*e.g.* atherosclerosis, hypercholesterolemia, thrombosis, clotting disorders, angiogenic disorders such as macular degeneration); proliferative disorders (*e.g.* cancer, benign neoplasms); respiratory disorders (*e.g.* chronic obstructive pulmonary disease); digestive disorders (*e.g.* inflammatory bowel disease, ulcers); musculoskeletal disorders (*e.g.* fibromyalgia, arthritis); endocrine, metabolic, and nutritional disorders (*e.g.* diabetes, osteoporosis); urological disorders (*e.g.* renal disease); psychological disorders (*e.g.* depression, schizophrenia); skin disorders (*e.g.* wounds, eczema); blood and lymphatic disorders (*e.g.* anemia, hemophilia); *etc.*

[000755] Diseases characterized by dysfunctional or aberrant protein activity include cystic fibrosis, sickle cell anemia, epidermolysis bullosa, amyotrophic lateral sclerosis, and glucose-6-phosphate dehydrogenase deficiency. The present invention provides a method for treating such conditions or diseases in a subject by introducing nucleic acid or cell-based therapeutics containing the polynucleotide, primary construct or mmRNA provided herein, wherein the polynucleotide, primary construct or mmRNA encode for a protein that antagonizes or otherwise overcomes the aberrant protein activity present in the cell of the subject. Specific examples of a dysfunctional protein are the missense mutation variants of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which produce a dysfunctional protein variant of CFTR protein, which causes cystic fibrosis.

[000756] Diseases characterized by missing (or substantially diminished such that proper (normal or physiological protein function does not occur) protein activity include cystic fibrosis, Niemann-Pick type C, β thalassemia major, Duchenne muscular dystrophy, Hurler Syndrome, Hunter Syndrome, and Hemophilia A. Such proteins may not be present, or are essentially non-functional. The present invention provides a method for treating such conditions or diseases in a subject by introducing nucleic acid or cell-based therapeutics containing the polynucleotide, primary construct or mmRNA provided herein, wherein the polynucleotide, primary construct or mmRNA encode for a protein that replaces the protein activity missing from the target cells of the subject. Specific examples of a dysfunctional protein are the nonsense mutation variants of the

cystic fibrosis transmembrane conductance regulator (CFTR) gene, which produce a nonfunctional protein variant of CFTR protein, which causes cystic fibrosis.

[000757] Thus, provided are methods of treating cystic fibrosis in a mammalian subject by contacting a cell of the subject with a polynucleotide, primary construct or mmRNA having a translatable region that encodes a functional CFTR polypeptide, under conditions such that an effective amount of the CTFR polypeptide is present in the cell. Preferred target cells are epithelial, endothelial and mesothelial cells, such as the lung, and methods of administration are determined in view of the target tissue; i.e., for lung delivery, the RNA molecules are formulated for administration by inhalation.

[000758] In another embodiment, the present invention provides a method for treating hyperlipidemia in a subject, by introducing into a cell population of the subject with a modified mRNA molecule encoding Sortilin, a protein recently characterized by genomic studies, thereby ameliorating the hyperlipidemia in a subject. The *SORT1* gene encodes a trans-Golgi network (TGN) transmembrane protein called Sortilin. Genetic studies have shown that one of five individuals has a single nucleotide polymorphism, rs12740374, in the 1p13 locus of the SORT1 gene that predisposes them to having low levels of low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). Each copy of the minor allele, present in about 30% of people, alters LDL cholesterol by 8 mg/dL, while two copies of the minor allele, present in about 5% of the population, lowers LDL cholesterol 16 mg/dL. Carriers of the minor allele have also been shown to have a 40% decreased risk of myocardial infarction. Functional *in vivo* studies in mice describes that overexpression of *SORT1* in mouse liver tissue led to significantly lower LDL-cholesterol levels, as much as 80% lower, and that silencing SORT1 increased LDL cholesterol approximately 200% (Musunuru K et al. From noncoding variant to phenotype via *SORT1* at the 1p13 cholesterol locus. *Nature* 2010; 466: 714-721).

[000759] In another embodiment, the present invention provides a method for treating hematopoietic disorders, cardiovascular disease, oncology, diabetes, cystic fibrosis, neurological diseases, inborn errors of metabolism, skin and systemic disorders, and blindness. The identity of molecular targets to treat these specific diseases has been described (Templeton ed., Gene and Cell Therapy: Therapeutic Mechanisms and

Strategies, 3rd Edition, Bota Raton, FL:CRC Press; herein incorporated by reference in its entirety).

[000760] Provided herein, are methods to prevent infection and/or sepsis in a subject at risk of developing infection and/or sepsis, the method comprising administering to a subject in need of such prevention a composition comprising a polynucleotide, primary construct or mmRNA precursor encoding an anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide), or a partially or fully processed form thereof in an amount sufficient to prevent infection and/or sepsis. In certain embodiments, the subject at risk of developing infection and/or sepsis may be a cancer patient. In certain embodiments, the cancer patient may have undergone a conditioning regimen. In some embodiments, the conditioning regiment may include, but is not limited to, chemotherapy, radiation therapy, or both. As a non-limiting example, a polynucleotide, primary construct or mmRNA can encode Protein C, its zymogen or prepro-protein, the activated form of Protein C (APC) or variants of Protein C which are known in the art. The polynucleotides, primary constructs or mmRNA may be chemically modified and delivered to cells. Non-limiting examples of polypeptides which may be encoded within the chemically modified mRNAs of the present invention include those taught in US Patents 7,226,999; 7,498,305; 6,630,138 each of which is incorporated herein by reference in its entirety. These patents teach Protein C like molecules, variants and derivatives, any of which may be encoded within the chemically modified molecules of the present invention.

[000761] Further provided herein, are methods to treat infection and/or sepsis in a subject, the method comprising administering to a subject in need of such treatment a composition comprising a polynucleotide, primary construct or mmRNA precursor encoding an anti-microbial polypeptide (*e.g.*, an anti-bacterial polypeptide), *e.g.*, an anti-microbial polypeptide described herein, or a partially or fully processed form thereof in an amount sufficient to treat an infection and/or sepsis. In certain embodiments, the subject in need of treatment is a cancer patient. In certain embodiments, the cancer patient has undergone a conditioning regimen. In some embodiments, the conditioning regiment may include, but is not limited to, chemotherapy, radiation therapy, or both.

[000762] In certain embodiments, the subject may exhibits acute or chronic microbial infections (*e.g.*, bacterial infections). In certain embodiments, the subject may have received or may be receiving a therapy. In certain embodiments, the therapy may include, but is not limited to, radiotherapy, chemotherapy, steroids, ultraviolet radiation, or a combination thereof. In certain embodiments, the patient may suffer from a microvascular disorder. In some embodiments, the microvascular disorder may be diabetes. In certain embodiments, the patient may have a wound. In some embodiments, the wound may be an ulcer. In a specific embodiment, the wound may be a diabetic foot ulcer. In certain embodiments, the subject may have one or more burn wounds. In certain embodiments, the administration may be local or systemic. In certain embodiments, the administration may be subcutaneous. In certain embodiments, the administration may be intravenous. In certain embodiments, the administration may be oral. In certain embodiments, the administration may be topical. In certain embodiments, the administration may be by inhalation. In certain embodiments, the administration may be rectal. In certain embodiments, the administration may be vaginal.

[000763] Other aspects of the present disclosure relate to transplantation of cells containing polynucleotide, primary construct, or mmRNA to a mammalian subject. Administration of cells to mammalian subjects is known to those of ordinary skill in the art, and include, but is not limited to, local implantation (e.g., topical or subcutaneous administration), organ delivery or systemic injection (e.g., intravenous injection or inhalation), and the formulation of cells in pharmaceutically acceptable carrier. Such compositions containing polynucleotide, primary construct, or mmRNA can be formulated for administration intramuscularly, transarterially, intraperitoneally, intravenously, intranasally, subcutaneously, endoscopically, transdermally, or intrathecally. In some embodiments, the composition may be formulated for extended release.

[000764] The subject to whom the therapeutic agent may be administered suffers from or may be at risk of developing a disease, disorder, or deleterious condition. Provided are methods of identifying, diagnosing, and classifying subjects on these bases, which may include clinical diagnosis, biomarker levels, genome-wide association studies (GWAS), and other methods known in the art.

Wound Management

[000765] The polynucleotides, primary constructs or mmRNA of the present invention may be used for wound treatment, *e.g.* of wounds exhibiting delayed healing. Provided herein are methods comprising the administration of polynucleotide, primary construct or mmRNA in order to manage the treatment of wounds. The methods herein may further comprise steps carried out either prior to, concurrent with or post administration of the polynucleotide, primary construct or mmRNA. For example, the wound bed may need to be cleaned and prepared in order to facilitate wound healing and hopefully obtain closure of the wound. Several strategies may be used in order to promote wound healing and achieve wound closure including, but not limited to: (i) debridement, optionally repeated, sharp debridement (surgical removal of dead or infected tissue from a wound), optionally including chemical debriding agents, such as enzymes, to remove necrotic tissue; (ii) wound dressings to provide the wound with a moist, warm environment and to promote tissue repair and healing.

[000766] Examples of materials that are used in formulating wound dressings include, but are not limited to: hydrogels (*e.g.*, AQUASORB®; DUODERM®), hydrocolloids (*e.g.*, AQUACEL®; COMFEEL®), foams (*e.g.*, LYOFOAM®; SPYROSORB®), and alginates (*e.g.*, ALGISITE®; CURASORB®); (iii) additional growth factors to stimulate cell division and proliferation and to promote wound healing *e.g.* becaplermin (REGRANEX GEL®), a human recombinant platelet-derived growth factor that is approved by the FDA for the treatment of neuropathic foot ulcers; (iv) soft-tissue wound coverage, a skin graft may be necessary to obtain coverage of clean, non-healing wounds. Examples of skin grafts that may be used for soft-tissue coverage include, but are not limited to: autologous skin grafts, cadaveric skin graft, bioengineered skin substitutes (*e.g.*, APLIGRAF®; DERMAGRAFT®).

[000767] In certain embodiments, the polynucleotide, primary construct or mmRNA of the present invention may further include hydrogels (*e.g.*, AQUASORB®; DUODERM®), hydrocolloids (*e.g.*, AQUACEL®; COMFEEL®), foams (*e.g.*, LYOFOAM®; SPYROSORB®), and/or alginates (*e.g.*, ALGISITE®; CURASORB®). In certain embodiments, the polynucleotide, primary construct or mmRNA of the present invention may be used with skin grafts including, but not limited to, autologous skin

grafts, cadaveric skin graft, or bioengineered skin substitutes (*e.g.*, APLIGRAF®; DERMAGRAFT®). In some embodiments, the polynucleotide, primary construct or mmRNA may be applied with would dressing formulations and/or skin grafts or they may be applied separately but methods such as, but not limited to, soaking or spraying.

[000768] In some embodiments, compositions for wound management may comprise a polynucleotide, primary construct or mmRNA encoding for an anti-microbial polypeptide (e.g., an anti-bacterial polypeptide) and/or an anti-viral polypeptide. A precursor or a partially or fully processed form of the anti-microbial polypeptide may be encoded. The composition may be formulated for administration using a bandage (e.g., an adhesive bandage). The anti-microbial polypeptide and/or the anti-viral polypeptide may be intermixed with the dressing compositions or may be applied separately, e.g., by soaking or spraying.

Production of Antibodies

[000769] In one embodiment of the invention, the polynucleotides, primary constructs or mmRNA may encode antibodies and fragments of such antibodies. These may be produced by any one of the methods described herein. The antibodies may be of any of the different subclasses or isotypes of immunoglobulin such as, but not limited to, IgA, IgG, or IgM, or any of the other subclasses. Exemplary antibody molecules and fragments that may be prepared according to the invention include, but are not limited to, immunoglobulin molecules, substantially intact immunoglobulin molecules and those portions of an immunoglobulin molecule that may contain the paratope. Such portion of antibodies that contain the paratope include, but are not limited to Fab, Fab', $F(ab')_2$, F(v) and those portions known in the art.

[000770] The polynucleotides of the invention may encode variant antibody polypeptides which may have a certain identity with a reference polypeptide sequence, or have a similar or dissimilar binding characteristic with the reference polypeptide sequence.

[000771] Antibodies obtained by the methods of the present invention may be chimeric antibodies comprising non-human antibody-derived variable region(s) sequences, derived from the immunized animals, and human antibody-derived constant region(s) sequences. In addition, they can also be humanized antibodies comprising complementary

determining regions (CDRs) of non-human antibodies derived from the immunized animals and the framework regions (FRs) and constant regions derived from human antibodies. In another embodiment, the methods provided herein may be useful for enhancing antibody protein product yield in a cell culture process.

Managing Infection

[000772] In one embodiment, provided are methods for treating or preventing a microbial infection (*e.g.*, a bacterial infection) and/or a disease, disorder, or condition associated with a microbial or viral infection, or a symptom thereof, in a subject, by administering a polynucleotide, primary construct or mmRNA encoding an anti-microbial polypeptide. Said administration may be in combination with an anti-microbial agent (*e.g.*, an anti-bacterial agent), *e.g.*, an anti-microbial polypeptide or a small molecule anti-microbial compound described herein. The anti-microbial agents include, but are not limited to, anti-bacterial agents, anti-viral agents, anti-fungal agents, anti-protozoal agents, anti-parasitic agents, and anti-prion agents.

[000773] The agents can be administered simultaneously, for example in a combined unit dose (*e.g.*, providing simultaneous delivery of both agents). The agents can also be administered at a specified time interval, such as, but not limited to, an interval of minutes, hours, days or weeks. Generally, the agents may be concurrently bioavailable, *e.g.*, detectable, in the subject. In some embodiments, the agents may be administered essentially simultaneously, for example two unit dosages administered at the same time, or a combined unit dosage of the two agents. In other embodiments, the agents may be delivered in separate unit dosages. The agents may be administered in any order, or as one or more preparations that includes two or more agents. In a preferred embodiment, at least one administration of one of the agents, *e.g.*, the first agent, may be made within minutes, one, two, three, or four hours, or even within one or two days of the other agent, *e.g.*, the second agent. In some embodiments, combinations can achieve synergistic results, *e.g.*, greater than additive results, *e.g.*, at least 25, 50, 75, 100, 200, 300, 400, or 500% greater than additive results.

Conditions associated with bacterial infection

[000774] Diseases, disorders, or conditions which may be associated with bacterial infections include, but are not limited to one or more of the following: abscesses,

actinomycosis, acute prostatitis, aeromonas hydrophila, annual ryegrass toxicity, anthrax, bacillary peliosis, bacteremia, bacterial gastroenteritis, bacterial meningitis, bacterial pneumonia, bacterial vaginosis, bacterium-related cutaneous conditions, bartonellosis, BCG-oma, botryomycosis, botulism, Brazilian purpuric fever, Brodie abscess, brucellosis, Buruli ulcer, campylobacteriosis, caries, Carrion's disease, cat scratch disease, cellulitis, chlamydia infection, cholera, chronic bacterial prostatitis, chronic recurrent multifocal osteomyelitis, clostridial necrotizing enteritis, combined periodontic-endodontic lesions, contagious bovine pleuropneumonia, diphtheria, diphtheritic stomatitis, ehrlichiosis, erysipelas, piglottitis, erysipelas, Fitz-Hugh–Curtis syndrome, flea-borne spotted fever, foot rot (infectious pododermatitis), Garre's sclerosing osteomyelitis, Gonorrhea, Granuloma inguinale, human granulocytic anaplasmosis, human monocytotropic ehrlichiosis, hundred days' cough, impetigo, late congenital syphilitic oculopathy, legionellosis, Lemierre's syndrome, leprosy (Hansen's Disease), leptospirosis, listeriosis, Lyme disease, lymphadenitis, melioidosis, meningococcal disease, meningococcal septicaemia, methicillin-resistant Staphylococcus aureus (MRSA) infection, mycobacterium avium-intracellulare (MAI), mycoplasma pneumonia, necrotizing fasciitis, nocardiosis, noma (cancrum oris or gangrenous stomatitis), omphalitis, orbital cellulitis, osteomyelitis, overwhelming post-splenectomy infection (OPSI), ovine brucellosis, pasteurellosis, periorbital cellulitis, pertussis (whooping cough), plague, pneumococcal pneumonia, Pott disease, proctitis, pseudomonas infection, psittacosis, pyaemia, pyomyositis, Q fever, relapsing fever (typhinia), rheumatic fever, Rocky Mountain spotted fever (RMSF), rickettsiosis, salmonellosis, scarlet fever, sepsis, serratia infection, shigellosis, southern tick-associated rash illness, staphylococcal scalded skin syndrome, streptococcal pharyngitis, swimming pool granuloma, swine brucellosis, syphilis, syphilitic aortitis, tetanus, toxic shock syndrome (TSS), trachoma, trench fever, tropical ulcer, tuberculosis, tularemia, typhoid fever, typhus, urogenital tuberculosis, urinary tract infections, vancomycin-resistant Staphylococcus aureus infection, Waterhouse–Friderichsen syndrome, pseudotuberculosis (Yersinia) disease, and yersiniosis. Other diseases, disorders, and/or conditions associated with bacterial infections can include, for example, Alzheimer's disease, anorexia nervosa, asthma, atherosclerosis, attention deficit hyperactivity disorder, autism, autoimmune diseases,

bipolar disorder, cancer (e.g., colorectal cancer, gallbladder cancer, lung cancer, pancreatic cancer, and stomach cancer), chronic fatigue syndrome, chronic obstructive pulmonary disease, Crohn's disease, coronary heart disease, dementia, depression, Guillain–Barré syndrome, metabolic syndrome, multiple sclerosis, myocardial infarction, obesity, obsessive–compulsive disorder, panic disorder, psoriasis, rheumatoid arthritis, sarcoidosis, schizophrenia, stroke, thromboangiitis obliterans (Buerger's disease), and Tourette syndrome.

Bacterial Pathogens

[000775] The bacterium described herein can be a Gram-positive bacterium or a Gram-negative bacterium. Bacterial pathogens include, but are not limited to, *Acinetobacter baumannii, Bacillus anthracis, Bacillus subtilis, Bordetella pertussis, Borrelia burgdorferi, Brucella abortus, Brucella canis, Brucella melitensis, Brucella suis, Campylobacter jejuni, Chlamydia pneumoniae, Chlamydia trachomatis, Chlamydophila psittaci, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Clostridium tetani,* coagulase Negative *Staphylococcus, Corynebacterium diphtheria, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, enterotoxigenic Escherichia coli* (ETEC), enteropathogenic *E. coli, E. coli* O157:H7, *Enterobacter sp., Francisella tularensis, Haemophilus influenzae, Helicobacter pylori, Klebsiella pneumoniae, Legionella pneumophila, Leptospira interrogans, Listeria monocytogenes, Moraxella catarralis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma pneumoniae, Neisseria gonorrhoeae, Neisseria meningitides, Preteus mirabilis, Proteus sps., Pseudomonas aeruginosa, Rickettsia rickettsii, Salmonella typhi, Salmonella typhimurium, Serratia marcesens, Shigella flexneri, Shigella sonnei, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus agalactiae, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Treponema pallidum, Vibrio cholerae, and Yersinia pestis*. Bacterial pathogens may also include bacteria that cause resistant bacterial infections, for example, clindamycin-resistant *Clostridium difficile,* fluoroquinolon-resistant *Clostridium difficile,* methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Enterococcus faecalis*, multidrug-resistant *Enterococcus faecium,* multidrug-resistance *Pseudomonas*

aeruginosa, multidrug-resistant *Acinetobacter baumannii,* and vancomycin-resistant *Staphylococcus aureus* (VRSA).

Antibiotic Combinations

[000776] In one embodiment, the modified mRNA of the present invention may be administered in conjunction with one or more antibiotics. These include, but are not limited to Aknilox , Ambisome, Amoxycillin, Ampicillin, Augmentin, Avelox, Azithromycin, Bactroban, Betadine, Betnovate, Blephamide, Cefaclor, Cefadroxil, Cefdinir, Cefepime, Cefix, Cefixime, Cefoxitin, Cefpodoxime, Cefprozil, Cefuroxime, Cefzil, Cephalexin, Cephazolin, Ceptaz, Chloramphenicol, Chlorhexidine, Chloromycetin, Chlorsig, Ciprofloxacin, Clarithromycin, Clindagel, Clindamycin, Clindatech, Cloxacillin, Colistin, Co-trimoxazole, Demeclocycline, Diclocil, Dicloxacillin, Doxycycline, Duricef, Erythromycin, Flamazine, Floxin, Framycetin, Fucidin, Furadantin, Fusidic, Gatifloxacin, Gemifloxacin, Gemifloxacin, Ilosone, Iodine, Levaquin, Levofloxacin, Lomefloxacin, Maxaquin, Mefoxin, Meronem, Minocycline, Moxifloxacin, Myambutol, Mycostatin, Neosporin, Netromycin, Nitrofurantoin, Norfloxacin, Norilet, Ofloxacin, Omnicef, Ospamox, Oxytetracycline, Paraxin, Penicillin, Pneumovax, Polyfax, Povidone, Rifadin, Rifampin, Rifaximin, Rifinah, Rimactane, Rocephin, Roxithromycin, Seromycin, Soframycin, Sparfloxacin, Staphlex, Targocid, Tetracycline, Tetradox, Tetralysal, tobramycin, Tobramycin, Trecator, Tygacil, Vancocin, Velosef, Vibramycin, Xifaxan, Zagam, Zitrotek, Zoderm, Zymar, and Zyvox.

Antibacterial agents

[000777] Exemplary anti-bacterial agents include, but are not limited to, aminoglycosides (*e.g.*, amikacin (AMIKIN®), gentamicin (GARAMYCIN®), kanamycin (KANTREX®), neomycin (MYCIFRADIN®), netilmicin (NETROMYCIN®), tobramycin (NEBCIN®), Paromomycin (HUMATIN®)), ansamycins (*e.g.*, geldanamycin, herbimycin), carbacephem (*e.g.*, loracarbef (LORABID®), Carbapenems (*e.g.*, ertapenem (INVANZ®), doripenem (DORIBAX®), imipenem/cilastatin (PRIMAXIN®), meropenem (MERREM®), cephalosporins (first generation) (*e.g.*, cefadroxil (DURICEF®), cefazolin (ANCEF®), cefalotin or cefalothin (KEFLIN®), cefalexin (KEFLEX®), cephalosporins (second generation) (*e.g.*, cefaclor (CECLOR®), cefamandole (MANDOL®), cefoxitin (MEFOXIN®), cefprozil (CEFZIL®), cefuroxime

(CEFTIN®, ZINNAT®)), cephalosporins (third generation) (*e.g.*, cefixime (SUPRAX®), cefdinir (OMNICEF®, CEFDIEL®), cefditoren (SPECTRACEF®), cefoperazone (CEFOBID®), cefotaxime (CLAFORAN®), cefpodoxime (VANTIN®), ceftazidime (FORTAZ®), ceftibuten (CEDAX®), ceftizoxime (CEFIZOX®), ceftriaxone (ROCEPHIN®)), cephalosporins (fourth generation) (*e.g.*, cefepime (MAXIPIME®)), cephalosporins (fifth generation) (*e.g.*, ceftobiprole (ZEFTERA®)), glycopeptides (*e.g.*, teicoplanin (TARGOCID®), vancomycin (VANCOCIN®), telavancin (VIBATIV®)), lincosamides (*e.g.*, clindamycin (CLEOCIN®), lincomycin (LINCOCIN®)), lipopeptide (*e.g.*, daptomycin (CUBICIN®)), macrolides (*e.g.*, azithromycin (ZITHROMAX®, SUMAMED®, ZITROCIN®), clarithromycin (BIAXIN®), dirithromycin (DYNABAC®), erythromycin (ERYTHOCIN®, ERYTHROPED®), roxithromycin, troleandomycin (TAO®), telithromycin (KETEK®), spectinomycin (TROBICIN®)), monobactams (*e.g.*, aztreonam (AZACTAM®)), nitrofurans (*e.g.*, furazolidone (FUROXONE®), nitrofurantoin (MACRODANTIN®, MACROBID®)), penicillins (*e.g.*, amoxicillin (NOVAMOX®, AMOXIL®), ampicillin (PRINCIPEN®), azlocillin, carbenicillin (GEOCILLIN®), cloxacillin (TEGOPEN®), dicloxacillin (DYNAPEN®), flucloxacillin (FLOXAPEN®), mezlocillin (MEZLIN®), methicillin (STAPHCILLIN®), nafcillin (UNIPEN®), oxacillin (PROSTAPHLIN®), penicillin G (PENTIDS®), penicillin V (PEN-VEE-K®), piperacillin (PIPRACIL®), temocillin (NEGABAN®), ticarcillin (TICAR®)), penicillin combinations (*e.g.*, amoxicillin/clavulanate (AUGMENTIN®), ampicillin/sulbactam (UNASYN®), piperacillin/tazobactam (ZOSYN®), ticarcillin/clavulanate (TIMENTIN®)), polypeptides (*e.g.*, bacitracin, colistin (COLY-MYCIN-S®), polymyxin B, quinolones (*e.g.*, ciprofloxacin (CIPRO®, CIPROXIN®, CIPROBAY®), enoxacin (PENETREX®), gatifloxacin (TEQUIN®), levofloxacin (LEVAQUIN®), lomefloxacin (MAXAQUIN®), moxifloxacin (AVELOX®), nalidixic acid (NEGGRAM®), norfloxacin (NOROXIN®), ofloxacin (FLOXIN®, OCUFLOX®), trovafloxacin (TROVAN®), grepafloxacin (RAXAR®), sparfloxacin (ZAGAM®), temafloxacin (OMNIFLOX®)), sulfonamides (*e.g.*, mafenide (SULFAMYLON®), sulfonamidochrysoidine (PRONTOSIL®), sulfacetamide (SULAMYD®, BLEPH-10®), sulfadiazine (MICRO-SULFON®), silver sulfadiazine (SILVADENE®), sulfamethizole (THIOSULFIL FORTE®), sulfamethoxazole

(GANTANOL®), sulfanilimide, sulfasalazine (AZULFIDINE®), sulfisoxazole (GANTRISIN®), trimethoprim (PROLOPRIM®), TRIMPEX®), trimethoprim-sulfamethoxazole (co-trimoxazole) (TMP-SMX) (BACTRIM®, SEPTRA®)), tetracyclines (*e.g.*, demeclocycline (DECLOMYCIN®), doxycycline (VIBRAMYCIN®), minocycline (MINOCIN®), oxytetracycline (TERRAMYCIN®), tetracycline (SUMYCIN®, ACHROMYCIN® V, STECLIN®)), drugs against mycobacteria (*e.g.*, clofazimine (LAMPRENE®), dapsone (AVLOSULFON®), capreomycin (CAPASTAT®), cycloserine (SEROMYCIN®), ethambutol (MYAMBUTOL®), ethionamide (TRECATOR®), isoniazid (I.N.H.®), pyrazinamide (ALDINAMIDE®), rifampin (RIFADIN®, RIMACTANE®), rifabutin (MYCOBUTIN®), rifapentine (PRIFTIN®), streptomycin), and others (*e.g.*, arsphenamine (SALVARSAN®), chloramphenicol (CHLOROMYCETIN®), fosfomycin (MONUROL®), fusidic acid (FUCIDIN®), linezolid (ZYVOX®), metronidazole (FLAGYL®), mupirocin (BACTROBAN®), platensimycin, quinupristin/dalfopristin (SYNERCID®), rifaximin (XIFAXAN®), thiamphenicol, tigecycline (TIGACYL®), tinidazole (TINDAMAX®, FASIGYN®)).

Conditions associated with viral infection

[000778] In another embodiment, provided are methods for treating or preventing a viral infection and/or a disease, disorder, or condition associated with a viral infection, or a symptom thereof, in a subject, by administering a polynucleotide, primary construct or mmRNA encoding an anti-viral polypeptide, *e.g.*, an anti-viral polypeptide described herein in combination with an anti-viral agent, *e.g.*, an anti-viral polypeptide or a small molecule anti-viral agent described herein.

[000779] Diseases, disorders, or conditions associated with viral infections include, but are not limited to, acute febrile pharyngitis, pharyngoconjunctival fever, epidemic keratoconjunctivitis, infantile gastroenteritis, Coxsackie infections, infectious mononucleosis, Burkitt lymphoma, acute hepatitis, chronic hepatitis, hepatic cirrhosis, hepatocellular carcinoma, primary HSV-1 infection (*e.g.*, gingivostomatitis in children, tonsillitis and pharyngitis in adults, keratoconjunctivitis), latent HSV-1 infection (*e.g.*, herpes labialis and cold sores), primary HSV-2 infection, latent HSV-2 infection, aseptic meningitis, infectious mononucleosis, Cytomegalic inclusion disease, Kaposi sarcoma,

multicentric Castleman disease, primary effusion lymphoma, AIDS, influenza, Reye syndrome, measles, postinfectious encephalomyelitis, Mumps, hyperplastic epithelial lesions (*e.g.*, common, flat, plantar and anogenital warts, laryngeal papillomas, epidermodysplasia verruciformis), cervical carcinoma, squamous cell carcinomas, croup, pneumonia, bronchiolitis, common cold, Poliomyelitis, Rabies, bronchiolitis, pneumonia, influenza-like syndrome, severe bronchiolitis with pneumonia, German measles, congenital rubella, Varicella, and herpes zoster.

Viral pathogens

[000780] Viral pathogens include, but are not limited to, adenovirus, coxsackievirus, dengue virus, encephalitis virus, Epstein-Barr virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, human herpesvirus type 8, human immunodeficiency virus, influenza virus, measles virus, mumps virus, human papillomavirus, parainfluenza virus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, varicella-zoster virus, West Nile virus, and yellow fever virus. Viral pathogens may also include viruses that cause resistant viral infections.

Antiviral agents

[000781] Exemplary anti-viral agents include, but are not limited to, abacavir (ZIAGEN®), abacavir/lamivudine/zidovudine (trizivir®), aciclovir or acyclovir (CYCLOVIR®, HERPEX®, ACIVIR®, ACIVIRAX®, ZOVIRAX®, ZOVIR®), adefovir (Preveon®, Hepsera®), amantadine (SYMMETREL®), amprenavir (AGENERASE®), ampligen, arbidol, atazanavir (REYATAZ®), boceprevir, cidofovir, darunavir (PREZISTA®), delavirdine (RESCRIPTOR®), didanosine (VIDEX®), docosanol (ABREVA®), edoxudine, efavirenz (SUSTIVA®, STOCRIN®), emtricitabine (EMTRIVA®), emtricitabine/tenofovir/efavirenz (ATRIPLA®), enfuvirtide (FUZEON®), entecavir (BARACLUDE®, ENTAVIR®), famciclovir (FAMVIR®), fomivirsen (VITRAVENE®), fosamprenavir (LEXIVA®, TELZIR®), foscarnet (FOSCAVIR®), fosfonet, ganciclovir (CYTOVENE®, CYMEVENE®, VITRASERT®), GS 9137 (ELVITEGRAVIR®), imiquimod (ALDARA®, ZYCLARA®, BESELNA®), indinavir (CRIXIVAN®), inosine, inosine pranobex (IMUNOVIR®), interferon type I, interferon type II, interferon type III, kutapressin

(NEXAVIR®), lamivudine (ZEFFIX®, HEPTOVIR®, EPIVIR®), lamivudine/zidovudine (COMBIVIR®), lopinavir, loviride, maraviroc (SELZENTRY®, CELSENTRI®), methisazone, MK-2048, moroxydine, nelfinavir (VIRACEPT®), nevirapine (VIRAMUNE®), oseltamivir (TAMIFLU®), peginterferon alfa-2a (PEGASYS®), penciclovir (DENAVIR®), peramivir, pleconaril, podophyllotoxin (CONDYLOX®), raltegravir (ISENTRESS®), ribavirin (COPEGUs®, REBETOL®, RIBASPHERE®, VILONA® AND VIRAZOLE®), rimantadine (FLUMADINE®), ritonavir (NORVIR®), pyramidine, saquinavir (INVIRASE®, FORTOVASE®), stavudine, tea tree oil (melaleuca oil), tenofovir (VIREAD®), tenofovir/emtricitabine (TRUVADA®), tipranavir (APTIVUS®), trifluridine (VIROPTIC®), tromantadine (VIRU-MERZ®), valaciclovir (VALTREX®), valganciclovir (VALCYTE®), vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir (RELENZA®), and zidovudine (azidothymidine (AZT), RETROVIR®, RETROVIS®).

Conditions associated with fungal infections

[000782] Diseases, disorders, or conditions associated with fungal infections include, but are not limited to, aspergilloses, blastomycosis, candidasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mycetomas, paracoccidioidomycosis, and tinea pedis. Furthermore, persons with immuno-deficiencies are particularly susceptible to disease by fungal genera such as Aspergillus, Candida, Cryptoccocus, Histoplasma, and Pneumocystis. Other fungi can attack eyes, nails, hair, and especially skin, the so-called dermatophytic fungi and keratinophilic fungi, and cause a variety of conditions, of which ringworms such as athlete's foot are common. Fungal spores are also a major cause of allergies, and a wide range of fungi from different taxonomic groups can evoke allergic reactions in some people.

Fungal pathogens

[000783] Fungal pathogens include, but are not limited to, Ascomycota (e.g., Fusarium oxysporum, Pneumocystis jirovecii, Aspergillus spp., Coccidioides immitis/posadasii, Candida albicans), Basidiomycota (e.g., Filobasidiella neoformans, Trichosporon), Microsporidia (e.g., Encephalitozoon cuniculi, Enterocytozoon bieneusi), and Mucoromycotina (e.g., Mucor circinelloides, Rhizopus oryzae, Lichtheimia corymbifera).

Anti-fungal agents

[000784] Exemplary anti-fungal agents include, but are not limited to, polyene antifungals (*e.g.*, natamycin, rimocidin, filipin, nystatin, amphotericin B, candicin, hamycin), imidazole antifungals (*e.g.*, miconazole (MICATIN®, DAKTARIN®), ketoconazole (NIZORAL®, FUNGORAL®, SEBIZOLE®), clotrimazole (LOTRIMIN®, LOTRIMIN® AF, CANESTEN®), econazole, omoconazole, bifonazole, butoconazole, fenticonazole, isoconazole, oxiconazole, sertaconazole (ERTACZO®), sulconazole, tioconazole), triazole antifungals (*e.g.*, albaconazole fluconazole, itraconazole, isavuconazole, ravuconazole, posaconazole, voriconazole, terconazole), thiazole antifungals (*e.g.*, abafungin), allylamines (*e.g.*, terbinafine (LAMISIL®), naftifine (NAFTIN®), butenafine (LOTRIMIN® Ultra)), echinocandins (*e.g.*, anidulafungin, caspofungin, micafungin), and others (*e.g.*, polygodial, benzoic acid, ciclopirox, tolnaftate (TINACTIN®, DESENEX®, AFTATE®), undecylenic acid, flucytosine or 5-fluorocytosine, griseofulvin, haloprogin, sodium bicarbonate, allicin).

Conditions associated with protozoal infection

[000785] Diseases, disorders, or conditions associated with protozoal infections include, but are not limited to, amoebiasis, giardiasis, trichomoniasis, African Sleeping Sickness, American Sleeping Sickness, leishmaniasis (Kala-Azar), balantidiasis, toxoplasmosis, malaria, acanthamoeba keratitis, and babesiosis.

Protozoan pathogens

[000786] Protozoal pathogens include, but are not limited to, Entamoeba histolytica, Giardia lambila, Trichomonas vaginalis, Trypanosoma brucei, T. cruzi, Leishmania donovani, Balantidium coli, Toxoplasma gondii, Plasmodium spp., and Babesia microti.

Anti-protozoan agents

[000787] Exemplary anti-protozoal agents include, but are not limited to, eflornithine, furazolidone (FUROXONE®, DEPENDAL-M®), melarsoprol, metronidazole (FLAGYL®), ornidazole, paromomycin sulfate (HUMATIN®), pentamidine, pyrimethamine (DARAPRIM®), and tinidazole (TINDAMAX®, FASIGYN®).

Conditions associated with parasitic infection

[000788] Diseases, disorders, or conditions associated with parasitic infections include, but are not limited to, acanthamoeba keratitis, amoebiasis, ascariasis, babesiosis,

balantidiasis, baylisascariasis, chagas disease, clonorchiasis, cochliomyia, cryptosporidiosis, diphyllobothriasis, dracunculiasis, echinococcosis, elephantiasis, enterobiasis, fascioliasis, fasciolopsiasis, filariasis, giardiasis, gnathostomiasis, hymenolepiasis, isosporiasis, katayama fever, leishmaniasis, lyme disease, malaria, metagonimiasis, myiasis, onchocerciasis, pediculosis, scabies, schistosomiasis, sleeping sickness, strongyloidiasis, taeniasis, toxocariasis, toxoplasmosis, trichinosis, and trichuriasis.

Parasitic pathogens

[000789] Parasitic pathogens include, but are not limited to, Acanthamoeba, Anisakis, Ascaris lumbricoides, botfly, Balantidium coli, bedbug, Cestoda, chiggers, Cochliomyia hominivorax, Entamoeba histolytica, Fasciola hepatica, Giardia lamblia, hookworm, Leishmania, Linguatula serrata, liver fluke, Loa loa, Paragonimus, pinworm, Plasmodium falciparum, Schistosoma, Strongyloides stercoralis, mite, tapeworm, Toxoplasma gondii, Trypanosoma, whipworm, Wuchereria bancrofti.

A*nti-parasitic agents*

[000790] Exemplary anti-parasitic agents include, but are not limited to, antinematodes (*e.g.*, mebendazole, pyrantel pamoate, thiabendazole, diethylcarbamazine, ivermectin), anticestodes (*e.g.*, niclosamide, praziquantel, albendazole), antitrematodes (*e.g.*, praziquantel), antiamoebics (*e.g.*, rifampin, amphotericin B), and antiprotozoals (*e.g.*, melarsoprol, eflornithine, metronidazole, tinidazole).

Conditions associated with prion infection

[000791] Diseases, disorders, or conditions associated with prion infections include, but are not limited to Creutzfeldt–Jakob disease (CJD), iatrogenic Creutzfeldt–Jakob disease (iCJD), variant Creutzfeldt–Jakob disease (vCJD), familial Creutzfeldt–Jakob disease (fCJD), sporadic Creutzfeldt–Jakob disease (sCJD), Gerstmann–Sträussler–Scheinker syndrome (GSS), fatal familial insomnia (FFI), Kuru, Scrapie, bovine spongiform encephalopathy (BSE), mad cow disease, transmissible mink encephalopathy (TME), chronic wasting disease (CWD), feline spongiform encephalopathy (FSE), exotic ungulate encephalopathy (EUE), and spongiform encephalopathy.

Anti-prion agents

[000792] Exemplary anti-prion agents include, but are not limited to, flupirtine, pentosan polysuphate, quinacrine, and tetracyclic compounds.

Modulation of the Immune Response

Avoidance of the immune response

[000793] As described herein, a useful feature of the polynucleotides, primary constructs or mmRNA of the invention is the capacity to reduce, evade or avoid the innate immune response of a cell. In one aspect, provided herein are polynucleotides, primary constructs or mmRNA encoding a polypeptide of interest which when delivered to cells, results in a reduced immune response from the host as compared to the response triggered by a reference compound, e.g. an unmodified polynucleotide corresponding to a polynucleotide, primary construct or mmRNA of the invention, or a different polynucleotide, primary construct or mmRNA of the invention. As used herein, a "reference compound" is any molecule or substance which when administered to a mammal, results in an innate immune response having a known degree, level or amount of immune stimmulation. A reference compound need not be a nucleic acid molecule and it need not be any of the polynucleotides, primary constructs or mmRNA of the invention. Hence, the measure of a polynucleotides, primary constructs or mmRNA avoidance, evasion or failure to trigger an immune response can be expressed in terms relative to any compound or substance which is known to trigger such a response.

[000794] The term "innate immune response" includes a cellular response to exogenous single stranded nucleic acids, generally of viral or bacterial origin, which involves the induction of cytokine expression and release, particularly the interferons, and cell death. As used herein, the innate immune response or interferon response operates at the single cell level causing cytokine expression, cytokine release, global inhibition of protein synthesis, global destruction of cellular RNA, upregulation of major histocompatibility molecules, and/or induction of apoptotic death, induction of gene transcription of genes involved in apoptosis, anti-growth, and innate and adaptive immune cell activation. Some of the genes induced by type I IFNs include PKR, ADAR (adenosine deaminase acting on RNA), OAS (2',5'-oligoadenylate synthetase), RNase L, and Mx proteins. PKR and ADAR lead to inhibition of translation initiation and RNA editing, respectively. OAS is a

dsRNA-dependent synthetase that activates the endoribonuclease RNase L to degrade ssRNA.

[000795] In some embodiments, the innate immune response comprises expression of a Type I or Type II interferon, and the expression of the Type I or Type II interferon is not increased more than two-fold compared to a reference from a cell which has not been contacted with a polynucleotide, primary construct or mmRNA of the invention.

[000796] In some embodiments, the innate immune response comprises expression of one or more IFN signature genes and where the expression of the one of more IFN signature genes is not increased more than three-fold compared to a reference from a cell which has not been contacted with the polynucleotide, primary construct or mmRNA of the invention.

[000797] While in some circumstances, it might be advantageous to eliminate the innate immune response in a cell, the invention provides polynucleotides, primary constructs and mmRNA that upon administration result in a substantially reduced (significantly less) the immune response, including interferon signaling, without entirely eliminating such a response.

[000798] In some embodiments, the immune response is lower by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.9%, or greater than 99.9% as compared to the immune response induced by a reference compound. The immune response itself may be measured by determining the expression or activity level of Type 1 interferons or the expression of interferon-regulated genes such as the toll-like receptors (e.g., TLR7 and TLR8). Reduction of innate immune response can also be measured by measuring the level of decreased cell death following one or more administrations to a cell population; e.g., cell death is 10%, 25%, 50%, 75%, 85%, 90%, 95%, or over 95% less than the cell death frequency observed with a reference compound. Moreover, cell death may affect fewer than 50%, 40%, 30%, 20%, 10%, 5%, 1%, 0.1%, 0.01% or fewer than 0.01% of cells contacted with the polynucleotide, primary construct or mmRNA.

[000799] In another embodiment, the polynucleotide, primary construct or mmRNA of the present invention is significantly less immunogenic than an unmodified in vitro-synthesized RNA molecule polynucleotide, or primary construct with the same sequence or a reference compound. As used herein, "significantly less immunogenic" refers to a

detectable decrease in immunogenicity. In another embodiment, the term refers to a fold decrease in immunogenicity. In another embodiment, the term refers to a decrease such that an effective amount of the polynucleotide, primary construct or mmRNA can be administered without triggering a detectable immune response. In another embodiment, the term refers to a decrease such that the polynucleotide, primary construct or mmRNA can be repeatedly administered without eliciting an immune response sufficient to detectably reduce expression of the recombinant protein. In another embodiment, the decrease is such that the polynucleotide, primary construct or mmRNA can be repeatedly administered without eliciting an immune response sufficient to eliminate detectable expression of the recombinant protein.

[000800] In another embodiment, the polynucleotide, primary construct or mmRNA is 2-fold less immunogenic than its unmodified counterpart or reference compound. In another embodiment, immunogenicity is reduced by a 3-fold factor. In another embodiment, immunogenicity is reduced by a 5-fold factor. In another embodiment, immunogenicity is reduced by a 7-fold factor. In another embodiment, immunogenicity is reduced by a 10-fold factor. In another embodiment, immunogenicity is reduced by a 15-fold factor. In another embodiment, immunogenicity is reduced by a fold factor. In another embodiment, immunogenicity is reduced by a 50-fold factor. In another embodiment, immunogenicity is reduced by a 100-fold factor. In another embodiment, immunogenicity is reduced by a 200-fold factor. In another embodiment, immunogenicity is reduced by a 500-fold factor. In another embodiment, immunogenicity is reduced by a 1000-fold factor. In another embodiment, immunogenicity is reduced by a 2000-fold factor. In another embodiment, immunogenicity is reduced by another fold difference.

[000801] Methods of determining immunogenicity are well known in the art, and include, e.g. measuring secretion of cytokines (e.g. IL-12, IFNalpha, TNF-alpha, RANTES, MIP-1alpha or beta, IL-6, IFN-beta, or IL-8), measuring expression of DC activation markers (e.g. CD83, HLA-DR, CD80 and CD86), or measuring ability to act as an adjuvant for an adaptive immune response.

[000802] The the polynucleotide, primary construct or mmRNA of the invention, including the combination of modifications taught herein may have superior properties making them more suitable as therapeutic modalities.

[000803] It has been determined that the "all or none" model in the art is sorely insufficient to describe the biological phenomena associated with the therapeutic utility of modified mRNA. The present inventors have determined that to improve protein production, one may consider the nature of the modification, or combination of modifications, the percent modification and survey more than one cytokine or metric to determine the efficacy and risk profile of a particular modified mRNA.

[000804] In one aspect of the invention, methods of determining the effectiveness of a modified mRNA as compared to unmodified involves the measure and analysis of one or more cytokines whose expression is triggered by the administration of the exogenous nucleic acid of the invention. These values are compared to administration of an umodified nucleic acid or to a standard metric such as cytokine response, PolyIC, R-848 or other standard known in the art.

[000805] One example of a standard metric developed herein is the measure of the ratio of the level or amount of encoded polypeptide (protein) produced in the cell, tissue or organism to the level or amount of one or more (or a panel) of cytokines whose expression is triggered in the cell, tissue or organism as a result of administration or contact with the modified nucleic acid. Such ratios are referred to herein as the Protein:Cytokine Ratio or "PC" Ratio. The higher the PC ratio, the more efficacioius the modified nucleic acid (polynucleotide encoding the protein measured). Preferred PC Ratios, by cytokine, of the present invention may be greater than 1, greater than 10, greater than 100, greater than 1000, greater than 10,000 or more. Modified nucleic acids having higher PC Ratios than a modified nucleic acid of a different or unmodified construct are preferred.

[000806] The PC ratio may be further qualified by the percent modification present in the polynucleotide. For example, normalized to a 100% modified nucleic acid, the protein production as a function of cytokine (or risk) or cytokine profile can be determined.

[000807] In one embodiment, the present invention provides a method for determining, across chemistries, cytokines or percent modification, the relative efficacy of any particular modified the polynucleotide, primary construct or mmRNA by comparing the PC Ratio of the modified nucleic acid (polynucleotide, primary construct or mmRNA).

[000808] mmRNA containing varying levels of nucleobase subsitutions could be produced that maintain increased protein production and decreased immunostimulatory potential. The relative percentage of any modified nucleotide to its naturally occurring nucleotide counterpart can be varied during the IVT reaction (for instance, 100, 50, 25, 10, 5, 2.5, 1, 0.1, 0.01% 5 methyl cytidine usage versus cytidine; 100, 50, 25, 10, 5, 2.5, 1, 0.1, 0.01% pseudouridine or N1-methyl-pseudouridine usage versus uridine). mmRNA can also be made that utilize different ratios using 2 or more different nucleotides to the same base (for instance, different ratios of pseudouridine and N1-methyl-pseudouridine). mmRNA can also be made with mixed ratios at more than 1 "base" position, such as ratios of 5 methyl cytidine/cytidine and pseudouridine/N1-methyl-pseudouridine/uridine at the same time. Use of modified mRNA with altered ratios of modified nucleotides can be beneficial in reducing potential exposure to chemically modified nucleotides. Lastly, positional introduction of modified nucleotides into the mmRNA which modulate either protein production or immunostimulatory potential or both is also possible. The ability of such mmRNA to demonstrate these improved properties can be assessed in vitro (using assays such as the PBMC assay described herein), and can also be assessed in vivo through measurement of both mmRNA-encoded protein production and mediators of innate immune recognition such as cytokines.

[000809] In another embodiment, the relative immunogenicity of the polynucleotide, primary construct or mmRNA and its unmodified counterpart are determined by determining the quantity of the polynucleotide, primary construct or mmRNA required to elicit one of the above responses to the same degree as a given quantity of the unmodified nucleotide or reference compound. For example, if twice as much polynucleotide, primary construct or mmRNA is required to elicit the same response, than the polynucleotide, primary construct or mmRNA is two-fold less immunogenic than the unmodified nucleotide or the reference compound.

[000810] In another embodiment, the relative immunogenicity of the polynucleotide, primary construct or mmRNA and its unmodified counterpart are determined by determining the quantity of cytokine (e.g. IL-12, IFNalpha, TNF-alpha, RANTES, MIP-1alpha or beta, IL-6, IFN-beta, or IL-8) secreted in response to administration of the

polynucleotide, primary construct or mmRNA, relative to the same quantity of the unmodified nucleotide or reference compound. For example, if one-half as much cytokine is secreted, than the polynucleotide, primary construct or mmRNA is two-fold less immunogenic than the unmodified nucleotide. In another embodiment, background levels of stimulation are subtracted before calculating the immunogenicity in the above methods.

[000811] Provided herein are also methods for performing the titration, reduction or elimination of the immune response in a cell or a population of cells. In some embodiments, the cell is contacted with varied doses of the same polynucleotides, primary constructs or mmRNA and dose response is evaluated. In some embodiments, a cell is contacted with a number of different polynucleotides, primary constructs or mmRNA at the same or different doses to determine the optimal composition for producing the desired effect. Regarding the immune response, the desired effect may be to avoid, evade or reduce the immune response of the cell. The desired effect may also be to alter the efficiency of protein production.

[000812] The polynucleotides, primary constructs and/or mmRNA of the present invention may be used to reduce the immune response using the method described in International Publication No. WO2013003475, herein incorporated by reference in its entirety.

Activation of the immune response: Vaccines

[000813] Additionally, certain modified nucleosides, or combinations thereof, when introduced into the polynucleotides, primary constructs or mmRNA of the invention will activate the innate immune response. Such activating molecules are useful as adjuvants when combined with polypeptides and/or other vaccines. In certain embodiments, the activating molecules contain a translatable region which encodes for a polypeptide sequence useful as a vaccine, thus providing the ability to be a self-adjuvant.

[000814] In one embodiment, the polynucleotides, primary constructs and/or mmRNA of the invention may encode an immunogen. The delivery of the polynucleotides, primary constructs and/or mmRNA encoding an immunogen may activate the immune response. As a non-limiting example, the polynucleotides, primary constructs and/or mmRNA encoding an immunogen may be delivered to cells to trigger multiple innate

response pathways (see International Pub. No. WO2012006377; herein incorporated by reference in its entirety). As another non-limiting example, the polynucleotides, primary constructs and mmRNA of the present invention encoding an immunogen may be delivered to a vertebrate in a dose amount large enough to be immunogenic to the vertebrate (see International Pub. No. WO2012006372 and WO2012006369; each of which is herein incorporated by reference in their entirety).

[000815] The polynucleotides, primary constructs or mmRNA of invention may encode a polypeptide sequence for a vaccine and may further comprise an inhibitor. The inhibitor may impair antigen presentation and/or inhibit various pathways known in the art. As a non-limiting example, the polynucleotides, primary constructs or mmRNA of the invention may be used for a vaccine in combination with an inhibitor which can impair antigen presentation (see International Pub. No. WO2012089225 and WO2012089338; each of which is herein incorporated by reference in their entirety).

[000816] In one embodiment, the polynucleotides, primary constructs or mmRNA of the invention may be self-replicating RNA. Self-replicating RNA molecules can enhance efficiency of RNA delivery and expression of the enclosed gene product. In one embodiment, the polynucleotides, primary constructs or mmRNA may comprise at least one modification described herein and/or known in the art. In one embodiment, the self-replicating RNA can be designed so that the self-replicating RNA does not induce production of infectious viral particles. As a non-limiting example the self-replicating RNA may be designed by the methods described in US Pub. No. US20110300205 and International Pub. No. WO2011005799, each of which is herein incorporated by reference in their entirety.

[000817] In one embodiment, the self-replicating polynucleotides, primary constructs or mmRNA of the invention may encode a protein which may raise the immune response. As a non-limiting example, the polynucleotides, primary constructs or mmRNA may be self-replicating mRNA may encode at least one antigen (see US Pub. No. US20110300205 and International Pub. Nos. WO2011005799, WO2013006838 and WO2013006842; each of which is herein incorporated by reference in their entirety).

[000818] In one embodiment, the self-replicating polynucleotides, primary constructs or mmRNA of the invention may be formulated using methods described herein or known

in the art. As a non-limiting example, the self-replicating RNA may be formulated for delivery by the methods described in Geall et al (Nonviral delivery of self-amplifying RNA vaccines, PNAS 2012; PMID: 22908294).

[000819] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may encode amphipathic and/or immunogenic amphipathic peptides.

[000820] In on embodiment, a formulation of the polynucleotides, primary constructs or mmRNA of the present invention may further comprise an amphipathic and/or immunogenic amphipathic peptide. As a non-limiting example, the polynucleotides, primary constructs or mmRNA comprising an amphipathic and/or immunogenic amphipathic peptide may be formulated as described in US. Pub. No. US20110250237 and International Pub. Nos. WO2010009277 and WO2010009065; each of which is herein incorporated by reference in their entirety.

[000821] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may be immunostimultory. As a non-limiting example, the polynucleotides, primary constructs or mmRNA may encode all or a part of a positive-sense or a negative-sense stranded RNA virus genome (see International Pub No. WO2012092569 and US Pub No. US20120177701, each of which is herein incorporated by reference in their entirety). In another non-limiting example, the immunostimultory polynucleotides, primary constructs or mmRNA of the present invention may be formulated with an excipient for administration as described herein and/or known in the art (see International Pub No. WO2012068295 and US Pub No. US20120213812, each of which is herein incorporated by reference in their entirety).

[000822] In one embodiment, the response of the vaccine formulated by the methods described herein may be enhanced by the addition of various compounds to induce the therapeutic effect. As a non-limiting example, the vaccine formulation may include a MHC II binding peptide or a peptide having a similar sequence to a MHC II binding peptide (see International Pub Nos. WO2012027365, WO2011031298 and US Pub No. US20120070493, US20110110965, each of which is herein incorporated by reference in their entirety). As another example, the vaccine formulations may comprise modified nicotinic compounds which may generate an antibody response to nicotine residue in a

subject (see International Pub No. WO2012061717 and US Pub No. US20120114677, each of which is herein incorporated by reference in their entirety).

Naturally Occuring Mutants

[000823] In another embodiment, the polynucleotides, primary construct and/or mmRNA can be utilized to express variants of naturally occurring proteins that have an improved disease modifying activity, including increased biological activity, improved patient outcomes, or a protective function, etc. Many such modifier genes have been described in mammals (Nadeau, Current Opinion in Genetics & Development 2003 13:290-295; Hamilton and Yu, PLoS Genet. 2012;8:e1002644; Corder et al., Nature Genetics 1994 7:180 – 184; all herein incorporated by reference in their entireties). Examples in humans include Apo E2 protein, Apo A-I variant proteins (Apo A-I Milano, Apo A-I Paris), hyperactive Factor IX protein (Factor IX Padua Arg338Lys), transthyretin mutants (TTR Thr119Met). Expression of ApoE2 (cys112, cys158) has been shown to confer protection relative to other ApoE isoforms (*ApoE3* (cys112, arg158), and *ApoE4* (arg112, arg158)) by reducing susceptibility to Alzheimer's disease and possibly other conditions such as cardiovascular disease (Corder et al., Nature Genetics 1994 7:180 – 184; Seripa et al., Rejuvenation Res. 2011 14:491-500; Liu et al. Nat Rev Neurol. 2013 9:106-118; all herein incorporated by reference in their entireties). Expression of Apo A-I variants has been associated with reduced cholesterol (deGoma and Rader, 2011 Nature Rev Cardiol 8:266-271; Nissen et al., 2003 JAMA 290:2292-2300; all herein incorporated by reference in its entirety). The amino acid sequence of ApoA-I in certain populations has been changed to cysteine in Apo A-I Milano (Arg 173 changed to Cys) and in Apo A-I Paris (Arg 151 changed to Cys). Factor IX mutation at position R338L (FIX Padua) results in a Factor IX protein that has ~10-fold increased activity (Simioni et al., N Engl J Med. 2009 361:1671-1675; Finn et al., Blood. 2012 120:4521-4523; Cantore et al., Blood. 2012 120:4517-20; all herein incorporated by reference in their entireties). Mutation of transthyretin at positions 104 or 119 (Arg104 His, Thr119Met) has been shown to provide protection to patients also harboring the disease causing Val30Met mutations (Saraiva, Hum Mutat. 2001 17:493-503; DATA BASE ON TRANSTHYRETIN MUTATIONS http://www.ibmc.up.pt/mjsaraiva/ttrmut.html; all herein incorporated by reference in its

entirety). Differences in clinical presentation and severity of symptoms among Portuguese and Japanese Met 30 patients carrying respectively the Met 119 and the His104 mutations are observed with a clear protective effect exerted by the non pathogenic mutant (Coelho et al. 1996 Neuromuscular Disorders (Suppl) 6: S20; Terazaki et al. 1999. Biochem Biophys Res Commun 264: 365-370; all herein incorporated by reference in its entirety), which confer more stability to the molecule. A modified mRNA encoding these protective TTR alleles can be expressed in TTR amyloidosis patients, thereby reducing the effect of the pathogenic mutant TTR protein.

Major Groove Interacting Partners

[000824] As described herein, the phrase "major groove interacting partner" refers to RNA recognition receptors that detect and respond to RNA ligands through interactions, *e.g.* binding, with the major groove face of a nucleotide or nucleic acid. As such, RNA ligands comprising modified nucleotides or nucleic acids such as the polynucleotide, primary construct or mmRNA as described herein decrease interactions with major groove binding partners, and therefore decrease an innate immune response.

[000825] Example major groove interacting, *e.g.* binding, partners include, but are not limited to the following nucleases and helicases. Within membranes, TLRs (Toll-like Receptors) 3, 7, and 8 can respond to single- and double-stranded RNAs. Within the cytoplasm, members of the superfamily 2 class of DE*X*(D/H) helicases and ATPases can sense RNAs to initiate antiviral responses. These helicases include the RIG-I (retinoic acid-inducible gene I) and MDA5 (melanoma differentiation-associated gene 5). Other examples include laboratory of genetics and physiology 2 (LGP2), HIN-200 domain containing proteins, or Helicase-domain containing proteins.

Targeting of pathogenic organisms or diseased cells

[000826] Provided herein are methods for targeting pathogenic microorganisms, such as bacteria, yeast, protozoa, helminthes and the like, or diseased cells such as cancer cells using polynucleotides, primary constructs or mmRNA that encode cytostatic or cytotoxic polypeptides. Preferably the mRNA introduced contains modified nucleosides or other nucleic acid sequence modifications that are translated exclusively, or preferentially, in the target pathogenic organism, to reduce possible off-target effects of the therapeutic. Such methods are useful for removing pathogenic organisms or killing diseased cells

found in any biological material, including blood, semen, eggs, and transplant materials including embryos, tissues, and organs.

Bioprocessing

[000827] The methods provided herein may be useful for enhancing protein product yield in a cell culture process. In a cell culture containing a plurality of host cells, introduction of a polynucleotide, primary construct or mmRNA described herein results in increased protein production efficiency relative to a corresponding unmodified nucleic acid. Such increased protein production efficiency can be demonstrated, e.g., by showing increased cell transfection, increased protein translation from the polynucleotide, primary construct or mmRNA, decreased nucleic acid degradation, and/or reduced innate immune response of the host cell. Protein production can be measured by enzyme-linked immunosorbent assay (ELISA), and protein activity can be measured by various functional assays known in the art. The protein production may be generated in a continuous or a batch-fed mammalian process.

[000828] Additionally, it is useful to optimize the expression of a specific polypeptide in a cell line or collection of cell lines of potential interest, particularly a polypeptide of interest such as a protein variant of a reference protein having a known activity. In one embodiment, provided is a method of optimizing expression of a polypeptide of interest in a target cell, by providing a plurality of target cell types, and independently contacting with each of the plurality of target cell types a polynucleotide, primary construct or mmRNA encoding a polypeptide of interest. The cells may be transfected with two or more polynucleotide, primary construct or mmRNA simultaneously or sequentially.

[000829] In certain embodiments, multiple rounds of the methods described herein may be used to obtain cells with increased expression of one or more nucleic acids or proteins of interest. For example, cells may be transfected with one or more polynucleotide, primary construct or mmRNA that encode a nucleic acid or protein of interest. The cells may be isolated according to methods described herein before being subjected to further rounds of transfections with one or more other nucleic acids which encode a nucleic acid or protein of interest before being isolated again. This method may be useful for generating cells with increased expression of a complex of proteins, nucleic acids or proteins in the same or related biological pathway, nucleic acids or proteins that act

upstream or downstream of each other, nucleic acids or proteins that have a modulating, activating or repressing function to each other, nucleic acids or proteins that are dependent on each other for function or activity, or nucleic acids or proteins that share homology.

[000830] Additionally, culture conditions may be altered to increase protein production efficiency. Subsequently, the presence and/or level of the polypeptide of interest in the plurality of target cell types is detected and/or quantitated, allowing for the optimization of a polypeptide's expression by selection of an efficient target cell and cell culture conditions relating thereto. Such methods are particularly useful when the polypeptide contains one or more post-translational modifications or has substantial tertiary structure, situations which often complicate efficient protein production.

[000831] In one embodiment, the cells used in the methods of the present invention may be cultured. The cells may be cultured in suspension or as adherent cultures. The cells may be cultured in a varied of vessels including, but not limited to, bioreactors, cell bags, wave bags, culture plates, flasks and other vessels well known to those of ordinary skill in the art. Cells may be cultured in IMDM (Invitrogen, Catalog number 12440-53) or any other suitable media including, but not limited to, chemically defined media formulations. The ambient conditions which may be suitable for cell culture, such as temperature and atmospheric composition, are well known to those skilled in the art. The methods of the invention may be used with any cell that is suitable for use in protein production.

[000832] The invention provides for the repeated introduction (e.g., transfection) of modified nucleic acids into a target cell population, e.g., *in vitro*, *ex vivo*, *in situ*, or *in vivo*. For example, contacting the same cell population may be repeated one or more times (such as two, three, four, five or more than five times). In some embodiments, the step of contacting the cell population with the polynucleotides, primary constructs or mmRNA is repeated a number of times sufficient such that a predetermined efficiency of protein translation in the cell population is achieved. Given the often reduced cytotoxicity of the target cell population provided by the nucleic acid modifications, repeated transfections are achievable in a diverse array of cell types and within a variety of tissues, as provided herein.

[000833] In one embodiment, the bioprocessing methods of the present invention may be used to produce antibodies or functional fragments thereof. The functional fragments may comprise a Fab, Fab', $F(ab')_2$, an Fv domain, an scFv, or a diabody. They may be variable in any region including the complement determining region (CDR). In one embodiment, there is complete diversity in the CDR3 region. In another embodiment, the antibody is substantially conserved except in the CDR3 region.

[000834] Antibodies may be made which bind or associate with any biomolecule, whether human, pathogenic or non-human in origin. The pathogen may be present in a non-human mammal, a clinical specimen or from a commercial product such as a cosmetic or pharmaceutical material. They may also bind to any specimen or sample including clinical specimens or tissue samples from any organism.

[000835] In some embodiments, the contacting step is repeated multiple times at a frequency selected from the group consisting of: 6 hour, 12 hour, 24 hour, 36 hour, 48 hour, 72 hour, 84 hour, 96 hour, and 108 hour and at concentrations of less than 20 nM, less than 50 nM, less than 80 nM or less than 100 nM. Compositions may also be administered at less than 1mM, less than 5mM, less than 10mM, less than 100mM or less than 500 mM.

[000836] In some embodiments, the polynucleotides, primary constructs or mmRNA are added at an amount of 50 molecules per cell, 100 molecules/cell, 200 molecules/cell, 300 molecules/cell, 400 molecules/cell, 500 molecules/ cell, 600 molecules/cell, 700 molecules/ cell, 800 molecules/cell, 900 molecules/cell, 1000 molecules/cell, 2000 molecules/cell, or 5000 molecules/cell.

[000837] In other embodiments, the polynucleotides, primary constructs or mmRNA are added at a concentration selected from the group consisting of: 0.01 fmol/106 cells, 0.1 fmol/106 cells, 0.5 fmol/106 cells, 0.75 fmol/106 cells, 1 fmol/106 cells, 2 fmol/106 cells, 5 fmol/106 cells, 10 fmol/106 cells, 20 fmol/106 cells, 30 fmol/106 cells, 40 fmol/106 cells, 50 fmol/106 cells, 60 fmol/106 cells, 100 fmol/106 cells, 200 fmol/106 cells, 300 fmol/106 cells, 400 fmol/106 cells, 500 fmol/106 cells, 700 fmol/106 cells, 800 fmol/106 cells, 900 fmol/106 cells, and 1 pmol/106 cells.

[000838] In some embodiments, the production of a biological product upon is detected by monitoring one or more measurable bioprocess parameters, such as a parameter

selected from the group consisting of: cell density, pH, oxygen levels, glucose levels, lactic acid levels, temperature, and protein production. Protein production can be measured as specific productivity (SP) (the concentration of a product, such as a heterologously expressed polypeptide, in solution) and can be expressed as mg/L or g/L; in the alternative, specific productivity can be expressed as pg/cell/day. An increase in SP can refer to an absolute or relative increase in the concentration of a product produced under two defined set of conditions (e.g., when compared with controls not treated with modified mRNA(s)).

Cells

[000839] In one embodiment, the cells are selected from the group consisting of mammalian cells, bacterial cells, plant, microbial, algal and fungal cells. In some embodiments, the cells are mammalian cells, such as, but not limited to, human, mouse, rat, goat, horse, rabbit, hamster or cow cells. In a further embodiment, the cells may be from an established cell line, including, but not limited to, HeLa, NS0, SP2/0, KEK 293T, Vero, Caco, Caco-2, MDCK, COS-1, COS-7, K562, Jurkat, CHO-K1, DG44, CHOK1SV, CHO-S, Huvec, CV-1, Huh-7, NIH3T3, HEK293, 293, A549, HepG2, IMR-90, MCF-7, U-20S, Per.C6, SF9, SF21 or Chinese Hamster Ovary (CHO) cells.

[000840] In certain embodiments, the cells are fungal cells, such as, but not limited to, Chrysosporium cells, Aspergillus cells, Trichoderma cells, Dictyostelium cells, Candida cells, Saccharomyces cells, Schizosaccharomyces cells, and Penicillium cells.

[000841] In certain embodiments, the cells are bacterial cells such as, but not limited to, E. coli, B. subtilis, or BL21 cells. Primary and secondary cells to be transfected by the methods of the invention can be obtained from a variety of tissues and include, but are not limited to, all cell types which can be maintained in culture. For examples, primary and secondary cells which can be transfected by the methods of the invention include, but are not limited to, fibroblasts, keratinocytes, epithelial cells (e.g., mammary epithelial cells, intestinal epithelial cells), endothelial cells, glial cells, neural cells, formed elements of the blood (e.g., lymphocytes, bone marrow cells), muscle cells and precursors of these somatic cell types. Primary cells may also be obtained from a donor of the same species or from another species (e.g., mouse, rat, rabbit, cat, dog, pig, cow, bird, sheep, goat, horse).

Purification and Isolation

[000842] Those of ordinary skill in the art should be able to make a determination of the methods to use to purify or isolate of a protein of interest from cultured cells. Generally, this is done through a capture method using affinity binding or non-affinity purification. If the protein of interest is not secreted by the cultured cells, then a lysis of the cultured cells should be performed prior to purification or isolation. One may use unclarified cell culture fluid containing the protein of interest along with cell culture media components as well as cell culture additives, such as anti-foam compounds and other nutrients and supplements, cells, cellular debris, host cell proteins, DNA, viruses and the like in the present invention. The process may be conducted in the bioreactor itself. The fluid may either be preconditioned to a desired stimulus such as pH, temperature or other stimulus characteristic or the fluid can be conditioned upon the addition of polymer(s) or the polymer(s) can be added to a carrier liquid that is properly conditioned to the required parameter for the stimulus condition required for that polymer to be solubilized in the fluid. The polymer may be allowed to circulate thoroughly with the fluid and then the stimulus may be applied (change in pH, temperature, salt concentration, etc) and the desired protein and polymer(s) precipitate can out of the solution. The polymer and the desired protein(s) can be separated from the rest of the fluid and optionally washed one or more times to remove any trapped or loosely bound contaminants. The desired protein may then be recovered from the polymer(s) by, for example, elution and the like. Preferably, the elution may be done under a set of conditions such that the polymer remains in its precipitated form and retains any impurities to it during the selected elution of the desired protein. The polymer and protein as well as any impurities may be solubilized in a new fluid such as water or a buffered solution and the protein may be recovered by a means such as affinity, ion exchanged, hydrophobic, or some other type of chromatography that has a preference and selectivity for the protein over that of the polymer or impurities. The eluted protein may then be recovered and may be subjected to additional processing steps, either batch like steps or continuous flow through steps if appropriate.

[000843] In another embodiment, it may be useful to optimize the expression of a specific polypeptide in a cell line or collection of cell lines of potential interest,

particularly a polypeptide of interest such as a protein variant of a reference protein having a known activity. In one embodiment, provided is a method of optimizing expression of a polypeptide of interest in a target cell, by providing a plurality of target cell types, and independently contacting with each of the plurality of target cell types a modified mRNA encoding a polypeptide. Additionally, culture conditions may be altered to increase protein production efficiency. Subsequently, the presence and/or level of the polypeptide of interest in the plurality of target cell types is detected and/or quantitated, allowing for the optimization of a polypeptide of interest's expression by selection of an efficient target cell and cell culture conditions relating thereto. Such methods may be useful when the polypeptide of interest contains one or more post-translational modifications or has substantial tertiary structure, which often complicate efficient protein production.

Protein recovery

[000844] The protein of interest may be preferably recovered from the culture medium as a secreted polypeptide, or it can be recovered from host cell lysates if expressed without a secretory signal. It may be necessary to purify the protein of interest from other recombinant proteins and host cell proteins in a way that substantially homogenous preparations of the protein of interest are obtained. The cells and/or particulate cell debris may be removed from the culture medium or lysate. The product of interest may then be purified from contaminant soluble proteins, polypeptides and nucleic acids by, for example, fractionation on immunoaffinity or ion-exchange columns, ethanol precipitation, reverse phase HPLC (RP-HPLC), SEPHADEX® chromatography, chromatography on silica or on a cation exchange resin such as DEAE. Methods of purifying a protein heterologous expressed by a host cell are well known in the art.

[000845] Methods and compositions described herein may be used to produce proteins which are capable of attenuating or blocking the endogenous agonist biological response and/or antagonizing a receptor or signaling molecule in a mammalian subject. For example, IL-12 and IL-23 receptor signaling may be enhanced in chronic autoimmune disorders such as multiple sclerosis and inflammatory diseases such as rheumatoid arthritis, psoriasis, lupus erythematosus, ankylosing spondylitis and Chron's disease (Kikly K, Liu L, Na S, Sedgwich JD (2006) Cur. Opin. Immunol. 18(6): 670-5). In

another embodiment, a nucleic acid encodes an antagonist for chemokine receptors. Chemokine receptors CXCR-4 and CCR-5 are required for HIV enry into host cells (Arenzana-Seisdedos F et al, (1996) Nature. Oct 3; 383 (6599):400).

Gene Silencing

[000846] The polynucleotides, primary constructs and mmRNA described herein are useful to silence (i.e., prevent or substantially reduce) expression of one or more target genes in a cell population. A polynucleotide, primary construct or mmRNA encoding a polypeptide of interest capable of directing sequence-specific histone H3 methylation is introduced into the cells in the population under conditions such that the polypeptide is translated and reduces gene transcription of a target gene via histone H3 methylation and subsequent heterochromatin formation. In some embodiments, the silencing mechanism is performed on a cell population present in a mammalian subject. By way of non-limiting example, a useful target gene is a mutated Janus Kinase-2 family member, wherein the mammalian subject expresses the mutant target gene suffers from a myeloproliferative disease resulting from aberrant kinase activity.

[000847] Co-administration of polynucleotides, primary constructs and mmRNA and RNAi agents are also provided herein.

Modulation of Biological Pathways

[000848] The rapid translation polynucleotides, primary constructs and mmRNA introduced into cells provides a desirable mechanism of modulating target biological pathways. Such modulation includes antagonism or agonism of a given pathway. In one embodiment, a method is provided for antagonizing a biological pathway in a cell by contacting the cell with an effective amount of a composition comprising a polynucleotide, primary construct or mmRNA encoding a polypeptide of interest, under conditions such that the polynucleotides, primary constructs and mmRNA is localized into the cell and the polypeptide is capable of being translated in the cell from the polynucleotides, primary constructs and mmRNA, wherein the polypeptide inhibits the activity of a polypeptide functional in the biological pathway. Exemplary biological pathways are those defective in an autoimmune or inflammatory disorder such as multiple sclerosis, rheumatoid arthritis, psoriasis, lupus erythematosus, ankylosing spondylitis colitis, or Crohn's disease; in particular, antagonism of the IL-12 and IL-23

signaling pathways are of particular utility. (See Kikly K, Liu L, Na S, Sedgwick JD (2006) Curr. Opin. Immunol. 18 (6): 670–5).

[000849] Further, provided are polynucleotide, primary construct or mmRNA encoding an antagonist for chemokine receptors; chemokine receptors CXCR-4 and CCR-5 are required for, e.g., HIV entry into host cells (Arenzana-Seisdedos F et al, (1996) Nature. Oct 3;383(6599):400).

[000850] Alternatively, provided are methods of agonizing a biological pathway in a cell by contacting the cell with an effective amount of a polynucleotide, primary construct or mmRNA encoding a recombinant polypeptide under conditions such that the nucleic acid is localized into the cell and the recombinant polypeptide is capable of being translated in the cell from the nucleic acid, and the recombinant polypeptide induces the activity of a polypeptide functional in the biological pathway. Exemplary agonized biological pathways include pathways that modulate cell fate determination. Such agonization is reversible or, alternatively, irreversible.

Expression of Ligand or Receptor on Cell Surface

[000851] In some aspects and embodiments of the aspects described herein, the polynucleotides, primary constructs or mmRNA described herein can be used to express a ligand or ligand receptor on the surface of a cell *(e.g.,* a homing moiety). A ligand or ligand receptor moiety attached to a cell surface can permit the cell to have a desired biological interaction with a tissue or an agent *in vivo.* A ligand can be an antibody, an antibody fragment, an aptamer, a peptide, a vitamin, a carbohydrate, a protein or polypeptide, a receptor, *e.g.*, cell-surface receptor, an adhesion molecule, a glycoprotein, a sugar residue, a therapeutic agent, a drug, a glycosaminoglycan, or any combination thereof. For example, a ligand can be an antibody that recognizes a cancer-cell specific antigen, rendering the cell capable of preferentially interacting with tumor cells to permit tumor-specific localization of a modified cell. A ligand can confer the ability of a cell composition to accumulate in a tissue to be treated, since a preferred ligand may be capable of interacting with a target molecule on the external face of a tissue to be treated. Ligands having limited cross-reactivity to other tissues are generally preferred.

[000852] In some cases, a ligand can act as a homing moiety which permits the cell to target to a specific tissue or interact with a specific ligand. Such homing moieties can

include, but are not limited to, any member of a specific binding pair, antibodies, monoclonal antibodies, or derivatives or analogs thereof, including without limitation: Fv fragments, single chain Fv (scFv) fragments, Fab' fragments, F(ab')2 fragments, single domain antibodies, camelized antibodies and antibody fragments, humanized antibodies and antibody fragments, and multivalent versions of the foregoing; multivalent binding reagents including without limitation: monospecific or bispecific antibodies, such as disulfide stabilized Fv fragments, scFv tandems ((SCFV)2 fragments), diabodies, tribodies or tetrabodies, which typically are covalently linked or otherwise stabilized *(i.e.,* leucine zipper or helix stabilized) scFv fragments; and other homing moieties include for example, aptamers, receptors, and fusion proteins.

[000853] In some embodiments, the homing moiety may be a surface-bound antibody, which can permit tuning of cell targeting specificity. This is especially useful since highly specific antibodies can be raised against an epitope of interest for the desired targeting site. In one embodiment, multiple antibodies are expressed on the surface of a cell, and each antibody can have a different specificity for a desired target. Such approaches can increase the avidity and specificity of homing interactions.

[000854] A skilled artisan can select any homing moiety based on the desired localization or function of the cell, for example an estrogen receptor ligand, such as tamoxifen, can target cells to estrogen-dependent breast cancer cells that have an increased number of estrogen receptors on the cell surface. Other non-limiting examples of ligand/receptor interactions include CCRI *(e.g.,* for treatment of inflamed joint tissues or brain in rheumatoid arthritis, and/or multiple sclerosis), CCR7, CCR8 *(e.g.,* targeting to lymph node tissue), CCR6, CCR9,CCR10 *(e.g.,* to target to intestinal tissue), CCR4, CCR10 *(e.g.,* for targeting to skin), CXCR4 *(e.g.,* for general enhanced transmigration), HCELL *(e.g.,* for treatment of inflammation and inflammatory disorders, bone marrow), Alpha4beta7 *(e.g.,* for intestinal mucosa targeting), VLA-4/VCAM-1 *(e.g.,* targeting to endothelium). In general, any receptor involved in targeting *(e.g.,* cancer metastasis) can be harnessed for use in the methods and compositions described herein.

Modulation of Cell Lineage

[000855] Provided are methods of inducing an alteration in cell fate in a target mammalian cell. The target mammalian cell may be a precursor cell and the alteration

may involve driving differentiation into a lineage, or blocking such differentiation. Alternatively, the target mammalian cell may be a differentiated cell, and the cell fate alteration includes driving de-differentiation into a pluripotent precursor cell, or blocking such de-differentiation, such as the dedifferentiation of cancer cells into cancer stem cells. In situations where a change in cell fate is desired, effective amounts of mRNAs encoding a cell fate inductive polypeptide is introduced into a target cell under conditions such that an alteration in cell fate is induced. In some embodiments, the modified mRNAs are useful to reprogram a subpopulation of cells from a first phenotype to a second phenotype. Such a reprogramming may be temporary or permanent.

Optionally, the reprogramming induces a target cell to adopt an intermediate phenotype.

[000856] Additionally, the methods of the present invention are particularly useful to generate induced pluripotent stem cells (iPS cells) because of the high efficiency of transfection, the ability to re-transfect cells, and the tenability of the amount of recombinant polypeptides produced in the target cells. Further, the use of iPS cells generated using the methods described herein is expected to have a reduced incidence of teratoma formation.

[000857] Also provided are methods of reducing cellular differentiation in a target cell population. For example, a target cell population containing one or more precursor cell types is contacted with a composition having an effective amount of a polynucleotides, primary constructs and mmRNA encoding a polypeptide, under conditions such that the polypeptide is translated and reduces the differentiation of the precursor cell. In non-limiting embodiments, the target cell population contains injured tissue in a mammalian subject or tissue affected by a surgical procedure. The precursor cell is, e.g., a stromal precursor cell, a neural precursor cell, or a mesenchymal precursor cell.

[000858] In a specific embodiment, provided are polynucleotide, primary construct or mmRNA that encode one or more differentiation factors Gata4, Mef2c and Tbx4. These mRNA-generated factors are introduced into fibroblasts and drive the reprogramming into cardiomyocytes. Such a reprogramming can be performed *in vivo*, by contacting an mRNA-containing patch or other material to damaged cardiac tissue to facilitate cardiac regeneration. Such a process promotes cardiomyocyte genesis as opposed to fibrosis.

Mediation of cell death

[000859] In one embodiment, polynucleotides, primary constructs or mmRNA compositions can be used to induce apoptosis in a cell *(e.g.,* a cancer cell) by increasing the expression of a death receptor, a death receptor ligand or a combination thereof. This method can be used to induce cell death in any desired cell and has particular usefulness in the treatment of cancer where cells escape natural apoptotic signals.

[000860] Apoptosis can be induced by multiple independent signaling pathways that converge upon a final effector mechanism consisting of multiple interactions between several "death receptors" and their ligands, which belong to the tumor necrosis factor (TNF) receptor/ligand superfamily. The best-characterized death receptors are CD95 ("Fas"), TNFRI (p55), death receptor 3 (DR3 or Apo3/TRAMO), DR4 and DR5 (apo2-TRAIL-R2). The final effector mechanism of apoptosis may be the activation of a series of proteinases designated as caspases. The activation of these caspases results in the cleavage of a series of vital cellular proteins and cell death. The molecular mechanism of death receptors/ligands-induced apoptosis is well known in the art. For example, Fas/FasL-mediated apoptosis is induced by binding of three FasL molecules which induces trimerization of Fas receptor via C-terminus death domains (DDs), which in turn recruits an adapter protein FADD (Fas-associated protein with death domain) and Caspase-8. The oligomerization of this trimolecular complex, Fas/FAIDD/caspase-8, results in proteolytic cleavage of proenzyme caspase-8 into active caspase-8 that, in turn, initiates the apoptosis process by activating other downstream caspases through proteolysis, including caspase-3. Death ligands in general are apoptotic when formed into trimers or higher order of structures. As monomers, they may serve as antiapoptotic agents by competing with the trimers for binding to the death receptors.

[000861] In one embodiment, the polynucleotides, primary constructs or mmRNA composition encodes for a death receptor *(e.g.,* Fas, TRAIL, TRAMO, TNFR, TLR etc). Cells made to express a death receptor by transfection of polynucleotides, primary constructs and mmRNA become susceptible to death induced by the ligand that activates that receptor. Similarly, cells made to express a death ligand, *e.g.,* on their surface, will induce death of cells with the receptor when the transfected cell contacts the target cell. In another embodiment, the polynucleotides, primary constructs and mmRNA

composition encodes for a death receptor ligand *(e.g.,* FasL, TNF, etc). In another embodiment, the polynucleotides, primary constructs and mmRNA composition encodes a caspase *(e.g.,* caspase 3, caspase 8, caspase 9 etc). Where cancer cells often exhibit a failure to properly differentiate to a non-proliferative or controlled proliferative form, in another embodiment, the synthetic, polynucleotides, primary constructs and mmRNA composition encodes for both a death receptor and its appropriate activating ligand. In another embodiment, the synthetic, polynucleotides, primary constructs and mmRNA composition encodes for a differentiation factor that when expressed in the cancer cell, such as a cancer stem cell, will induce the cell to differentiate to a non-pathogenic or nonself-renewing phenotype *(e.g.,* reduced cell growth rate, reduced cell division etc) or to induce the cell to enter a dormant cell phase *(e.g.,* G_0 resting phase).

[000862] One of skill in the art will appreciate that the use of apoptosis-inducing techniques may require that the polynucleotides, primary constructs or mmRNA are appropriately targeted to *e.g.,* tumor cells to prevent unwanted wide-spread cell death. Thus, one can use a delivery mechanism *(e.g.,* attached ligand or antibody, targeted liposome etc) that recognizes a cancer antigen such that the polynucleotides, primary constructs or mmRNA are expressed only in cancer cells.

Cosmetic Applications

[000863] In one embodiment, the polynucleotides, primary constructs and/or mmRNA may be used in the treatment, amelioration or prophylaxis of cosmetic conditions. Such conditions include acne, rosacea, scarring, wrinkles, eczema, shingles, psoriasis, age spots, birth marks, dry skin, calluses, rash (e.g., diaper, heat), scabies, hives, warts, insect bites, vitiligo, dandruff, freckles, and general signs of aging.

VI. Kits and Devices

Kits

[000864] The invention provides a variety of kits for conveniently and/or effectively carrying out methods of the present invention. Typically kits will comprise sufficient amounts and/or numbers of components to allow a user to perform multiple treatments of a subject(s) and/or to perform multiple experiments.

[000865] In one aspect, the present invention provides kits comprising the molecules (polynucleotides, primary constructs or mmRNA) of the invention. In one embodiment, the kit comprises one or more functional antibodies or function fragments thereof.

[000866] Said kits can be for protein production, comprising a first polynucleotide, primary construct or mmRNA comprising a translatable region. The kit may further comprise packaging and instructions and/or a delivery agent to form a formulation composition. The delivery agent may comprise a saline, a buffered solution, a lipidoid or any delivery agent disclosed herein.

[000867] In one embodiment, the buffer solution may include sodium chloride, calcium chloride, phosphate and/or EDTA. In another embodiment, the buffer solution may include, but is not limited to, saline, saline with 2mM calcium, 5% sucrose, 5% sucrose with 2mM calcium, 5% Mannitol, 5% Mannitol with 2mM calcium, Ringer's lactate, sodium chloride, sodium chloride with 2mM calcium and mannose (See e.g., U.S. Pub. No. 20120258046; herein incorporated by reference in its entirety). In a futher embodiment, the buffer solutions may be precipitated or it may be lyophilized. The amount of each component may be varied to enable consistent, reproducible higher concentration saline or simple buffer formulations. The components may also be varied in order to increase the stability of modified RNA in the buffer solution over a period of time and/or under a variety of conditions.In one aspect, the present invention provides kits for protein production, comprising: a polynucleotide, primary construct or mmRNA comprising a translatable region, provided in an amount effective to produce a desired amount of a protein encoded by the translatable region when introduced into a target cell; a second polynucleotide comprising an inhibitory nucleic acid, provided in an amount effective to substantially inhibit the innate immune response of the cell; and packaging and instructions.

[000868] In one aspect, the present invention provides kits for protein production, comprising a polynucleotide, primary construct or mmRNA comprising a translatable region, wherein the polynucleotide exhibits reduced degradation by a cellular nuclease, and packaging and instructions.

[000869] In one aspect, the present invention provides kits for protein production, comprising a polynucleotide, primary construct or mmRNA comprising a translatable

region, wherein the polynucleotide exhibits reduced degradation by a cellular nuclease, and a mammalian cell suitable for translation of the translatable region of the first nucleic acid.

[000870] In one embodiment, the levels of Protein C may be measured by immunoassay. The assay may be purchased and is available from any number of suppliers including BioMerieux, Inc. (Durham, NC), Abbott Laboratories (Abbott Park, IL), Siemens Medical Solutions USA, Inc. (Malvern, PA), BIOPORTO® Diagnostics A/S (Gentofte, Denmark), USCN® Life Science Inc. (Houston, TX) or Roche Diagnostic Corporation (Indianapolis, IN). In this embodiment, the assay may be used to assess levels of Protein C or its activated form or a variant delivered as or in response to administration of a modified mRNA molecule.

Devices

[000871] The present invention provides for devices which may incorporate polynucleotides, primary constructs or mmRNA that encode polypeptides of interest. These devices contain in a stable formulation the reagents to synthesize a polynucleotide in a formulation available to be immediately delivered to a subject in need thereof, such as a human patient. Non-limiting examples of such a polypeptide of interest include a growth factor and/or angiogenesis stimulator for wound healing, a peptide antibiotic to facilitate infection control, and an antigen to rapidly stimulate an immune response to a newly identified virus.

[000872] Devices may also be used in conjunction with the present invention. In one embodiment, a device is used to assess levels of a protein which has been administered in the form of a modified mRNA. The device may comprise a blood, urine or other biofluidic test. It may be as large as to include an automated central lab platform or a small decentralized bench top device. It may be point of care or a handheld device. In this embodiment, for example, Protein C or APC may be quatitated before, during or after treatment with a modified mRNA encoding Protein C (its zymogen), APC or any variants thereof. Protein C, also known as autoprothrombin IIA and blood coagulation factor XIV is a zymogen, or precursor, of a serine protease which plays an important role in the regulation of blood coagulation and generation of fibrinolytic activity in vivo. It is synthesized in the liver as a single-chain polypeptide but undergoes posttranslational

processing to give rise to a two-chain intermediate. The intermediate form of Protein C is converted via thrombin-mediated cleavage of a 12-residue peptide from the amino-terminus of the heavy chain to of the molecule to the active form, known as "activated protein C" (APC). The device may be useful in drug discovery efforts as a companion diagnostic test associated with Protein C, or APC treatment such as for sepsis or severe sepsis. In early studies it was suggested that APC had the ability to reduce mortality in severe sepsis. Following this line of work, clinical studies lead to the FDA approval of one compound, activated drotrecogin alfa (recombinant protein C). However, in late 2011, the drug was withdrawn from sale in all markets following results of the PROWESS-SHOCK study, which showed the study did not meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients with septic shock. The present invention provides modified mRNA molecules which may be used in the diagnosis and treatment of sepsis, severe sepsis and septicemia which overcome prior issues or problems associated with increasing protein expression efficiencies in mammals.

[000873] In some embodiments the device is self-contained, and is optionally capable of wireless remote access to obtain instructions for synthesis and/or analysis of the generated polynucleotide, primary construct or mmRNA. The device is capable of mobile synthesis of at least one polynucleotide, primary construct or mmRNA and preferably an unlimited number of different polynucleotides, primary constructs or mmRNA. In certain embodiments, the device is capable of being transported by one or a small number of individuals. In other embodiments, the device is scaled to fit on a benchtop or desk. In other embodiments, the device is scaled to fit into a suitcase, backpack or similarly sized object. In another embodiment, the device may be a point of care or handheld device. In further embodiments, the device is scaled to fit into a vehicle, such as a car, truck or ambulance, or a military vehicle such as a tank or personnel carrier. The information necessary to generate a modified mRNA encoding polypeptide of interest is present within a computer readable medium present in the device.

[000874] In one embodiment, a device may be used to assess levels of a protein which has been administered in the form of a polynucleotide, primary construct or mmRNA. The device may comprise a blood, urine or other biofluidic test.

[000875] In some embodiments, the device is capable of communication (e.g., wireless communication) with a database of nucleic acid and polypeptide sequences. The device contains at least one sample block for insertion of one or more sample vessels. Such sample vessels are capable of accepting in liquid or other form any number of materials such as template DNA, nucleotides, enzymes, buffers, and other reagents. The sample vessels are also capable of being heated and cooled by contact with the sample block. The sample block is generally in communication with a device base with one or more electronic control units for the at least one sample block. The sample block preferably contains a heating module, such heating molecule capable of heating and/or cooling the sample vessels and contents thereof to temperatures between about -20C and above +100C. The device base is in communication with a voltage supply such as a battery or external voltage supply. The device also contains means for storing and distributing the materials for RNA synthesis.

[000876] Optionally, the sample block contains a module for separating the synthesized nucleic acids. Alternatively, the device contains a separation module operably linked to the sample block. Preferably the device contains a means for analysis of the synthesized nucleic acid. Such analysis includes sequence identity (demonstrated such as by hybridization), absence of non-desired sequences, measurement of integrity of synthesized mRNA (such has by microfluidic viscometry combined with spectrophotometry), and concentration and/or potency of modified RNA (such as by spectrophotometry).

[000877] In certain embodiments, the device is combined with a means for detection of pathogens present in a biological material obtained from a subject, e.g., the IBIS PLEX-ID system (Abbott, Abbott Park, IL) for microbial identification.

[000878] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662; each of which is herein incorporated by reference in their entirety. Intradermal compositions may be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 (herein incorporated by reference in its entirety) and functional

equivalents thereof. Jet injection devices which deliver liquid compositions to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144; 5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537; each of which are hrein incorporated by reference in their entirety. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes may be used in the classical mantoux method of intradermal administration.

[000879] In some embodiments, the device may be a pump or comprise a catheter for administration of compounds or compositions of the invention across the blood brain barrier. Such devices include but are not limited to a pressurized olfactory delivery device, iontophoresis devices, multi-layered microfluidic devices, and the like. Such devices may be portable or stationary. They may be implantable or externally tethered to the body or combinations thereof.

[000880] Devices for administration may be employed to deliver the polynucleotides, primary constructs or mmRNA of the present invention according to single, multi- or split-dosing regimens taught herein. Such devices are described below.

[000881] Method and devices known in the art for multi-administration to cells, organs and tissues are contemplated for use in conjunction with the methods and compositions disclosed herein as embodiments of the present invention. These include, for example, those methods and devices having multiple needles, hybrid devices employing for example lumens or catheters as well as devices utilizing heat, electric current or radiation driven mechanisms.

[000882] According to the present invention, these multi-administration devices may be utilized to deliver the single, multi- or split doses contemplated herein.

[000883] A method for delivering therapeutic agents to a solid tissue has been described by Bahrami et al. and is taught for example in US Patent Publication 20110230839, the contents of which are incorporated herein by reference in their entirety. According to

Bahrami, an array of needles is incorporated into a device which delivers a substantially equal amount of fluid at any location in said solid tissue along each needle's length.

[000884] A device for delivery of biological material across the biological tissue has been described by Kodgule et al. and is taught for example in US Patent Publication 20110172610, the contents of which are incorporated herein by reference in their entirety. According to Kodgule, multiple hollow micro-needles made of one or more metals and having outer diameters from about 200 microns to about 350 microns and lengths of at least 100 microns are incorporated into the device which delivers peptides, proteins, carbohydrates, nucleic acid molecules, lipids and other pharmaceutically active ingredients or combinations thereof.

[000885] A delivery probe for delivering a therapeutic agent to a tissue has been described by Gunday et al. and is taught for example in US Patent Publication 20110270184, the contents of each of which are incorporated herein by reference in their entirety. According to Gunday, multiple needles are incorporated into the device which moves the attached capsules between an activated position and an inactivated position to force the agent out of the capsules through the needles.

[000886] A multiple-injection medical apparatus has been described by Assaf and is taught for example in US Patent Publication 20110218497, the contents of which are incorporated herein by reference in their entirety. According to Assaf, multiple needles are incorporated into the device which has a chamber connected to one or more of said needles and a means for continuously refilling the chamber with the medical fluid after each injection.

[000887] In one embodiment, the polynucleotide, primary construct, or mmRNA is administered subcutaneously or intramuscularly via at least 3 needles to three different, optionally adjacent, sites simultaneously, or within a 60 minutes period (e.g., administration to 4 ,5, 6, 7, 8, 9, or 10 sites simultaneously or within a 60 minute period). The split doses can be administered simultaneously to adjacent tissue using the devices described in U.S. Patent Publication Nos. 20110230839 and 20110218497, each of which is incorporated herein by reference in their entirety.

[000888] An at least partially implantable system for injecting a substance into a patient's body, in particular a penis erection stimulation system has been described by

Forsell and is taught for example in US Patent Publication 20110196198, the contents of which are incorporated herein by reference in their entirety. According to Forsell, multiple needles are incorporated into the device which is implanted along with one or more housings adjacent the patient's left and right corpora cavernosa. A reservoir and a pump are also implanted to supply drugs through the needles.

[000889] A method for the transdermal delivery of a therapeutic effective amount of iron has been described by Berenson and is taught for example in US Patent Publication 20100130910, the contents of which are incorporated herein by reference in their entirety. According to Berenson, multiple needles may be used to create multiple micro channels in stratum corneum to enhance transdermal delivery of the ionic iron on an iontophoretic patch.

[000890] A method for delivery of biological material across the biological tissue has been described by Kodgule et al and is taught for example in US Patent Publication 20110196308, the contents of which are incorporated herein by reference in their entirety. According to Kodgule, multiple biodegradable microneedles containing a therapeutic active ingredient are incorporated in a device which delivers proteins, carbohydrates, nucleic acid molecules, lipids and other pharmaceutically active ingredients or combinations thereof.

[000891] A transdermal patch comprising a botulinum toxin composition has been described by Donovan and is taught for example in US Patent Publication 20080220020, the contents of which are incorporated herein by reference in their entirety. According to Donovan, multiple needles are incorporated into the patch which delivers botulinum toxin under stratum corneum through said needles which project through the stratum corneum of the skin without rupturing a blood vessel.

[000892] A small, disposable drug reservoir, or patch pump, which can hold approximately 0.2 to 15 mL of liquid formulations can be placed on the skin and deliver the formulation continuously subcutaneously using a small bore needed (e.g., 26 to 34 gauge). As non-limiting examples, the patch pump may be 50 mm by 76 mm by 20 mm spring loaded having a 30 to 34 gauge needle (BD™ Microinfuser, Franklin Lakes NJ), 41 mm by 62 mm by 17 mm with a 2 mL reservoir used for drug delivery such as insulin (OMNIPOD®, Insulet Corporation Bedford, MA), or 43-60 mm diameter, 10 mm thick

with a 0.5 to 10 mL reservoir (PATCHPUMP®, SteadyMed Therapeutics, San Francisco, CA). Further, the patch pump may be battery powered and/or rechargeable.

[000893] A cryoprobe for administration of an active agent to a location of cryogenic treatment has been described by Toubia and is taught for example in US Patent Publication 20080140061, the contents of which are incorporated herein by reference in their entirety. According to Toubia, multiple needles are incorporated into the probe which receives the active agent into a chamber and administers the agent to the tissue.

[000894] A method for treating or preventing inflammation or promoting healthy joints has been described by Stock et al and is taught for example in US Patent Publication 20090155186, the contents of which are incorporated herein by reference in their entirety. According to Stock, multiple needles are incorporated in a device which administers compositions containing signal transduction modulator compounds.

[000895] A multi-site injection system has been described by Kimmell et al. and is taught for example in US Patent Publication 20100256594, the contents of which are incorporated herein by reference in their entirety. According to Kimmell, multiple needles are incorporated into a device which delivers a medication into a stratum corneum through the needles.

[000896] A method for delivering interferons to the intradermal compartment has been described by Dekker et al. and is taught for example in US Patent Publication 20050181033, the contents of which are incorporated herein by reference in their entirety. According to Dekker, multiple needles having an outlet with an exposed height between 0 and 1 mm are incorporated into a device which improves pharmacokinetics and bioavailability by delivering the substance at a depth between 0.3 mm and 2 mm.

[000897] A method for delivering genes, enzymes and biological agents to tissue cells has described by Desai and is taught for example in US Patent Publication 20030073908, the contents of which are incorporated herein by reference in their entirety. According to Desai, multiple needles are incorporated into a device which is inserted into a body and delivers a medication fluid through said needles.

[000898] A method for treating cardiac arrhythmias with fibroblast cells has been described by Lee et al and is taught for example in US Patent Publication 20040005295, the contents of which are incorporated herein by reference in their entirety. According to

Lee, multiple needles are incorporated into the device which delivers fibroblast cells into the local region of the tissue.

[000899] A method using a magnetically controlled pump for treating a brain tumor has been described by Shachar et al. and is taught for example in US Patent 7799012 (method) and 7799016 (device), the contents of which are incorporated herein by reference in their entirety. According Shachar, multiple needles were incorporated into the pump which pushes a medicating agent through the needles at a controlled rate.

[000900] Methods of treating functional disorders of the bladder in mammalian females have been described by Versi et al. and are taught for example in US Patent 8,029,496, the contents of which are incorporated herein by reference in their entirety. According to Versi, an array of micro-needles is incorporated into a device which delivers a therapeutic agent through the needles directly into the trigone of the bladder.

[000901] A micro-needle transdermal transport device has been described by Angel et al and is taught for example in US Patent 7,364,568, the contents of which are incorporated herein by reference in their entirety. According to Angel, multiple needles are incorporated into the device which transports a substance into a body surface through the needles which are inserted into the surface from different directions. The micro-needle transdermal transport device may be a solid micro-needle system or a hollow micro-needle system. As a non-limiting example, the solid micro-needle system may have up to a 0.5 mg capacity, with 300-1500 solid micro-needles per cm^2 about 150-700 μm tall coated with a drug. The micro-needles penetrate the stratum corneum and remain in the skin for short duration (e.g., 20 seconds to 15 minutes). In another example, the hollow micro-needle system has up to a 3 mL capacity to deliver liquid formulations using 15-20 microneedles per cm2 being approximately 950 μm tall. The micro-needles penetrate the skin to allow the liquid formulations to flow from the device into the skin. The hollow micro-needle system may be worn from 1 to 30 minutes depending on the formulation volume and viscocity.

[000902] A device for subcutaneous infusion has been described by Dalton et al and is taught for example in US Patent 7,150,726, the contents of which are incorporated herein by reference in their entirety. According to Dalton, multiple needles are incorporated into the device which delivers fluid through the needles into a subcutaneous tissue.

[000903] A device and a method for intradermal delivery of vaccines and gene therapeutic agents through microcannula have been described by Mikszta et al. and are taught for example in US Patent 7,473,247, the contents of which are incorporated herein by reference in their entirety. According to Mitszta, at least one hollow micro-needle is incorporated into the device which delivers the vaccines to the subject's skin to a depth of between 0.025 mm and 2 mm.

[000904] A method of delivering insulin has been described by Pettis et al and is taught for example in US Patent 7,722,595, the contents of which are incorporated herein by reference in their entirety. According to Pettis, two needles are incorporated into a device wherein both needles insert essentially simultaneously into the skin with the first at a depth of less than 2.5 mm to deliver insulin to intradermal compartment and the second at a depth of greater than 2.5 mm and less than 5.0 mm to deliver insulin to subcutaneous compartment.

[000905] Cutaneous injection delivery under suction has been described by Kochamba et al. and is taught for example in US Patent 6,896,666, the contents of which are incorporated herein by reference in their entirety. According to Kochamba, multiple needles in relative adjacency with each other are incorporated into a device which injects a fluid below the cutaneous layer.

[000906] A device for withdrawing or delivering a substance through the skin has been described by Down et al and is taught for example in US Patent 6,607,513, the contents of which are incorporated herein by reference in their entirety. According to Down, multiple skin penetrating members which are incorporated into the device have lengths of about 100 microns to about 2000 microns and are about 30 to 50 gauge.

[000907] A device for delivering a substance to the skin has been described by Palmer et al and is taught for example in US Patent 6,537,242, the contents of which are incorporated herein by reference in their entirety. According to Palmer, an array of micro-needles is incorporated into the device which uses a stretching assembly to enhance the contact of the needles with the skin and provides a more uniform delivery of the substance.

[000908] A perfusion device for localized drug delivery has been described by Zamoyski and is taught for example in US Patent 6,468,247, the contents of which are

incorporated herein by reference in their entirety. According to Zamoyski, multiple hypodermic needles are incorporated into the device which injects the contents of the hypodermics into a tissue as said hypodermics are being retracted.

[000909] A method for enhanced transport of drugs and biological molecules across tissue by improving the interaction between micro-needles and human skin has been described by Prausnitz et al. and is taught for example in US Patent 6,743,211, the contents of which are incorporated herein by reference in their entirety. According to Prausnitz, multiple micro-needles are incorporated into a device which is able to present a more rigid and less deformable surface to which the micro-needles are applied.

[000910] A device for intraorgan administration of medicinal agents has been described by Ting et al and is taught for example in US Patent 6,077,251, the contents of which are incorporated herein by reference in their entirety. According to Ting, multiple needles having side openings for enhanced administration are incorporated into a device which by extending and retracting said needles from and into the needle chamber forces a medicinal agent from a reservoir into said needles and injects said medicinal agent into a target organ.

[000911] A multiple needle holder and a subcutaneous multiple channel infusion port has been described by Brown and is taught for example in US Patent 4,695,273, the contents of which are incorporated herein by reference in their entirety. According to Brown, multiple needles on the needle holder are inserted through the septum of the infusion port and communicate with isolated chambers in said infusion port.

[000912] A dual hypodermic syringe has been described by Horn and is taught for example in US Patent 3,552,394, the contents of which are incorporated herein by reference in their entirety. According to Horn, two needles incorporated into the device are spaced apart less than 68 mm and may be of different styles and lengths, thus enabling injections to be made to different depths.

[000913] A syringe with multiple needles and multiple fluid compartments has been described by Hershberg and is taught for example in US Patent 3,572,336, the contents of which are incorporated herein by reference in their entirety. According to Hershberg, multiple needles are incorporated into the syringe which has multiple fluid compartments

and is capable of simultaneously administering incompatible drugs which are not able to be mixed for one injection.

[000914] A surgical instrument for intradermal injection of fluids has been described by Eliscu et al. and is taught for example in US Patent 2,588,623, the contents of which are incorporated herein by reference in their entirety. According to Eliscu, multiple needles are incorporated into the instrument which injects fluids intradermally with a wider disperse.

[000915] An apparatus for simultaneous delivery of a substance to multiple breast milk ducts has been described by Hung and is taught for example in EP 1818017, the contents of which are incorporated herein by reference in their entirety. According to Hung, multiple lumens are incorporated into the device which inserts though the orifices of the ductal networks and delivers a fluid to the ductal networks.

[000916] A catheter for introduction of medications to the tissue of a heart or other organs has been described by Tkebuchava and is taught for example in WO2006138109, the contents of which are incorporated herein by reference in their entirety. According to Tkebuchava, two curved needles are incorporated which enter the organ wall in a flattened trajectory.

[000917] Devices for delivering medical agents have been described by Mckay et al. and are taught for example in WO2006118804, the content of which are incorporated herein by reference in their entirety. According to Mckay, multiple needles with multiple orifices on each needle are incorporated into the devices to facilitate regional delivery to a tissue, such as the interior disc space of a spinal disc.

[000918] A method for directly delivering an immunomodulatory substance into an intradermal space within a mammalian skin has been described by Pettis and is taught for example in WO2004020014, the contents of which are incorporated herein by reference in their entirety. According to Pettis, multiple needles are incorporated into a device which delivers the substance through the needles to a depth between 0.3 mm and 2 mm.

[000919] Methods and devices for administration of substances into at least two compartments in skin for systemic absorption and improved pharmacokinetics have been described by Pettis et al. and are taught for example in WO2003094995, the contents of which are incorporated herein by reference in their entirety. According to Pettis, multiple

needles having lengths between about 300 μm and about 5 mm are incorporated into a device which delivers to intradermal and subcutaneous tissue compartments simultaneously.

[000920] A drug delivery device with needles and a roller has been described by Zimmerman et al. and is taught for example in WO2012006259, the contents of which are incorporated herein by reference in their entirety. According to Zimmerman, multiple hollow needles positioned in a roller are incorporated into the device which delivers the content in a reservoir through the needles as the roller rotates.

[000921] A drug delivery device such as a stent is known in the art and is taught for example in U.S. Pat. No. 8,333,799, U.S. Pub. Nos. US20060020329, US20040172127 and US20100161032; the contents of each of which are herein incorporated by reference in their entirety. Formulations of the polynucleotides, primary constructs, mmRNA described herein may be delivered using stents. Additionally, stents used herein may be able to deliver multiple polynucleotides, primary constructs and/or mmRNA and/or formulations at the same or varied rates of delivery. Non-limiting examples of manufacturers of stents include CORDIS® (Miami, FL) (CYPHER®), Boston Scientific Corporation (Natick, MA) (TAXUS®), Medtronic (Minneapolis, MN) (ENDEAVOUR®) and Abbott (Abbott Park, IL) (XIENCE V®).

Methods and Devices utilizing catheters and/or lumens

[000922] Methods and devices using catheters and lumens may be employed to administer the mmRNA of the present invention on a single, multi- or split dosing schedule. Such methods and devices are described below.

[000923] A catheter-based delivery of skeletal myoblasts to the myocardium of damaged hearts has been described by Jacoby et al and is taught for example in US Patent Publication 20060263338, the contents of which are incorporated herein by reference in their entirety. According to Jacoby, multiple needles are incorporated into the device at least part of which is inserted into a blood vessel and delivers the cell composition through the needles into the localized region of the subject's heart.

[000924] An apparatus for treating asthma using neurotoxin has been described by Deem et al and is taught for example in US Patent Publication 20060225742, the contents of which are incorporated herein by reference in their entirety. According to Deem,

multiple needles are incorporated into the device which delivers neurotoxin through the needles into the bronchial tissue.

[000925] A method for administering multiple-component therapies has been described by Nayak and is taught for example in US Patent 7,699,803, the contents of which are incorporated herein by reference in their entirety. According to Nayak, multiple injection cannulas may be incorporated into a device wherein depth slots may be included for controlling the depth at which the therapeutic substance is delivered within the tissue.

[000926] A surgical device for ablating a channel and delivering at least one therapeutic agent into a desired region of the tissue has been described by McIntyre et al and is taught for example in US Patent 8,012,096, the contents of which are incorporated herein by reference in their entirety. According to McIntyre, multiple needles are incorporated into the device which dispenses a therapeutic agent into a region of tissue surrounding the channel and is particularly well suited for transmyocardial revascularization operations.

[000927] Methods of treating functional disorders of the bladder in mammalian females have been described by Versi et al and are taught for example in US Patent 8,029,496, the contents of which are incorporated herein by reference in their entirety. According to Versi, an array of micro-needles is incorporated into a device which delivers a therapeutic agent through the needles directly into the trigone of the bladder.

[000928] A device and a method for delivering fluid into a flexible biological barrier have been described by Yeshurun et al. and are taught for example in US Patent 7,998,119 (device) and 8,007,466 (method), the contents of which are incorporated herein by reference in their entirety. According to Yeshurun, the micro-needles on the device penetrate and extend into the flexible biological barrier and fluid is injected through the bore of the hollow micro-needles.

[000929] A method for epicardially injecting a substance into an area of tissue of a heart having an epicardial surface and disposed within a torso has been described by Bonner et al and is taught for example in US Patent 7,628,780, the contents of which are incorporated herein by reference in their entirety. According to Bonner, the devices have elongate shafts and distal injection heads for driving needles into tissue and injecting medical agents into the tissue through the needles.

[000930] A device for sealing a puncture has been described by Nielsen et al and is taught for example in US Patent 7,972,358, the contents of which are incorporated herein by reference in their entirety. According to Nielsen, multiple needles are incorporated into the device which delivers a closure agent into the tissue surrounding the puncture tract.

[000931] A method for myogenesis and angiogenesis has been described by Chiu et al. and is taught for example in US Patent 6,551,338, the contents of which are incorporated herein by reference in their entirety. According to Chiu, 5 to 15 needles having a maximum diameter of at least 1.25 mm and a length effective to provide a puncture depth of 6 to 20 mm are incorporated into a device which inserts into proximity with a myocardium and supplies an exogeneous angiogenic or myogenic factor to said myocardium through the conduits which are in at least some of said needles.

[000932] A method for the treatment of prostate tissue has been described by Bolmsj et al. and is taught for example in US Patent 6,524,270, the contents of which are incorporated herein by reference in their entirety. According to Bolmsj, a device comprising a catheter which is inserted through the urethra has at least one hollow tip extendible into the surrounding prostate tissue. An astringent and analgesic medicine is administered through said tip into said prostate tissue.

[000933] A method for infusing fluids to an intraosseous site has been described by Findlay et al. and is taught for example in US Patent 6,761,726, the contents of which are incorporated herein by reference in their entirety. According to Findlay, multiple needles are incorporated into a device which is capable of penetrating a hard shell of material covered by a layer of soft material and delivers a fluid at a predetermined distance below said hard shell of material.

[000934] A device for injecting medications into a vessel wall has been described by Vigil et al. and is taught for example in US Patent 5,713,863, the contents of which are incorporated herein by reference in their entirety. According to Vigil, multiple injectors are mounted on each of the flexible tubes in the device which introduces a medication fluid through a multi-lumen catheter, into said flexible tubes and out of said injectors for infusion into the vessel wall.

[000935] A catheter for delivering therapeutic and/or diagnostic agents to the tissue surrounding a bodily passageway has been described by Faxon et al. and is taught for example in US Patent 5,464,395, the contents of which are incorporated herein by reference in their entirety. According to Faxon, at least one needle cannula is incorporated into the catheter which delivers the desired agents to the tissue through said needles which project outboard of the catheter.

[000936] Balloon catheters for delivering therapeutic agents have been described by Orr and are taught for example in WO2010024871, the contents of which are incorporated herein by reference in their entirety. According to Orr, multiple needles are incorporated into the devices which deliver the therapeutic agents to different depths within the tissue. In another aspect, drug-eluting balloons may be used to deliver the formulations described herein. The drug-eluting balloons may be used in target lesion applications such as, but are not limited to, in-stent restenosis, treating lesion in tortuous vessels, bifurcation lesions, femoral/popliteal lesions and below the knee lesions.

[000937] A device for deliverying therapeutic agents (e.g., polynucleotides, primary constructs or mmRNA) to tissue disposed about a lumin has been described by Perry et al. and is taught for example in U.S. Pat. Pub. US20100125239, the contents of which are herein incorporated by reference in their entirety. According to Perry, the catheter has a balloon which may be coated with a therapeutic agent by methods known in the art and described in Perry. When the balloon expands, the therapeutic agent will contact the surrounding tissue. The device may additionally have a heat source to change the temperature of the coating on the balloon to release the thereapeutic agent to the tissue.

Methods and Devices utilizing electrical current

[000938] Methods and devices utilizing electric current may be employed to deliver the mmRNA of the present invention according to the single, multi- or split dosing regimens taught herein. Such methods and devices are described below.

[000939] An electro collagen induction therapy device has been described by Marquez and is taught for example in US Patent Publication 20090137945, the contents of which are incorporated herein by reference in their entirety. According to Marquez, multiple needles are incorporated into the device which repeatedly pierce the skin and draw in the skin a portion of the substance which is applied to the skin first.

[000940] An electrokinetic system has been described by Etheredge et al. and is taught for example in US Patent Publication 20070185432, the contents of which are incorporated herein by reference in their entirety. According to Etheredge, micro-needles are incorporated into a device which drives by an electrical current the medication through the needles into the targeted treatment site.

[000941] An iontophoresis device has been described by Matsumura et al. and is taught for example in US Patent 7,437,189, the contents of which are incorporated herein by reference in their entirety. According to Matsumura, multiple needles are incorporated into the device which is capable of delivering ionizable drug into a living body at higher speed or with higher efficiency.

[000942] Intradermal delivery of biologically active agents by needle-free injection and electroporation has been described by Hoffmann et al and is taught for example in US Patent 7,171,264, the contents of which are incorporated herein by reference in their entirety. According to Hoffmann, one or more needle-free injectors are incorporated into an electroporation device and the combination of needle-free injection and electroporation is sufficient to introduce the agent into cells in skin, muscle or mucosa.

[000943] A method for electropermeabilization-mediated intracellular delivery has been described by Lundkvist et al. and is taught for example in US Patent 6,625,486, the contents of which are incorporated herein by reference in their entirety. According to Lundkvist, a pair of needle electrodes is incorporated into a catheter. Said catheter is positioned into a body lumen followed by extending said needle electrodes to penetrate into the tissue surrounding said lumen. Then the device introduces an agent through at least one of said needle electrodes and applies electric field by said pair of needle electrodes to allow said agent pass through the cell membranes into the cells at the treatment site.

[000944] A delivery system for transdermal immunization has been described by Levin et al. and is taught for example in WO2006003659, the contents of which are incorporated herein by reference in their entirety. According to Levin, multiple electrodes are incorporated into the device which applies electrical energy between the electrodes to generate micro channels in the skin to facilitate transdermal delivery.

[000945] A method for delivering RF energy into skin has been described by Schomacker and is taught for example in WO2011163264, the contents of which are incorporated herein by reference in their entirety. According to Schomacker, multiple needles are incorporated into a device which applies vacuum to draw skin into contact with a plate so that needles insert into skin through the holes on the plate and deliver RF energy.

VII. Definitions

[000946] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

[000947] *About:* As used herein, the term "about" means +/- 10% of the recited value.

[000948] *Administered in combination:* As used herein, the term "administered in combination" or "combined administration" means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[000949] *Animal:* As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans at any stage of development. In some embodiments, "animal" refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[000950] *Antigens of interest or desired antigens*: As used herein, the terms "antigens of interest" or "desired antigens" include those proteins and other biomolecules provided herein that are immunospecifically bound by the antibodies and fragments, mutants,

variants, and alterations thereof described herein. Examples of antigens of interest include, but are not limited to, insulin, insulin-like growth factor, hGH, tPA, cytokines, such as interleukins (IL), e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, interferon (IFN) alpha, IFN beta, IFN gamma, IFN omega or IFN tau, tumor necrosis factor (TNF), such as TNF alpha and TNF beta, TNF gamma, TRAIL; G-CSF, GM-CSF, M-CSF, MCP-1 and VEGF.

[000951] *Approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[000952] *Associated with:* As used herein, the terms "associated with," "conjugated," "linked," "attached," and "tethered," when used with respect to two or more moieties, means that the moieties are physically associated or connected with one another, either directly or via one or more additional moieties that serves as a linking agent, to form a structure that is sufficiently stable so that the moieties remain physically associated under the conditions in which the structure is used, *e.g.*, physiological conditions. An "association" need not be strictly through direct covalent chemical bonding. It may also suggest ionic or hydrogen bonding or a hybridization based connectivity sufficiently stable such that the "associated" entities remain physically associated.

[000953] *Bifunctional:* As used herein, the term "bifunctional" refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may effect the same outcome or a different outcome. The structure that produces the function may be the same or different. For example, bifunctional modified RNAs of the present invention may encode a cytotoxic peptide (a first function) while those nucleosides which comprise the encoding RNA are, in and of themselves, cytotoxic (second function). In this example, delivery of the bifunctional modified RNA to a cancer cell would produce not only a peptide or protein molecule which may ameliorate or treat

the cancer but would also deliver a cytotoxic payload of nucleosides to the cell should degradation, instead of translation of the modified RNA, occur.

[000954] *Biocompatible*: As used herein, the term "biocompatible" means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[000955] *Biodegradable*: As used herein, the term "biodegradable" means capable of being broken down into innocuous products by the action of living things.

[000956] *Biologically active*: As used herein, the phrase "biologically active" refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active. In particular embodiments, a polynucleotide, primary construct or mmRNA of the present invention may be considered biologically active if even a portion of the polynucleotide, primary construct or mmRNA is biologically active or mimics an activity considered biologically relevant.

[000957] *Chemical terms*: The following provides the definition of various chemical terms from "acyl" to "thiol."

[000958] The term "acyl," as used herein, represents a hydrogen or an alkyl group (e.g., a haloalkyl group), as defined herein, that is attached to the parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxyaldehyde group), acetyl, propionyl, butanoyl and the like. Exemplary unsubstituted acyl groups include from 1 to 7, from 1 to 11, or from 1 to 21 carbons. In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein.

[000959] The term "acylamino," as used herein, represents an acyl group, as defined herein, attached to the parent molecular group though an amino group, as defined herein (i.e., $-N(R^{N1})-C(O)-R$, where R is H or an optionally substituted C_{1-6}, C_{1-10}, or C_{1-20} alkyl group and R^{N1} is as defined herein). Exemplary unsubstituted acylamino groups include from 1 to 41 carbons (e.g., from 1 to 7, from 1 to 13, from 1 to 21, from 2 to 7, from 2 to 13, from 2 to 21, or from 2 to 41 carbons). In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein, and/or the amino

group is $-NH_2$ or $-NHR^{N1}$, wherein R^{N1} is, independently, OH, NO_2, NH_2, $NR^{N2}{}_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, alkyl, or aryl, and each R^{N2} can be H, alkyl, or aryl.

[000960] The term "acyloxy," as used herein, represents an acyl group, as defined herein, attached to the parent molecular group though an oxygen atom (i.e., –O-C(O)-R, where R is H or an optionally substituted C_{1-6}, C_{1-10}, or C_{1-20} alkyl group). Exemplary unsubstituted acyloxy groups include from 1 to 21 carbons (e.g., from 1 to 7 or from 1 to 11 carbons). In some embodiments, the alkyl group is further substituted with 1, 2, 3, or 4 substituents as described herein, and/or the amino group is $-NH_2$ or $-NHR^{N1}$, wherein R^{N1} is, independently, OH, NO_2, NH_2, $NR^{N2}{}_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, alkyl, or aryl, and each R^{N2} can be H, alkyl, or aryl.

[000961] The term "alkaryl," as used herein, represents an aryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted alkaryl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{1-6} alk-C_{6-10} aryl, C_{1-10} alk-C_{6-10} aryl, or C_{1-20} alk-C_{6-10} aryl). In some embodiments, the alkylene and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups. Other groups preceded by the prefix "alk-" are defined in the same manner, where "alk" refers to a C_{1-6} alkylene, unless otherwise noted, and the attached chemical structure is as defined herein.

[000962] The term "alkcycloalkyl" represents a cycloalkyl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein (e.g., an alkylene group of from 1 to 4, from 1 to 6, from 1 to 10, or form 1 to 20 carbons). In some embodiments, the alkylene and the cycloalkyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

[000963] The term "alkenyl," as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 20 carbons (e.g., from 2 to 6 or from 2 to 10 carbons) containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. Alkenyls include both cis and trans isomers. Alkenyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected,

independently, from amino, aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

[000964] The term "alkenyloxy" represents a chemical substituent of formula –OR, where R is a C_{2-20} alkenyl group (e.g., C_{2-6} or C_{2-10} alkenyl), unless otherwise specified. Exemplary alkenyloxy groups include ethenyloxy, propenyloxy, and the like. In some embodiments, the alkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein (e.g., a hydroxy group).

[000965] The term "alkheteroaryl" refers to a heteroaryl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted alkheteroaryl groups are from 2 to 32 carbons (e.g., from 2 to 22, from 2 to 18, from 2 to 17, from 2 to 16, from 3 to 15, from 2 to 14, from 2 to 13, or from 2 to 12 carbons, such as C_{1-6} alk-C_{1-12} heteroaryl, C_{1-10} alk-C_{1-12} heteroaryl, or C_{1-20} alk-C_{1-12} heteroaryl). In some embodiments, the alkylene and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group. Alkheteroaryl groups are a subset of alkheterocyclyl groups.

[000966] The term "alkheterocyclyl" represents a heterocyclyl group, as defined herein, attached to the parent molecular group through an alkylene group, as defined herein. Exemplary unsubstituted alkheterocyclyl groups are from 2 to 32 carbons (e.g., from 2 to 22, from 2 to 18, from 2 to 17, from 2 to 16, from 3 to 15, from 2 to 14, from 2 to 13, or from 2 to 12 carbons, such as C_{1-6} alk-C_{1-12} heterocyclyl, C_{1-10} alk-C_{1-12} heterocyclyl, or C_{1-20} alk-C_{1-12} heterocyclyl). In some embodiments, the alkylene and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

[000967] The term "alkoxy" represents a chemical substituent of formula –OR, where R is a C_{1-20} alkyl group (e.g., C_{1-6} or C_{1-10} alkyl), unless otherwise specified. Exemplary alkoxy groups include methoxy, ethoxy, propoxy (e.g., n-propoxy and isopropoxy), t-butoxy, and the like. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein (e.g., hydroxy or alkoxy).

[000968] The term "alkoxyalkoxy" represents an alkoxy group that is substituted with an alkoxy group. Exemplary unsubstituted alkoxyalkoxy groups include between 2 to 40 carbons (e.g., from 2 to 12 or from 2 to 20 carbons, such as C_{1-6} alkoxy-C_{1-6} alkoxy, C_{1-10}

alkoxy-C_{1-10} alkoxy, or C_{1-20} alkoxy-C_{1-20} alkoxy). In some embodiments, the each alkoxy group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[000969] The term "alkoxyalkyl" represents an alkyl group that is substituted with an alkoxy group. Exemplary unsubstituted alkoxyalkyl groups include between 2 to 40 carbons (e.g., from 2 to 12 or from 2 to 20 carbons, such as C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-10} alkoxy-C_{1-10} alkyl, or C_{1-20} alkoxy-C_{1-20} alkyl). In some embodiments, the alkyl and the alkoxy each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective group.

[000970] The term "alkoxycarbonyl," as used herein, represents an alkoxy, as defined herein, attached to the parent molecular group through a carbonyl atom (e.g., -C(O)-OR, where R is H or an optionally substituted C_{1-6}, C_{1-10}, or C_{1-20} alkyl group). Exemplary unsubstituted alkoxycarbonyl include from 1 to 21 carbons (e.g., from 1 to 11 or from 1 to 7 carbons). In some embodiments, the alkoxy group is further substituted with 1, 2, 3, or 4 substituents as described herein.

[000971] The term "alkoxycarbonylalkoxy," as used herein, represents an alkoxy group, as defined herein, that is substituted with an alkoxycarbonyl group, as defined herein (e.g., -O-alkyl-C(O)-OR, where R is an optionally substituted C_{1-6}, C_{1-10}, or C_{1-20} alkyl group). Exemplary unsubstituted alkoxycarbonylalkoxy include from 3 to 41 carbons (e.g., from 3 to 10, from 3 to 13, from 3 to 17, from 3 to 21, or from 3 to 31 carbons, such as C_{1-6} alkoxycarbonyl-C_{1-6} alkoxy, C_{1-10} alkoxycarbonyl-C_{1-10} alkoxy, or C_{1-20} alkoxycarbonyl-C_{1-20} alkoxy). In some embodiments, each alkoxy group is further independently substituted with 1, 2, 3, or 4 substituents, as described herein (e.g., a hydroxy group).

[000972] The term "alkoxycarbonylalkyl," as used herein, represents an alkyl group, as defined herein, that is substituted with an alkoxycarbonyl group, as defined herein (e.g., -alkyl-C(O)-OR, where R is an optionally substituted C_{1-20}, C_{1-10}, or C_{1-6} alkyl group). Exemplary unsubstituted alkoxycarbonylalkyl include from 3 to 41 carbons (e.g., from 3 to 10, from 3 to 13, from 3 to 17, from 3 to 21, or from 3 to 31 carbons, such as C_{1-6} alkoxycarbonyl-C_{1-6} alkyl, C_{1-10} alkoxycarbonyl-C_{1-10} alkyl, or C_{1-20} alkoxycarbonyl-C_{1-20}

alkyl). In some embodiments, each alkyl and alkoxy group is further independently substituted with 1, 2, 3, or 4 substituents as described herein (e.g., a hydroxy group).

[000973] The term "alkyl," as used herein, is inclusive of both straight chain and branched chain saturated groups from 1 to 20 carbons (e.g., from 1 to 10 or from 1 to 6), unless otherwise specified. Alkyl groups are exemplified by methyl, ethyl, n- and iso-propyl, n-, sec-, iso- and tert-butyl, neopentyl, and the like, and may be optionally substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four substituents independently selected from the group consisting of: (1) C_{1-6} alkoxy; (2) C_{1-6} alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$, where R^{N1} is as defined for amino); (4) C_{6-10} aryl-C_{1-6} alkoxy; (5) azido; (6) halo; (7) (C_{2-9} heterocyclyl)oxy; (8) hydroxy; (9) nitro; (10) oxo (e.g., carboxyaldehyde or acyl); (11) C_{1-7} spirocyclyl; (12) thioalkoxy; (13) thiol; (14) $-CO_2R^{A'}$, where $R^{A'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (15) $-C(O)NR^{B'}R^{C'}$, where each of $R^{B'}$ and $R^{C'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (16) $-SO_2R^{D'}$, where $R^{D'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) C_{1-6} alk-C_{6-10} aryl, and (d) hydroxy; (17) $-SO_2NR^{E'}R^{F'}$, where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl and (d) C_{1-6} alk-C_{6-10} aryl; (18) $-C(O)R^{G'}$, where $R^{G'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6

or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (19) $-NR^{H'}C(O)R^{I'}$, wherein $R^{H'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{I'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk-C_{6-10} aryl, (f2) amino-C_{1-20} alkyl, (g2) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (20) $-NR^{J'}C(O)OR^{K'}$, wherein $R^{J'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{K'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk-C_{6-10} aryl, (f2) amino-C_{1-20} alkyl, (g2) polyethylene glycol of $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein. For

example, the alkylene group of a C_1-alkaryl can be further substituted with an oxo group to afford the respective aryloyl substituent.

[000974] The term "alkylene" and the prefix "alk-," as used herein, represent a saturated divalent hydrocarbon group derived from a straight or branched chain saturated hydrocarbon by the removal of two hydrogen atoms, and is exemplified by methylene, ethylene, isopropylene, and the like. The term "C_{x-y} alkylene" and the prefix "C_{x-y} alk-" represent alkylene groups having between x and y carbons. Exemplary values for x are 1, 2, 3, 4, 5, and 6, and exemplary values for y are 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, or 20 (e.g., C_{1-6}, C_{1-10}, C_{2-20}, C_{2-6}, C_{2-10}, or C_{2-20} alkylene). In some embodiments, the alkylene can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for an alkyl group.

[000975] The term "alkylsulfinyl," as used herein, represents an alkyl group attached to the parent molecular group through an -S(O)- group. Exemplary unsubstituted alkylsulfinyl groups are from 1 to 6, from 1 to 10, or from 1 to 20 carbons. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[000976] The term "alkylsulfinylalkyl," as used herein, represents an alkyl group, as defined herein, substituted by an alkylsulfinyl group. Exemplary unsubstituted alkylsulfinylalkyl groups are from 2 to 12, from 2 to 20, or from 2 to 40 carbons. In some embodiments, each alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[000977] The term "alkynyl," as used herein, represents monovalent straight or branched chain groups from 2 to 20 carbon atoms (e.g., from 2 to 4, from 2 to 6, or from 2 to 10 carbons) containing a carbon-carbon triple bond and is exemplified by ethynyl, 1-propynyl, and the like. Alkynyl groups may be optionally substituted with 1, 2, 3, or 4 substituent groups that are selected, independently, from aryl, cycloalkyl, or heterocyclyl (e.g., heteroaryl), as defined herein, or any of the exemplary alkyl substituent groups described herein.

[000978] The term "alkynyloxy" represents a chemical substituent of formula –OR, where R is a C_{2-20} alkynyl group (e.g., C_{2-6} or C_{2-10} alkynyl), unless otherwise specified. Exemplary alkynyloxy groups include ethynyloxy, propynyloxy, and the like. In some

embodiments, the alkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein (e.g., a hydroxy group).

[000979] The term "amidine," as used herein, represents a $-C(=NH)NH_2$ group.

[000980] The term "amino," as used herein, represents $-N(R^{N1})_2$, wherein each R^{N1} is, independently, H, OH, NO_2, $N(R^{N2})_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, an *N*-protecting group, alkyl, alkenyl, alkynyl, alkoxy, aryl, alkaryl, cycloalkyl, alkcycloalkyl, carboxyalkyl, sulfoalkyl, heterocyclyl (e.g., heteroaryl), or alkheterocyclyl (e.g., alkheteroaryl), wherein each of these recited R^{N1} groups can be optionally substituted, as defined herein for each group; or two R^{N1} combine to form a heterocyclyl or an *N*-protecting group, and wherein each R^{N2} is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$). In a preferred embodiment, amino is $-NH_2$ or $-NHR^{N1}$, wherein R^{N1} is, independently, OH, NO_2, NH_2, $NR^{N2}{}_2$, SO_2OR^{N2}, SO_2R^{N2}, SOR^{N2}, alkyl, carboxyalkyl, sulfoalkyl, or aryl, and each R^{N2} can be H, $C_{1\text{-}20}$ alkyl (e.g., $C_{1\text{-}6}$ alkyl), or $C_{6\text{-}10}$ aryl.

[000981] The term "amino acid," as described herein, refers to a molecule having a side chain, an amino group, and an acid group (e.g., a carboxy group of $-CO_2H$ or a sulfo group of $-SO_3H$), wherein the amino acid is attached to the parent molecular group by the side chain, amino group, or acid group (e.g., the side chain). In some embodiments, the amino acid is attached to the parent molecular group by a carbonyl group, where the side chain or amino group is attached to the carbonyl group. Exemplary side chains include an optionally substituted alkyl, aryl, heterocyclyl, alkaryl, alkheterocyclyl, aminoalkyl, carbamoylalkyl, and carboxyalkyl. Exemplary amino acids include alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, hydroxynorvaline, isoleucine, leucine, lysine, methionine, norvaline, ornithine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, taurine, threonine, tryptophan, tyrosine, and valine. Amino acid groups may be optionally substituted with one, two, three, or, in the case of amino acid groups of two carbons or more, four substituents independently selected from the group consisting of: (1) $C_{1\text{-}6}$ alkoxy; (2) $C_{1\text{-}6}$ alkylsulfinyl; (3) amino, as defined herein (e.g., unsubstituted amino (i.e., $-NH_2$) or a substituted amino (i.e., $-N(R^{N1})_2$, where R^{N1} is as defined for amino); (4) $C_{6\text{-}10}$ aryl-$C_{1\text{-}6}$ alkoxy; (5) azido; (6) halo; (7) ($C_{2\text{-}9}$ heterocyclyl)oxy; (8) hydroxy; (9) nitro; (10) oxo

(e.g., carboxyaldehyde or acyl); (11) C_{1-7} spirocyclyl; (12) thioalkoxy; (13) thiol; (14) -$CO_2R^{A'}$, where $R^{A'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (15) -$C(O)NR^{B'}R^{C'}$, where each of $R^{B'}$ and $R^{C'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (16) -$SO_2R^{D'}$, where $R^{D'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) C_{1-6} alk-C_{6-10} aryl, and (d) hydroxy; (17) -$SO_2NR^{E'}R^{F'}$, where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl and (d) C_{1-6} alk-C_{6-10} aryl; (18) -$C(O)R^{G'}$, where $R^{G'}$ is selected from the group consisting of (a) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c) C_{6-10} aryl, (d) hydrogen, (e) C_{1-6} alk-C_{6-10} aryl, (f) amino-C_{1-20} alkyl, (g) polyethylene glycol of -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h) amino-polyethylene glycol of -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (19) -$NR^{H'}C(O)R^{I'}$, wherein $R^{H'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{I'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk-C_{6-10} aryl, (f2) amino-C_{1-20} alkyl, (g2) polyethylene glycol of -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1

to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; (20) -$NR^{J'}C(O)OR^{K'}$, wherein $R^{J'}$ is selected from the group consisting of (a1) hydrogen and (b1) C_{1-6} alkyl, and $R^{K'}$ is selected from the group consisting of (a2) C_{1-20} alkyl (e.g., C_{1-6} alkyl), (b2) C_{2-20} alkenyl (e.g., C_{2-6} alkenyl), (c2) C_{6-10} aryl, (d2) hydrogen, (e2) C_{1-6} alk-C_{6-10} aryl, (f2) amino-C_{1-20} alkyl, (g2) polyethylene glycol of -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and R' is H or C_{1-20} alkyl, and (h2) amino-polyethylene glycol of -$NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 0 to 10 (e.g., from 0 to 4, from 0 to 6, from 1 to 4, from 1 to 6, or from 1 to 10), and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl; and (21) amidine. In some embodiments, each of these groups can be further substituted as described herein.

[000982] The term "aminoalkoxy," as used herein, represents an alkoxy group, as defined herein, substituted by an amino group, as defined herein. The alkyl and amino each can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for the respective group (e.g., $CO_2R^{A'}$, where $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk-C_{6-10} aryl, e.g., carboxy).

[000983] The term "aminoalkyl," as used herein, represents an alkyl group, as defined herein, substituted by an amino group, as defined herein. The alkyl and amino each can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for the respective group (e.g., $CO_2R^{A'}$, where $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk-C_{6-10} aryl, e.g., carboxy).

[000984] The term "aryl," as used herein, represents a mono-, bicyclic, or multicyclic carbocyclic ring system having one or two aromatic rings and is exemplified by phenyl,

naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, anthracenyl, phenanthrenyl, fluorenyl, indanyl, indenyl, and the like, and may be optionally substituted with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of: (1) C_{1-7} acyl (e.g., carboxyaldehyde); (2) C_{1-20} alkyl (e.g., C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} alkylsulfinyl-C_{1-6} alkyl, amino-C_{1-6} alkyl, azido-C_{1-6} alkyl, (carboxyaldehyde)-C_{1-6} alkyl, halo-C_{1-6} alkyl (e.g., perfluoroalkyl), hydroxy-C_{1-6} alkyl, nitro-C_{1-6} alkyl, or C_{1-6} thioalkoxy-C_{1-6} alkyl); (3) C_{1-20} alkoxy (e.g., C_{1-6} alkoxy, such as perfluoroalkoxy); (4) C_{1-6} alkylsulfinyl; (5) C_{6-10} aryl; (6) amino; (7) C_{1-6} alk-C_{6-10} aryl; (8) azido; (9) C_{3-8} cycloalkyl; (10) C_{1-6} alk-C_{3-8} cycloalkyl; (11) halo; (12) C_{1-12} heterocyclyl (e.g., C_{1-12} heteroaryl); (13) (C_{1-12} heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C_{1-20} thioalkoxy (e.g., C_{1-6} thioalkoxy); (17) $-(CH_2)_qCO_2R^{A'}$, where q is an integer from zero to four, and $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk-C_{6-10} aryl; (18) $-(CH_2)_qCONR^{B'}R^{C'}$, where q is an integer from zero to four and where $R^{B'}$ and $R^{C'}$ are independently selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (19) $-(CH_2)_qSO_2R^{D'}$, where q is an integer from zero to four and where $R^{D'}$ is selected from the group consisting of (a) alkyl, (b) C_{6-10} aryl, and (c) alk-C_{6-10} aryl; (20) $-(CH_2)_qSO_2NR^{E'}R^{F'}$, where q is an integer from zero to four and where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (21) thiol; (22) C_{6-10} aryloxy; (23) C_{3-8} cycloalkoxy; (24) C_{6-10} aryl-C_{1-6} alkoxy; (25) C_{1-6} alk-C_{1-12} heterocyclyl (e.g., C_{1-6} alk-C_{1-12} heteroaryl); (26) C_{2-20} alkenyl; and (27) C_{2-20} alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C_1-alkaryl or a C_1-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

[000985] The term "arylalkoxy," as used herein, represents an alkaryl group, as defined herein, attached to the parent molecular group through an oxygen atom. Exemplary unsubstituted alkoxyalkyl groups include from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C_{6-10} aryl-C_{1-6} alkoxy, C_{6-10} aryl-C_{1-10} alkoxy, or C_{6-10} aryl-C_{1-20} alkoxy). In some embodiments, the arylalkoxy group can be substituted with 1, 2, 3, or 4 substituents as defined herein

[000986] The term "aryloxy" represents a chemical substituent of formula –OR′, where R′ is an aryl group of 6 to 18 carbons, unless otherwise specified. In some embodiments, the aryl group can be substituted with 1, 2, 3, or 4 substituents as defined herein.

[000987] The term "aryloyl," as used herein, represents an aryl group, as defined herein, that is attached to the parent molecular group through a carbonyl group. Exemplary unsubstituted aryloyl groups are of 7 to 11 carbons. In some embodiments, the aryl group can be substituted with 1, 2, 3, or 4 substituents as defined herein.

[000988] The term "azido" represents an $-N_3$ group, which can also be represented as –N=N=N.

[000989] The term "bicyclic," as used herein, refer to a structure having two rings, which may be aromatic or non-aromatic. Bicyclic structures include spirocyclyl groups, as defined herein, and two rings that share one or more bridges, where such bridges can include one atom or a chain including two, three, or more atoms. Exemplary bicyclic groups include a bicyclic carbocyclyl group, where the first and second rings are carbocyclyl groups, as defined herein; a bicyclic aryl groups, where the first and second rings are aryl groups, as defined herein; bicyclic heterocyclyl groups, where the first ring is a heterocyclyl group and the second ring is a carbocyclyl (e.g., aryl) or heterocyclyl (e.g., heteroaryl) group; and bicyclic heteroaryl groups, where the first ring is a heteroaryl group and the second ring is a carbocyclyl (e.g., aryl) or heterocyclyl (e.g., heteroaryl) group. In some embodiments, the bicyclic group can be substituted with 1, 2, 3, or 4 substituents as defined herein for cycloalkyl, heterocyclyl, and aryl groups.

[000990] The terms "carbocyclic" and "carbocyclyl," as used herein, refer to an optionally substituted C_{3-12} monocyclic, bicyclic, or tricyclic structure in which the rings, which may be aromatic or non-aromatic, are formed by carbon atoms. Carbocyclic structures include cycloalkyl, cycloalkenyl, and aryl groups.

[000991] The term "carbamoyl," as used herein, represents $-C(O)-N(R^{N1})_2$, where the meaning of each R^{N1} is found in the definition of "amino" provided herein.

[000992] The term "carbamoylalkyl," as used herein, represents an alkyl group, as defined herein, substituted by a carbamoyl group, as defined herein. The alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[000993] The term "carbamyl," as used herein, refers to a carbamate group having the structure
$-NR^{N1}C(=O)OR$ or $-OC(=O)N(R^{N1})_2$, where the meaning of each R^{N1} is found in the definition of "amino" provided herein, and R is alkyl, cycloalkyl , alkcycloalkyl, aryl, alkaryl, heterocyclyl (e.g., heteroaryl), or alkheterocyclyl (e.g., alkheteroaryl), as defined herein.

[000994] The term "carbonyl," as used herein, represents a C(O) group, which can also be represented as C=O.

[000995] The term "carboxyaldehyde" represents an acyl group having the structure –CHO.

[000996] The term "carboxy," as used herein, means $-CO_2H$.

[000997] The term "carboxyalkoxy," as used herein, represents an alkoxy group, as defined herein, substituted by a carboxy group, as defined herein. The alkoxy group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for the alkyl group.

[000998] The term "carboxyalkyl," as used herein, represents an alkyl group, as defined herein, substituted by a carboxy group, as defined herein. The alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[000999] The term "cyano," as used herein, represents an –CN group.

[0001000] The term "cycloalkoxy" represents a chemical substituent of formula –OR, where R is a C_{3-8} cycloalkyl group, as defined herein, unless otherwise specified. The cycloalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein. Exemplary unsubstituted cycloalkoxy groups are from 3 to 8 carbons. In some embodiment, the cycloalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[0001001] The term "cycloalkyl," as used herein represents a monovalent saturated or unsaturated non-aromatic cyclic hydrocarbon group from three to eight carbons, unless otherwise specified, and is exemplified by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1.]heptyl, and the like. When the cycloalkyl group includes one carbon-carbon double bond, the cycloalkyl group can be referred to as a "cycloalkenyl" group. Exemplary cycloalkenyl groups include cyclopentenyl,

cyclohexenyl, and the like. The cycloalkyl groups of this invention can be optionally substituted with: (1) C_{1-7} acyl (e.g., carboxyaldehyde); (2) C_{1-20} alkyl (e.g., C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} alkylsulfinyl-C_{1-6} alkyl, amino-C_{1-6} alkyl, azido-C_{1-6} alkyl, (carboxyaldehyde)-C_{1-6} alkyl, halo-C_{1-6} alkyl (e.g., perfluoroalkyl), hydroxy-C_{1-6} alkyl, nitro-C_{1-6} alkyl, or C_{1-6} thioalkoxy-C_{1-6} alkyl); (3) C_{1-20} alkoxy (e.g., C_{1-6} alkoxy, such as perfluoroalkoxy); (4) C_{1-6} alkylsulfinyl; (5) C_{6-10} aryl; (6) amino; (7) C_{1-6} alk-C_{6-10} aryl; (8) azido; (9) C_{3-8} cycloalkyl; (10) C_{1-6} alk-C_{3-8} cycloalkyl; (11) halo; (12) C_{1-12} heterocyclyl (e.g., C_{1-12} heteroaryl); (13) (C_{1-12} heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C_{1-20} thioalkoxy (e.g., C_{1-6} thioalkoxy); (17) $-(CH_2)_qCO_2R^{A'}$, where q is an integer from zero to four, and $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk-C_{6-10} aryl; (18) $-(CH_2)_qCONR^{B'}R^{C'}$, where q is an integer from zero to four and where $R^{B'}$ and $R^{C'}$ are independently selected from the group consisting of (a) hydrogen, (b) C_{6-10} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (19) $-(CH_2)_qSO_2R^{D'}$, where q is an integer from zero to four and where $R^{D'}$ is selected from the group consisting of (a) C_{6-10} alkyl, (b) C_{6-10} aryl, and (c) C_{1-6} alk-C_{6-10} aryl; (20) $-(CH_2)_qSO_2NR^{E'}R^{F'}$, where q is an integer from zero to four and where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{6-10} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (21) thiol; (22) C_{6-10} aryloxy; (23) C_{3-8} cycloalkoxy; (24) C_{6-10} aryl-C_{1-6} alkoxy; (25) C_{1-6} alk-C_{1-12} heterocyclyl (e.g., C_{1-6} alk-C_{1-12} heteroaryl); (26) oxo; (27) C_{2-20} alkenyl; and (28) C_{2-20} alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C_1-alkaryl or a C_1-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

[0001002] The term "diastereomer," as used herein means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

[0001003] The term "effective amount" of an agent, as used herein, is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment, as defined herein, of cancer, as compared to the response obtained without administration of the agent.

[0001004] The term "enantiomer," as used herein, means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e., at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

[0001005] The term "halo," as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

[0001006] The term "haloalkoxy," as used herein, represents an alkoxy group, as defined herein, substituted by a halogen group (i.e., F, Cl, Br, or I). A haloalkoxy may be substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four halogens. Haloalkoxy groups include perfluoroalkoxys (e.g., $-OCF_3$), $-OCHF_2$, $-OCH_2F$, $-OCCl_3$, $-OCH_2CH_2Br$, $-OCH_2CH(CH_2CH_2Br)CH_3$, and $-OCHICH_3$. In some embodiments, the haloalkoxy group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

[0001007] The term "haloalkyl," as used herein, represents an alkyl group, as defined herein, substituted by a halogen group (i.e., F, Cl, Br, or I). A haloalkyl may be substituted with one, two, three, or, in the case of alkyl groups of two carbons or more, four halogens. Haloalkyl groups include perfluoroalkyls (e.g., $-CF_3$), $-CHF_2$, $-CH_2F$, $-CCl_3$, $-CH_2CH_2Br$, $-CH_2CH(CH_2CH_2Br)CH_3$, and $-CHICH_3$. In some embodiments, the haloalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups.

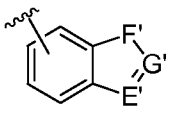
[0001008] The term "heteroalkylene," as used herein, refers to an alkylene group, as defined herein, in which one or two of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkylene group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkylene groups.

[0001009] The term "heteroaryl," as used herein, represents that subset of heterocyclyls, as defined herein, which are aromatic: i.e., they contain $4n+2$ pi electrons within the mono- or multicyclic ring system. Exemplary unsubstituted heteroaryl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. In some

embodiment, the heteroaryl is substituted with 1, 2, 3, or 4 substituents groups as defined for a heterocyclyl group.

[0001010] The term "heterocyclyl," as used herein represents a 5-, 6- or 7-membered ring, unless otherwise specified, containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The 5-membered ring has zero to two double bonds, and the 6- and 7-membered rings have zero to three double bonds. Exemplary unsubstituted heterocyclyl groups are of 1 to 12 (e.g., 1 to 11, 1 to 10, 1 to 9, 2 to 12, 2 to 11, 2 to 10, or 2 to 9) carbons. The term "heterocyclyl" also represents a heterocyclic compound having a bridged multicyclic structure in which one or more carbons and/or heteroatoms bridges two non-adjacent members of a monocyclic ring, e.g., a quinuclidinyl group. The term "heterocyclyl" includes bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one, two, or three carbocyclic rings, e.g., an aryl ring, a cyclohexane ring, a cyclohexene ring, a cyclopentane ring, a cyclopentene ring, or another monocyclic heterocyclic ring, such as indolyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzofuryl, benzothienyl and the like. Examples of fused heterocyclyls include tropanes and 1,2,3,5,8,8a-hexahydroindolizine. Heterocyclics include pyrrolyl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, homopiperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidiniyl, morpholinyl, thiomorpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, indazolyl, quinolyl, isoquinolyl, quinoxalinyl, dihydroquinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzothiadiazolyl, furyl, thienyl, thiazolidinyl, isothiazolyl, triazolyl, tetrazolyl, oxadiazolyl (e.g., 1,2,3-oxadiazolyl), purinyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl), tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, dihydrothienyl, dihydroindolyl, dihydroquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dihydroisoquinolyl, pyranyl, dihydropyranyl, dithiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, and the like, including dihydro and tetrahydro forms thereof, where one or more double bonds are reduced and replaced with hydrogens. Still other exemplary heterocyclyls include: 2,3,4,5-tetrahydro-2-oxo-oxazolyl; 2,3-dihydro-2-oxo-1H-imidazolyl; 2,3,4,5-tetrahydro-5-oxo-1H-pyrazolyl (e.g.,

2,3,4,5-tetrahydro-2-phenyl-5-oxo-1H-pyrazolyl); 2,3,4,5-tetrahydro-2,4-dioxo-1H-imidazolyl (e.g., 2,3,4,5-tetrahydro-2,4-dioxo-5-methyl-5-phenyl-1H-imidazolyl); 2,3-dihydro-2-thioxo-1,3,4-oxadiazolyl (e.g., 2,3-dihydro-2-thioxo-5-phenyl-1,3,4-oxadiazolyl); 4,5-dihydro-5-oxo-1*H*-triazolyl (e.g., 4,5-dihydro-3-methyl-4-amino 5-oxo-1*H*-triazolyl); 1,2,3,4-tetrahydro-2,4-dioxopyridinyl (e.g., 1,2,3,4-tetrahydro-2,4-dioxo-3,3-diethylpyridinyl); 2,6-dioxo-piperidinyl (e.g., 2,6-dioxo-3-ethyl-3-phenylpiperidinyl); 1,6-dihydro-6-oxopyridiminyl; 1,6-dihydro-4-oxopyrimidinyl (e.g., 2-(methylthio)-1,6-dihydro-4-oxo-5-methylpyrimidin-1-yl); 1,2,3,4-tetrahydro-2,4-dioxopyrimidinyl (e.g., 1,2,3,4-tetrahydro-2,4-dioxo-3-ethylpyrimidinyl); 1,6-dihydro-6-oxo-pyridazinyl (e.g., 1,6-dihydro-6-oxo-3-ethylpyridazinyl); 1,6-dihydro-6-oxo-1,2,4-triazinyl (e.g., 1,6-dihydro-5-isopropyl-6-oxo-1,2,4-triazinyl); 2,3-dihydro-2-oxo-1*H*-indolyl (e.g., 3,3-dimethyl-2,3-dihydro-2-oxo-1*H*-indolyl and 2,3-dihydro-2-oxo-3,3′-spiropropane-1*H*-indol-1-yl); 1,3-dihydro-1-oxo-2*H*-iso-indolyl; 1,3-dihydro-1,3-dioxo-2*H*-iso-indolyl; 1*H*-benzopyrazolyl (e.g., 1-(ethoxycarbonyl)- 1*H*-benzopyrazolyl); 2,3-dihydro-2-oxo-1*H*-benzimidazolyl (e.g., 3-ethyl-2,3-dihydro-2-oxo-1*H*-benzimidazolyl); 2,3-dihydro-2-oxo-benzoxazolyl (e.g., 5-chloro-2,3-dihydro-2-oxo-benzoxazolyl); 2,3-dihydro-2-oxo-benzoxazolyl; 2-oxo-2H-benzopyranyl; 1,4-benzodioxanyl; 1,3-benzodioxanyl; 2,3-dihydro-3-oxo,4*H*-1,3-benzothiazinyl; 3,4-dihydro-4-oxo-3*H*-quinazolinyl (e.g., 2-methyl-3,4-dihydro-4-oxo-3*H*-quinazolinyl); 1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolyl (e.g., 1-ethyl-1,2,3,4-tetrahydro-2,4-dioxo-3*H*-quinazolyl); 1,2,3,6-tetrahydro-2,6-dioxo-7*H*-purinyl (e.g., 1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxo-7 *H* -purinyl); 1,2,3,6-tetrahydro-2,6-dioxo-1 *H* –purinyl (e.g., 1,2,3,6-tetrahydro-3,7-dimethyl-2,6-dioxo-1 *H* -purinyl); 2-oxobenz[*c,d*]indolyl; 1,1-dioxo-2H-naphth[1,8-*c,d*]isothiazolyl; and 1,8-naphthylenedicarboxamido. Additional heterocyclics include 3,3a,4,5,6,6a-hexahydro-pyrrolo[3,4-b]pyrrol-(2H)-yl, and 2,5-diazabicyclo[2.2.1]heptan-2-yl, homopiperazinyl (or diazepanyl), tetrahydropyranyl, dithiazolyl, benzofuranyl, benzothienyl, oxepanyl, thiepanyl, azocanyl, oxecanyl, and thiocanyl. Heterocyclic groups also include groups of the formula



, where

[0001011] E′ is selected from the group consisting of -N- and -CH-; F′ is selected from the group consisting of -N=CH-, -NH-CH_2-, -NH-C(O)-, -NH-, -CH=N-, -CH_2-NH-, -C(O)-NH-, -CH=CH-, -CH_2-, -CH_2CH_2-, -CH_2O-, -OCH_2-, -O-, and -S-; and G′ is selected from the group consisting of -CH- and -N-. Any of the heterocyclyl groups mentioned herein may be optionally substituted with one, two, three, four or five substituents independently selected from the group consisting of: (1) C_{1-7} acyl (e.g., carboxyaldehyde); (2) C_{1-20} alkyl (e.g., C_{1-6} alkyl, C_{1-6} alkoxy-C_{1-6} alkyl, C_{1-6} alkylsulfinyl-C_{1-6} alkyl, amino-C_{1-6} alkyl, azido-C_{1-6} alkyl, (carboxyaldehyde)-C_{1-6} alkyl, halo-C_{1-6} alkyl (e.g., perfluoroalkyl), hydroxy-C_{1-6} alkyl, nitro-C_{1-6} alkyl, or C_{1-6} thioalkoxy-C_{1-6} alkyl); (3) C_{1-20} alkoxy (e.g., C_{1-6} alkoxy, such as perfluoroalkoxy); (4) C_{1-6} alkylsulfinyl; (5) C_{6-10} aryl; (6) amino; (7) C_{1-6} alk-C_{6-10} aryl; (8) azido; (9) C_{3-8} cycloalkyl; (10) C_{1-6} alk-C_{3-8} cycloalkyl; (11) halo; (12) C_{1-12} heterocyclyl (e.g., C_{2-12} heteroaryl); (13) (C_{1-12} heterocyclyl)oxy; (14) hydroxy; (15) nitro; (16) C_{1-20} thioalkoxy (e.g., C_{1-6} thioalkoxy); (17) -$(CH_2)_qCO_2R^{A'}$, where q is an integer from zero to four, and $R^{A'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, (c) hydrogen, and (d) C_{1-6} alk-C_{6-10} aryl; (18) -$(CH_2)_qCONR^{B'}R^{C'}$, where q is an integer from zero to four and where $R^{B'}$ and $R^{C'}$ are independently selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (19) -$(CH_2)_qSO_2R^{D'}$, where q is an integer from zero to four and where $R^{D'}$ is selected from the group consisting of (a) C_{1-6} alkyl, (b) C_{6-10} aryl, and (c) C_{1-6} alk-C_{6-10} aryl; (20) -$(CH_2)_qSO_2NR^{E'}R^{F'}$, where q is an integer from zero to four and where each of $R^{E'}$ and $R^{F'}$ is, independently, selected from the group consisting of (a) hydrogen, (b) C_{1-6} alkyl, (c) C_{6-10} aryl, and (d) C_{1-6} alk-C_{6-10} aryl; (21) thiol; (22) C_{6-10} aryloxy; (23) C_{3-8} cycloalkoxy; (24) arylalkoxy; (25) C_{1-6} alk-C_{1-12} heterocyclyl (e.g., C_{1-6} alk-C_{1-12} heteroaryl); (26) oxo; (27) (C_{1-12} heterocyclyl)imino; (28) C_{2-20} alkenyl; and (29) C_{2-20} alkynyl. In some embodiments, each of these groups can be further substituted as described herein. For example, the alkylene group of a C_1-alkaryl or a C_1-alkheterocyclyl can be further substituted with an oxo group to afford the respective aryloyl and (heterocyclyl)oyl substituent group.

[0001012] The term "(heterocyclyl)imino," as used herein, represents a heterocyclyl group, as defined herein, attached to the parent molecular group through an imino group.

In some embodiments, the heterocyclyl group can be substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[0001013] The term "(heterocyclyl)oxy," as used herein, represents a heterocyclyl group, as defined herein, attached to the parent molecular group through an oxygen atom. In some embodiments, the heterocyclyl group can be substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[0001014] The term "(heterocyclyl)oyl," as used herein, represents a heterocyclyl group, as defined herein, attached to the parent molecular group through a carbonyl group. In some embodiments, the heterocyclyl group can be substituted with 1, 2, 3, or 4 substituent groups as defined herein.

[0001015] The term "hydrocarbon," as used herein, represents a group consisting only of carbon and hydrogen atoms.

[0001016] The term "hydroxy," as used herein, represents an –OH group.

[0001017] The term "hydroxyalkenyl," as used herein, represents an alkenyl group, as defined herein, substituted by one to three hydroxy groups, with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group, and is exemplified by dihydroxypropenyl, hydroxyisopentenyl, and the like.

[0001018] The term "hydroxyalkyl," as used herein, represents an alkyl group, as defined herein, substituted by one to three hydroxy groups, with the proviso that no more than one hydroxy group may be attached to a single carbon atom of the alkyl group, and is exemplified by hydroxymethyl, dihydroxypropyl, and the like.

[0001019] The term "isomer," as used herein, means any tautomer, stereoisomer, enantiomer, or diastereomer of any compound of the invention. It is recognized that the compounds of the invention can have one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric E/Z isomers) or diastereomers (e.g., enantiomers (i.e., (+) or (-)) or cis/trans isomers). According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding stereoisomers, that is, both the stereomerically pure form (e.g., geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures, e.g., racemates. Enantiomeric and stereoisomeric mixtures of compounds of the invention can typically

be resolved into their component enantiomers or stereoisomers by well-known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically or enantiomerically pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0001020] The term "*N*-protected amino," as used herein, refers to an amino group, as defined herein, to which is attached one or two *N*-protecting groups, as defined herein.

[0001021] The term "*N*-protecting group," as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used *N*-protecting groups are disclosed in Greene, "Protective Groups in Organic Synthesis," 3rd Edition (John Wiley & Sons, New York, 1999), which is incorporated herein by reference. *N*-protecting groups include acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L or D, L-amino acids such as alanine, leucine, phenylalanine, and the like; sulfonyl-containing groups such as benzenesulfonyl, p-toluenesulfonyl, and the like; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl, and the like, alkaryl groups such as benzyl, triphenylmethyl, benzyloxymethyl, and the like and silyl groups, such as trimethylsilyl, and the like. Preferred *N*-protecting groups are formyl, acetyl,

benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).

[0001022] The term "nitro," as used herein, represents an $-NO_2$ group.

[0001023] The term "oxo" as used herein, represents =O.

[0001024] The term "perfluoroalkyl," as used herein, represents an alkyl group, as defined herein, where each hydrogen radical bound to the alkyl group has been replaced by a fluoride radical. Perfluoroalkyl groups are exemplified by trifluoromethyl, pentafluoroethyl, and the like.

[0001025] The term "perfluoroalkoxy," as used herein, represents an alkoxy group, as defined herein, where each hydrogen radical bound to the alkoxy group has been replaced by a fluoride radical. Perfluoroalkoxy groups are exemplified by trifluoromethoxy, pentafluoroethoxy, and the like.

[0001026] The term "spirocyclyl," as used herein, represents a C_{2-7} alkylene diradical, both ends of which are bonded to the same carbon atom of the parent group to form a spirocyclic group, and also a C_{1-6} heteroalkylene diradical, both ends of which are bonded to the same atom. The heteroalkylene radical forming the spirocyclyl group can containing one, two, three, or four heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. In some embodiments, the spirocyclyl group includes one to seven carbons, excluding the carbon atom to which the diradical is attached. The spirocyclyl groups of the invention may be optionally substituted with 1, 2, 3, or 4 substituents provided herein as optional substituents for cycloalkyl and/or heterocyclyl groups.

[0001027] The term "stereoisomer," as used herein, refers to all possible different isomeric as well as conformational forms which a compound may possess (e.g., a compound of any formula described herein), in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

[0001028] The term "sulfoalkyl," as used herein, represents an alkyl group, as defined herein, substituted by a sulfo group of $-SO_3H$. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[0001029] The term "sulfonyl," as used herein, represents an $-S(O)_2-$ group.

[0001030] The term "thioalkaryl," as used herein, represents a chemical substituent of formula –SR, where R is an alkaryl group. In some embodiments, the alkaryl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[0001031] The term "thioalkheterocyclyl," as used herein, represents a chemical substituent of formula –SR, where R is an alkheterocyclyl group. In some embodiments, the alkheterocyclyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[0001032] The term "thioalkoxy," as used herein, represents a chemical substituent of formula –SR, where R is an alkyl group, as defined herein. In some embodiments, the alkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein.

[0001033] The term "thiol" represents an –SH group.

~~**[0001034]**~~ *Compound:* As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

[0001035] The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present disclosure that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically active starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present disclosure. Cis and trans geometric isomers of the compounds of the present disclosure are described and may be isolated as a mixture of isomers or as separated isomeric forms.

[0001036] Compounds of the present disclosure also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double

bond and the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Examples prototropic tautomers include ketone – enol pairs, amide – imidic acid pairs, lactam – lactim pairs, amide – imidic acid pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, such as, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

[0001037] Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. "Isotopes" refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[0001038] The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

[0001039] *Conserved*: As used herein, the term "conserved" refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[0001040] In some embodiments, two or more sequences are said to be "completely conserved" if they are 100% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "highly conserved" if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at

least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be "conserved" if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of an oligonucleotide or polypeptide or may apply to a portion, region or feature thereof.

[0001041] *Controlled Release:* As used herein, the term "controlled release" refers to a pharmaceutical composition or compound release profile that conforms to a particular pattern of release to effect a therapeutic outcome.

[0001042] *Cyclic or Cyclized:* As used herein, the term "cyclic" refers to the presence of a continuous loop. Cyclic molecules need not be circular, only joined to form an unbroken chain of subunits. Cyclic molecules such as the engineered RNA or mRNA of the present invention may be single units or multimers or comprise one or more components of a complex or higher order structure.

[0001043] *Cytostatic*: As used herein, "cytostatic" refers to inhibiting, reducing, suppressing the growth, division, or multiplication of a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[0001044] *Cytotoxic*: As used herein, "cytotoxic" refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[0001045] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

[0001046] *Delivery Agent*: As used herein, "delivery agent" refers to any substance which facilitates, at least in part, the *in vivo* delivery of a polynucleotide, primary construct or mmRNA to targeted cells.

[0001047] *Destabilized:* As used herein, the term "destable," "destabilize," or "destabilizing region" means a region or molecule that is less stable than a starting, wild-type or native form of the same region or molecule.

[0001048] *Detectable label:* As used herein, "detectable label" refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another

entity that is readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include radioisotopes, fluorophores, chromophores, enzymes, dyes, metal ions, ligands such as biotin, avidin, streptavidin and haptens, quantum dots, and the like. Detectable labels may be located at any position in the peptides or proteins disclosed herein. They may be within the amino acids, the peptides, or proteins, or located at the N- or C- termini.

[0001049] *Digest*: As used herein, the term "digest" means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[0001050] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[0001051] *Dosing regimen*: As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[0001052] *Dose splitting factor (DSF)*-ratio of PUD of dose split treatment divided by PUD of total daily dose or single unit dose. The value is derived from comparison of dosing regimens groups.

[0001053] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase.

[0001054] *Encoded protein cleavage signal*: As used herein, "encoded protein cleavage signal" refers to the nucleotide sequence which encodes a protein cleavage signal.

[0001055] *Engineered:* As used herein, embodiments of the invention are "engineered" when they are designed to have a feature or property, whether structural or chemical, that varies from a starting point, wild type or native molecule.

[0001056] *Exosome:* As used herein, "exosome" is a vesicle secreted by mammalian cells or a complex involved in RNA degradation.

[0001057] *Expression*: As used herein, "expression" of a nucleic acid sequence refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (*e.g.*, by transcription); (2) processing of an RNA transcript (*e.g.*, by splicing,

editing, 5′ cap formation, and/or 3′ end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0001058] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[0001059] *Formulation*: As used herein, a "formulation" includes at least a polynucleotide, primary construct or mmRNA and a delivery agent.

[0001060] *Fragment:* A "fragment," as used herein, refers to a portion. For example, fragments of proteins may comprise polypeptides obtained by digesting full-length protein isolated from cultured cells.

[0001061] *Functional*: As used herein, a "functional" biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

[0001062] *Homology*: As used herein, the term "homology" refers to the overall relatedness between polymeric molecules, *e.g.* between nucleic acid molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "homologous" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term "homologous" necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the invention, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the invention, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0001063] *Identity*: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, *e.g.*, between oligonucleotide molecules (*e.g.* DNA

molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H., and Lipman, D., SIAM J Applied

Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[0001064] *Inhibit expression of a gene:* As used herein, the phrase "inhibit expression of a gene" means to cause a reduction in the amount of an expression product of the gene. The expression product can be an RNA transcribed from the gene (*e.g.*, an mRNA) or a polypeptide translated from an mRNA transcribed from the gene. Typically a reduction in the level of an mRNA results in a reduction in the level of a polypeptide translated therefrom. The level of expression may be determined using standard techniques for measuring mRNA or protein.

[0001065] *In vitro*: As used herein, the term "*in vitro*" refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[0001066] *In vivo*: As used herein, the term "*in vivo*" refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[0001067] *Isolated*: As used herein, the term "isolated" refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is "pure" if it is substantially free of other components. *Substantially isolated*: By "substantially isolated" is meant that the compound is substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compound of the present disclosure. Substantial separation can include

compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[0001068] *Linker:* As used herein, a linker refers to a group of atoms, e.g., 10-1,000 atoms, and can be comprised of the atoms or groups such as, but not limited to, carbon, amino, alkylamino, oxygen, sulfur, sulfoxide, sulfonyl, carbonyl, and imine. The linker can be attached to a modified nucleoside or nucleotide on the nucleobase or sugar moiety at a first end, and to a payload, e.g., a detectable or therapeutic agent, at a second end. The linker may be of sufficient length as to not interfere with incorporation into a nucleic acid sequence. The linker can be used for any useful purpose, such as to form mmRNA multimers (e.g., through linkage of two or more polynucleotides, primary constructs, or mmRNA molecules) or mmRNA conjugates, as well as to administer a payload, as described herein. Examples of chemical groups that can be incorporated into the linker include, but are not limited to, alkyl, alkenyl, alkynyl, amido, amino, ether, thioether, ester, alkylene, heteroalkylene, aryl, or heterocyclyl, each of which can be optionally substituted, as described herein. Examples of linkers include, but are not limited to, unsaturated alkanes, polyethylene glycols (e.g., ethylene or propylene glycol monomeric units, e.g., diethylene glycol, dipropylene glycol, triethylene glycol, tripropylene glycol, tetraethylene glycol, or tetraethylene glycol), and dextran polymers and derivatives thereof., Other examples include, but are not limited to, cleavable moieties within the linker, such as, for example, a disulfide bond (-S-S-) or an azo bond (-N=N-), which can be cleaved using a reducing agent or photolysis. Non-limiting examples of a selectively cleavable bond include an amido bond can be cleaved for example by the use of tris(2-carboxyethyl)phosphine (TCEP), or other reducing agents, and/or photolysis, as well as an ester bond can be cleaved for example by acidic or basic hydrolysis.

[0001069] *MicroRNA (miRNA) binding site:* As used herein, a microRNA (miRNA) binding site represents a nucleotide location or region of a nucleic acid transcript to which at least the "seed" region of a miRNA binds.

[0001070] *Modified:* As used herein "modified" refers to a changed state or structure of a molecule of the invention. Molecules may be modified in many ways including

chemically, structurally, and functionally. In one embodiment, the mRNA molecules of the present invention are modified by the introduction of non-natural nucleosides and/or nucleotides, e.g., as it relates to the natural ribonucleotides A, U, G, and C. Noncanonical nucleotides such as the cap structures are not considered "modified" although they differ from the chemical structure of the A, C, G, U ribonucleotides.

[0001071] *Mucus*: As used herein, "mucus" refers to the natural substance that is viscous and comprises mucin glycoproteins.

[0001072] *Naturally occurring:* As used herein, "naturally occurring" means existing in nature without artificial aid.

[0001073] *Non-human vertebrate:* As used herein, a "non human vertebrate" includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, rabbit, reindeer, sheep water buffalo, and yak.

[0001074] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[0001075] *Open reading frame:* As used herein, "open reading frame" or "ORF" refers to a sequence which does not contain a stop codon in a given reading frame.

[0001076] *Operably linked:* As used herein, the phrase "operably linked" refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[0001077] *Optionally substituted:* Herein a phrase of the form "optionally substituted X" (*e.g.*, optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (*e.g.*, "alkyl, wherein said alkyl is optionally substituted"). It is not intended to mean that the feature "X" (*e.g.* alkyl) *per se* is optional.

[0001078] *Peptide:* As used herein, "peptide" is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0001079] *Paratope:* As used herein, a "paratope" refers to the antigen-binding site of an antibody.

[0001080] *Patient:* As used herein, "patient" refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[0001081] *Pharmaceutically acceptable*: The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0001082] *Pharmaceutically acceptable excipients:* The phrase "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0001083] *Pharmaceutically acceptable salts*: The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety

to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al., *Journal of Pharmaceutical Science*, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety.

[0001084] *Pharmaceutically acceptable solvate*: The term "pharmaceutically acceptable solvate," as used herein, means a compound of the invention wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a "hydrate."

[0001085] *Pharmacokinetic:* As used herein, "pharmacokinetic" refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[0001086] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[0001087] *Polypeptide per unit drug (PUD)*: As used herein, a PUD or product per unit drug, is defined as a subdivided portion of total daily dose, usually 1 mg, pg, kg, etc., of a product (such as a polypeptide) as measured in body fluid or tissue, usually defined in concentration such as pmol/mL, mmol/mL, etc divided by the measure in the body fluid.

[0001088] *Preventing*: As used herein, the term "preventing" refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or

completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0001089] *Prodrug*: The present disclosure also includes prodrugs of the compounds described herein. As used herein, "prodrugs" refer to any substance, molecule or entity which is in a form predicate for that substance, molecule or entity to act as a therapeutic upon chemical or physical alteration. Prodrugs may by covalently bonded or sequestered in some way and which release or are converted into the active drug moiety prior to, upon or after administered to a mammalian subject. Prodrugs can be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Preparation and use of prodrugs is discussed in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

[0001090] *Proliferate:* As used herein, the term "proliferate" means to grow, expand or increase or cause to grow, expand or increase rapidly. "Proliferative" means having the ability to proliferate. "Anti-proliferative" means having properties counter to or inapposite to proliferative properties.

[0001091] *Protein cleavage site*: As used herein, "protein cleavage site" refers to a site where controlled cleavage of the amino acid chain can be accomplished by chemical, enzymatic or photochemical means.

[0001092] *Protein cleavage signal:* As used herein "protein cleavage signal" refers to at least one amino acid that flags or marks a polypeptide for cleavage.

[0001093] *Protein of interest:* As used herein, the terms "proteins of interest" or "desired proteins" include those provided herein and fragments, mutants, variants, and alterations thereof.

[0001094] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[0001095] *Pseudouridine:* As used herein, pseudouridine refers to the C-glycoside isomer of the nucleoside uridine. A "pseudouridine analog" is any modification, variant, isoform or derivative of pseudouridine. For example, pseudouridine analogs include but are not limited to 1-carboxymethyl-pseudouridine, 1-propynyl-pseudouridine, 1-taurinomethyl-pseudouridine, 1-taurinomethyl-4-thio-pseudouridine, 1-methylpseudouridine ($m^1\psi$), 1-methyl-4-thio-pseudouridine ($m^1s^4\psi$), 4-thio-1-methyl-pseudouridine, 3-methyl-pseudouridine ($m^3\psi$), 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydropseudouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, N1-methyl-pseudouridine, 1-methyl-3-(3-amino-3-carboxypropyl)pseudouridine ($acp^3\ \psi$), and 2′-O-methyl-pseudouridine (ψm).

[0001096] *Purified:* As used herein, "purify," "purified," "purification" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection.

[0001097] *Sample:* As used herein, the term "sample" or "biological sample" refers to a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). A sample further may include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. A sample further refers to a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecule.

[0001098] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization of a protein.

[0001099] *Single unit dose*: As used herein, a "single unit dose" is a dose of any therapeutic administed in one dose/at one time/single route/single point of contact, i.e., single administration event.

[0001100] *Similarity*: As used herein, the term "similarity" refers to the overall relatedness between polymeric molecules, *e.g.* between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of percent similarity of polymeric molecules to one another can be performed in the same manner as a calculation of percent identity, except that calculation of percent similarity takes into account conservative substitutions as is understood in the art.

[0001101] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

[0001102] *Stable:* As used herein "stable" refers to a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and preferably capable of formulation into an efficacious therapeutic agent.

[0001103] *Stabilized:* As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable.

[0001104] *Subject:* As used herein, the term "subject" or "patient" refers to any organism to which a composition in accordance with the invention may be administered, *e.g.*, for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and humans) and/or plants.

[0001105] *Substantially*: As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0001106] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[0001107] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

[0001108] *Suffering from*: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[0001109] *Susceptible to*: An individual who is "susceptible to" a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, cancer) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0001110] *Sustained release:* As used herein, the term "sustained release" refers to a pharmaceutical composition or compound release profile that conforms to a release rate over a specific period of time.

[0001111] *Synthetic*: The term "synthetic" means produced, prepared, and/or manufactured by the hand of man. Synthesis of polynucleotides or polypeptides or other molecules of the present invention may be chemical or enzymatic.

[0001112] *Targeted Cells:* As used herein, "targeted cells" refers to any one or more cells of interest. The cells may be found *in vitro*, *in vivo*, *in situ* or in the tissue or organ

of an organism. The organism may be an animal, preferably a mammal, more preferably a human and most preferably a patient.

[0001113] *Therapeutic Agent:* The term "therapeutic agent" refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect.

[0001114] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" means an amount of an agent to be delivered (*e.g.*, nucleic acid, drug, therapeutic agent, diagnostic agent, prophylactic agent, *etc.*) that is sufficient, when administered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0001115] *Therapeutically effective outcome*: As used herein, the term "therapeutically effective outcome" means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0001116] *Total daily dose:* As used herein, a "total daily dose" is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

[0001117] *Transcription factor:* As used herein, the term "transcription factor" refers to a DNA-binding protein that regulates transcription of DNA into RNA, for example, by activation or repression of transcription. Some transcription factors effect regulation of transcription alone, while others act in concert with other proteins. Some transcription factor can both activate and repress transcription under certain conditions. In general, transcription factors bind a specific target sequence or sequences highly similar to a specific consensus sequence in a regulatory region of a target gene. Transcription factors may regulate transcription of a target gene alone or in a complex with other molecules.

[0001118] *Treating*: As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, "treating" cancer may refer to inhibiting survival, growth, and/or spread of a tumor. Treatment may

be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0001119] *Unmodified*: As used herein, "unmodified" refers to any substance, compound or molecule prior to being changed in any way. Unmodified may, but does not always, refer to the wild type or native form of a biomolecule. Molecules may undergo a series of modifications whereby each modified molecule may serve as the "unmodified" starting molecule for a subsequent modification.

Equivalents and Scope

[0001120] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0001121] In the claims, articles such as "a," "an," and "the" may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[0001122] It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.

[0001123] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and

understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0001124] In addition, it is to be understood that any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions of the invention (*e.g.*, any nucleic acid or protein encoded thereby; any method of production; any method of use; *etc.*) can be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

[0001125] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation. In case of conflicting statements of a cited source and the instant application, the statement in the instant application shall control.

[0001126] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Modified mRNA Production

[0001127] Modified mRNAs (mmRNA) according to the invention may be made using standard laboratory methods and materials. The open reading frame (ORF) of the gene of interest may be flanked by a 5' untranslated region (UTR) which may contain a strong Kozak translational initiation signal and/or an alpha-globin 3' UTR which may include an oligo(dT) sequence for templated addition of a poly-A tail. The modified mRNAs may be modified to reduce the cellular innate immune response. The modifications to reduce the cellular response may include pseudouridine (ψ) and 5-methyl-cytidine (5meC, 5mc or m^5C). (See, Kariko K et al. Immunity 23:165-75 (2005), Kariko K et al. Mol Ther 16:1833-40 (2008), Anderson BR et al. NAR (2010); each of which are herein incorporated by reference in their entireties).

[0001128] The ORF may also include various upstream or downstream additions (such as, but not limited to, β-globin, tags, etc.) may be ordered from an optimization service

such as, but limited to, DNA2.0 (Menlo Park, CA) and may contain multiple cloning sites which may have XbaI recognition. Upon receipt of the construct, it may be reconstituted and transformed into chemically competent *E. coli*.

[0001129] For the present invention, NEB DH5-alpha Competent *E. coli* are used. Transformations are performed according to NEB instructions using 100 ng of plasmid. The protocol is as follows:

1 Thaw a tube of NEB 5-alpha Competent *E. coli* cells on ice for 10 minutes.
2 Add 1-5 µl containing 1 pg-100 ng of plasmid DNA to the cell mixture. Carefully flick the tube 4-5 times to mix cells and DNA. Do not vortex.
3 Place the mixture on ice for 30 minutes. Do not mix.
4 Heat shock at 42°C for exactly 30 seconds. Do not mix.
5 Place on ice for 5 minutes. Do not mix.
6 Pipette 950 µl of room temperature SOC into the mixture.
7 Place at 37°C for 60 minutes. Shake vigorously (250 rpm) or rotate.
8 Warm selection plates to 37°C.
9 Mix the cells thoroughly by flicking the tube and inverting.

[0001130] Spread 50-100 µl of each dilution onto a selection plate and incubate overnight at 37°C. Alternatively, incubate at 30°C for 24-36 hours or 25°C for 48 hours.

[0001131] A single colony is then used to inoculate 5 ml of LB growth media using the appropriate antibiotic and then allowed to grow (250 RPM, 37° C) for 5 hours. This is then used to inoculate a 200 ml culture medium and allowed to grow overnight under the same conditions.

[0001132] To isolate the plasmid (up to 850 µg), a maxi prep is performed using the Invitrogen PURELINK™ HiPure Maxiprep Kit (Carlsbad, CA), following the manufacturer's instructions.

[0001133] In order to generate cDNA for *In Vitro* Transcription (IVT), the plasmid (an Example of which is shown in Figure 3) is first linearized using a restriction enzyme such as XbaI. A typical restriction digest with XbaI will comprise the following: Plasmid 1.0 µg; 10x Buffer 1.0 µl; XbaI 1.5 µl; dH_20 up to 10 µl; incubated at 37° C for 1 hr. If performing at lab scale (< 5µg), the reaction is cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA) per manufacturer's instructions. Larger

scale purifications may need to be done with a product that has a larger load capacity such as Invitrogen's standard PURELINK™ PCR Kit (Carlsbad, CA). Following the cleanup, the linearized vector is quantified using the NanoDrop and analyzed to confirm linearization using agarose gel electrophoresis.

[0001134] The methods described herein to make modified mRNA may be used to produce molecules of all sizes including long molecules. Modified mRNA using the described methods has been made for different sized molecules including glucosidase, alpha; acid (GAA) (3.2 kb), cystic fibrosis transmembrane conductance regulator (CFTR) (4.7 kb), Factor VII (7.3 kb), lysosomal acid lipase (45.4kDa), glucocerebrosidase (59.7 kDa) and iduronate 2-sulfatase (76 kDa).

[0001135] As a non-limiting example, G-CSF may represent the polypeptide of interest. Sequences used in the steps outlined in Examples 1-5 are shown in Table 11. It should be noted that the start codon (ATG) has been underlined in each sequence of Table 11.

Table 11. G-CSF Sequences

SEQ ID NO	Description
61645	cDNA sequence: ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCT GCAGCTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAG CCACCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGC TCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGCGATGGCGC AGCGCTCCAGGAGAAGCTGTGTGCCACCTACAAGCTGTGCCACC CCGAGGAGCTGGTGCTGCTCGGACACTCTCTGGGCATCCCCTGG GCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGG CTGCTTGAGCCAACTCCATAGCGGCCTTTTCCTCTACCAGGGGCT CCTGCAGGCCCTGGAAGGGATCTCCCCCGAGTTGGGTCCCACCT TGGACACACTGCAGCTGGACGTCGCCGACTTTGCCACCACCATC TGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCC CACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCCAGCGCCG GGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGG AGGTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGA
61646	cDNA having T7 polymerase site, AfeI and Xba restriction site: TAATACGACTCACTATA GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAG CCACC ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCT GCAGCTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAG CCACCCCCCTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGC TCAAGTGCTTAGAGCAAGTGAGGAAGATCCAGGGCGATGGCGC AGCGCTCCAGGAGAAGCTGTGTGCCACCTACAAGCTGTGCCACC

	CCGAGGAGCTGGTGCTGCTCGGACACTCTCTGGGCATCCCCTGG GCTCCCCTGAGCAGCTGCCCCAGCCAGGCCCTGCAGCTGGCAGG CTGCTTGAGCCAACTCCATAGCGGCCTTTTCCTCTACCAGGGGCT CCTGCAGGCCCTGGAAGGGATCTCCCCCGAGTTGGGTCCCACCT TGGACACACTGCAGCTGGACGTCGCCGACTTTGCCACCACCATC TGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCCTGCAGCC CACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCCAGCGCCG GGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGG AGGTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGA AGCGCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTC TCTCCCTTGCACCTGTACCTCTTGGTCTTTGAATAAAGCCTGAGT AGGAAGGCGGCCGCTCGAGCATGCATCTAGA
61647	Optimized sequence; containing T7 polymerase site, AfeI and Xba restriction site TAATACGACTCACTATA GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAG CCACC ATGGCCGGTCCCGCGACCCAAAGCCCCATGAAACTTATGGCCCT GCAGTTGCTGCTTTGGCACTCGGCCCTCTGGACAGTCCAAGAAG CGACTCCTCTCGGACCTGCCTCATCGTTGCCGCAGTCATTCCTTT TGAAGTGTCTGGAGCAGGTGCGAAAGATTCAGGGCGATGGAGCC GCACTCCAAGAGAAGCTCTGCGCGACATACAAACTTTGCCATCC CGAGGAGCTCGTACTGCTCGGGCACAGCTTGGGGATTCCCTGGG CTCCTCTCTCGTCCTGTCCGTCGCAGGCTTTGCAGTTGGCAGGGT GCCTTTCCCAGCTCCACTCCGGTTTGTTCTTGTATCAGGGACTGC TGCAAGCCCTTGAGGGAATCTCGCCAGAATTGGGCCCGACGCTG GACACGTTGCAGCTCGACGTGGCGGATTTCGCAACAACCATCTG GCAGCAGATGGAGGAACTGGGGATGGCACCCGCGCTGCAGCCC ACGCAGGGGGCAATGCCGGCCTTTGCGTCCGCGTTTCAGCGCAG GGCGGGTGGAGTCCTCGTAGCGAGCCACCTTCAATCATTTTTGG AAGTCTCGTACCGGGTGCTGAGACATCTTGCGCAGCCGTGA AGCGCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTC TCTCCCTTGCACCTGTACCTCTTGGTCTTTGAATAAAGCCTGAGT AGGAAGGCGGCCGCTCGAGCATGCATCTAGA
61648	mRNA sequence (transcribed) GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAG CCACC AUGGCCGGUCCCGCGACCCAAAGCCCCAUGAAACUUAUGGCCC UGCAGUUGCUGCUUUGGCACUCGGCCCUCUGGACAGUCCAAGA AGCGACUCCUCUCGGACCUGCCUCAUCGUUGCCGCAGUCAUUC CUUUUGAAGUGUCUGGAGCAGGUGCGAAAGAUUCAGGGCGAU GGAGCCGCACUCCAAGAGAAGCUCUGCGCGACAUACAAACUUU GCCAUCCCGAGGAGCUCGUACUGCUCGGGCACAGCUUGGGGAU UCCCUGGGCUCCUCUCUCGUCCUGUCCGUCGCAGGCUUUGCAG UUGGCAGGGUGCCUUUCCCAGCUCCACUCCGGUUUGUUCUUGU

	AUCAGGGACUGCUGCAAGCCCUUGAGGGAAUCUCGCCAGAAUU GGGCCCGACGCUGGACACGUUGCAGCUCGACGUGGCGGAUUUC GCAACAACCAUCUGGCAGCAGAUGGAGGAACUGGGGAUGGCAC CCGCGCUGCAGCCCACGCAGGGGGCAAUGCCGGCCUUUGCGUC CGCGUUUCAGCGCAGGGCGGGUGGAGUCCUCGUAGCGAGCCAC CUUCAAUCAUUUUUGGAAGUCUCGUACCGGGUGCUGAGACAUC UUGCGCAGCCGUGA AGCGCUGCCUUCUGCGGGGCUUGCCUUCUGGCCAUGCCCUUCU UCUCUCCCUUGCACCUGUACCUCUUGGUCUUUGAAUAAAGCCU GAGUAGGAAG

Example 2: PCR for cDNA Production

[0001136] PCR procedures for the preparation of cDNA are performed using 2x KAPA HIFI™ HotStart ReadyMix by Kapa Biosystems (Woburn, MA). This system includes 2x KAPA ReadyMix12.5 µl; Forward Primer (10 uM) 0.75 µl; Reverse Primer (10 uM) 0.75 µl; Template cDNA 100 ng; and dH_20 diluted to 25.0 µl. The reaction conditions are at 95° C for 5 min. and 25 cycles of 98° C for 20 sec, then 58° C for 15 sec, then 72° C for 45 sec, then 72° C for 5 min. then 4° C to termination.

[0001137] The reverse primer of the instant invention incorporates a poly-T_{120} for a poly-A_{120} in the mRNA. Other reverse primers with longer or shorter poly(T) tracts can be used to adjust the length of the poly(A) tail in the mRNA.

[0001138] The reaction is cleaned up using Invitrogen's PURELINK™ PCR Micro Kit (Carlsbad, CA) per manufacturer's instructions (up to 5 µg). Larger reactions will require a cleanup using a product with a larger capacity. Following the cleanup, the cDNA is quantified using the NANODROP™ and analyzed by agarose gel electrophoresis to confirm the cDNA is the expected size. The cDNA is then submitted for sequencing analysis before proceeding to the *in vitro* transcription reaction.

Example 3. *In vitro* Transcription (IVT)

[0001139] The *in vitro* transcription reaction generates mRNA containing modified nucleotides or modified RNA. The input nucleotide triphosphate (NTP) mix is made in-house using natural and un-natural NTPs.

[0001140] A typical *in vitro* transcription reaction includes the following:

1 Template cDNA 1.0 µg

2 10x transcription buffer (400 mM Tris-HCl pH 8.0, 190 mM $MgCl_2$, 50 mM DTT, 10 mM Spermidine) 2.0 µl

3 Custom NTPs (25mM each) 7.2 µl

4 RNase Inhibitor 20 U

5 T7 RNA polymerase 3000 U

6 dH_20 Up to 20.0 µl. and

7 Incubation at 37° C for 3 hr-5 hrs.

[0001141] The crude IVT mix may be stored at 4° C overnight for cleanup the next day. 1 U of RNase-free DNase is then used to digest the original template. After 15 minutes of incubation at 37° C, the mRNA is purified using Ambion's MEGACLEAR™ Kit (Austin, TX) following the manufacturer's instructions. This kit can purify up to 500 µg of RNA. Following the cleanup, the RNA is quantified using the NanoDrop and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA has occurred.

Example 4. Enzymatic Capping of mRNA

[0001142] Capping of the mRNA is performed as follows where the mixture includes: IVT RNA 60 µg-180µg and dH_20 up to 72 µl. The mixture is incubated at 65° C for 5 minutes to denature RNA, and then is transferred immediately to ice.

[0001143] The protocol then involves the mixing of 10x Capping Buffer (0.5 M Tris-HCl (pH 8.0), 60 mM KCl, 12.5 mM $MgCl_2$) (10.0 µl); 20 mM GTP (5.0 µl); 20 mM S-Adenosyl Methionine (2.5 µl); RNase Inhibitor (100 U); 2′-O-Methyltransferase (400U); Vaccinia capping enzyme (Guanylyl transferase) (40 U); dH_20 (Up to 28 µl); and incubation at 37° C for 30 minutes for 60 µg RNA or up to 2 hours for 180 µg of RNA.

[0001144] The mRNA is then purified using Ambion's MEGACLEAR™ Kit (Austin, TX) following the manufacturer's instructions. Following the cleanup, the RNA is quantified using the NANODROP™ (ThermoFisher, Waltham, MA) and analyzed by agarose gel electrophoresis to confirm the RNA is the proper size and that no degradation of the RNA has occurred. The RNA product may also be sequenced by running a reverse-transcription-PCR to generate the cDNA for sequencing.

Example 5. PolyA Tailing Reaction

[0001145] Without a poly-T in the cDNA, a poly-A tailing reaction must be performed before cleaning the final product. This is done by mixing Capped IVT RNA (100 µl); RNase Inhibitor (20 U); 10x Tailing Buffer (0.5 M Tris-HCl (pH 8.0), 2.5 M NaCl, 100 mM $MgCl_2$)(12.0 µl); 20 mM ATP (6.0 µl); Poly-A Polymerase (20 U); dH_20 up to 123.5 µl and incubation at 37° C for 30 min. If the poly-A tail is already in the transcript, then the tailing reaction may be skipped and proceed directly to cleanup with Ambion's MEGACLEAR™ kit (Austin, TX) (up to 500 µg). Poly-A Polymerase is preferably a recombinant enzyme expressed in yeast.

[0001146] For studies performed and described herein, the poly-A tail is encoded in the IVT template to comprise160 nucleotides in length. However, it should be understood that the processivity or integrity of the polyA tailing reaction may not always result in exactly 160 nucleotides. Hence polyA tails of approximately 160 nucleotides, e.g, about 150-165, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164 or 165 are within the scope of the invention.

Example 6. Natural 5′ Caps and 5′ Cap Analogues

[0001147] 5′-capping of modified RNA may be completed concomitantly during the *in vitro*-transcription reaction using the following chemical RNA cap analogs to generate the 5′-guanosine cap structure according to manufacturer protocols: 3′-O-Me-m7G(5')ppp(5') G [the ARCA cap];G(5')ppp(5')A; G(5')ppp(5')G; m7G(5')ppp(5')A; m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). 5′-capping of modified RNA may be completed post-transcriptionally using a Vaccinia Virus Capping Enzyme to generate the "Cap 0" structure: m7G(5')ppp(5')G (New England BioLabs, Ipswich, MA). Cap 1 structure may be generated using both Vaccinia Virus Capping Enzyme and a 2′-O methyl-transferase to generate: m7G(5')ppp(5')G-2′-O-methyl. Cap 2 structure may be generated from the Cap 1 structure followed by the 2′-O-methylation of the 5′-antepenultimate nucleotide using a 2′-O methyl-transferase. Cap 3 structure may be generated from the Cap 2 structure followed by the 2′-O-methylation of the 5′-preantepenultimate nucleotide using a 2′-O methyl-transferase. Enzymes are preferably derived from a recombinant source.

[0001148] When transfected into mammalian cells, the modified mRNAs have a stability of between 12-18 hours or more than 18 hours, e.g., 24, 36, 48, 60, 72 or greater than 72 hours.

Example 7. Capping

A. Protein Expression Assay

[0001149] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 61645; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 61648 with a polyA tail approximately 160 nucletodies in length not shown in sequence) containing the ARCA (3′ O-Me-m7G(5')ppp(5')G) cap analog or the Cap1 structure can be transfected into human primary keratinocytes at equal concentrations. 6, 12, 24 and 36 hours post-transfection the amount of G-CSF secreted into the culture medium can be assayed by ELISA. Synthetic mRNAs that secrete higher levels of G-CSF into the medium would correspond to a synthetic mRNA with a higher translationally-competent Cap structure.

B. Purity Analysis Synthesis

[0001150] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 61645; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 61648 with a polyA tail approximately 160 nucletodies in length not shown in sequence) containing the ARCA cap analog or the Cap1 structure crude synthesis products can be compared for purity using denaturing Agarose-Urea gel electrophoresis or HPLC analysis. Synthetic mRNAs with a single, consolidated band by electrophoresis correspond to the higher purity product compared to a synthetic mRNA with multiple bands or streaking bands. Synthetic mRNAs with a single HPLC peak would also correspond to a higher purity product. The capping reaction with a higher efficiency would provide a more pure mRNA population.

C. Cytokine Analysis

[0001151] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 61645; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 61648 with a polyA tail approximately 160 nucletodies in length not shown in sequence) containing the

ARCA cap analog or the Cap1 structure can be transfected into human primary keratinocytes at multiple concentrations. 6, 12, 24 and 36 hours post-transfection the amount of pro-inflammatory cytokines such as TNF-alpha and IFN-beta secreted into the culture medium can be assayed by ELISA. Synthetic mRNAs that secrete higher levels of pro-inflammatory cytokines into the medium would correspond to a synthetic mRNA containing an immune-activating cap structure.

D. Capping Reaction Efficiency

[0001152] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 61645; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 61648 with a polyA tail approximately 160 nucletodies in length not shown in sequence) containing the ARCA cap analog or the Cap1 structure can be analyzed for capping reaction efficiency by LC-MS after capped mRNA nuclease treatment. Nuclease treatment of capped mRNAs would yield a mixture of free nucleotides and the capped 5′-5-triphosphate cap structure detectable by LC-MS. The amount of capped product on the LC-MS spectra can be expressed as a percent of total mRNA from the reaction and would correspond to capping reaction efficiency. The cap structure with higher capping reaction efficiency would have a higher amount of capped product by LC-MS.

Example 8. Agarose Gel Electrophoresis of Modified RNA or RT PCR Products

[0001153] Individual modified RNAs (200-400 ng in a 20 µl volume) or reverse transcribed PCR products (200-400 ng) are loaded into a well on a non-denaturing 1.2% Agarose E-Gel (Invitrogen, Carlsbad, CA) and run for 12-15 minutes according to the manufacturer protocol.

Example 9. Nanodrop Modified RNA Quantification and UV Spectral Data

[0001154] Modified RNAs in TE buffer (1 µl) are used for Nanodrop UV absorbance readings to quantitate the yield of each modified RNA from an *in vitro* transcription reaction.

Example 10. Formulation of Modified mRNA Using Lipidoids

[0001155] Modified mRNAs (mmRNA) are formulated for *in vitro* experiments by mixing the mmRNA with the lipidoid at a set ratio prior to addition to cells. *In vivo* formulation may require the addition of extra ingredients to facilitate circulation

throughout the body. To test the ability of these lipidoids to form particles suitable for *in vivo* work, a standard formulation process used for siRNA-lipidoid formulations was used as a starting point. Initial mmRNA-lipidoid formulations may consist of particles composed of 42% lipidoid, 48% cholesterol and 10% PEG, with further optimization of ratios possible. After formation of the particle, mmRNA is added and allowed to integrate with the complex. The encapsulation efficiency is determined using a standard dye exclusion assays.

Materials and Methods for Examples 11-15

A. Lipid Synthesis

[0001156] Six lipids, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 and DLin-MC3-DMA, were synthesized by methods outlined in the art in order to be formulated with modified RNA. DLin-DMA and precursorswere synthesized as described in Heyes et. al, J. Control Release, 2005, 107, 276-287. DLin-K-DMA and DLin-KC2-DMA and precursors were synthesized as described in Semple et. al, Nature Biotechnology, 2010, 28, 172-176. 98N12-5 and precursor were synthesized as described in Akinc et. al, *Nature Biotechnology*, 2008, 26, 561-569.

[0001157] C12-200 and precursors were synthesized according to the method outlined in Love et. al, PNAS, 2010, 107, 1864-1869. 2-epoxydodecane (5.10 g, 27.7 mmol, 8.2 eq) was added to a vial containing Amine 200 (0.723 g, 3.36 mmol, 1 eq) and a stirring bar. The vial was sealed and warmed to 80°C. The reaction was stirred for 4 days at 80°C. Then the mixture was purified by silica gel chromatography using a gradient from pure dichloromethane (DCM) to DCM:MeOH 98:2. The target compound was further purified by RP-HPLC to afford the desired compound.

[0001158] DLin-MC3-DMA and precursors were synthesized according to procedures described in WO 2010054401 herein incorporated by reference in its entirety. A mixture of dilinoleyl methanol (1.5 g, 2.8 mmol, 1 eq), N,N-dimethylaminobutyric acid (1.5 g, 2.8 mmol, 1eq), DIPEA (0.73 mL, 4.2 mmol, 1.5 eq) and TBTU(1.35 g, 4.2 mmol, 1.5 eq) in 10 mL of DMF was stirred for 10 h at room temperature. Then the reaction mixture was diluted in ether and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using a gradient DCM to DCM:MeOH 98:2.

Subsequently the target compound was subjected to an additional RP-HPLC purification which was done using a YMC – Pack C4 column to afford the target compound.

B. Formulation of Modified RNA Nanoparticles

[0001159] Solutions of synthesized lipid, 1,2-distearoyl-3-phosphatidylcholine (DSPC) (Avanti Polar Lipids, Alabaster, AL), cholesterol (Sigma-Aldrich, Taufkirchen, Germany), and α-[3'-(1,2-dimyristoyl-3-propanoxy)-carboxamide-propyl]-ω-methoxy-polyoxyethylene (PEG-c-DOMG) (NOF, Bouwelven, Belgium) were prepared at concentrations of 50 mM in ethanol and stored at -20°C. The lipids were combined to yield molar ratio of 50:10:38.5:1.5 (Lipid: DSPC: Cholesterol: PEG-c-DOMG) and diluted with ethanol to a final lipid concentration of 25 mM. Solutions of modified mRNA at a concentration of 1-2 mg/mL in water were diluted in 50 mM sodium citrate buffer at a pH of 3 to form a stock modified mRNA solution. Formulations of the lipid and modified mRNA were prepared by combining the synthesized lipid solution with the modified mRNA solution at total lipid to modified mRNA weight ratio of 10:1, 15:1, 20:1 and 30:1. The lipid ethanolic solution was rapidly injected into aqueous modified mRNA solution to afford a suspension containing 33% ethanol. The solutions were injected either manually (MI) or by the aid of a syringe pump (SP) (Harvard Pump 33 Dual Syringe Pump Harvard Apparatus Holliston, MA).

[0001160] To remove the ethanol and to achieve the buffer exhange, the formulations were dialyzed twice against phosphate buffered saline (PBS), pH 7.4 at volumes 200-times of the primary product using a Slide-A-Lyzer cassettes (Thermo Fisher Scientific Inc. Rockford, IL) with a molecular weight cutoff (MWCO) of 10 kD. The first dialysis was carried at room temperature for 3 hours and then the formulations were dialyzed overnight at 4°C. The resulting nanoparticle suspension was filtered through 0.2 μm sterile filter (Sarstedt, Nümbrecht, Germany) into glass vials and sealed with a crimp closure.

C. Characterization of formulations

[0001161] A Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK) was used to determine the particle size, the polydispersity index (PDI) and the zeta potential of the modified mRNA nanoparticles in 1X PBS in determining particle size and 15 mM PBS in determining zeta potential.

[0001162] Ultraviolet–visible spectroscopy was used to determine the concentration of modified mRNA nanoparticle formulation. 100 μL of the diluted formulation in 1X PBS was added to 900 μL of a 4:1 (v/v) mixture of methanol and chloroform. After mixing, the absorbance spectrum of the solution was recorded between 230 nm and 330 nm on a DU 800 spectrophotometer (Beckman Coulter, Beckman Coulter, Inc., Brea, CA). The modified RNA concentration in the nanoparicle formulation was calculated based on the extinction coefficient of the modified RNA used in the formulation and on the difference between the absorbance at a wavelength of 260 nm and the baseline value at a wavelength of 330 nm.

[0001163] QUANT-IT™ RIBOGREEN® RNA assay (Invitrogen Corporation Carlsbad, CA) was used to evaluate the encapsulation of modified RNA by the nanoparticle. The samples were diluted to a concentration of approximately 5 μg/mL in TE buffer (10 mM Tris-HCl, 1 mM EDTA, pH 7.5). 50 μL of the diluted samples were transferred to a polystyrene 96 well plate, then either 50 μL of TE buffer or 50 μL of a 2% Triton X-100 solution was added. The plate was incubated at a temperature of 37°C for 15 minutes. The RIBOGREEN® reagent was diluted 1:100 in TE buffer, 100 μL of this solution was added to each well. The fluorescence intensity was measured using a fluorescence plate reader (Wallac Victor 1420 Multilablel Counter; Perkin Elmer, Waltham, MA) at an excitation wavelength of ~480 nm and an emission wavelength of ~520 nm. The fluorescence values of the reagent blank were subtracted from that of each of the samples and the percentage of free modified RNA was determined by dividing the fluorescence intensity of the intact sample (without addition of Triton X-100) by the fluorescence value of the disrupted sample (caused by the addition of Triton X-100).

D. *In Vitro* Incubation

[0001164] Human embryonic kidney epithelial (HEK293) and hepatocellular carcinoma epithelial (HepG2) cells (LGC standards GmbH, Wesel, Germany) were seeded on 96-well plates (Greiner Bio-one GmbH, Frickenhausen, Germany) and plates for HEK293 cells were precoated with collagen type1. HEK293 were seeded at a density of 30,000 and HepG2 were seeded at a density of 35,000 cells per well in 100 μl cell culture medium. For HEK293 the cell culture medium was DMEM, 10% FCS, adding 2mM L-Glutamine, 1 mM Sodiumpyruvate and 1x non-essential amino acids (Biochrom AG,

Berlin, Germany) and 1.2 mg/ml Sodiumbicarbonate (Sigma-Aldrich, Munich, Germany) and for HepG2 the culture medium was MEM (Gibco Life Technologies, Darmstadt, Germany), 10% FCS adding 2mM L-Glutamine, 1 mM Sodiumpyruvate and 1x non-essential amino acids (Biochrom AG, Berlin, Germany. Formulations containing mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were added in quadruplicates directly after seeding the cells and incubated. The mCherry cDNA with the T7 promoter, 5′untranslated region (UTR) and 3′ UTR used in *in vitro* transcription (IVT) is given in SEQ ID NO: 61650. The mCherry mRNA was modified with a 5meC at each cytosine and pseudouridine replacement at each uridine site.

[0001165] Cells were harvested by transferring the culture media supernatants to a 96-well Pro-Bind U-bottom plate (Beckton Dickinson GmbH, Heidelberg, Germany). Cells were trypsinized with ½ volume Trypsin/EDTA (Biochrom AG, Berlin, Germany), pooled with respective supernatants and fixed by adding one volume PBS/2%FCS (both Biochrom AG, Berlin, Germany)/0.5% formaldehyde (Merck, Darmstadt, Germany). Samples then were submitted to a flow cytometer measurement with a 532nm excitation laser and the 610/20 filter for PE-Texas Red in a LSRII cytometer (Beckton Dickinson GmbH, Heidelberg, Germany). The mean fluorescence intensity (MFI) of all events and the standard deviation of four independent wells are presented in for samples analyzed.

Example 11. Purification of Nanoparticle Formulations

[0001166] Nanoparticle formulations of DLin-KC2-DMA and 98N12-5 in HEK293 and HepG2 were tested to determine if the mean fluorescent intensity (MFI) was dependent on the lipid to modified RNA ratio and/or purification. Three formulations of DLin-KC2-DMA and two formulations of 98N12-5 were produced using a syringe pump to the specifications described in Table 12. Purified samples were purified by SEPHADEX™ G-25 DNA grade (GE Healthcare, Sweden). Each formulation before and after purification (aP) was tested at concentration of 250 ng modified RNA per well in a 24 well plate. The percentage of cells that are positive for the marker for FL4 channel (%FL4-positive) when analyzed by the flow cytometer for each formulation and the background sample, and the MFI of the marker for the FL4 channel for each formulation

and the background sample are shown in Table 13. The formulations which had been purified had a slightly higher MFI than those formulations tested before purification.

Table 12. Formulations

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)
NPA-001-1	DLin-KC2-DMA	10	155 nm PDI: 0.08
NPA-001-1 aP	DLin-KC2-DMA	10	141 nm PDI: 0.14
NPA-002-1	DLin-KC2-DMA	15	140 nm PDI: 0.11
NPA-002-1 aP	DLin-KC2-DMA	15	125 nm PDI: 0.12
NPA-003-1	DLin-KC2-DMA	20	114 nm PDI: 0.08
NPA-003-1 aP	DLin-KC2-DMA	20	104 nm PDI: 0.06
NPA-005-1	98N12-5	15	127 nm PDI: 0.12
NPA-005-1 aP	98N12-5	15	134 nm PDI: 0.17
NPA-006-1	98N12	20	126 nm PDI: 0.08
NPA-006-1 aP	98N12	20	118 nm PDI: 0.13

Table 13. HEK293 and HepG2, 24-well, 250 ng Modified RNA/well

Formulation	%FL4-positive		FL4 MFI	
	HEK293	HepG2	HEK293	HepG2
Untreated	0.33	0.40	0.25	0.30
NPA-001-1	62.42	5.68	1.49	0.41
NPA-001-ap	87.32	9.02	3.23	0.53
NPA-002-1	91.28	9.90	4.43	0.59
NPA-002-ap	92.68	14.02	5.07	0.90
NPA-003-1	87.70	11.76	6.83	0.88
NPA-003-ap	88.88	15.46	8.73	1.06
NPA-005-1	50.60	4.75	1.83	0.46
NPA-005-ap	38.64	5.16	1.32	0.46
NPA-006-1	54.19	13.16	1.30	0.60
NPA-006-ap	49.97	13.74	1.27	0.61

Example 12. Concentration Response Curve

[0001167] Nanoparticle formulations of 98N12-5 (NPA-005) and DLin-KC2-DMA (NPA-003) were tested at varying concentrations to determine the MFI of FL4 or mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately

160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) over a range of doses. The formulations tested are outlined in Table 14. To determine the optimal concentration of nanoparticle formulations of 98N12-5, varying concentrations of formulated modified RNA (100 ng, 10 ng, 1.0 ng, 0.1 ng and 0.01 ng per well) were tested in a 24-well plate of HEK293, and the results of the FL4 MFI of each dose are shown in Table 15. Likewise, to determine the optimal concentration of nanoparticle formulations of DLin-KC2-DMA, varying concentrations of formulated modified RNA (250 ng 100 ng, 10 ng, 1.0 ng, 0.1 ng and 0.01 ng per well) were tested in a 24-well plate of HEK293, and the results of the FL4 MFI of each dose are shown in Table 16. Nanoparticle formulations of DLin-KC2-DMA were also tested at varying concentrations of formulated modified RNA (250 ng, 100 ng and 30 ng per well) in a 24 well plate of HEK293, and the results of the FL4 MFI of each dose are shown in Table 17. A dose of 1 ng/well for 98N12-5 and a dose of 10 ng/well for DLin-KC2-DMA were found to resemble the FL4 MFI of the background.

[0001168] To determine how close the concentrations resembled the background, we utilized a flow cytometer with optimized filter sets for detection of mCherry expression, and were able to obtain results with increased sensitivity relative to background levels. Doses of 25 ng/well, 0.25 ng/well, 0.025 ng/well and 0.0025 ng/well were analyzed for 98N12-5 (NPA-005) and DLin-KC2-DMA (NPA-003) to determine the MFI of mCherry. As shown in Table 18, the concentration of 0.025 ng/well and lesser concentrations are similar to the background MFI level of mCherry which is about 386.125.

Table 14. Formulations

Formulation #	NPA-003	NPA-005
Lipid	DLin-KC2-DMA	98N12-5
Lipid/RNA wt/wt	20	15
Mean size	114 nm PDI: 0.08	106 nm PDI: 0.12

Table 15. HEK293, NPA-005, 24-well, n=4

Formulation	FL4 MFI
Untreated control	0.246
NPA-005 100 ng	2.2175
NPA-005 10 ng	0.651

NPA-005 1.0 ng	0.28425
NPA-005 0.1 ng	0.27675
NPA-005 0.01 ng	0.2865

Table 16. HEK293, NPA-003, 24-well, n=4

Formulation	FL4 MFI
Untreated control	0.3225
NPA-003 250 ng	2.9575
NPA-003 100 ng	1.255
NPA-003 10 ng	0.40025
NPA-003 1 ng	0.33025
NPA-003 0.1 ng	0.34625
NPA-003 0.01 ng	0.3475

Table 17. HEK293, NPA-003, 24-well, n=4

Formulation	FL4 MFI
Untreated control	0.27425
NPA-003 250 ng	5.6075
NPA-003 100 ng	3.7825
NPA-003 30 ng	1.5525

Table 18. Concentration and MFI

	MFI mCherry	
Formulation	NPA-003	NPA-005
25 ng/well	11963.25	12256.75
0.25 ng/well	1349.75	2572.75
0.025 ng/well	459.50	534.75
0.0025 ng/well	310.75	471.75

Example 13. Manual Injection and Syringe Pump Formulations

[0001169] Two formulations of DLin-KC2-DMA and 98N12-5 were prepared by manual injection (MI) and syringe pump injection (SP) and analyzed along with a background sample to compare the MFI of mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) of the different formulations. Table 19 shows that the syringe pump formulations had a higher MFI as compared to the manual injection formulations of the same lipid and lipid/RNA ratio.

Table 19. Formulations and MFI

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)	Method of formulation	MFI
Untreated Control	N/A	N/A	N/A	N/A	674.67
NPA-002	DLin-KC2-DMA	15	140 nm PDI: 0.11	MI	10318.25
NPA-002-2	DLin-KC2-DMA	15	105 nm PDI: 0.04	SP	37054.75
NPA-003	DLin-KC2-DMA	20	114 nm PDI: 0.08	MI	22037.5
NPA-003-2	DLin-KC2-DMA	20	95 nm PDI: 0.02	SP	37868.75
NPA-005	98N12-5	15	127 nm PDI: 0.12	MI	11504.75
NPA-005-2	98N12-5	15	106 nm PDI: 0.07	SP	9343.75
NPA-006	98N12-5	20	126 nm PDI: 0.08	MI	11182.25
NPA-006-2	98N12-5	20	93 nm PDI: 0.08	SP	5167

Example 14. Lipid Nanoparticle Formulations

[0001170] Formulations of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200 and DLin-MC3-DMA were incubated at a concentration of 60 ng/well or 62.5 ng/well in a plate of HEK293 and 62.5 ng/well in a plate of HepG2 cells for 24 hours to determine the MFI of mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) for each formulation. The formulations tested are outlined in Table 20 below. As shown in Table 21 for the 60 ng/well and Tables 22, 23, 24 and 25 for the 62.5 ng/well,the formulation of NPA-003 and NPA-018 have the highest mCherry MFI and the formulations of NPA-008, NPA-010 and NPA-013 are most the similar to the background sample mCherry MFI value.

Table 20. Formulations

Formulation #	Lipid	Lipid/RNA wt/wt	Mean size (nm)
NPA-001	DLin-KC2-DMA	10	155 nm PDI: 0.08
NPA-002	DLin-KC2-DMA	15	140 nm PDI: 0.11
NPA-002-2	DLin-KC2-DMA	15	105 nm PDI: 0.04
NPA-003	DLin-KC2-DMA	20	114 nm PDI: 0.08

NPA-003-2	DLin-KC2-DMA	20	95 nm PDI: 0.02
NPA-005	98N12-5	15	127 nm PDI: 0.12
NPA-006	98N12-5	20	126 nm PDI: 0.08
NPA-007	DLin-DMA	15	148 nm PDI: 0.09
NPA-008	DLin-K-DMA	15	121 nm PDI: 0.08
NPA-009	C12-200	15	138 nm PDI: 0.15
NPA-010	DLin-MC3-DMA	15	126 nm PDI: 0.09
NPA-012	DLin-DMA	20	86 nm PDI: 0.08
NPA-013	DLin-K-DMA	20	104 nm PDI: 0.03
NPA-014	C12-200	20	101 nm PDI: 0.06
NPA-015	DLin-MC3-DMA	20	109 nm PDI: 0.07

Table 21. HEK293, 96-well, 60 ng Modified RNA/well

Formulation	MFI mCherry
Untreated	871.81
NPA-001	6407.25
NPA-002	14995
NPA-003	29499.5
NPA-005	3762
NPA-006	2676
NPA-007	9905.5
NPA-008	1648.75
NPA-009	2348.25
NPA-010	4426.75
NPA-012	11466
NPA-013	2098.25
NPA-014	3194.25
NPA-015	14524

Table 22. HEK293, 62.5 ng /well

Formulation	MFI mCherry
Untreated	871.81
NPA-001	6407.25
NPA-002	14995
NPA-003	29499.5
NPA-005	3762

NPA-006	2676
NPA-007	9905.5
NPA-008	1648.75
NPA-009	2348.25
NPA-010	4426.75
NPA-012	11466
NPA-013	2098.25
NPA-014	3194.25
NPA-015	14524

Table 23. HEK293, 62.5 ng /well

Formulation	MFI mCherry
Untreated	295
NPA-007	3504
NPA-012	8286
NPA-017	6128
NPA-003-2	17528
NPA-018	34142
NPA-010	1095
NPA-015	5859
NPA-019	3229

Table 24. HepG2, 62.5 ng /well

Formulation	MFI mCherry
Untreated	649.94
NPA-001	6006.25
NPA-002	8705
NPA-002-2	15860.25
NPA-003	15059.25
NPA-003-2	28881
NPA-005	1676
NPA-006	1473
NPA-007	15678
NPA-008	2976.25
NPA-009	961.75
NPA-010	3301.75
NPA-012	18333.25
NPA-013	5853
NPA-014	2257
NPA-015	16225.75

Table 25. HepG2, 62.5 ng /well

Formulation	MFI mCherry

Untreated control	656
NPA-007	16798
NPA-012	21993
NPA-017	20377
NPA-003-2	35651
NPA-018	40154
NPA-010	2496
NPA-015	19741
NPA-019	16373

Example 15. *In vivo* formulation studies

[0001171] Rodents (n=5) are administered intravenously, subcutaneously or intramuscularly a single dose of a formulation containing a modified mRNA and a lipid. The modified mRNA administered to the rodents is selected from G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), erythropoietin (EPO) (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Factor IX (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1). The erythropoietin cDNA with the T7 promoter, 5′untranslated region (UTR) and 3′ UTR used in *in vitro* transcription (IVT) is given in SEQ ID NO: 61653 and SEQ ID NO: 61654.

[0001172] Each formulation also contains a lipid which is selected from one of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200, DLin-MC3-DMA, reLNP, ATUPLEX®, DACC and DBTC. The rodents are injected with 100ug, 10 ug or 1 ug of the formulated modified mRNA and samples are collected at specified time intervals.

[0001173] Serum from the rodents administered formulations containing human G-CSF modified mRNA are measured by specific G-CSF ELISA and serum from mice administered human factor IX modified RNA is analyzed by specific factor IX ELISA or chromogenic assay. The liver and spleen from the mice administered with mCherry modified mRNA are analyzed by immunohistochemistry (IHC) or fluorescence-activated cell sorting (FACS). As a control, a group of mice are not injected with any formulation and their serum and tissue are collected analyzed by ELISA, FACS and/or IHC.

A. Time Course

[0001174] The rodents are administered formulations containing at least one modified mRNA to study the time course of protein expression for the administered formulation. The rodents are bled at specified time intervals prior to and after administration of the modified mRNA formulations to determine protein expression and complete blood count. Samples are also collected from the site of administration of rodents administered modified mRNA formulations subcutaneously and intramuscularly to determine the protein expression in the tissue.

B. Dose Response

[0001175] The rodents are administered formulations containing at least one modified mRNA to determine dose response of each formulation. The rodents are bled at specified time intervals prior to and after administration of the modified mRNA formulations to determine protein expression and complete blood count. The rodents are also sacrified to analyze the effect of the modified mRNA formulation on the internal tissue. Samples are also collected from the site of administration of rodents administered modified mRNA formulations subcutaneously and intramuscularly to determine the protein expression in the tissue.

C. Toxicity

[0001176] The rodents are administered formulations containing at least one modified mRNA to study toxicity of each formulation. The rodents are bled at specified time intervals prior to and after administration of the modified mRNA formulations to determine protein expression and complete blood count. The rodents are also sacrificedto analyze the effect of the modified mRNA formulation on the internal tissue. Samples are also collected from the site of administration of rodents administered modified mRNA formulations subcutaneously and intramuscularly to determine the protein expression in the tissue.

Example 16. PLGA Microsphere Formulations

[0001177] Optimization of parameters used in the formulation of PLGA microspheres may allow for tunable release rates and high encapsulation efficiencies while maintaining the integrity of the modified RNA encapsulated in the microspheres. Parameters such as, but not limited to, particle size, recovery rates and encapsulation efficiency may be optimized to achieve the optimal formulation.

A. Synthesis of PLGA microspheres

[0001178] Polylacticglycolic acid (PLGA) microspheres were synthesized using the water/oil/water double emulsification methods known in the art using PLGA (Lactel, Cat# B6010-2, inherent viscosity 0.55-0.75, 50:50 LA:GA), polyvinylalcohol (PVA) (Sigma, Cat# 348406-25G, MW 13-23k) dichloromethane and water. Briefly, 0.1 ml of water (W1) was added to 2 ml of PLGA dissolved in dichloromethane (DCM) (O1) at concentrations ranging from 50 – 200 mg/ml of PLGA. The W1/O1 emulsion was homogenized (IKA Ultra-Turrax Homogenizer, T18) for 30 seconds at speed 4 (~15,000 rpm). The W1/O1 emulsion was then added to 100 to 200 ml of 0.3 to 1% PVA (W2) and homogenized for 1 minute at varied speeds. Formulations were left to stir for 3 hours and then washed by centrifugation (20-25 min, 4,000 rpm, 4°C). The supernatant was discarded and the PLGA pellets were resuspended in 5-10 ml of water, which was repeated 2x. Average particle size (represents 20 -30 particles) for each formulation was determined by microscopy after washing. Table 26 shows that an increase in the PLGA concentration led to larger sized microspheres. A PLGA concentration of 200 mg/mL gave an average particle size of 14.8 μm, 100 mg/mL was 8.7 μm, and 50 mg/mL of PLGA gave an average particle size of 4.0 μm.

Table 26. Varied PLGA Concentration

Sample ID	O1 Volume (mL)	PLGA Concentration (mg/mL)	W2 Volume (mL)	PVA Concentration (%)	Speed	Average Size (μm)
1	2	200	100	0.3	5	14.8
2	2	100	100	0.3	5	8.7
3	2	50	100	0.3	5	4.0

[0001179] Table 27 shows that decreasing the homogenization speed from 5 (~20,000 rpm) to speed 4 (~15,000 rpm) led to an increase in particle size from 14.8 μm to 29.7 μm.

Table 27. Varied Homogenization Speed

Sample ID	O1 Volume (mL)	PLGA Concentration (mg/mL)	W2 Volume (mL)	PVA Concentration (%)	Speed	Average Size (μm)
1	2	200	100	0.3	5	14.8
4	2	200	100	0.3	4	29.7

[0001180] Table 28 shows that increasing the W2 volume (i.e. increasing the ratio of W2:O1 from 50:1 to 100:1), decreased average particle size slightly. Altering the PVA concentration from 0.3 to 1 wt% had little impact on PLGA microsphere size.

Table 28. Varied W2 Volume and Concentration

Sample ID	O1 Volume (mL)	PLGA Concentration (mg/mL)	W2 Volume (mL)	PVA Concentration (%)	Speed	Average Size (µm)
1	2	200	100	0.3	5	14.8
5	2	200	200	0.3	5	11.7
6	2	200	190	0.3	5	11.4
7	2	200	190	1.0	5	12.3

B. Encapsulation of modified mRNA

[0001181] Modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was dissolved in water at a concentration of 2 mg/ml (W3). Three batches of PLGA microsphere formulations were made as described above with the following parameters: 0.1 ml of W3 at 2 mg/ml, 1.6 ml of O1 at 200 mg/ml, 160 ml of W2 at 1%, and homogenized at a speed of 4 for the first emulsion (W3/O1) and homogenized at a speed of 5 for the second emulstion (W3/O1/W2). After washing by centrifugation, the formulations were frozen in liquid nitrogen and then lyophilized for 3 days. To test the encapsulation efficiency of the formulations, the lyophilized material was deformulated in DCM for 6 hours followed by an overnight extraction in water. The modified RNA concentration in the samples was then determined by OD260. Encapsulation efficiency was calculated by taking the actual amount of modified RNA and dividing by the starting amount of modified RNA. In the three batches tested, there was an encapsulation efficiency of 59.2, 49.8 and 61.3.

C. Integrity of modified mRNA encapsulated in PLGA microspheres

[0001182] Modified Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was dissolved in water at varied concentrations (W4) to vary the weight percent loading in the formulation (mg modified RNA/mg PLGA * 100) and to determine encapsulation efficiency. The parameters in

Table 29 were used to make four different batches of PLGA microsphere formulations with a homogenization speed of 4 for the first emulstion (W4/O1) and a homogenization speed of 5 for the second emulsion (W4/O1/W2).

Table 29. Factor IX PLGA Microsphere Formulation Parameters

ID	W4 Volume (uL)	Factor IX Concentration (mg/ml)	Factor IX Amount (ug)	O1 Volume (ml)	PLGA Concentration (mg/ml)	W2 Volume (ml)	PVA Concentration (%)	Weight % (wt%) Loading
A	100	2.0	200.0	2.0	200	200	1.0	0.05
B	100	4.0	400.0	2.0	200	200	1.0	0.10
C	400	2.0	800.0	2.0	200	200	1.0	0.20
D	400	4.0	1600.0	2.0	200	200	1.0	0.40

[0001183] After lyophilization, PLGA microspheres were weighed out in 2 ml eppendorf tubes to correspond to ~ 10 ug of modified RNA. Lyophilization was found to not destroy the overall structure of the PLGA microspheres. To increase weight percent loading (wt%) for the PLGA microspheres, increasing amounts of modified RNA were added to the samples. PLGA microspheres were deformulated by adding 1.0 ml of DCM to each tube and then shaking the samples for 6 hours. For modified RNA extraction, 0.5 ml of water was added to each sample and the samples were shaken overnight before the concentration of modified RNA in the samples was determined by OD260. To determine the recovery of the extraction process, unformulated Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) (deformulation control) was spiked into DCM and was subjected to the deformulation process. Table 30 shows the loading and encapsulation efficiency for the samples. All encapsulation efficiency samples were normalized to the deformulation control.

Table 30. Weight Percent Loading and Encapsulation Efficiency

ID	Theoretical modified RNA loading (wt%)	Actual modified RNA loading (wt%)	Encapsulation Efficiency (%)
A	0.05	0.06	97.1
B	0.10	0.10	85.7
C	0.20	0.18	77.6

D	0.40	0.31	68.1
Control	-	-	100.0

D. Release study of modified mRNA encapsulated in PLGA microspheres

[0001184] PLGA microspheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were deformulated as described above and the integrity of the extracted modified RNA was determined by automated electrophoresis (Bio-Rad Experion). The extracted modified mRNA was compared against unformulated modified mRNA and the deformulation control in order to test the integrity of the encapsulated modified mRNA. As shown in Figure 4, the majority of modRNA was intact for batch ID A, B, C and D, for the deformulated control (Deform control) and the unformulated control (Unform control).

E. Protein Expression of modified mRNA encapsulated in PLGA microspheres

[0001185] PLGA microspheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were deformulated as described above and the protein expression of the extracted modified RNA was determined by an *in vitro* transfection assay. HEK293 cells were reverse transfected with 250 ng of Factor IX modified RNA complexed with RNAiMAX (Invitrogen) in triplicate.

[0001186] Factor IX modified RNA was diluted in nuclease-free water to a concentration of 25 ng/µl and RNAiMAX was diluted 13.3x in serum-free EMEM. Equal volumes of diluted modified RNA and diluted RNAiMAX were mixed together and were allowed to stand for 20 to 30 minutes at room temperature. Subsequently, 20 µl of the transfection mix containing 250 ng of Factor IX modified RNA was added to 80 µl of a cell suspension containing 30,000 cells. Cells were then incubated for 16h in a humidified 37°C/5% CO2 cell culture incubator before harvesting the cell culture supernatant. Factor IX protein expression in the cell supernatant was analyzed by an ELISA kit specific for Factor IX (Molecular Innovations, Cat # HFIXKT-TOT) and the protein expression is shown in Table 31 and Figure 5. In all PLGA microsphere batches tested,

Factor IX modified RNA remained active and expressed Factor IX protein after formulation in PLGA microspheres and subsequent deformulation.

Table 31. Protein Expression

Sample	Factor IX Protein Expression (ng/ml)
Batch A	0.83
Batch B	1.83
Batch C	1.54
Batch D	2.52
Deformulated Control	4.34
Unformulated Control	3.35

F. Release study of modified mRNA encapsulated in PLGA microspheres

[0001187] PLGA micropsheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were resuspended in water to a PLGA microsphere concentration of 24 mg/ml. After resuspension, 150 ul of the PLGA microsphere suspension was aliquoted into eppendorf tubes. Samples were kept incubating and shaking at 37°C during the course of the study. Triplicate samples were pulled at 0.2, 1, 2, 8, 14, and 21 days. To determine the amount of modified RNA released from the PLGA microspheres, samples were centrifuged, the supernatant was removed, and the modified RNA concentration in the supernatant was determined by OD 260. The percent release, shown in Table 32, was calculated based on the total amount of modified RNA in each sample. After 31 days, 96% of the Factor IX modified RNA was released from the PLGA microsphere formulations.

Table 32. Percent Release

Time (days)	% Release
0	0.0
0.2	27.0
1	37.7
2	45.3
4	50.9
8	57.0
14	61.8
21	75.5

31	96.4

G. Particle size reproducibility of PLGA microspheres

[0001188] Three batches of Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) PLGA microspheres were made using the same conditions described for Batch D, shown in Table 29, (0.4 ml of W4 at 4 mg/ml, 2.0 ml of O1 at 200 mg/ml, 200 ml of W2 at 1%, and homogenized at a speed of 5 for the W4/O1/W2 emulsion). To improve the homogeneity of the PLGA microsphere suspension, filtration was incorporated prior to centrifugation. After stirring for 3 hours and before centrifuging, all formulated material was passed through a 100 μm nylon mesh strainer (Fisherbrand Cell Strainer, Cat # 22-363-549) to remove larger aggregates. After washing and resuspension with water, 100-200 μl of a PLGA microspheres sample was used to measure particle size of the formulations by laser diffraction (Malvern Mastersizer2000). The particle size of the samples is shown in Table 33.

Table 33. Particle Size Summary

ID	D10 (μm)	D50 (μm)	D90 (μm)	Volume Weighted Mean (um)	Filtration
Control	19.2	62.5	722.4	223.1	No
A	9.8	31.6	65.5	35.2	Yes
B	10.5	32.3	66.9	36.1	Yes
C	10.8	35.7	79.8	41.4	Yes

[0001189] Results of the 3 PLGA microsphere batches using filtration were compared to a PLGA microsphere batch made under the same conditions without filtration. The inclusion of a filtration step before washing reduced the mean particle size and demonstrated a consistent particle size distribution between 3 PLGA microsphere batches.

H. Serum Stability of Factor IX PLGA Microspheres

[0001190] Factor IX mRNA RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully

modified with 5-methylcytosine and pseudouridine) in buffer (TE) or 90% serum (Se), or Factor IX mRNA in PLGA in buffer, 90% serum or 1% serum was incubated in buffer, 90% serum or 1% serum at an mRNA concentration of 50 ng/ul in a total volume of 70 ul. The samples were removed at 0, 30, 60 or 120 minutes. RNases were inactivated with proteinase K digestion for 20 minutes at 55°C by adding 25 ul of 4x proteinase K buffer (0.4 ml 1M TRIS-HCl pH 7.5, 0.1 ml 0.5M EDTA, 0.12 ml 5M NaCl, and 0.4ml 10% SDS) and 8 ul of proteinase K at 20 mg/ml. The Factor IX mRNA was precipitated (add 250 ul 95% ethanol for 1 hour, centrifuge for 10 min at 13 k rpm and remove supernatant, add 200 ul 70% ethanol to the pellet, centrifuge again for 5 min at 13 k rpm and remove supernatant and resuspend the pellet in 70 ul water) or extracted from PLGA microspheres (centrifuge 5 min at 13k rpm and remove supernatant, wash pellet with 1 ml water, centrifuge 5 min at 13k rpm and remove supernatant, add 280 ul dichloromethane to the pellet and shake for 15 minutes, add 70 ul water and then shake for 2 hours and remove the aqueous phase) before being analyzed by bioanalyzer. PLGA microspheres protect Factor IX modified mRNA from degradation in 90% and 1% serum over 2 hours. Factor IX modified mRNA completely degrades in 90% serum at the initial time point.

Example 17. Lipid nanoparticle *in vivo* studies

[0001191] G-CSF (cDNA with the T7 promoter, 5' Untranslated region (UTR) and 3'UTR used in in vitro transcription is given in SEQ ID NO: 61647. mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) and Factor IX (cDNA with the T7 promoter, 5' UTR and 3'UTR used in in vitro transcription is given in SEQ ID NO: 61655. mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) modified mRNA were formulated as lipid nanoparticles (LNPs) using the syringe pump method. The LNPs were formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: PEG-c-DOMG). Formulations, listed in Table 34, were characterized by particle size, zeta potential, and encapsulation.

Table 34. Formulations

Formulation #	NPA-029-1	NPA-030-1
Modified mRNA	Factor IX	G-CSF
Mean size	91 nm PDI: 0.04	106 nm PDI: 0.06
Zeta at pH 7.4	1.8 mV	0.9 mV
Encaps. (RiboGr)	92%	100%

[0001192] LNP formulations were administered to mice (n=5) intravenously at a modified mRNA dose of 100, 10, or 1 ug. Mice were sacrificed at 8 hrs after dosing. Serum was collected by cardiac puncture from mice that were administered with G-CSF or Factor IX modified mRNA formulations. Protein expression was determined by ELISA.

[0001193] There was no significant body weight loss (<5%) in the G-CSF or Factor IX dose groups. Protein expression for G-CSF or Factor IX dose groups was determined by ELISA from a standard curve. Serum samples were diluted (about 20-2500x for G-CSF and about 10-250x for Factor IX) to ensure samples were within the linear range of the standard curve. As shown in Table 35, G-CSF protein expression determined by ELISA was approximately 17, 1200, and 4700 ng /ml for the 1, 10, and 100 ug dose groups, respectively. As shown in Table 36, Factor IX protein expression determined by ELISA was approximately 36, 380, and 3000-11000 ng/ml for the 1, 10, and 100 ug dose groups, respectively.

Table 35. G-CSF Protein Expression

Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume
1	17.73	20x	5 ul
10	1204.82	2500x	0.04 ul
100	4722.20	2500x	0.04 ul

Table 36. Factor IX Protein Expression

Dose (ug)	Conc (ng/ml)	Dilution Factor	Sample Volume

1	36.05	10x	5 ul
10	383.04	10x	5 ul
100*	3247.75	50x	1 ul
100*	11177.20	250x	0.2 ul

[0001194] As shown in Table 37, the LNP formulations described above have about a 10,000-100,000-fold increase in protein production compared to an administration of an intravenous (IV)-lipoplex formulation for the same dosage of modified mRNA and intramuscular (IM) or subcutaneous (SC) administration of the same dose of modified mRNA in saline. As used in Table 37, the symbol "~" means about.

Table 37. Protein Production

G-CSF	**Dose (ug)**	**Serum Concentration (pg/ml) 8-12 hours after administration**
IM	100	~20-80
SC	100	~10-40
IV (Lipoplex)	100	~30
IV (LNP)	100	~5,000,000
IV (LNP)	10	~1,000,000
IV (LNP)	1	~20,000
Factor IX	**Dose (ug)**	**Serum Concentration (ng/ml) 8-12 hours after administration**
IM	2 x 100	~1.6 ng/ml
IV (LNP)	100	~3,000-10,000 ng/ml
IV (LNP)	10	~400 ng/ml
IV (LNP)	1	~40 ng/ml

Materials and Methods for Examples 18-23

[0001195] G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nulceotides not shown in sequence; 5'cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) and EPO (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nulceotides not shown in sequence; 5'cap, Cap 1; fully modified with 5-methylcytosine and pseudouridine) modified mRNA were formulated as lipid nanoparticles (LNPs) using the syringe pump method. The LNPs were formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: PEG-c-DOMG).

Formulations, listed in Table 38, were characterized by particle size, zeta potential, and encapsulation.

Table 38. Formulations

Formulation #	NPA-030-2	NPA-060-1
Modified mRNA	G-CSF	EPO
Mean size	84 nm PDI: 0.04	85 nm PDI: 0.03
Zeta at pH 7.4	0.8 mV	1.5 mV
Encapsulation (RiboGreen)	95%	98%

Example 18. Lipid nanoparticle *in vivo* studies with modified mRNA

[0001196] LNP formulations, shown in Table 38 (above), were administered to rats (n=5) intravenously (IV), intramuscularly (IM) or subcutaneously (SC) at a single modified mRNA dose of 0.05 mg/kg. A control group of rats (n=4) was untreated. The rats were bled at 2 hours, 8 hours, 24 hours, 48 hours and 96 hours and after they were administered with G-CSF or EPO modified mRNA formulations to determine protein expression using ELISA. The rats administered EPO modified mRNA intravenously were also bled at 7 days.

[0001197] As shown in Table 39, EPO protein expression in the rats intravenously administered modified EPO mRNA was detectable out to 5 days. G-CSF in the rats intravenously administered modified G-CSF mRNA was detectable to 7 days. Subcutaneous and intramuscular administration of EPO modified mRNA was detectable to at least 24 hours and G-CSF modified mRNA was detectable to at least 8 hours. In Table 39, "OSC" refers to values that were outside the standard curve and "NT" means not tested.

Table 39. G-CSF and EPO Protein Expression

Route	Time	EPO Serum Concentration (pg/ml)	G-CSF Serum Concentration (pg/ml)
IV	2 hours	36,981.0	31,331.9
IV	8 hours	62,053.3	70,532.4
IV	24 hours	42,077.0	5,738.6
IV	48 hours	5,561.5	233.8

IV	5 days	0.0	60.4
IV	7 days	0.0	NT
IM	2 hours	1395.4	1620.4
IM	8 hours	8974.6	7910.4
IM	24 hours	4678.3	893.3
IM	48 hours	NT	OSC
IM	5 days	NT	OSC
SC	2 hours	386.2	80.3
SC	8 hours	985.6	164.2
SC	24 hours	544.2	OSC
SC	48 hours	NT	OSC
SC	5 days	NT	OSC
Untreated	All bleeds	0	0

Example 19. Time course *in vivo* study

[0001198] LNP formulations, shown in Table 38 (above), were administered to mice (n=5) intravenously (IV) at a single modified mRNA dose of 0.5, 0.05 or 0.005 mg/kg. The mice were bled at 8 hours, 24 hours, 72 hours and 6 days after they were administered with G-CSF or EPO modified mRNA formulations to determine protein expression using ELISA.

[0001199] As shown in Table 40, EPO and G-CSF protein expression in the mice administered with the modified mRNA intravenously was detectable out to 72 hours for the mice dosed with 0.005 mg/kg and 0.05 mg/kg of modified mRNA and out to 6 days for the mice administered the EPO modified mRNA. In Table 40, ">" means greater than and "ND" means not detected.

Table 40. Protein Expression

Dose (mg/kg)	Time	EPO Serum Concentration (pg/ml)	G-CSF Serum Concentration (pg/ml)
0.005	8 hours	12,508.3	11,550.6
0.005	24 hours	6,803.0	5,068.9
0.005	72 hours	ND	ND
0.005	6 days	ND	ND
0.05	8 hours	92,139.9	462,312.5
0.05	24 hours	54,389.4	80,903.8
0.05	72 hours	ND	ND

0.05	6 days	ND	ND
0.5	8 hours	498,515.3	>1,250,000
0.5	24 hours	160,566.3	495,812.5
0.5	72 hours	3,492.5	1,325.6
0.5	6 days	21.2	ND

Example 20. LNP formulations *in vivo* study in rodents

A. LNP Formulations in Mice

[0001200] LNP formulations, shown in Table 38 (above), were administered to mice (n=4) intravenously (IV) at a single modified mRNA dose 0.05 mg/kg or 0.005 mg/kg. There was also 3 control groups of mice (n=4) that were untreated. The mice were bled at 2 hours, 8 hours, 24 hours, 48 hours and 72 hours after they were administered with G-CSF or EPO modified mRNA formulations to determine the protein expression. Protein expression of G-CSF and EPO were determined using ELISA.

[0001201] As shown in Table 41, EPO and G-CSF protein expression in the mice was detectable at least out to 48 hours for the mice that received a dose of 0.005 mg/kg modified RNA and 72 hours for the mice that received a dose of 0.05 mg/kg modified RNA. In Table 41, "OSC" refers to values that were outside the standard curve and "NT" means not tested.

Table 41. Protein Expression in Mice

Dose (mg/kg)	Time	EPO Serum Concentration (pg/ml)	G-CSF Serum Concentration (pg/ml)
0.005	2 hours	OSC	3,447.8
0.005	8 hours	1,632.8	11,454.0
0.005	24 hours	1,141.0	4,960.2
0.005	48 hours	137.4	686.4
0.005	72 hours	0	NT
0.05	2 hours	10,027.3	20,951.4
0.05	8 hours	56,547.2	70,012.8
0.05	24 hours	25,027.3	19,356.2

0.05	48 hours	1,432.3	1,963.0
0.05	72 hours	82.2	47.3

B. LNP Formulations in Rodents

[0001202] LNP formulations, shown in Table 38 (above), are administered to rats (n=4) intravenously (IV) at a single modified mRNA dose 0.05 mg/kg. There is also a control group of rats (n=4) that are untreated. The rats are bled at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours, 7 days and 14 days after they were administered with G-CSF or EPO modified mRNA formulations to determine the protein expression. Protein expression of G-CSF and EPO are determined using ELISA.

Example 21. Early Time Course Study of LNPs

[0001203] LNP formulations, shown in Table 38 (above), are administered to mammals intravenously (IV), intramuscularly (IM) or subcutaneously (SC) at a single modified mRNA dose of 0.5 mg/kg, 0.05 mg/kg or 0.005 mg/kg. A control group of mammals are not treated. The mammals are bled at 5 minutes, 10 minutes, 20 minutes, 30 minutes, 45 minutes, 1 hour, 1.5 hours and/or 2 hours after they are administered with the modified mRNA LNP formulations to determine protein expression using ELISA. The mammals are also bled to determine the complete blood count such as the granulocyte levels and red blood cell count.

Example 22. Non-human primate *in vivo* study

[0001204] LNP formulations, shown in Table 38 (above), were administered to non-human primates (NHP) (cynomolgus monkey) (n=2) as a bolus intravenous injection (IV) over approximately 30 seconds using a hypodermic needle, which may be attached to a syringe/abbocath or butterfly if needed. The NHP were administered a single modified mRNA IV dose of 0.05mg/kg of EPO or G-CSF or 0.005 mg/kg of EPO in a dose volume of 0.5 mL/kg. The NHPs were bled 5-6 days before dosing with the modified mRNA LNP formulations to determine protein expression in the serum and a baseline complete blood count. After administration with the modified mRNA formulation the NHP were bled at 8, 24, 48 and 72 hours to determined protein expression. At 24 and 72 hours after administration the complete blood count of the NHP was also determined. Protein expression of G-CSF and EPO was determined by ELISA.Urine from the NHPs was

collected over the course of the entire experiment and analyzed to evaluate clinical safety. Samples were collected from the NHPs after they were administered with G-CSF or EPO modified mRNA formulations to determine protein expression using ELISA. Clinical chemistry, hematology, urinalysis and cytokines of the non-human primates were also analyzed.

[0001205] As shown in Table 42, EPO protein expression in the NHPs administered 0.05 mg/kg is detectable out to 72 hours and the 0.005 mg/kg dosing of the EPO formulation is detectable out to 48 hours. In Table 42, the "<" means less than a given value. G-CSF protein expression was seen out to 24 hours after administration with the modified mRNA formulation. Preliminarily, there was an increase in granulocytes and reticulocytes levels seen in the NHP after administration with the modified mRNA formulations.

Table 42. Protein Expression in Non-Human Primates

Modified mRNA	Dose (mg/kg)	Time	Female NHP Serum Concentration (pg/ml)	Male NHP Serum Concentration (pg/ml)	Average Serum Conentration (pg/ml)
G-CSF	0.05	Pre-bleed	0	0	0
		8 hours	3289	1722	2,506
		24 hours	722	307	515
		48 hours	0	0	0
		72 hours	0	0	0
EPO	0.05	Pre-bleed	0	0	0
		8 hours	19,858	7,072	13,465
		24 hours	18,178	4,913	11,546
		48 hours	5,291	498	2,895
		72 hours	744	60	402
EPO	0.005	Pre-bleed	0	0	0
		8 hours	523	250	387
		24 hours	302	113	208

		48 hours	<7.8	<7.8	<7.8
		72 hours	0	0	0

Example 23. Non-human primate *in vivo* study for G-CSF and EPO

[0001206] LNP formulations, shown in Table 38 (above), were administered to non-human primates (NHP) (cynomolgus monkey) (n=2) as intravenous injection (IV). The NHP were administered a single modified mRNA IV dose of 0.5 mg/kg, 0.05mg/kg or 0.005 mg/kg of G-CSF or EPO in a dose volume of 0.5 mL/kg. The NHPs were bled before dosing with the modified mRNA LNP formulations to determine protein expression in the serum and a baseline complete blood count. After administration with the G-CSF modified mRNA formulation the NHP were bled at 8, 24, 48 and 72 hours to determined protein expression. After administration with the EPO modified mRNA formulation the NHP were bled at 8, 24, 48, 72 hours and 7 days to determined protein expression.

[0001207] Samples collected from the NHPs after they were administered with G-CSF or EPO modified mRNA formulations were analyzed by ELISA to determine protein expression. Neutrophil and reticulocyte count was also determined pre-dose, 24 hours, 3 days, 7 days, 14 days and 18 days after administration of the modified G-CSF or EPO formulation.

[0001208] As shown in Table 43, G-CSF protein expression was not detected beyond 72 hours. In Table 43, "<39" refers to a value below the lower limit of detection of 39 pg/ml.

Table 43. G-CSF Protein Expression

Modified mRNA	Dose (mg/kg)	Time	Female NHP Serum G-CSF Concentration (pg/ml)	Male NHP Serum G-CSF Concentration (pg/ml)
G-CSF	0.5	Pre-bleed	<39	<39
		8 hours	43,525	43,594
		24 hours	11,374	3,628
		48 hours	1,100	833
		72 hours	<39	306

G-CSF	0.05	Pre-bleed	<39	<39
		8 hours	3,289	1,722
		24 hours	722	307
		48 hours	<39	<39
		72 hours	<39	<39
G-CSF	0.005	Pre-bleed	<39	<39
		8 hours	559	700
		24 hours	155	<39
		48 hours	<39	<39
		72 hours	<39	<39

[0001209] As shown in Table 44, EPO protein expression was not detected beyond 7 days. In Table 44, "<7.8" refers to a value below the lower limit of detection of 7.8 pg/ml.

Table 44. EPO Protein Expression

Modified mRNA	Dose (mg/kg)	Time	Female NHP Serum EPO Concentration (pg/ml)	Male NHP Serum EPO Concentration (pg/ml)
EPO	0.5	Pre-bleed	<7.8	<7.8
		8 hours	158,771	119,086
		24 hours	133,978	85,825
		48 hours	45,250	64,793
		72 hours	15,097	20,407
		7 days	<7.8	<7.8
EPO	0.05	Pre-bleed	<7.8	<7.8
		8 hours	19,858	7,072
		24 hours	18,187	4,913
		48 hours	5,291	498
		72 hours	744	60
		7 days	<7.8	<7.8
EPO	0.005	Pre-bleed	<7.8	<7.8
		8 hours	523	250
		24 hours	302	113

		48 hours	11	29
		72 hours	<7.8	<7.8
		7 days	<7.8	<7.8

[0001210] As shown in Table 45, there was an increase in neutrophils in all G-CSF groups relative to pre-dose levels.

Table 45. Pharmacologic Effect of G-CSF mRNA in NHP

Dose (mg/kg)	Time	Male NHP (G-CSF) Neutrophils (10^9/L)	Female NHP (G-CSF) Neutrophils (10^9/L)	Male NHP (EPO) Neutrophils (10^9/L)	Female NHP (EPO) Neutrophils (10^9/L)
0.5	Pre-dose	1.53	1.27	9.72	1.82
	24 hours	14.92	13.96	7.5	11.85
	3 days	9.76	13.7	11.07	5.22
	7 days	2.74	3.81	11.8	2.85
	14/18 days	2.58	1.98	7.16	2.36
0.05	Pre-dose	13.74	3.05	0.97	2.15
	24 hours	19.92	29.91	2.51	2.63
	3 days	7.49	10.77	1.73	4.08
	7 days	4.13	3.8	1.23	2.77
	14/18 days	3.59	1.82	1.53	1.27
0.005	Pre-dose	1.52	2.54	5.46	5.96
	24 hours	16.44	8.6	5.37	2.59
	3 days	3.74	1.78	6.08	2.83
	7 days	7.28	2.27	3.51	2.23
	14/18 days	4.31	2.28	1.52	2.54

[0001211] As shown in Table 46, there was an increase in reticulocytes in all EPO groups 3 days to 14/18 days after dosing relative to reticulocyte levels 24 hours after dosing.

Table 46. Pharmacologic Effect of EPO mRNA on Neutrophil Count

Dose (mg/kg)	Time	Male NHP (G-CSF) Neutrophils (10^{12}/L)	Female NHP (G-CSF) Neutrophils (10^{12}/L)	Male NHP (EPO) Neutrophils (10^{12}/L)	Female NHP (EPO) Neutrophils (10^{12}/L)
0.5	Pre-dose	0.067	0.055	0.107	0.06
	24 hours	0.032	0.046	0.049	0.045
	3 days	0.041	0.017	0.09	0.064
	7 days	0.009	0.021	0.35	0.367
	14/18 days	0.029	0.071	0.066	0.071
0.05	Pre-dose	0.055	0.049	0.054	0.032
	24 hours	0.048	0.046	0.071	0.04
	3 days	0.101	0.061	0.102	0.105
	7 days	0.157	0.094	0.15	0.241
	14/18 days	0.107	0.06	0.067	0.055
0.005	Pre-dose	0.037	0.06	0.036	0.052
	24 hours	0.037	0.07	0.034	0.061
	3 days	0.037	0.054	0.079	0.118
	7 days	0.046	0.066	0.049	0.087
	14/18 days	0.069	0.057	0.037	0.06

[0001212] As shown in Tables 47-49, the administration of EPO modified RNA had an effect on other erythropoetic parameters including hemoglobin (HGB), hematocrit (HCT) and red blood cell (RBC) count.

Table 47. Pharmacologic Effect of EPO mRNA on Hemoglobin

Dose (mg/kg)	Time	Male NHP (G-CSF) HGB (g/L)	Female NHP (G-CSF) HGB (g/L)	Male NHP (EPO) HGB (g/L)	Female NHP (EPO) HGB (g/L)
0.5	Pre-dose	133	129	134	123
	24 hours	113	112	127	108
	3 days	118	114	126	120
	7 days	115	116	140	134
	14/18 days	98	113	146	133
0.05	Pre-dose	137	129	133	133
	24 hours	122	117	123	116
	3 days	126	115	116	120

	7 days	126	116	126	121
	14/18 days	134	123	133	129
0.005	Pre-dose	128	129	132	136
	24 hours	117	127	122	128
	3 days	116	127	125	130
	7 days	116	129	119	127
	14/18 days	118	129	128	129

Table 48. Pharmacologic Effect of EPO mRNA on Hematocrit

Dose (mg/kg)	Time	Male NHP (G-CSF) HCT (L/L)	Female NHP (G-CSF) HCT (L/L)	Male NHP (EPO) HCT (L/L)	Female NHP (EPO) HCT (L/L)
0.5	Pre-dose	0.46	0.43	0.44	0.4
	24 hours	0.37	0.38	0.4	0.36
	3 days	0.39	0.38	0.41	0.39
	7 days	0.39	0.38	0.45	0.45
	14/18 days	0.34	0.37	0.48	0.46
0.05	Pre-dose	0.44	0.44	0.45	0.43
	24 hours	0.39	0.4	0.43	0.39
	3 days	0.41	0.39	0.38	0.4
	7 days	0.42	0.4	0.45	0.41
	14/18 days	0.44	0.4	0.46	0.43
0.005	Pre-dose	0.42	0.42	0.48	0.45
	24 hours	0.4	0.42	0.42	0.43
	3 days	0.4	0.41	0.44	0.42
	7 days	0.39	0.42	0.41	0.42
	14/18 days	0.41	0.42	0.42	0.42

Table 49. Pharmacologic Effect of EPO mRNA on Red Blood Cells

Dose (mg/kg)	Time	Male NHP (G-CSF) RBC (10^{12}/L)	Female NHP (G-CSF) RBC (10^{12}/L)	Male NHP (EPO) RBC (10^{12}/L)	Female NHP (EPO) RBC (10^{12}/L)
0.5	Pre-dose	5.57	5.57	5.43	5.26
	24 hours	4.66	4.96	5.12	4.69
	3 days	4.91	4.97	5.13	5.15

	7 days	4.8	5.04	5.55	5.68
	14/18 days	4.21	4.92	5.83	5.72
0.05	Pre-dose	5.68	5.64	5.57	5.84
	24 hours	4.96	5.08	5.25	5.18
	3 days	5.13	5.04	4.81	5.16
	7 days	5.17	5.05	5.37	5.31
	14/18 days	5.43	5.26	5.57	5.57
0.005	Pre-dose	5.67	5.36	6.15	5.72
	24 hours	5.34	5.35	5.63	5.35
	3 days	5.32	5.24	5.77	5.42
	7 days	5.25	5.34	5.49	5.35
	14/18 days	5.37	5.34	5.67	5.36

[0001213] As shown in Tables 50 and 51, the administration of modified RNA had an effect on serum chemistry parameters including alanine transaminase (ALT) and aspartate transaminase (AST).

Table 50. Pharmacologic Effect of EPO mRNA on Alanine Transaminase

Dose (mg/kg)	Time	Male NHP (G-CSF) ALT (U/L)	Female NHP (G-CSF) ALT (U/L)	Male NHP (EPO) ALT (U/L)	Female NHP (EPO) ALT (U/L)
0.5	Pre-dose	29	216	50	31
	2 days	63	209	98	77
	4 days	70	98	94	87
	7 days	41	149	60	59
	14days	43	145	88	44
0.05	Pre-dose	58	53	56	160
	2 days	82	39	95	254
	4 days	88	56	70	200
	7 days	73	73	64	187
	14days	50	31	29	216
0.005	Pre-dose	43	51	45	45
	2 days	39	32	62	48
	4 days	48	58	48	50
	7 days	29	55	21	48

	14days	44	46	43	51

Table 51. Pharmacologic Effect of EPO mRNA on Aspartate Transaminase

Dose (mg/kg)	Time	Male NHP (G-CSF) AST (U/L)	Female NHP (G-CSF) AST (U/L)	Male NHP (EPO) AST (U/L)	Female NHP (EPO) AST (U/L)
0.5	Pre-dose	32	47	59	20
	2 days	196	294	125	141
	4 days	67	63	71	60
	7 days	53	68	56	47
	14days	47	67	82	44
0.05	Pre-dose	99	33	74	58
	2 days	95	34	61	80
	4 days	69	42	48	94
	7 days	62	52	53	78
	14days	59	20	32	47
0.005	Pre-dose	35	54	39	40
	2 days	70	34	29	25
	4 days	39	36	43	55
	7 days	28	31	55	31
	14days	39	20	35	54

[0001214] As shown in Table 52, the administration of lipid nanoparticle-formulated modified RNA at high doses (0.5 mg/kg) caused an increase in cytokines, interferon-alpha (IFN-alpha) after administration of modified mRNA.

Table 52. Pharmacologic Effect of EPO mRNA on Alanine Transaminase

Dose (mg/kg)	Time	Male NHP (G-CSF) IFN-alpha (pg/mL)	Female NHP (G-CSF) IFN-alpha (pg/mL)	Male NHP (EPO) IFN-alpha (pg/mL)	Female NHP (EPO) IFN-alpha (pg/mL)
0.5	Pre-dose	0	0	0	0
	Day 1 + 8 hr	503.8	529.2	16.79	217.5
	4 days	0	0	0	0
0.05	Pre-dose	0	0	0	0
	Day 1 + 8 hr	0	0	0	0

	4 days	0	0	0	0
0.005	Pre-dose	0	0	0	0
	Day 1 + 8 hr	0	0	0	0
	4 days	0	0	0	0

Example 24. Study of Intramuscular and/or Subcutaneous Administration in Non-Human Primates

[0001215] Formulations containing modified EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) or G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) in saline were administered to non-human primates (Cynomolgus monkey) (NHP) intramuscularly (IM) or subcutaneously (SC). The single modified mRNA dose of 0.05mg/kg or 0.005 mg/kg was in a dose volume of 0.5 mL/kg. The non-human primates are bled 5-6 days prior to dosing to determine serum protein concentration and a baseline complete blood count. After administration with the modified mRNA formulation the NHP are bled at 8 hours, 24 hours, 48 hours, 72 hours, 7 days and 14 days to determined protein expression. Protein expression of G-CSF and EPO is determined by ELISA.At 24 hours, 72 hours, 7 days and 14 days after administration the complete blood count of the NHP is also determined. Urine from the NHPs is collected over the course of the entire experiment and analyzed to evaluate clinical safety. Tissue near the injection site is also collected and analyzed to determine protein expression.

Example 25. Modified mRNA Trafficking

[0001216] In order to determine localization and/or trafficking of the modified mRNA, studies may be performed as follows.

[0001217] LNP formulations of siRNA and modified mRNA are formulated according to methods known in the art and/or described herein. The LNP formulations may include at least one modified mRNA which may encode a protein such as G-CSF, EPO, Factor VII, and/or any protein described herein. The formulations may be administered locally into muscle of mammals using intramuscular or subcutaneous injection. The dose of

modified mRNA and the size of the LNP may be varied to determine the effect on trafficking in the body of the mammal and/or to assess the impact on a biologic reaction such as, but not limited to, inflammation. The mammal may be bled at different time points to determine the expression of protein encoded by the modified mRNA administered present in the serum and/or to determine the complete blood count in the mammal.

[0001218] For example, modified mRNA encoding Factor VII, expressed in the liver and secreted into the serum, may be administered intramuscularly and/or subcutaneously. Coincident or prior to modified mRNA administration, siRNA is administered to knock out endogenous Factor VII. Factor VII arising from the intramuscular and/or subcutaneous injection of modified mRNA is administered is measured in the blood. Also, the levels of Factor VII is measured in the tissues near the injection site. If Factor VII is expressed in blood then there is trafficking of the modified mRNA. If Factor VII is expressed in tissue and not in the blood than there is only local expression of Factor VII.

Example 26. Formulations of Multiple Modified mRNA

[0001219] LNP formulations of modified mRNA are formulated according to methods known in the art and/or described herein or known in the art. The LNP formulations may include at least one modified mRNA which may encode a protein such as G-CSF, EPO, thrombopoietin and/or any protein described herein. The at least one modified mRNA may include 1, 2, 3, 4 or 5 modified mRNA molecules. The formulations containing at least one modified mRNA may be administered intravenously, intramuscularly or subcutaneously in a single or multiple dosing regimens. Biological samples such as, but not limited to, blood and/or serum may be collected and analyzed at different time points before and/or after administration of the at least one modified mRNA formulation. An expression of a protein in a biological sample of 50-200 pg/ml after the mammal has been administered a formulation containing at least one modified mRNA encoding said protein would be considered biologically effective.

Example 27. Polyethylene Glycol Ratio Studies

A. Formulation and Characterization of PEG LNPs

[0001220] Lipid nanoparticles (LNPs) were formulated using the syringe pump method. The LNPs were formulated at a 20:1 weight ratio of total lipid to modified G-CSF mRNA

(mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine). The molar ratio ranges of the formulations are shown in Table 53.

Table 53. Molar Ratios

	DLin-KC2-DMA	DSPC	Cholesterol	PEG-c-DOMG
Mole Percent (mol%)	50.0	10.0	37-38.5	1.5-3

[0001221] Two types of PEG lipid, 1,2-Dimyristoyl-sn-glycerol, methoxypolyethylene Glycol (PEG-DMG, NOF Cat # SUNBRIGHT® GM-020) and 1,2-Distearoyl-sn-glycerol, methoxypolyethylene Glycol (PEG-DSG, NOF Cat # SUNBRIGHT® GS-020), were tested at 1.5 or 3.0 mol%. After the formation of the LNPs and the encapsulation of the modified G-CSF mRNA, the LNP formulations were characterized by particle size, zeta potential and encapsulation percentage and the results are shown in Table 54.

Table 54. Characterization of LNP Formulations

Formulation No.	NPA-071-1	NPA-072-1	NPA-073-1	NPA-074-1
Lipid	PEG-DMG 1.5%	PEG-DMG 3%	PEG-DSA 1.5%	PEG-DSA 3%
Mean Size	95 nm PDI: 0.01	85 nm PDI: 0.06	95 nm PDI: 0.08	75 nm PDI: 0.08
Zeta at pH 7.4	-1.1 mV	-2.6 mV	1.7 mV	0.7 mV
Encapsulation (RiboGreen)	88%	89%	98%	95%

B. *In Vivo* Screening of PEG LNPs

[0001222] Formulations of the PEG LNPs described in Table 55 were administered to mice (n=5) intravenously at a dose of 0.5 mg/kg. Serum was collected from the mice at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours and 8 days after administration of the formulation. The serum was analyzed by ELISA to determine the protein expression of G-CSF and the expression levels are shown in Table 55. LNP formulations using PEG-DMG gave substantially higher levels of protein expression than LNP formulations with PEG-DSA.

Table 55. Protein Expression

Lipid	Formulation No.	Time	Protein Expression (pg/ml)
PEG-DMG, 1.5%	NPA-071-1	2 hours	114,102
		8 hours	357,944
		24 hours	104,832
		48 hours	6,697
		72 hours	980
		8 days	0
PEG-DMG, 3%	NPA-072-1	2 hours	154,079
		8 hours	354,994
		24 hours	164,311
		48 hours	13,048
		72 hours	1,182
		8 days	13
PEG-DSA, 1.5%	NPA-073-1	2 hours	3,193
		8 hours	6,162
		24 hours	446
		48 hours	197
		72 hours	124
		8 days	5
PEG-DSA, 3%	NPA-074-1	2 hours	259
		8 hours	567
		24 hours	258
		48 hours	160
		72 hours	328
		8 days	33

Example 28. Cationic Lipid Formulation Studies

A. Formulation and Characterization of Cationic Lipid Nanoparticles

[0001223] Lipid nanoparticles (LNPs) were formulated using the syringe pump method. The LNPs were formulated at a 20:1 weight ratio of total lipid to modified mRNA. The final lipid molar ratio ranges of cationic lipid, DSPC, cholesterol and PEG-c-DOMG are outlined in Table 56.

Table 56. Molar Ratios

	Cationic Lipid	DSPC	Cholesterol	PEG-c-DOMG

Mole Percent (mol%)	50.0	10.0	38.5	1.5

[0001224] A 25 mM lipid solution in ethanol and modified RNA in 50mM citrate at a pH of 3 were mixed to create spontaneous vesicle formation. The vesicles were stabilized in ethanol before the ethanol was removed and there was a buffer exchange by dialysis. The LNPs were then characterized by particle size, zeta potential, and encapsulation percentage. Table 57 describes the characterization of LNPs encapsulating EPO modified mRNA (mRNA sequence shown in SEQ ID NO: 61651 polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) or G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotdies not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) using DLin-MC3-DMA, DLin-DMA or C12-200 as the cationic lipid.

Table 57. Characterization of Cationic Lipid Formulations

Formulation No.	**NPA-071-1**	**NPA-072-1**	**NPA-073-1**	**NPA-074-1**	**NPA-075-1**	**NPA-076-1**
Lipid	DLin-MC3-DMA	DLin-MC3-DMA	DLin-DMA	DLin-DMA	C12-200	C12-200
Modified RNA	EPO	G-CSF	EPO	G-CSF	EPO	G-CSF
Mean Size	89 nm PDI: 0.07	96 nm PDI: 0.08	70 nm PDI: 0.04	73 nm PDI: 0.06	97 nm PDI: 0.05	103 nm PDI: 0.09
Zeta at pH 7.4	-1.1 mV	-1.4 mV	-1.6 mV	-0.4 mV	1.4 mV	0.9 mV
Encapsulation (RiboGreen)	100%	100%	99%	100%	88%	98%

B. *In Vivo* Screening of Cationic LNP Formulations

[0001225] Formulations of the cationic lipid formulations described in Table 57 were administered to mice (n=5) intravenously at a dose of 0.5 mg/kg. Serum was collected from the mice at 2 hours, 24 hours, 72 hours and/or 7 days after administration of the formulation. The serum was analyzed by ELISA to determine the protein expression of EPO or G-CSF and the expression levels are shown in Table 58.

Table 58. Protein Expression

Modified mRNA	Formulation No.	Time	Protein Expression (pg/ml)
EPO	NPA-071-1	2 hours	304,190.0
		24 hours	166,811.5
		72 hours	1,356.1
		7 days	20.3
EPO	NPA-073-1	2 hours	73,852.0
		24 hours	75,559.7
		72 hours	130.8
EPO	NPA-075-1	2 hours	413,010.2
		24 hours	56,463.8
G-CSF	NPA-072-1	2 hours	62,113.1
		24 hours	53,206.6
G-CSF	NPA-074-1	24 hours	25,059.3
G-CSF	NPA-076-1	2 hours	219,198.1
		24 hours	8,470.0

[0001226] Toxcity was seen in the mice administered the LNPs formulations with the cationic lipid C12-200 (NPA-075-1 and NPA-076-1) and they were sacrificed at 24 hours because they showed symptoms such as scrubby fur, cowering behavior and weight loss of greater than 10%. C12-200 was expected to be more toxic but also had a high level of expression over a short period. The cationic lipid DLin-DMA (NPA-073-1 and NPA-074-1) had the lowest expression out of the three cationic lipids tested. DLin-MC3-DMA (NPA-071-1 and NPA-072-1) showed good expression up to day three and was above the background sample out to day 7 for EPO formulations.

Example 29. Method of Screening for Protein Expression

A. Electrospray Ionization

[0001227] A biological sample which may contain proteins encoded by modified RNA administered to the subject is prepared and analyzed according to the manufacturer protocol for electrospray ionization (ESI) using 1, 2, 3 or 4 mass analyzers. A biologic sample may also be analyzed using a tandem ESI mass spectrometry system.

Patterns of protein fragments, or whole proteins, are compared to known controls for a given protein and identity is determined by comparison.

B. Matrix-Assisted Laser Desorption/Ionization

[0001228] A biological sample which may contain proteins encoded by modified RNA administered to the subject is prepared and analyzed according to the manufacturer protocol for matrix-assisted laser desorption/ionization (MALDI).

[0001229] Patterns of protein fragments, or whole proteins, are compared to known controls for a given protein and identity is determined by comparison.

C. Liquid Chromatography-Mass spectrometry-Mass spectrometry

[0001230] A biological sample, which may contain proteins encoded by modified RNA, may be treated with a trypsin enzyme to digest the proteins contained within. The resulting peptides are analyzed by liquid chromatography-mass spectrometry-mass spectrometry (LC/MS/MS). The peptides are fragmented in the mass spectrometer to yield diagnostic patterns that can be matched to protein sequence databases via computer algorithms. The digested sample may be diluted to achieve 1 ng or less starting material for a given protein. Biological samples containing a simple buffer background (e.g. water or volatile salts) are amenable to direct in-solution digest; more complex backgrounds (e.g. detergent, non-volatile salts, glycerol) require an additional clean-up step to facilitate the sample analysis.

[0001231] Patterns of protein fragments, or whole proteins, are compared to known controls for a given protein and identity is determined by comparison.

Example 30. Lipid Nanoparticle *in vivo* studies

[0001232] mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61656; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was formulated as a lipid nanoparticle (LNP) using the syringe pump method. The LNP was formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: PEG-c-DOMG). The mCherry formulation, listed in Table 59, was characterized by particle size, zeta potential, and encapsulation.

Table 59. mCherry Formulation

Formulation #	**NPA-003-5**
Modified mRNA	mCherry
Mean size	105 nm PDI: 0.09
Zeta at pH 7.4	1.8 mV

Encaps. (RiboGr)	100%

[0001233] The LNP formulation was administered to mice (n=5) intravenously at a modified mRNA dose of 100 ug. Mice were sacrificed at 24 hrs after dosing. The liver and spleen from the mice administered with mCherry modified mRNA formulations were analyzed by immunohistochemistry (IHC), western blot, or fluorescence-activated cell sorting (FACS).

[0001234] Histology of the liver showed uniform mCherry expression throughout the section, while untreated animals did not express mCherry. Western blots were also used to confirm mCherry expression in the treated animals, whereas mCherry was not detected in the untreated animals. Tubulin was used as a control marker and was detected in both treated and untreated mice, indicating that normal protein expression in hepatocytes was unaffected.

[0001235] FACS and IHC were also performed on the spleens of mCherry and untreated mice. All leukocyte cell populations were negative for mCherry expression by FACS analysis. By IHC, there were also no observable differences in the spleen in the spleen between mCherry treated and untreated mice.

Example 31. Syringe Pump *in vivo* studies

[0001236] mCherry modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) is formulated as a lipid nanoparticle (LNP) using the syringe pump method. The LNP is formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: PEG-c-DOMG). The mCherry formulation is characterized by particle size, zeta potential, and encapsulation.

[0001237] The LNP formulation is administered to mice (n=5) intravenously at a modified mRNA dose of 10 or 100 ug. Mice are sacrificed at 24 hrs after dosing. The liver and spleen from the mice administered with mCherry modified mRNA formulations are analyzed by immunohistochemistry (IHC), western blot, and/or fluorescence-activated cell sorting (FACS).

Example 32. *In vitro* and *in vivo* Expression

A. *In vitro* Expression in Human Cells Using Lipidoid Formulations

[0001238] The ratio of mmRNA to lipidoid used to test for *in vitro* transfection is tested empirically at different lipidoid:mmRNA ratios. Previous work using siRNA and lipidoids have utilized 2.5:1, 5:1, 10:1, and 15:1 lipidoid:siRNA wt:wt ratios. Given the longer length of mmRNA relative to siRNA, a lower wt:wt ratio of lipidoid to mmRNA may be effective. In addition, for comparison mmRNA were also formulated using RNAIMAX™ (Invitrogen, Carlsbad, CA) or TRANSIT-mRNA (Mirus Bio, Madison, WI) cationic lipid delivery vehicles.

[0001239] The ability of lipidoid-formulated Luciferase (IVT cDNA sequence as shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site), green fluorescent protein (GFP) (IVT cDNA sequence as shown in SEQ ID NO: 61659; mRNA sequence shown in SEQ ID NO: 61660, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site), G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), and EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1)to express the desired protein product can be confirmed by luminescence for luciferase expression, flow cytometry for GFP expression, and by ELISA for G-CSF and Erythropoietin (EPO) secretion.

B. *In vivo* Expression Following Intravenous Injection

[0001240] Systemic intravenous administration of the formulations are created using various different lipidoids including, but not limited to, 98N12-5, C12-200, and MD1.

[0001241] Lipidoid formulations containing mmRNA are injected intravenously into animals. The expression of the modified mRNA (mmRNA)-encoded proteins are assessed in blood and/or other organs samples such as, but not limited to, the liver and spleen collected from the animal. Conducting single dose intravenous studies will also allow an assessment of the magnitude, dose responsiveness, and longevity of expression of the desired product.

[0001242] In one embodiment, lipidoid based formulations of 98N12-5, C12-200, MD1 and other lipidoids, are used to deliver luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human Factor IX, or human Erythropoietin (EPO) mmRNA into the animal. After formulating mmRNA with a lipid, as described previously, animals are divided into groups to receive either a saline formulation, or a lipidoid-formulation which contains one of a different mmRNA selected from luciferase, GFP, mCherry, sAP, human G-CSF, human Factor IX, and human EPO. Prior to injection into the animal, mmRNA-containing lipidoid formulations are diluted in PBS. Animals are then administered a single dose of formulated mmRNA ranging from a dose of 10 mg/kg to doses as low as 1 ng/kg, with a preferred range to be 10 mg/kg to 100 ng/kg, where the dose of mmRNA depends on the animal body weight such as a 20 gram mouse receiving a maximum formulation of 0.2 ml (dosing is based no mmRNA per kg body weight). After the administration of the mmRNA-lipidoid formulation, serum, tissues, and/or tissue lysates are obtained and the level of the mmRNA-encoded product is determined at a single and/or a range of time intervals. The ability of lipidoid-formulated Luciferase, GFP, mCherry, sAP, G-CSF, Factor IX, and EPO mmRNA to express the desired protein product is confirmed by luminescence for the expression of Luciferase, flow cytometry for the expression of GFP and mCherry expression, by enzymatic activity for sAP, or by ELISA for the section of G-CSF, Factor IX and/or EPO.

[0001243] Further studies for a multi-dose regimen are also performed to determine the maximal expression of mmRNA, to evaluate the saturability of the mmRNA-driven expression (by giving a control and active mmRNA formulation in parallel or in sequence), and to determine the feasibility of repeat drug administration (by giving mmRNA in doses separated by weeks or months and then determining whether expression level is affected by factors such as immunogenicity). An assessment of the physiological function of proteins such as G-CSF and EPO are also determined through analyzing samples from the animal tested and detecting increases in granulocyte and red blood cell counts, respectively. . Activity of an expressed protein product such as Factor IX, in animals can also be assessed through analysis of Factor IX enzymatic activity (such as an activated partial thromboplastin time assay) and effect of clotting times.

C. *In vitro* Expression Following Intramuscular and/or Subcutaneous Injection

[0001244] The use of lipidoid formulations to deliver oligonucleotides, including mRNA, via an intramuscular route or a subcutaneous route of injection needs to be evaluated as it has not been previously reported. Intramuscular and/or subcutaneous injection of mmRNA are evaluated to determine if mmRNA-containing lipidoid formulations are capabable to produce both localized and systemic expression of a desired portiens.

[0001245] Lipidoid formulations of 98N12-5, C12-200, and MD1containing mmRNA selected from luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human factor IX, or human Erythropoietin (EPO) mmRNA are injected intramuscularly and/or subcutaneously into animals. The expression of mmRNA-encoded proteins are assessed both within the muscle or subcutaneous tissue and systemically in blood and other organs such as the liver and spleen. Single dose studies allow an assessment of the magnitude, dose responsiveness, and longevity of expression of the desired product.

[0001246] Animals are divided into groups to receive either a saline formulation or a formulation containing modified mRNA. Prior to injection mmRNA-containing lipidoid formulations are diluted in PBS. Animals are administered a single intramuscular dose of formulated mmRNA ranging from 50 mg/kg to doses as low as 1 ng/kg with a preferred range to be 10 mg/kg to 100 ng/kg. A maximum dose for intramuscular administration, for a mouse, is roughly 1 mg mmRNA or as low as 0.02 ng mmRNA for an intramuscular injection into the hind limb of the mouse. For subcutaneous administration, the animals are administered a single subcutaneous dose of formulated mmRNA ranging from 400 mg/kg to doses as low as 1 ng/kg with a preferred range to be 80 mg/kg to100 ng/kg. A maximum dose for subcutaneous administration, for a mouse, is roughly 8 mg mmRNA or as low as 0.02 ng mmRNA.

[0001247] For a 20 gram mouse the volume of a single intramuscular injection is maximally 0.025 ml and a single subcutaneous injection is maximally 0.2 ml. The optimal dose of mmRNA administered is calculated from the body weight of the animal. At various points in time points following the administration of the mmRNA-lipidoid, serum, tissues, and tissue lysates is obtained and the level of the mmRNA-encoded

product is determined. The ability of lipidoid-formulated luciferase, green fluorescent protein (GFP), mCherry fluorescent protein, secreted alkaline phosphatase (sAP), human G-CSF, human factor IX, or human Erythropoietin (EPO) mmRNA to express the desired protein product is confirmed by luminescence for luciferase expression, flow cytometry for GFP and mCherry expression, by enzymatic activity for sAP, and by ELISA for G-CSF, Factor IX and Erythropoietin (EPO) secretion.

[0001248] Additional studies for a multi-dose regimen are also performed to determine the maximal expression using mmRNA, to evaluate the saturability of the mmRNA-driven expression (achieved by giving a control and active mmRNA formulation in parallel or in sequence), and to determine the feasibility of repeat drug administration (by giving mmRNA in doses separated by weeks or months and then determining whether expression level is affected by factors such as immunogenicity). Studies utilizing multiple subcutaneous or intramuscular injection sites at one time point, are also utilized to further increase mmRNA drug exposure and improve protein production. An assessment of the physiological function of proteins, such as GFP, mCherry, sAP, human G-CSF, human factor IX, and human EPO, are determined through analyzing samples from the tested animals and detecting a change in granulocyte and/or red blood cell counts. Activity of an expressed protein product such as Factor IX, in animals can also be assessed through analysis of Factor IX enzymatic activity (such as an activated partial thromboplastin time assay) and effect of clotting times.

Example 33. Bifunctional mmRNA

[0001249] Using the teachings and synthesis methods described herein, modified RNAs are designed and synthesized to be bifunctional, thereby encoding one or more cytotoxic protein molecules as well as be synthesized using cytotoxic nucleosides.

[0001250] Administration of the bifunctional modified mRNAs is effected using either saline or a lipid carrier. Once administered, the bifunctional modified mRNA is translated to produce the encoded cytotoxic peptide. Upon degradation of the delivered modified mRNA, the cytotoxic nucleosides are released which also effect therapeutic benefit to the subject.

Example 34. Modified mRNA Transfection

A. Reverse Transfection

[0001251] For experiments performed in a 24-well collagen-coated tissue culture plate, Keratinocytes are seeded at a cell density of 1 x 10^5. For experiments performed in a 96-well collagen-coated tissue culture plate, Keratinocytes are seeded at a cell density of 0.5 x 10^5. For each modified mRNA (mmRNA) to be transfected, modified mRNA: RNAIMAX™ is prepared as described and mixed with the cells in the multi-well plate within a period of time, e.g., 6 hours, of cell seeding before cells had adhered to the tissue culture plate.

B. Forward Transfection

In a 24-well collagen-coated tissue culture plate, Keratinocytes are seeded at a cell density of 0.7 x 10^5. For experiments performed in a 96-well collagen-coated tissue culture plate, Keratinocytes are seeded at a cell density of 0.3 x 10^5. Keratinocytes are grown to a confluency of >70% for over 24 hours. For each modified mRNA (mmRNA) to be transfected, modified mRNA: RNAIMAX™ is prepared as described and transfected onto the cells in the multi-well plate over 24 hours after cell seeding and adherence to the tissue culture plate.

C. Modified mRNA Translation Screen: G-CSF ELISA

[0001252] Keratinocytes are grown in EPILIFE medium with Supplement S7 from Invitrogen (Carlsbad, CA) at a confluence of >70%. One set of keratinocytes were reverse transfected with 300 ng of the chemically modified mRNA (mmRNA) complexed with RNAIMAX™ from Invitrogen. Another set of keratinocytes are forward transfected with 300 ng modified mRNA complexed with RNAIMAX™ from Invitrogen. The modified mRNA: RNAIMAX™ complex is formed by first incubating the RNA with Supplement-free EPILIFE® media in a 5X volumetric dilution for 10 minutes at room temperature.

[0001253] In a second vial, RNAIMAX™ reagent was incubated with Supplement-free EPILIFE® Media in 10X volumetric dilution for 10 minutes at room temperature. The RNA vial was then mixed with the RNAIMAX™ vial and incubated for 20-30 minutes at room temperature before being added to the cells in a drop-wise fashion. Secreted human Granulocyte-Colony Stimulating Factor (G-CSF) concentration in the culture medium is measured at 18 hours post-transfection for each of the chemically modified mRNA in triplicate.

[0001254] Secretion of Human G-CSF from transfected human keratinocytes is quantified using an ELISA kit from Invitrogen or R&D Systems (Minneapolis, MN) following the manufacturers recommended instructions.

D. Modified mRNA Dose and Duration: G-CSF ELISA

[0001255] Keratinocytes are grown in EPILIFE® medium with Supplement S7 from Invitrogen at a confluence of >70%. Keratinocytes are reverse transfected with either 0ng, 46.875ng, 93.75ng, 187.5ng, 375ng, 750ng, or 1500ng modified mRNA complexed with the RNAIMAX™ from Invitrogen (Carlsbad, CA). The modified mRNA:RNAIMAX™ complex is formed as described. Secreted human G-CSF concentration in the culture medium is measured at 0, 6, 12, 24, and 48 hours post-transfection for each concentration of each modified mRNA in triplicate. Secretion of human G-CSF from transfected human keratinocytes is quantified using an ELISA kit from Invitrogen or R&D Systems following the manufacturers recommended instructions.

Example 35. Split dose studies

[0001256] Studies utilizing multiple subcutaneous or intramuscular injection sites at one time point were designed and performed to investigate ways to increase mmRNA drug exposure and improve protein production. In addition to detection of the expressed protein product, an assessment of the physiological function of proteins was also determined through analyzing samples from the animal tested.

[0001257] Surprisingly, it has been determined that split dosing of mmRNA produces greater protein production and phenotypic responses than those produced by single unit dosing or multi-dosing schemes.

[0001258] The design of a single unit dose, multi-dose and split dose experiment involved using human erythropoietin (EPO) mmRNA (mRNA shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) administered in buffer alone. The dosing vehicle (F. buffer) consisted of 150mM NaCl, 2 mM $CaCl_2$, 2 mM Na^+-phosphate (1.4mM monobasic sodium phosphate; 0.6mM dibasic sodium phosphate), and 0.5 mM EDTA, pH 6.5. The pH was adjusted using sodium hydroxide and the final solution was filter sterilized. The mmRNA was modified with 5meC at each cytosine and pseudouridine replacement at each uridine site.

[0001259] Animals (n=5) were injected IM (intramuscular) for the single unit dose of 100 ug. For multi-dosing, two schedules were used, 3 doses of 100 ug and 6 doses of 100 ug. For the split dosing scheme, two schedules were used, 3 doses at 33.3 ug and 6 doses of 16.5 ug mmRNA. Control dosing involved use of buffer only at 6 doses. Control mmRNA involved the use of luciferase mmRNA (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) dosed 6 times at 100 ug. Blood and muscle tissue were evaluated 13 hrs post injection.

[0001260] Human EPO protein was measured in mouse serum 13h post I.M. single, multi- or split dosing of the EPO mmRNA in buffer. Seven groups of mice (n=5 mice per group) were treated and evaluated. The results are shown in Table 60.

Table 60. Split dose study

Group	Treatment	Dose of mmRNA	Total Dose	Avg. pmol/mL human EPO	Polypeptide per unit drug (pmol/ug)	Dose Splitting Factor
1	Human EPO mmRNA	1 x 100 ug	100 ug	14.3	.14	1
2	Human EPO mmRNA	3 x 100 ug	300 ug	82.5	.28	2
3	Human EPO mmRNA	6 x 100 ug	600 ug	273.0	.46	3.3
4	Human EPO mmRNA	3 x 33.3 ug	100 ug	104.7	1.1	7.9
5	Human EPO mmRNA	6 x 16.5 ug	100 ug	127.9	1.3	9.3
6	Luciferase mmRNA	6 x 100 ug	600 ug	0	--	--
7	Buffer Alone	--	--	0	--	--

[0001261] The splitting factor is defined as the product per unit drug divided by the single dose product per unit drug (PUD). For example for treatment group 2 the value .28 or product (EPO) per unit drug (mmRNA) is divided by the single dose product per unit drug of 0.14. The result is 2. Likewise, for treatment group 4, the value 1.1 or product (EPO) per unit drug (mmRNA) is divided by the single dose product per unit drug of 0.14. The result is 7.9. Consequently, the dose splitting factor (DSF) may be used as an indicator of the efficacy of a split dose regimen. For any single administration of a total daily dose, the DSF should be equal to 1. Therefore any DSF greater than this value in a split dose regimen is an indication of increased efficacy.

[0001262] To determine the dose response trends, impact of injection site and impact of injection timing, studies are performed. In these studies, varied doses of 1ug, 5ug, 10 ug, 25 ug, 50 ug, and values in between are used to determine dose response outcomes. Split dosing for a 100 ug total dose includes three or six doses of 1.6 ug, 4.2 ug, 8.3 ug, 16.6 ug, or values and total doses equal to administration of the total dose selected.

[0001263] Injection sites are chosen from the limbs or any body surface presenting enough area suitable for injection. This may also include a selection of injection depth to target the dermis (Intradermal), epidermis (Epidermal), subcutaneous tissue (SC) or muscle (IM). Injection angle will vary based on targeted delivery site with injections targeting the intradermal site to be 10-15 degree angles from the plane of the surface of the skin, between 20-45 degrees from the plane of the surface of the skin for subcutaneous injections and angles of between 60-90 degrees for injections substantially into the muscle.

Example 36. Quantification in Exosomes

[0001264] The quantity and localization of the mmRNA of the present invention can be determined by measuring the amounts (initial, timecourse, or residual basis) in isolated exosomes. In this study, since the mmRNA are typically codon-optimized and distinct in sequence from endogenous mRNA, the levels of mmRNA are quantitated as compared to endogenous levels of native or wild type mRNA by using the methods of Gibbings, PCT/IB2009/005878, the contents of which are incorporated herein by reference in their entirety.

[0001265] In these studies, the method is performed by first isolating exosomes or vesicles preferably from a bodily fluid of a patient previously treated with a polynucleotide, primary construct or mmRNA of the invention, then measuring, in said exosomes, the polynucleotide, primary construct or mmRNA levels by one of mRNA microarray, qRT-PCR, or other means for measuring RNA in the art including by suitable antibody or immunohistochemical methods.

Example 37. Effect of Modified mRNA on Cellular Viability, Cytotoxicity and Apoptosis

[0001266] This experiment demonstrates cellular viability, cytotoxicity and apoptosis for distinct modified mRNA *in-vitro* transfected Human Keratinocyte cells. Keratinocytes

are grown in EPILIFE® medium with Human Keratinocyte Growth Supplement in the absence of hydrocortisone from Invitrogen (Carlsbad, CA) at a confluence of >70%. Keratinocytes are reverse transfected with 0ng, 46.875ng, 93.75ng, 187.5ng, 375ng, 750ng, 1500ng, 3000ng, or 6000ng of modified mRNA complexed with RNAIMAX™ from Invitrogen. The modified mRNA:RNAIMAX™ complex is formed. Secreted human G-CSF concentration in the culture medium is measured at 0, 6, 12, 24, and 48 hours post-transfection for each concentration of each modified m RNA in triplicate. Secretion of human G-CSF from transfected human keratinocytes is quantified using an ELISA kit from Invitrogen or R&D Systems following the manufacturers recommended instructions.

[0001267] Cellular viability, cytotoxicity and apoptosis is measured at 0, 12, 48, 96, and 192 hours post-transfection using the APOTOX-GLO™ kit from Promega (Madison, WI) according to manufacturer instructions.

Example 38. Detection of a Cellular Innate Immune Response to Modified mRNA Using an ELISA Assay

[0001268] An enzyme-linked immunosorbent assay (ELISA) for Human Tumor Necrosis Factor-α (TNF-α), Human Interferon-β (IFN-β) and Human Granulocyte-Colony Stimulating Factor (G-CSF) secreted from *in vitro*-transfected Human Keratinocyte cells is tested for the detection of a cellular innate immune response. Keratinocytes are grown in EPILIFE® medium with Human Keratinocyte Growth Supplement in the absence of hydrocortisone from Invitrogen (Carlsbad, CA) at a confluence of >70%. Secreted TNF-α keratinocytes are reverse transfected with 0ng, 93.75ng, l 87.5ng, 375ng, 750ng, 1500ng or 3000ng of the chemically modified mRNA (mmRNA) complexed with RNAIMAX™ from Invitrogen as described in triplicate. Secreted TNF-α in the culture medium is measured 24 hours post-transfection for each of the chemically modified mRNA using an ELISA kit from Invitrogen according to the manufacturer protocols.

[0001269] Secreted IFN-β in the same culture medium is measured 24 hours post-transfection for each of the chemically modified mRNA using an ELISA kit from Invitrogen according to the manufacturer protocols. Secreted human G-CSF concentration in the same culture medium is measured at 24 hours post-transfection for each of the chemically modified mRNA. Secretion of human G-CSF from transfected

human keratinocytes is quantified using an ELISA kit from Invitrogen or R&D Systems (Minneapolis, MN) following the manufacturers recommended instructions. These data indicate which modified mRNA (mmRNA) are capable eliciting a reduced cellular innate immune response in comparison to natural and other chemically modified polynucleotides or reference compounds by measuring exemplary type 1 cytokines TNF-α and IFN-β.

Example 39. Human Granulocyte –Colony Stimulating Factor (G-CSF) Modified mRNA-induced Cell Proliferation Assay

[0001270] Human keratinocytes are grown in EPILIFE® medium with Supplement S7 from Invitrogen at a confluence of >70% in a 24-well collagen-coated TRANSWELL® (Coming, Lowell, MA) co-culture tissue culture plate. Keratinocytes are reverse transfected with 750ng of the indicated chemically modified mRNA (mmRNA) complexed with RNAIMAX from Invitrogen as described in triplicate. The modified mRNA:RNAIMAX complex is formed as described. Keratinocyte media is exchanged 6-8 hours post-transfection. 42-hours post-transfection, the 24-well TRANSWELL® plate insert with a 0.4 μm-pore semi-permeable polyester membrane is placed into the human G-CSF modified mRNA-transfected keratinocyte containing culture plate

[0001271] Human myeloblast cells, Kasumi-1 cells or KG- 1 (0.2×10^5 cells), are seeded into the insert well and cell proliferation is quantified 42 hours post-co-culture initiation using the CyQuant Direct Cell Proliferation Assay (Invitrogen, Carlsbad, CA) in a 100-120μl volume in a 96-well plate. Modified mRNA-encoding human G-CSF-induced myeloblast cell proliferation is expressed as a percent cell proliferation normalized to untransfected keratinocyte/myeloblast co-culture control wells. Secreted human G-CSF concentration in both the keratinocyte and myeloblast insert co-culture wells is measured at 42 hours post-co-culture initiation for each modified mRNA in duplicate. Secretion of human G-CSF is quantified using an ELISA kit from Invitrogen following the manufacturer recommended instructions.

[0001272] Transfected human G-CSF modified mRNA in human keratinocyte feeder cells and untransfected human myeloblast cells are detected by RT -PCR. Total RNA from sample cells is extracted and lysed using RNEASY® kit (Qiagen, Valencia, CA) according to the manufacturer instructions. Extracted total RNA is submitted to RT-PCR

for specific amplification of modified mRNA-G-CSF using PROTOSCRIPT® M-MuLV *Taq* RT-PCR kit (New England BioLabs, Ipswich, MA) according to the manufacturer instructions with human G-CSF-specific primers. RT-PCR products are visualized by 1.2% agarose gel electrophoresis.

Example 40: Co-Culture Assay

Modified mRNA comprised of chemically-distinct modified nucleotides encoding human Granulocyte-Colony Stimulating Factor (G-CSF) may stimulate the cellular proliferation of a transfection incompetent cell in a co-culture environment. The co-culture includes a highly transfectable cell type such as a human keratinocyte and a transfection incompetent cell type such as a white blood cell (WBC). The modified mRNA encoding G-CSF are transfected into the highly transfectable cell allowing for the production and secretion of G-CSF protein into the extracellular environment where G-CSF acts in a paracrine-like manner to stimulate the white blood cell expressing the G-CSF receptor to proliferate. The expanded WBC population may be used to treat immune-compromised patients or partially reconstitute the WBC population of an immunosuppressed patient and thus reduce the risk of opportunistic infections.

In another example, a highly transfectable cell such as a fibroblast are transfected with certain growth factors support and simulate the growth, maintenance, or differentiation of poorly transfectable embryonic stem cells or induced pluripotent stem cells.

Example 41: Detection Assays of Human IgG Antibodies

A. ELISA Detection of Human IgG Antibodies

[0001273] This example describes an ELISA for Human IgG from Chinese Hamster Ovary's (CHO) and Human Embryonic Kidney (HEK, HER-2 Negative) 293 cells transfected with human IgG modified mRNA (mmRNA). The Human Embryonic Embryonic Kidney (HEK) 293 are grown in CD 293 Medium with Supplement of L-Glutamine from Invitrogen until they reach a confluence of 80-90%. The CHO cells are grown in CD CHO Medium with Supplement of L- Glutamine, Hypoxanthine and Thymidine. In one aspect, 2 x 106 cells are transfected with 24 µg modified mRNA complexed with RNAIMAXTM from Invitrogen in a 75cm2 culture flask from Corning in 7 ml of medium. In another aspect, 80,000 cells are transfected with 1 µg modified mRNA complexed with RNAIMAXTM from Invitrogen in a 24-well plate. The modified

mRNA:RNAIMAXTM complex is formed by incubating in a vial the mmRNA with either the CD 293 or CD CHO medium in a 5X volumetric dilution for 10 minutes at room temperature. In a second vial, RNAIMAXTM reagent is incubated with CD 293 medium or CD CHO medium in a 10X volumetric dilution for 10 minutes at room temperature. The mmRNA vial is then mixed with the RNAIMAXTM vial and incubated for 20-30 minutes at room temperature before it isadded to the CHO or HEK cells in a drop-wise fashion. The culture supernatants are stored at 4 degrees celsius. The concentration of the secreted human IgG in the culture medium in the 24 μg mmRNA transfections is measured at 12, 24, 36 hours post-transfection and the 1 μg mmRNA transfection is measured at 36 hours. Secretion of Trastuzumab from transfected HEK 293 cells is quantified using an ELISA kit from Abcam (Cambridge, MA) following the manufacturers recommended instructions. The data shows that a Humanized IgG antibody (such as Trastuzumab) mmRNA is capable of being translated in HEK Cells and that Trastuzumab is secreted out of the cells and released into the extracellular environment. Furthermore, the data demonstrate that transfection of cells with mmRNA encoding Trastuzumab for the production of secreted protein can be scaled up to a bioreactor or large cell culture conditions.

B. Western Detection of Modified mRNA Produced Human IgG Antibody

[0001274] A Western Blot of CHO-K1 cells is co-transfected with 1 μg each of Heavy and Light Chain of Trastuzumab modified mRNA (mmRNA). CHO cells are grown using standard protocols in 24-well plates. The cell supernatants or cell lysates are collected 24 hours post-transfection, separated on a 12% SDS-Page gel and transferred onto a nitrocellulose membrane using the IBOT® by Invitrogen (Carlsbad, CA). The cells are incubated with a first conjugation of a rabbit polyclonal antibody to Human IgG conjugated to DYLIGHT594 (ab96904, abcam, Cambridge, MA) and a second conjugation of a goat polyclonal antibody to Rb IgG which is conjugated to alkaline phosphatase. After incubation, the antibody is detected using Novex® alkaline phosphatase chromogenic substrate by Invitrogen (Carlsbad, CA).

C. Cell Immuno Staining of Modified mRNA Produced Trastuzumab and Rituximab

[0001275] CHO-K1 cells are co-transfected with 500 ng each of Heavy and Light Chain of either Trastuzumab or Rituximab. Cells are grown in F-12K Medium from GIBCO®

(Grand Island, NY) and 10% FBS. Cells are fixed with 4% paraformaldehyde in PBS, permeabilized with 0.1% Triton X-100 in PBS for 5-10 minutes at room temperature and cells are washed 3 times with room temperature PBS. Trastuzumab and Rituximab staining is performed using rabbit polyclonal antibody to Human IgG conjugated to DYLIGHT®594 (ab96904, abcam, Cambridge, MA) according to the manufacture's recommended dilutions. Nuclear DNA staining is performed with DAPI dye from Invitrogen (Carlsbad, CA). The protein for Trastuzumab and Rituximab is translated and localized to the cytoplasm upon modified mRNA transfections. Pictures are taken 13 hours post-transfection.

D. Binding Immunoblot Assay for Modified mRNA Produced Trastuzumab and Rituximab

[0001276] Trastuzumab and Rituximab are detected using a binding immunoblot detection assay. Varying concentrations (100ng/ul to 0ng/ul) of the ErB2 peptide (ab40048, abeam, Cambridge, MA), antigen for Trastuzumab and the CD20 peptide (ab97360, abeam, Cambridge, MA), antigen for Rituximab are run on a 12% SDS-Page gel and transferred onto a membrane using the iBlot from Invitrogen. The membranes are incubated for 1 hour with their respective cell supernatants from CHO-K1 cells which are co-transfected with 500ng each of Heavy and Light Chain of either Trastuzumab or Rituximab. The membranes are blocked with 1% BSA and a secondary anti-human IgG antibody conjugated to alkaline phosphatase (abcam, Cambridge, MA) is added. Antibody detection is conducted using the NOVEX alkaline phosphatase chromogenic substrate by Invitrogen (Carlsbad, CA). The data shows that a humanized IgG antibodies generated from modified mRNA is capable of recognizing and binding to their respective antigens.

E. Cell Proliferation Assay

[0001277] The SK-BR-3 cell line, an adherent cell line derived from a human breast adenocarcinoma, which overexpresses the HER2/neu receptor can be used to compare the anti-proliferative properties of modified mRNA (mmRNA) generated Trastuzumab. Varying concentrations of purified Trastuzumab generated from modified mRNA and trastuzumab are be added to cell cultures, and their effects on cell growth are be assessed in triplicate cytotoxicity and viability assays.

Example 42: Bulk Transfection of Modified mRNA into Cell Culture

A. Cationic Lipid Delivery Vehicles

[0001278] RNA transfections are carried out using RNAIMAX™ (Invitrogen, Carlsbad, CA) or TRANSIT-mRNA (Mirus Bio, Madison, WI) cationic lipid delivery vehicles. RNA and reagent are first diluted in Opti-MEM basal media (Invitrogen, Carlsbad, CA). 100 ng/uL RNA is diluted 5x and 5 μL of RNAIMax per μg of RNA is diluted 10x. The diluted components are pooled and incubated 15 minutes at room temperature before they are dispensed to culture media. For TRANSIT-mRNA transfections, 100 ng/uL RNA is diluted 10x in Opti-MEM and BOOST reagent is added (at a concentration of 2 μL per μg of RNA), TRANSIT-mRNA is added (at a concentration of 2 μL per μg of RNA), and then the RNA-lipid complexes are delivered to the culture media after a 2-minute incubation at room temperature. RNA transfections are performed in Nutristem xenofree hES media (Stemgent, Cambridge, MA) for RiPS derivations, Dermal Cell Basal Medium plus Keratinocyte Growth Kit (ATCC) for keratinocyte experiments, and Opti-MEM plus 2% FBS for all other experiments. Successful introduction of a modified mRNA (mmRNA) into host cells can be monitored using various known methods, such as a fluorescent marker, such as Green Fluorescent Protein (GFP). Successful transfection of a modified mRNA can also be determined by measuring the protein expression level of the target polypeptide by e.g., Western Blotting or immunocytochemistry. Similar methods may be followed for large volume scale-up to multi-liter (5-10,000L) culture format following similar RNA-lipid complex ratios.

B. Electroporation Delivery of Exogenous Synthetic mRNA Transcripts

[0001279] Electroporation parameters are optimized by transfecting MRC-5 fibroblasts with in vitro synthetic modified mRNA (mmRNA) transcripts and measuring transfection efficiency by quantitative RT-PCR with primers designed to specifically detect the exogenous transcripts. Discharging a 150uF capacitor charged to F into $2.5x10^6$ cells suspended in 50 μl of Opti-MEM (Invitrogen, Carlsbad, CA) in a standard electroporation cuvette with a 2mm gap is sufficient for repeated delivery in excess of 10,000 copies of modified mRNA transcripts per cell, as determined using the standard curve method, while maintaining high viability (>70%). Further experiments may reveal that the voltage required to efficiently transfect cells with mmRNA transcripts can

depend on the cell density during electroporation. Cell density may vary from $1x10^6$ cell/50 µl to a density of $2.5x10^6$ cells/50µl and require from 110V to 145V to transfect cells with similar efficiencies measured in transcript copies per cell. Large multi-liter (5-10,000 L) electroporation may be performed similar to large volume flow electroporation strategies similar to methods described with the above described constraints (Li et al., 2002; Geng et al., 2010).

Example 43: *In Vivo* Delivery Using Lipoplexes

A. Human EPO Modified RNA Lipoplex

[0001280] A formulation containing 100 µg of modified human erythropoietin mRNA(mRNA shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) (EPO; fully modified 5-methylcytosine; N1-methyl-pseudouridine) was lipoplexed with 30% by volume of RNAIMAX™ (Lipoplex-h-Epo-46; Generation 2 or Gen2) in 50-70 uL delivered intramuscularly to four C57/BL6 mice. Other groups consisted of mice receiving an injection of the lipoplexed modified luciferase mRNA (Lipoplex-luc) (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) which served as a control containing 100 µg of modified luciferase mRNA was lipoplexed with 30% by volume of RNAiMAX™ or mice receiving an injection of the formulation buffer as negative control at a dose volume of 65ul. 13 hours after the intramuscular injection, serum was collected from each mouse to measure the amount of human EPO protein in the mouse serum by human EPO ELISA and the results are shown in Table 61.

Table 61. Human EPO Production (IM Injection Route)

Formualtion	Average
Lipoplex-h-Epo-46	251.95
Lipoplex-Luc	0
Formulation Buffer	0

B. Human G-CSF Modified RNA Lipoplex

[0001281] A formulation containing 100 µg of one of two versions of modified human G-CSF mRNA(mRNA sequence shown in SEQ ID NO: 61649; polyA tail of

approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) (G-CSF fully modified with 5-methylcytosine and pseudouridine (G-CSF) or G-CSF fully modified with 5-methylcytosine and N1-methyl-pseudouridine (G-CSF-N1) lipoplexed with 30% by volume of RNAIMAX™ and delivered in 150 uL intramuscularly (I.M), in 150 uL subcutaneously (S.C) and in 225uL intravenously (I.V) to C57/BL6 mice.

[0001282] Three control groups were administered either 100 μg of modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) intramuscularly (Luc-unsp I.M.) or 150 μg of modified luciferase mRNA intravenously (Luc-unsp I.V.) or 150 uL of the formulation buffer intramuscularly (Buffer I.M.). 6 hours after administration of a formulation, serum was collected from each mouse to measure the amount of human G-CSF protein in the mouse serum by human G-CSF ELISA and the results are shown in Table 62.

[0001283] These results demonstrate that both 5-methylcytosine/pseudouridine and 5-methylcytosine/N1-methyl-pseudouridine modified human G-CSF mRNA can result in specific human G-CSF protein expression in serum when delivered via I.V. or I.M. route of administration in a lipoplex formulation.

Table 62. Human G-CSF in Serum (I.M., I.V., S.C. Injection Route)

Formulation	Route	G-CSF (pg/ml)
G-CSF	I.M.	85.6
G-CSF N1	I.M.	40.1
G-CSF	S.C.	3.9
G-CSF N1	S.C.	0.0
G-CSF	I.V.	31.0
G-CSF N1	I.V.	6.1
Luc-unsp	I.M.	0.0
Luc-unsp	I.V.	0.0
Buffer	I.M.	0.0

C. Human G-CSF Modified RNA Lipoplex Comparison

[0001284] A formulation containing 100 μg of either modified human G-CSF mRNA lipoplexed with 30% by volume of RNAIMAX™ with a 5-methylcytosine (5mc) and a pseudouridine (ψ) modification (G-CSF-Gen1-Lipoplex), modified human G-CSF

mRNA with a 5mc and ψ modification in saline (G-CSF-Gen1-Saline), modified human G-CSF mRNA with a N1-5-methylcytosine (N1-5mc) and a ψ modification lipoplexed with 30% by volume of RNAIMAX™ (G-CSF-Gen2-Lipoplex), modified human G-CSF mRNA with a N1-5mc and ψ modification in saline (G-CSF-Gen2-Saline), modified luciferase with a 5mc and ψ modification lipoplexed with 30% by volume of RNAIMAX™ (Luc-Lipoplex), or modified luciferase mRNA with a a 5mc and ψ modification in saline (Luc-Saline) was delivered intramuscularly (I.M.) or subcutaneously (S.C.) and a control group for each method of administration was giving a dose of 80uL of the formulation buffer (F. Buffer) to C57/BL6 mice. 13 hours post injection serum and tissue from the site of injection were collected from each mouse and analyzed by G-CSF ELISA to compare human G-CSF protein levels. The results of the human G-CSF protein in mouse serum from the intramuscular administration, and the subcutaneous administration results are shown in Table 63.

[0001285] These results demonstrate that 5-methylcytosine/pseudouridine and 5-methylcytosine/N1-methyl-pseudouridine modified human G-CSF mRNA can result in specific human G-CSF protein expression in serum when delivered via I.M. or S.C. route of administration whether in a saline formulation or in a lipoplex formulation. As shown in Table 63, 5-methylcytosine/N1-methyl-pseudouridine modified human G-CSF mRNA generally demonstrates increased human G-CSF protein production relative to 5-methylcytosine/pseudouridine modified human G-CSF mRNA.

Table 63. Human G-CSF Protein in Mouse Serum

Formulation	G-CSF (pg/ml)	
	I.M. Injection Route	S.C. Injenction Route
G-CSF-Gen1-Lipoplex	13.988	42.855
G-CSF-Gen1-saline	9.375	4.614
G-CSF-Gen2-lipoplex	75.572	32.107
G-CSF-Gen2-saline	20.190	45.024
Luc lipoplex	0	3.754
Luc saline	0.0748	0
F. Buffer	4.977	2.156

D. mCherry Modified RNA Lipoplex Comparison

Intramuscular and Subcutaneous Administration

[0001286] A formulation containing 100 μg of either modified mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) lipoplexed with 30% by volume of RNAIMAX™ or modified mCherry mRNA in saline is delivered intramuscularly and subcutaneously to mice. A formulation buffer is also administered to a control group of mice either intramuscularly or subcutaneously. The site of injection on the mice may be collected 17 hours post injection for sectioning to determine the cell type(s) responsible for producing protein.

Intravitreal Administration

[0001287] A formulation containing 10 μg of either modified mCherry mRNA lipoplexed with RNAIMAX™, modified mCherry mRNA in a formulation buffer, modified luciferase mRNA lipoplexed with RNAMAX™, modified luciferase mRNA in a formulation buffer can be administered by intravitreal injection (IVT) in rats in a dose volume of 5 μl/eye. A formulation buffer is also administrered by IVT to a control group of rats in a dose volume of 5 μl/eye. Eyes from treated rats can be collected after 18 hours post injection for sectioning and lysating to determine whether mmRNA can be effectively delivered in vivo to the eye and result in protein production, and to also determine the cell type(s) responsible for producing protein *in vivo*.

Intranasal Administration

[0001288] A formulation containing 100 μg of either modified mCherry mRNA lipoplexed with 30% by volume of RNAIMAX™, modified mCherry mRNA in saline, modified luciferase mRNA lipoplexed with 30% by volume of RNAIMAX™ or modified luciferase mRNA in saline is delivered intranasally. A formulation buffer is also administered to a control group intranasally. Lungs may be collected about 13 hours post instillation for sectioning (for those receiving mCherry mRNA) or homogenization (for those receiving luciferase mRNA). These samples will be used to determine whether mmRNA can be effectively delivered in vivo to the lungs and result in protein production, and to also determine the cell type(s) responsible for producing protein *in vivo*.

Example 44: *In Vivo* Delivery Using Varying Lipid Ratios

[0001289] Modified mRNA was delivered to C57/BL6 mice to evaluate varying lipid ratios and the resulting protein expression. Formulations of 100µg modified human EPO mRNA (mRNA shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) lipoplexed with 10%, 30% or 50% RNAIMAX™, 100µg modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) lipoplexed with 10%, 30% or 50% RNAIMAX™ or a formulation buffer were administered intramuscularly to mice in a single 70 µl dose. Serum was collected 13 hours post injection to undergo a human EPO ELISA to determine the human EPO protein level in each mouse. The results of the human EPO ELISA, shown in Table 64, show that modified human EPO expressed in the muscle is secreted into the serum for each of the different percentage of RNAIMAX™.

Table 64. Human EPO Protein in Mouse Serum (IM Injection Route)

Formulation	EPO (pg/ml)
Epo + 10% RNAiMAX	11.4
Luc + 10% RNAiMAX	0
Epo + 30% RNAiMAX	27.1
Luc + 30% RNAiMAX	0
Epo + 50% RNAiMAX	19.7
Luc + 50% RNAiMAX	0
F. Buffer	0

Example 45: Intramuscular and Subcutaneous *In Vivo* Delivery in Mammals

[0001290] Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) formulated in formulation buffer was delivered to either C57/BL6 mice or Sprague-Dawley rats to evaluate the dose dependency on human EPO production. Rats were intramuscularlly injected with 50 µl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA (Luc) (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1,

fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) or the formulation buffer (F.Buffer) as described in the dosing chart Table 65.

[0001291] Mice were intramuscularly or subcutaneously injected with 50 µl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA (Luc) or the formulation buffer (F.Buffer) as described in the dosing chart Table 66. 13 hours post injection blood was collected and serum was analyzed to determine the amount human EPO for each mouse or rat. The average and geometric mean in pg/ml for the rat study are also shown in Table 65.

Table 65. Rat Study

	Group	Dose (ug)	Avg. pg/ml	Geometric-mean pg/ml
h-EPO	G#1	150	67.7	67.1
h-EPO	G#2	100	79.4	66.9
h-EPO	G#3	50	101.5	85.4
h-EPO	G#4	10	46.3	31.2
h-EPO	G#5	1	28.7	25.4
Luc	G#6	100	24.5	22.4
F.Buffer	G#7	-	18.7	18.5

Table 66. Mouse Study

Route	Treatment	Group	Dose	Average Level in serum pg/ml
IM	h-EPO	1	100 µg	96.2
IM	h-EPO	2	50 µg	63.5
IM	h-EPO	3	25 µg	18.7
IM	h-EPO	4	10 µg	25.9
IM	h-EPO	5	1 µg	2.6
IM	Luc	6	100 µg	0
IM	F.Buffer	7	-	1.0
SC	h-EPO	1	100 µg	72.0
SC	Luc	2	100 µg	26.7
SC	F.Buffer	3	--	17.4

Example 46: Duration of Activity after Intramuscular *In Vivo* Delivery

[0001292] Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) formulated in formulation

buffer was delivered to Sprague-Dawley rats to determine the duration of the dose response. Rats were intramuscularly injected with 50 µl of the modified human EPO mRNA (h-EPO), modified luciferase mRNA(IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) (Luc) or the formulation buffer (F.Buffer) as described in the dosing chart Table 67. The rats were bled 2, 6, 12, 24, 48 and 72 hours after the intramuscular injection to determine the concentration of human EPO in serum at a given time. The average and geometric mean in pg/ml for this study are also shown in Table 67.

Table 67. Dosing Chart

	Group	Dose (ug)	Avg. pg/ml	Geometric -mean (pg/ml)
h-EPO	2 hour	100	59.6	58.2
h-EPO	6 hour	100	68.6	55.8
h-EPO	12 hour	100	87.4	84.5
h-EPO	24 hour	100	108.6	95.3
h-EPO	48 hour	100	77.9	77.0
h-EPO	72 hour	100	80.1	75.8
Luc	24, 48 and 72 hour	100	37.2	29.2
F.Buffer	24, 48 and 72 hour	-	48.9	10.4

Example 47: Routes of Administration

[0001293] Further studies were performed to investigate dosing using different routes of administration. Following the protocol outlined in Example 35, 4 mice per group were dosed intramuscularly (I.M.), intravenously (IV) or subcutaneously (S.C.) by the dosing chart outlined in Table 68. Serum was collected 13 hours post injection from all mice, tissue was collected from the site of injection from the intramuscular and subcutaneous group and the spleen, liver and kidneys were collected from the intravenous group. The results from the intramuscular group and the subcutaneous group results are shown in Table 69.

Table 68. Dosing Chart

Group	Treatment	Route	Dose of mmRNA	Total Dose	Dosing Vehicle
1	Lipoplex-human EPO mmRNA	I.M.	4 x 100 ug + 30% Lipoplex	4x70 ul	Lipoplex

2	Lipoplex-human EPO mmRNA	I.M.	4 x 100 ug	4x70 ul	Buffer
3	Lipoplex-human EPO mmRNA	S.C.	4 x 100 ug + 30% Lipoplex	4x70 ul	Lipoplex
4	Lipoplex-human EPO mmRNA	S.C.	4 x 100 ug	4x70 ul	Buffer
5	Lipoplex-human EPO mmRNA	I.V.	200 ug + 30% Lipoplex	140 ul	Lipoplex
6	Lipoplexed-Luciferase mmRNA	I.M.	100 ug + 30% Lipoplex	4x70 ul	Lipoplex
7	Lipoplexed-Luciferase mmRNA	I.M.	100 ug	4x70 ul	Buffer
8	Lipoplexed-Luciferase mmRNA	S.C.	100 ug + 30% Lipoplex	4x70 ul	Lipoplex
9	Lipoplexed-Luciferase mmRNA	S.C.	100 ug	4x70 ul	Buffer
10	Lipoplexed-human EPO mmRNA	I.V.	200 ug + 30% Lipoplex	140 ul	Lipoplex
11	Formulation Buffer	I.M.	4x multi dosing	4x70 ul	Buffer

Table 69. Human EPO Protein in Mouse Serum (I.M. Injection Route)

Formulation	EPO (pg/ml)	
	I.M. Injection Route	S.C. Injection Route
Epo-Lipoplex	67.115	2.154
Luc-Lipoplex	0	0
Epo-Saline	100.891	11.37
Luc-Saline	0	0
Formulation Buffer	0	0

Example 48. Rapidly eliminated Lipid Nanoparticle (reLNP) Studies

A. Formulation of Modified RNA reLNPs

[0001294] Solutions of synthesized lipid, 1,2-distearoyl-3-phosphatidylcholine (DSPC) (Avanti Polar Lipids, Alabaster, AL), cholesterol (Sigma-Aldrich, Taufkirchen, Germany), and α-[3'-(1,2-dimyristoyl-3-propanoxy)-carboxamide-propyl]-ω-methoxy-polyoxyethylene (PEG-c-DOMG) (NOF, Bouwelven, Belgium) are prepared and stored at -20°C. The synthesized lipid is selected from DLin-DMA with an internal ester, DLin-DMA with a terminal ester, DLin-MC3-DMA-internal ester, and DLin-MC3-DMA with a terminal ester. The reLNPs are combined to yield a molar ratio of 50:10:38.5:1.5 (reLNP: DSPC: Cholesterol: PEG-c-DOMG). Formulations of the reLNPs and modified

mRNA are prepared by combining the lipid solution with the modified mRNA solution at total lipid to modified mRNA weight ratio of 10:1, 15:1, 20:1 and 30:1.

B. Characterization of formulations

[0001295] A Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, Worcestershire, UK) is used to determine the particle size, the polydispersity index (PDI) and the zeta potential of the modified mRNA nanoparticles in 1X PBS in determining particle size and 15 mM PBS in determining zeta potential.

[0001296] Ultraviolet–visible spectroscopy is used to determine the concentration of modified mRNA nanoparticle formulation. After mixing, the absorbance spectrum of the solution is recorded between 230 nm and 330 nm on a DU 800 spectrophotometer (Beckman Coulter, Beckman Coulter, Inc., Brea, CA). The modified RNA concentration in the nanoparicle formulation is calculated based on the extinction coefficient of the modified RNA used in the formulation and on the difference between the absorbance at a wavelength of 260 nm and the baseline value at a wavelength of 330 nm.

[0001297] QUANT-IT™ RIBOGREEN® RNA assay (Invitrogen Corporation Carlsbad, CA) is used to evaluate the encapsulation of modified RNA by the nanoparticle. The samples are diluted, transferred to a polystyrene 96 well plate, then either a TE buffer or a 2% Triton X-100 solution is added. The plate is incubated and the RIBOGREEN® reagent is diluted in TE buffer, and of this solution is added to each well. The fluorescence intensity is measured using a fluorescence plate reader (Wallac Victor 1420 Multilablel Counter; Perkin Elmer, Waltham, MA) The fluorescence values of the reagent blank are subtracted from each of the samples and the percentage of free modified RNA is determined by dividing the fluorescence intensity of the intact sample by the fluorescence value of the disrupted sample.

C. *In Vitro* Incubation

[0001298] Human embryonic kidney epithelial (HEK293) and hepatocellular carcinoma epithelial (HepG2) cells (LGC standards GmbH, Wesel, Germany) are seeded on 96-well plates (Greiner Bio-one GmbH, Frickenhausen, Germany) and plates for HEK293 cells are precoated with collagen type1. HEK293 are seeded at a density of about 30,000 and HepG2 are seeded at a density of about 35,000 cells per well in 100 µl cell culture medium. Formulations containing mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap,

Cap1) are added directly after seeding the cells and incubated. The mCherry cDNA with the T7 promoter, 5′untranslated region (UTR) and 3′ UTR used in *in vitro* transcription (IVT) is given in SEQ ID NO: 61650.

[0001299] Cells are harvested by transferring the culture media supernatants to a 96-well Pro-Bind U-bottom plate (Beckton Dickinson GmbH, Heidelberg, Germany). Cells are trypsinized with ½ volume Trypsin/EDTA (Biochrom AG, Berlin, Germany), pooled with respective supernatants and fixed by adding one volume PBS/2%FCS (both Biochrom AG, Berlin, Germany)/0.5% formaldehyde (Merck, Darmstadt, Germany). Samples are then submitted to a flow cytometer measurement with an excitation laser and a filter for PE-Texas Red in a LSRII cytometer (Beckton Dickinson GmbH, Heidelberg, Germany). The mean fluorescence intensity (MFI) of all events and the standard deviation of four independent wells are presented in for samples analyzed.

D. *In Vivo* Formulation Studies

[0001300] Mice are administered intravenously a single dose of a formulation containing a modified mRNA and a reLNP. The modified mRNA administered to the mice is selected from G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Factor IX (mRNA shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or mCherry (mRNA sequence shown in SEQ ID NO:61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1).

[0001301] The mice are injected with 100ug, 10 ug or 1 ug of the formulated modified mRNA and are sacrificed 8 hours after they are administered the formulation. Serum from the mice administered formulations containing human G-CSF modified mRNA are measured by specific G-CSF ELISA and serum from mice administered human Factor IX modified RNA is analyzed by specific factor IX ELISA or chromogenic assay. The liver and spleen from the mice administered with mCherry modified mRNA are analyzed by immunohistochemistry (IHC) or fluorescence-activated cell sorting (FACS). As a control, a group of mice are not injected with any formulation and their serum and tissue are collected analyzed by ELISA, FACS and/or IHC.

Example 49. *In Vitro* Transfection of VEGF-A

[0001302] Human vascular endothelial growth factor-isoform A (VEGF-A) modified mRNA (mRNA sequence shown in SEQ ID NO: 1672; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was transfected via reverse transfection in Human Keratinocyte cells in 24 multi-well plates. Human Keratinocytes cells were grown in EPILIFE® medium with Supplement S7 from Invitrogen (Carlsbad, CA) until they reached a confluence of 50-70%. The cells were transfected with 0, 46.875, 93.75, 187.5, 375, 750, and 1500 ng of modified mRNA (mmRNA) encoding VEGF-A which had been complexed with RNAIMAX™ from Invitrogen (Carlsbad, CA). The RNA:RNAIMAX™ complex was formed by first incubating the RNA with Supplement-free EPILIFE® media in a 5X volumetric dilution for 10 minutes at room temperature. In a second vial, RNAIMAX™ reagent was incubated with Supplement-free EPILIFE® Media in a 10X volumetric dilution for 10 minutes at room temperature. The RNA vial was then mixed with the RNAIMAX™ vial and incubated for 20-30 minutes at room temperature before being added to the cells in a drop-wise fashion.

[0001303] The fully optimized mRNA encoding VEGF-A (mRNA sequence shown in SEQ ID NO: 61661; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) transfected with the Human Keratinocyte cells included modifications during translation such as natural nucleoside triphosphates (NTP), pseudouridine at each uridine site and 5-methylcytosine at each cytosine site (pseudo-U/5mC), and N1-methyl-pseudouridine at each uridine site and 5-methylcytosine at each cytosine site (N1-methyl-Pseudo-U/5mC). Cells were transfected with the mmRNA encoding VEGF-A and secreted VEGF-A concentration (ρg/ml) in the culture medium was measured at 6, 12, 24, and 48 hours post-transfection for each of the concentrations using an ELISA kit from Invitrogen (Carlsbad, CA) following the manufacturers recommended instructions. These data, shown in Table 70 and Figures 6A, 6B and 6C, show that modified mRNA encoding VEGF-A is capable of being translated in Human Keratinocyte cells and that VEGF-A is transported out of the cells and released into the extracellular environment.

Table 70. VEGF-A Dosing and Protein Secretion

VEGF-A Dose Containing Natural NTPs				
Dose (ng)	**6 hours (pg/ml)**	**12 hours (pg/ml)**	**24 hours (pg/ml)**	**48 hours (pg/ml)**
46.875	10.37	18.07	33.90	67.02
93.75	9.79	20.54	41.95	65.75

187.5	14.07	24.56	45.25	64.39
375	19.16	37.53	53.61	88.28
750	21.51	38.90	51.44	61.79
1500	36.11	61.90	76.70	86.54
VEGF-A Dose Containing Pseudo-U/5mC				
Dose (ng)	**6 hours (pg/ml)**	**12 hours (pg/ml)**	**24 hours (pg/ml)**	**48 hours (pg/ml)**
46.875	10.13	16.67	33.99	72.88
93.75	11.00	20.00	46.47	145.61
187.5	16.04	34.07	83.00	120.77
375	69.15	188.10	448.50	392.44
750	133.95	304.30	524.02	526.58
1500	198.96	345.65	426.97	505.41
VEGF-A Dose Containing N1-methyl-Pseudo-U/5mC				
Dose (ng)	**6 hours (pg/ml)**	**12 hours (pg/ml)**	**24 hours (pg/ml)**	**48 hours (pg/ml)**
46.875	0.03	6.02	27.65	100.42
93.75	12.37	46.38	121.23	167.56
187.5	104.55	365.71	1025.41	1056.91
375	605.89	1201.23	1653.63	1889.23
750	445.41	1036.45	1522.86	1954.81
1500	261.61	714.68	1053.12	1513.39

Example 50. *In vivo* studies of Factor IX

[0001304] Human Factor IX mmRNA (Gen1; fully modified 5-methycytosine and pseudouridine) formulated in formulation buffer was delivered to mice via intramuscular injection. The results demonstrate that Factor IX protein was elevated in serum as measured 13 hours after administration.

[0001305] In this study, mice (N=5 for Factor IX, N=3 for Luciferase or Buffer controls) were intramuscularly injected with 50 µl of the Factor IX mmRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Luciferase (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) or the formulation buffer (F.Buffer) at 2x 100 ug/mouse. The mice were bled at 13 hours after the intramuscular injection to determine the concentration of human the polypeptide in serum in pg/mL. The results revealed that administration of Factor IX mmRNA resulted in

levels of 1600 pg/mL at 13 hours as compared to less than 100 pg/mL of Factor IX for either Luciferase or buffer control administration.

Example 51. Multi-site administration: Intramuscular and Subcutaneous

[0001306] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) modified as either Gen1 or Gen2 (5-methylcytosine (5mc) and a pseudouridine (ψ) modification, G-CSF-Gen1; or N1-5-methylcytosine (N1-5mc) and a ψ modification, G-CSF-Gen2) and formulated in formulation buffer were delivered to mice via intramuscular (IM) or subcutaneous (SC) injection. Injection of four doses or 2x 50ug (two sites) daily for three days (24 hrs interval) was performed. The fourth dose was administered 6 hrs before blood collection and CBC analysis. Controls included Luciferase (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) or the formulation buffer (F.Buffer). The mice were bled at 72 hours after the first mRNA injection (6 hours after the last modified mRNA dose) to determine the effect of mRNA-encoded human G-CSF on the neutrophil count. The dosing regimen is shown in Table 71 as are the resulting neutrophil counts (thousands/uL). In Table 71, an asterisk(*) indicates statistical significance at $p<0.05$.

[0001307] For intramuscular administration, the data reveal a four fold increase in neutrophil count above control at day 3 for the Gen1 G-CSF mRNA and a two fold increase for the Gen2 G-CSF mmRNA. For subcutaneous administration, the data reveal a two fold increase in neutrophil count above control at day 3 for the Gen2 G-CSF mRNA.

[0001308] These data demonstrate that both 5-methylcytidine/pseudouridine and 5-methylcytidine/N1-methyl-pseudouridine-modified mRNA can be biologically active, as evidenced by specific increases in blood neutrophil counts.

Table 71. Dosing Regimen

Gr.	Treatment	Route	N=	Dose (µg/mouse)	Dose Vol. (µl/mouse)	Dosing Vehicle	Neutroph Thous/uL
1	G-CSF (Gen1)	I.M	5	2x50ug (four doses)	50	F. buffer	840*

2	G-CSF (Gen1)	S.C	5	2x50ug (four doses)	50	F. buffer	430
3	G-CSF (Gen2)	I.M	5	2x50ug (four doses)	50	F. buffer	746*
4	G-CSF (Gen2)	S.C	5	2x50ug (four doses)	50	F. buffer	683
5	Luc (Gen1)	I.M.	5	2x50ug (four doses)	50	F. buffer	201
6	Luc (Gen1)	S.C.	5	2x50ug (four doses)	50	F. buffer	307
7	Luc (Gen2)	I.M	5	2x50ug (four doses)	50	F. buffer	336
8	Luc (Gen2)	S.C	5	2x50ug (four doses)	50	F. buffer	357
9	F. Buffer	I.M	4	0 (four doses)	50	F. buffer	245
10	F. Buffer	S.C.	4	0 (four doses)	50	F. buffer	509
11	Untreated	-	4			-	312

Example 52. Intravenous administration

[0001309] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) modified with 5-methylcytosine (5mc) and a pseudouridine (ψ) modification (Gen 1); or having no modifications and formulated in 10% lipoplex (RNAiMax) were delivered to mice at a dose of 50 ug RNA and in a volume of 100 ul via intravenous (IV) injection at days 0, 2 and 4. Neutrophils were measured at days 1, 5 and 8. Controls included non-specific mammalian RNA or the formulation buffer alone (F.Buffer). The mice were bled at days 1, 5 and 8 to determine the effect of modified mRNA-encoded human G-CSF to increase neutrophil count. The dosing regimen is shown in Table 72 as are the resulting neutrophil counts (thousands/uL; K/uL).

[0001310] For intravenous administration, the data reveal a four to five fold increase in neutrophil count above control at day 5 with G-CSF modified mRNA but not with unmodified G-CSF mRNA or non-specific controls. Blood count returned to baseline four days after the final injection. No other changes in leukocyte populations were observed.

[0001311] In Table 72, an asterisk(*) indicates statistical significance at $p<0.001$ compared to buffer.

[0001312] These data demonstrate that lipoplex-formulated 5-methylcytidine/pseudouridine-modified mRNA can be biologically active, when delivered through an I.V. route of administration as evidenced by specific increases in blood neutrophil counts. No other cell subsets were significantly altered. Unmodified G-CSF mRNA similarly administered showed no pharmacologic effect on neutrophil counts.

Table 72. Dosing Regimen

Gr.	Day	Treatment	N=	Dose Vol. (µl/mouse)	Dosing Vehicle	Neutrophil K/uL
1	1	G-CSF (Gen1)	5	100	10% lipoplex	2.91
2	5	G-CSF (Gen1)	5	100	10% lipoplex	5.32*
3	8	G-CSF (Gen1)	5	100	10% lipoplex	2.06
4	1	G-CSF (no modification)	5	100	10% lipoplex	1.88
5	5	G-CSF (no modification)	5	100	10% lipoplex	1.95
6	8	G-CSF (no modification)	5	100	10% lipoplex	2.09
7	1	RNA control	5	100	10% lipoplex	2.90
8	5	RNA control	5	100	10% lipoplex	1.68
9	8	RNA control	4	100	10% lipoplex	1.72
10	1	F. Buffer	4	100	10% lipoplex	2.51
11	5	F. Buffer	4	100	10% lipoplex	1.31
12	8	F. Buffer	4	100	10% lipoplex	1.92

Example 53. Saline formulation: Intramuscular Administration

A. Protein Expression

[0001313] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and human EPO mmRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1); G-CSF modified mRNA (modified with 5-methylcytosine (5mc) and pseudouridine (ψ)) and EPO modified mRNA (modified with N1-5-methylcytosine (N1-5mc) and ψ modification), were formulated in formulation buffer (150 mM sodium chloride, 2mM calcium chloride, 2mM phosphate, 0.5 mM EDTA at a pH of 6.5) and delivered to mice via intramuscular (IM) injection at a dose of 100 ug.

[0001314] Controls included Luciferase (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160

nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) or the formulation buffer (F.Buffer). The mice were bled at 13 hours after the injection to determine the concentration of the human polypeptide in serum in pg/mL. (G-CSF groups measured human G-CSF in mouse serum and EPO groups measured human EPO in mouse serum). The data are shown in Table 73.

Table 73. Dosing Regimen

Group	Treatment	N=	Dose Vol. (µl/mouse)	Dosing Vehicle	Average Protein Product pg/mL, serum
G-CSF	G-CSF	5	50	Saline	19.8
G-CSF	Luciferase	5	50	Saline	0.5
G-CSF	F. buffer	5	50	F. buffer	0.5
EPO	EPO	5	50	Saline	191.5
EPO	Luciferase	5	50	Saline	15.0
EPO	F. buffer			F. buffer	4.8

B. Dose Response

[0001315] Human EPO modified mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were formulated in formulation buffer and delivered to mice via intramuscular (IM) injection.

[0001316] Controls included Luciferase (mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine and pseudouridine) or the formulation buffer (F.Buffer). The mice were bled at 13 hours after the injection to determine the concentration of the human polypeptide in serum in pg/mL. The dose and expression are shown in Table 74.

Table 74. Dosing Regimen and Expression

Treatment	Dose Vol. (µl/mouse)	Average Protein Product pg/mL, serum
EPO	100	96.2
EPO	50	63.5
EPO	25	18.7

EPO	10	25.9
EPO	1	2.6
Luciferase	100	0.0
F. buffer	100	1.0

Example 54. EPO muti-dose/multi-administration

[0001317] Studies utilizing multiple intramuscular injection sites at one time point were designed and performed.

[0001318] The design of a single multi-dose experiment involved using human erythropoietin (EPO) mmRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or G-CSF mmRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) administered in formulation buffer. The dosing vehicle (F. buffer) was used as a control. The EPO and G-CSF modified mRNA were modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site.

[0001319] Animals (n=5), Sprague-Dawley rats, were injected IM (intramuscular) for the single unit dose of 100 ug (delivered to one thigh). For multi-dosing 6 doses of 100 ug (delivered to two thighs) were used for both EPO and G-CSF mmRNA. Control dosing involved use of buffer at a single dose. Human EPO blood levels were evaluated 13 hrs post injection.

[0001320] Human EPO protein was measured in rat serum 13 hrs post intramuscular injection. Five groups of rats were treated and evaluated. The results are shown in Table 75.

Table 75. Multi-dose study

Group	Treatment	Dose of mmRNA	Total Dose	Avg. Pg/mL human EPO, serum
1	Human EPO mmRNA	1 x 100 ug	100 ug	143
2	Human EPO mmRNA	6 x 100 ug	600 ug	256
3	G-CSF mmRNA	1 x 100 ug	100 ug	43
4	G-CSF mmRNA	6 x 100 ug	600 ug	58
5	Buffer Alone	--	--	20

Example 55. Signal Sequence Exchange Study

[0001321] Several variants of mmRNAs encoding human Granulocyte colony stimulating factor (G-CSF) (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were synthesized using modified nucleotides pseudouridine and 5-methylcytosine (pseudo-U/5mC). These variants included the G-CSF constructs encoding either the wild-type N terminal secretory signal peptide sequence (MAGPATQSPMKLMALQLLLWHSALWTVQEA; SEQ ID NO: 95), no secretory signal peptide sequence, or secretory signal peptide sequences taken from other mRNAs. These included sequences where the wild type G-CSF signal peptide sequence was replaced with the signal peptide sequence of either: human α-1-anti trypsin (AAT) (MMPSSVSWGILLLAGLCCLVPVSLA; SEQ ID NO: 94), human Factor IX (FIX) (MQRVNMIMAESPSLITICLLGYLLSAECTVFLDHENANKILNRPKR; SEQ ID NO: 96), human Prolactin (Prolac) (MKGSLLLLLVSNLLLCQSVAP; SEQ ID NO: 97), or human Albumin (Alb) (MKWVTFISLLFLFSSAYSRGVFRR; SEQ ID NO: 98).

[0001322] 250ng of modified mRNA encoding each G-CSF variant was transfected into HEK293A (293A in the table), mouse myoblast (MM in the table) (C2C12, CRL-1772, ATCC) and rat myoblast (RM in the table) (L6 line, CRL-1458, ATCC) cell lines in a 24 well plate using 1 ul of Lipofectamine 2000 (Life Technologies), each well containing 300,000 cells. The supernatants were harvested after 24 hrs and the secreted G-CSF protein was analyzed by ELISA using the Human G-CSF ELISA kit (Life Technologies). The data shown in Table 76 reveal that cells transfected with G-CSF mmRNA encoding the Albumin signal peptide secrete at least 12 fold more G-CSF protein than its wild type counterpart.

Table 76. Signal Peptide Exchange

Signal peptides	293A (pg/ml)	MM (pg/ml)	RM (pg/ml)
G-CSF Natural	9650	3450	6050
α-1-anti trypsin	9950	5000	8475
Factor IX	11675	6175	11675
Prolactin	7875	1525	9800
Albumin	122050	81050	173300
No Signal peptide	0	0	0

Example 56. Cytokine Study: PBMC

A. PBMC isolation and Culture

[0001323] 50 mL of human blood from two donors was received from Research Blood Components (lots KP30928 and KP30931) in sodium heparin tubes. For each donor, the blood was pooled and diluted to 70 mL with DPBS (SAFC Bioscience 59331C, lot 071M8408) and split evenly between two 50 mL conical tubes. 10 mL of Ficoll Paque (GE Healthcare 17-5442-03, lot 10074400) was gently dispensed below the blood layer. The tubes were centrifuged at 2000 rpm for 30 minutes with low acceleration and braking. The tubes were removed and the buffy coat PBMC layers were gently transferred to a fresh 50 mL conical and washed with DPBS. The tubes were centrifuged at 1450 rpm for 10 minutes.

[0001324] The supernatant was aspirated and the PBMC pellets were resuspended and washed in 50 mL of DPBS. The tubes were centrifuged at 1250 rpm for 10 minutes. This wash step was repeated, and the PBMC pellets were resuspended in 19 mL of Optimem I (Gibco 11058, lot 1072088) and counted. The cell suspensions were adjusted to a concentration of 3.0 x 10^6 cells / mL live cells.

[0001325] These cells were then plated on five 96 well tissue culture treated round bottom plates (Costar 3799) per donor at 50 uL per well. Within 30 minutes, transfection mixtures were added to each well at a volume of 50 uL per well. After 4 hours post transfection, the media was supplemented with 10 uL of Fetal Bovine Serum (Gibco 10082, lot 1012368)

B. Transfection Preparation

[0001326] mmRNA encoding human G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) (containing either (1) natural NTPs, (2) 100% substitution with 5-methyl cytidine and pseudouridine, or (3) 100% substitution with 5-methyl cytidine and N1-methyl-pseudouridine; mmRNA encoding luciferase (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site)

(containing either (1) natural NTPs or (2) 100% substitution with 5-methyl cytidine and pseudouridine) and TLR agonist R848 (Invivogen tlrl-r848) were diluted to 38.4 ng / uL in a final volume of 2500 uL Optimem I.

[0001327] Separately, 432 uL of Lipofectamine 2000 (Invitrogen 11668-027, lot 1070962) was diluted with 13.1 mL Optimem I. In a 96 well plate nine aliquots of 135 uL of each mmRNA, positive control (R-848) or negative control (Optimem I) was added to 135 uL of the diluted Lipofectamine 2000. The plate containing the material to be transfected was incubated for 20 minutes. The transfection mixtures were then transferred to each of the human PBMC plates at 50 uL per well. The plates were then incubated at 37 C. At 2, 4, 8, 20, and 44 hours each plate was removed from the incubator, and the supernatants were frozen.

[0001328] After the last plate was removed, the supernatants were assayed using a human G-CSF ELISA kit (Invitrogen KHC2032) and human IFN-alpha ELISA kit (Thermo Scientific 41105-2). Each condition was done in duplicate.

C. Results

[0001329] The ability of unmodified and modified mRNA (mmRNAs) to produce the encoded protein was assessed (G-CSF production) over time as was the ability of the mRNA to trigger innate immune recognition as measured by interferon-alpha production. Use of *in vitro* PBMC cultures is an accepted way to measure the immunostimulatory potential of oligonucleotides (Robbins et al., Oligonucleotides 2009 19:89-102; herein incorporated by reference in its entirety).

[0001330] Results were interpolated against the standard curve of each ELISA plate using a four parameter logistic curve fit. Shown in Tables 77 and 78 are the average from 2 separate PBMC donors of the G-CSF and IFN-alpha production over time as measured by specific ELISA.

[0001331] In the G-CSF ELISA, background signal from the Lipofectamine 2000 untreated condition was subtracted at each timepoint. The data demonstrated specific production of human G-CSF protein by human peripheral blood mononuclear is seen with G-CSF mRNA containing natural NTPs, 100% substitution with 5-methyl cytidine and pseudouridine, or 100% substitution with 5-methyl cytidine and N1-methyl-pseudouridine. Production of G-CSF was significantly increased through the use of

modified mRNA relative to unmodified mRNA, with the 5-methyl cytidine and N1-methyl-pseudouridine containing G-CSF mmRNA showing the highest level of G-CSF production. With regards to innate immune recognition, unmodified mRNA resulted in substantial IFN-alpha production, while the modified mRNA largely prevented interferon-alpha production. G-CSF mRNA fully modified with 5-methyl cytidine and N1-methyl-pseudouridine did not significantly increase cytokines whereas G-CSF mRNA fully modified with 5-methyl cytidine and pseudouridine induced IFN-alpha, TNF-alpha and IP10. Many other cytokines were not affected by either modification.

Table 77. G-CSF Signal

G-CSF signal - 2 Donor Average					
pg / mL	**2 Hr**	**4 Hr**	**8 Hr**	**20 Hr**	**44 Hr**
G-CSF (5mC/pseudouridine)	120.3	136.8	421.0	346.1	431.8
G-CSF (5mC/N1-methyl-pseudouridine)	256.3	273.7	919.3	1603.3	1843.3
G-CSF(Natural-no modification)	63.5	92.6	129.6	258.3	242.4
Luciferase (5mC/pseudouridine)	4.5	153.7	33.0	186.5	58.0

Table 78. IFN-alpha signal

IFN-alpha signal - 2 donor average					
pg / mL	**2 Hr**	**4 Hr**	**8 Hr**	**20 Hr**	**44 Hr**
G-CSF (5mC/pseudouridine)	21.1	2.9	3.7	22.7	4.3
G-CSF (5mC/N1-methyl-pseudouridine)	0.5	0.4	3.0	2.3	2.1
G-CSF(Natural)	0.0	2.1	23.3	74.9	119.7
Luciferase (5mC/pseudouridine)	0.4	0.4	4.7	1.0	2.4
R-848	39.1	151.3	278.4	362.2	208.1
Lpf. 2000 control	0.8	17.2	16.5	0.7	3.1

Example 57. Chemical modification ranges of modified mRNA

[0001332] Modified nucleotides such as, but not limited to, the chemical modifications 5-methylcytosine and pseudouridine have been shown to lower the innate immune response and increase expression of RNA in mammalian cells. Surprisingly, and not previously known, the effects manifested by the chemical modifications can be titrated when the amount of chemical modification is less than 100%. Previously, it was believed

that full modification was necessary and sufficient to elicit the beneficial effects of the chemical modifications and that less than 100% modification of an mRNA had little effect. However, it has now been shown that the benefits of chemical modification can be derived using less than complete modification and that the effects are target, concentration and modification dependent.

A. Modified RNA transfected in PBMC

[0001333] 960 ng of G-CSF mRNA modified with 5-methylcytosine (5mC) and pseudouridine (pseudoU) or unmodified G-CSF mRNA was transfected with 0.8 uL of Lipofectamine 2000 into peripheral blood mononuclear cells (PBMC) from three normal blood donors (D1, D2, D3). The G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was completely modified with 5mC and pseudoU (100% modification), not modified with 5mC and pseudoU (0% modification) or was partially modified with 5mC and pseudoU so the mRNA would contain 50% modification, 25% modification, 10% modification, %5 modification, 1% modification or 0.1% modification. A control sample of Luciferase (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified 5meC and pseudoU) was also analyzed for G-CSF expression. For TNF-alpha and IFN-alpha control samples of Lipofectamine2000, LPS, R-848, Luciferase (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified 5mC and pseudo), and P(I)P(C) were also analyzed. The supernatant was harvested and run by ELISA 22 hours after transfection to determine the protein expression. The expression of G-CSF is shown in Table 79 and the expression of IFN-alpha and TNF-alpha is shown in Table 80. The expression of IFN-alpha and TNF-alpha may be a secondary effect from the transfection of the G-CSF mRNA. Tables 79 and 80 show that the amount of chemical modification of G-CSF, IFN-alpha and TNF-alpha is titratable when the mRNA is not fully modified and the titratable trend is not the same for each target.

Table 79. G-CSF Expression

	G-CSF Expression (pg/ml)		
	D1	D2	D3
100% modification	270.3	151.6	162.2
50% modification	45.6	19.8	26.3

25% modification	23.6	10.8	8.9
10% modification	39.4	12.9	12.9
5% modification	70.9	26.8	26.3
1 % modification	70.3	26.9	66.9
0.1% modification	67.5	25.2	28.7
Luciferase	14.5	3.1	10.0

Table 80. IFN-alpha and TNF-alpha Expression

	IFN-alpha Expression (pg/ml)			TNF-alpha Expression (pg/ml)		
	D1	D2	D3	D1	D2	D3
100% modification	76.8	6.8	15.1	5.6	1.4	21.4
50% modification	22.0	5.5	257.3	4.7	1.7	12.1
25% modification	64.1	14.9	549.7	3.9	0.7	10.1
10% modification	150.2	18.8	787.8	6.6	0.9	13.4
5% modification	143.9	41.3	1009.6	2.5	1.8	12.0
1 % modification	189.1	40.5	375.2	9.1	1.2	25.7
0.1% modification	261.2	37.8	392.8	9.0	2.	13.7
0% modification	230.3	45.1	558.3	10.9	1.4	10.9
LF 200	0	0	1.5	45.8	2.8	53.6
LPS	0	0	1.0	114.5	70.0	227.0
R-848	39.5	11.9	183.5	389.3	256.6	410.6
Luciferase	9.1	0	3.9	4.5	2.7	13.6
P(I)P(C)	1498.1	216.8	238.8	61.2	4.4	69.1

B. Modified RNA transfected in HEK293

[0001334] Human embryonic kidney epithelial (HEK293) cells were seeded on 96-well plates at a density of 30,000 cells per well in 100 ul cell culture medium. 250 ng of modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) formulated with RNAiMAX™ (Invitrogen, Carlsbad, CA) was added to a well. The G-CSF was completely modified with 5mC and pseudoU (100% modification), not modified with 5mC and pseudoU (0% modification) or was partially modified with 5mC and pseudoU so the mRNA would contain 75% modification, 50% modification or 25% modification. Control samples (AK 5/2, mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1;

fully modified 5mC and pseudoU) and untreated) were also analyzed. The half-life of G-CSF mRNA fully modified with 5-methylcytosine and pseudouridine is approximately 8-10 hours. The supernatants were harvested after 16 hours and the secreted G-CSF protein was analyzed by ELISA. Table 81 shows that the amount of chemical modification of G-CSF is titratable when the mRNA is not fully modified.

Table 81. G-CSF Expression

	G-CSF Expression (ng/ml)
100% modification	118.4
75% modification	101.9
50% modification	105.7
25% modification	231.1
0% modification	270.9
AK 5/2	166.8
mCherry	0
Untreated	0

Example 58: *In Vivo* Delivery of Modified mRNA (mmRNA)

[0001335] Modified RNA was delivered to C57/BL6 mice intramuscularly, subcutaneously, or intravenously to evaluate the bio-distribution of modified RNA using luciferase. A formulation buffer used with all delivery methods contained 150mM sodium chloride, 2mM calcium chloride, 2 mM Na+-phosphate which included 1.4mM monobasic sodium phosphate and 0.6 mM of dibasic sodium phosphate, and 0.5 mM ethylenediaminetetraacetic acid (EDTA) was adjusted using sodium hydroxide to reach a final pH of 6.5 before being filtered and sterilized. A 1X concentration was used as the delivery buffer. To create the lipoplexed solution delivered to the mice, in one vial 50 μg of RNA was equilibrated for 10 minutes at room temperature in the delivery buffer and in a second vial 10 μl RNAiMAX™ was equilibrated for 10 minutes at room temperature in the delivery buffer. After equilibrium, the vials were combined and delivery buffer was added to reach a final volume of 100 μl which was then incubated for 20 minutes at room temperature. Luciferin was administered by intraperitoneal injection (IP) at 150 mg/kg to each mouse prior to imaging during the plateau phase of the luciferin exposure curve which was between 15 and 30 minutes. To create luciferin, 1 g of D-luciferin potassium or sodium salt was dissolved in 66.6 ml of distilled phosphate buffer solution (DPBS), not containing Mg2+ or Ca2+, to make a 15 mg/ml solution. The solution was gently

mixed and passed through a 0.2 μm syringe filter, before being purged with nitrogen, aliquoted and frozen at -80°C while being protected from light as much as possible. The solution was thawed using a waterbath if luciferin was not dissolved, gently mixed and kept on ice on the day of dosing.

[0001336] Whole body images were taken of each mouse 2, 8 and 24 hours after dosing. Tissue images and serum was collected from each mouse 24 hours after dosing. Mice administered doses intravenously had their liver, spleen, kidneys, lungs, heart, peri-renal adipose tissue and thymus imaged. Mice administered doses intramuscularly or subcutaneously had their liver, spleen, kidneys, lungs, peri-renal adipose tissue, and muscle at the injection site. From the whole body images the bioluminescence was measured in photon per second for each route of administration and dosing regimen.

A. Intramuscular Administration

[0001337] Mice were intramuscularly (I.M.) administered either modified luciferase mRNA fully modified with 5-methylcytosine and pseudouridine (Naked-Luc), lipoplexed modified luciferase mRNA fully modified with 5-methylcytosine and pseudouridine (Lipoplex-luc) (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site), lipoplexed modified granulocyte colony-stimulating factor (G-CSF) mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) (Lipoplex-Cytokine) or the formation buffer at a single dose of 50 μg of modified RNA in an injection volume of 50μl for each formulation in the right hind limb and a single dose of 5 μg of modified RNA in an injection volume of 50 μl in the left hind limb. The bioluminescence average for the luciferase expression signals for each group at 2, 8 and 24 hours after dosing are shown in Table 82. The bioluminescence showed a positive signal at the injection site of the 5 μg and 50 μg modified RNA formulations containing and not containing lipoplex.

Table 82. *In vivo* Biophotoic Imaging (I.M. Injection Route)

Formulation	Dose (ug)	Bioluminescence (photon/sec)		
		2 hours	8 hours	24 hours
Naked-Luc	5	224,000	683,000	927,000

Lipolplex-Luc	5	579,000	639,000	186,000
Lipoplex-G-CSF	5	64,600	85,600	75,100
Formulation Buffer	5	102,000	86,000	90,700
Naked-Luc	50	446,000	766,000	509,000
Lipolplex-Luc	50	374,000	501,000	332,000
Lipoplex-G-CSF	50	49,400	74,800	74,200
Formulation Buffer	50	59,300	69,200	63,600

B. Subcutaneous Administration

[0001338] Mice were subcutaneously (S.C.) administered either modified luciferase mRNA (Naked-Luc), lipoplexed modified luciferase mRNA (Lipoplex-luc), lipoplexed modified G-CSF mRNA (Lipoplex-G-CSF) or the formation buffer at a single dose of 50 μg of modified mRNA in an injection volume of 100 μl for each formulation. The bioluminescence average for the luciferase expression signals for each group at 2, 8 and 24 hours after dosing are shown in Table 83. The bioluminescence showed a positive signal at the injection site of the 50 μg modified mRNA formulations containing and not containing lipoplex.

Table 83. *In vivo* Biophotoic Imaging (S.C. Injection Route)

Formulation	Bioluminescence (photon/sec)		
	2 hours	8 hours	24 hours
Naked-Luc	3,700,000	8,060,000	2,080,000
Lipolplex-Luc	3,960,000	1,700,000	1,290,000
Lipoplex-G-CSF	123,000	121,000	117,000
Formulation Buffer	116,000	127,000	123,000

C. Intravenous Administration

[0001339] Mice were intravenously (I.V.) administered either modified luciferase mRNA (Naked-Luc), lipoplexed modified luciferase mRNA (Lipoplex-luc), lipoplexed modified G-CSF mRNA (Lipoplex-G-CSF) or the formation buffer at a single dose of 50 μg of modified mRNA in an injection volume of 100 μl for each formulation. The bioluminescence average for the luciferase expression signal in the spleen from each group at 2 hours after dosing is shown in Table 84. The bioluminescence showed a positive signal in the spleen of the 50 μg modified mRNA formulations containing lipoplex.

Table 84. *In vivo* Biophotoic Imaging (I.V. Injection Route)

Formulation	Bioluminescence (photon/sec) of the Spleen
Naked-Luc	58,400
Lipolplex-Luc	65,000
Lipoplex-G-CSF	57,100
Formulation Buffer	58,300

Example 59. Buffer Formulation Studies

[0001340] G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with N1-pseudouridine and 5-methylcytosine) or Factor IX modified mRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with N1-pseudouridine and 5-methylcytosine) in a buffer solution is administered intramuscularly to rats in an injection volume of 50 µl (n=5) at a modified mRNA dose of 200 ug per rat as described in Table 85. The modified mRNA is lyophilized in water for 1-2 days. It is then reconstituted in the buffers listed below to a target concentration of 6 mg/ml. Concentration is determined by OD 260. Samples are diluted to 4 mg/ml in the appropriate buffer before dosing.

[0001341] To precipitate the modified mRNA, 3M sodium acetate, pH 5.5 and pure ethanol are added at $1/10^{th}$ the total volume and 4 times the total volume of modified mRNA, respectively. The material is placed at -80C for a minimum of 1 hour. The material is then centrifuged for 30 minutes at 4000 rpm, 4C. The supernatant is removed and the pellet is centrifuged and washed 3x with 75% ethanol. Finally, the pellet is reconstituted with buffer to a target concentration of 6 mg/ml. Concentration is determined by OD 260. Samples are diluted to 4 mg/ml in the appropriate buffer before dosing. All samples are prepared by lyophilization unless noted below.

Table 85. Buffer Dosing Groups

Group	Treatment	Buffer	Dose (ug/rat)
1	G-CSF	0.9% Saline	200
	Factor IX	0.9% Saline	200
2	G-CSF	0.9% Saline + 2mM Calcium	200
	Factor IX	0.9% Saline + 2mM Calcium	200

3	G-CSF	Lactated Ringer's	200
	Factor IX	Lactated Ringer's	200
4	G-CSF	5% Sucrose	200
	Factor IX	5% Sucrose	200
5	G-CSF	5% Sucrose + 2mM Calcium	200
	Factor IX	5% Sucrose + 2mM Calcium	200
6	G-CSF	5% Mannitol	200
	Factor IX	5% Mannitol	200
7	G-CSF	5% Mannitol + 2mM Calcium	200
	Factor IX	5% Mannitol + 2mM Calcium	200
8	G-CSF	0.9% saline (precipitation)	200
	Factor IX	0.9% saline (precipitation)	200

[0001342] Serum samples are collected from the rats at various time intervals and analyzed for G-CSF or Factor IX protein expression using G-CSF or Factor IX ELISA.

Example 60. Multi-Dose Study

[0001343] Sprague-Dawley rats (n=8) are injected intravenously eight times (twice a week) over 28 days. The rats are injected with 0.5 mg/kg, 0.05 mg/kg, 0.005 mg/kg or 0.0005 mg/kg of human G-CSF modified mRNA of luciferase modified mRNA formulated in a lipid nanoparticle, 0.5 mg/kg of human G-CSF modified mRNA in saline, 0.2 mg/kg of the human G-CSF protein Neupogen or non-translatable human G-CSF modified mRNA formulated in a lipid nanoparticle. Serum is collected during pre-determined time intervals to evaluate G-CSF protein expression (8, 24 and 72 hours after the first dose of the week), complete blood count and white blood count (24 and 72 hours after the first dose of the week) and clinical chemistry (24 and 72 hours after the first dose of the week). The rats are sacrificed at day 29, 4 days after the final dosing, to determine the complete blood count, white blood count, clinical chemistry, protein expression and to evaluate the effect on the major organs by histopathology and necropsy. Further, an antibody assay is performed on the rats on day 29.

Example 61. LNP *in vivo* study

[0001344] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence, 5' cap, Cap1; fully modified with 5-methylcytosine and pseudouridine was formulated as a lipid nanoparticle

(LNP) using the syringe pump method. The LNP was formulated at a 20:1 weight ratio of total lipid to modified mRNA with a final lipid molar ratio of 50:10:38.5:1.5 (DLin-KC2-DMA: DSPC: Cholesterol: PEG-DMG). As shown in Table 86, the luciferase LNP formulation was characterized by particle size, zeta potential, and encapsulation.

Table 86. Luciferase Formulation

Formulation	NPA-098-1
Modified mRNA	Luciferase
Mean size	135 nm
	PDI: 0.08
Zeta at pH 7.4	-0.6 mV
Encaps. (RiboGr)	91 %

[0001345] As outlined in Table 87, the luciferase LNP formulation was administered to Balb-C mice (n=3) intramuscularly, intravenously and subcutaneously and a luciferase modified RNA formulated in PBS was administered to mice intravenously.

Table 87. Luciferase Formulations

Formulation	Vehicle	Route	Concentration (mg/ml)	Injection Volume (ul)	Amount of modified RNA (ug)	Dose (mg/kg)
Luc-LNP	PBS	IV	0.20	50	10	0.50
Luc-LNP	PBS	IM	0.20	50	10	0.50
Luc-LNP	PBS	SC	0.20	50	10	0.50
Luc-PBS	PBS	IV	0.20	50	10	0.50

[0001346] The mice administered the luciferase LNP formulation intravenously and intramuscularly were imaged at 2, 8, 24, 48, 120 and 192 hours and the mice administered the luciferase LNP formulation subcutaneously were imaged at 2, 8, 24, 48 and 120 hours to determine the luciferase expression as shown in Table 88. In Table 88, "NT" means not tested. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse.

Table 88. Luciferase Expression

Formulation	Route of Administration	Average Expression (photon/second)					
		2 hours	8 hours	24 hours	48 hours	120 hours	192 hours

Luc-LNP	IV	1.62E+08	3.00E+09	7.77E+08	4.98E+08	1.89E+08	6.08E+07
Luc-LNP	IM	4.85E+07	4.92E+08	9.02E+07	3.17E+07	1.22E+07	2.38E+06
Luc-LNP	SC	1.85E+07	9.79E+08	3.09E+08	4.94E+07	1.98E+06	NT
Luc-PBS	IV	3.61E+05	5.64E+05	3.19E+05	NT	NT	NT

[0001347] One mouse administered the LNP formulation intravenously was sacrificed at 8 hours to determine the luciferase expression in the liver and spleen. Also, one mouse administered the LNP formulation intramuscular was sacrificed at 8 hours to determine the luciferase expression of the muscle around the injection site and in the liver and spleen. As shown in Table 89, expression was seen in the both the liver and spleen after intravenous and intramuscular administration and in the muscle around the intramuscular injection site.

Table 89. Luciferase Expression in Tissue

Luciferase LNP: IV Administration	Expression (photon/second)
Liver	7.984E+08
Spleen	3.951E+08
Luciferase LNP: IM Administration	Expression (photon/second)
Muscle around the injection site	3.688E+07
Liver	1.507E+08
Spleen	1.096E+07

Example 62. Cytokine Study: PBMC

A. PBMC isolation and Culture

[0001348] 50 mL of human blood from two donors was received from Research Blood Components (lots KP30928 and KP30931) in sodium heparin tubes. For each donor, the blood was pooled and diluted to 70 mL with DPBS (SAFC Bioscience 59331C, lot 071M8408) and split evenly between two 50 mL conical tubes. 10 mL of Ficoll Paque (GE Healthcare 17-5442-03, lot 10074400) was gently dispensed below the blood layer. The tubes were centrifuged at 2000 rpm for 30 minutes with low acceleration and braking. The tubes were removed and the buffy coat PBMC layers were gently

transferred to a fresh 50 mL conical and washed with DPBS. The tubes were centrifuged at 1450 rpm for 10 minutes.

[0001349] The supernatant was aspirated and the PBMC pellets were resuspended and washed in 50 mL of DPBS. The tubes were centrifuged at 1250 rpm for 10 minutes. This wash step was repeated, and the PBMC pellets were resuspended in 19 mL of Optimem I (Gibco 11058, lot 1072088) and counted. The cell suspensions were adjusted to a concentration of 3.0 x 10^6 cells / mL live cells.

[0001350] These cells were then plated on five 96 well tissue culture treated round bottom plates (Costar 3799) per donor at 50 uL per well. Within 30 minutes, transfection mixtures were added to each well at a volume of 50 uL per well. After 4 hours post transfection, the media was supplemented with 10 uL of Fetal Bovine Serum (Gibco 10082, lot 1012368).

B. Transfection Preparation

[0001351] Modified mRNA encoding human G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) (containing either (1) natural NTPs, (2) 100% substitution with 5-methyl cytidine and pseudouridine, or (3) 100% substitution with 5-methyl cytidine and N1-methyl-pseudouridine; mRNA encoding luciferase (IVT cDNA sequence shown in SEQ ID NO: 61657; mRNA sequence shown in SEQ ID NO: 61658, polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1, fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site) (containing either (1) natural NTPs or (2) 100% substitution with 5-methyl cytidine and pseudouridine) and TLR agonist R848 (Invivogen tlrl-r848) were diluted to 38.4 ng / uL in a final volume of 2500 uL Optimem I.

[0001352] Separately, 110 uL of Lipofectamine 2000 (Invitrogen 11668-027, lot 1070962) was diluted with 6.76 mL Optimem I. In a 96 well plate nine aliquots of 135 uL of each mRNA, positive control (R-848) or negative control (Optimem I) was added to 135 uL of the diluted Lipofectamine 2000. The plate containing the material to be transfected was incubated for 20 minutes. The transfection mixtures were then transferred to each of the human PBMC plates at 50 uL per well. The plates were then incubated at

37°C. At 2, 4, 8, 20, and 44 hours each plate was removed from the incubator, and the supernatants were frozen.

[0001353] After the last plate was removed, the supernatants were assayed using a human G-CSF ELISA kit (Invitrogen KHC2032) and human IFN-alpha ELISA kit (Thermo Scientific 41105-2). Each condition was done in duplicate.

C. Protein and Innate Immune Response Analysis

[0001354] The ability of unmodified and modified mRNA to produce the encoded protein was assessed (G-CSF production) over time as was the ability of the mRNA to trigger innate immune recognition as measured by interferon-alpha production. Use of *in vitro* PBMC cultures is an accepted way to measure the immunostimulatory potential of oligonucleotides (Robbins et al., Oligonucleotides 2009 19:89-102).

[0001355] Results were interpolated against the standard curve of each ELISA plate using a four parameter logistic curve fit. Shown in Tables 90 and 91 are the average from 3 separate PBMC donors of the G-CSF, interferon-alpha (IFN-alpha) and tumor necrosis factor alpha (TNF-alpha) production over time as measured by specific ELISA.

[0001356] In the G-CSF ELISA, background signal from the Lipofectamine 2000 (LF2000) untreated condition was subtracted at each time point. The data demonstrated specific production of human G-CSF protein by human peripheral blood mononuclear is seen with G-CSF mRNA containing natural NTPs, 100% substitution with 5-methyl cytidine and pseudouridine, or 100% substitution with 5-methyl cytidine and N1-methyl-pseudouridine. Production of G-CSF was significantly increased through the use of 5-methyl cytidine and N1-methyl-pseudouridine modified mRNA relative to 5-methyl cytidine and pseudouridine modified mRNA.

[0001357] With regards to innate immune recognition, while both modified mRNA chemistries largely prevented IFN-alpha and TNF-alpha production relative to positive controls (R848, p(I)p(C)), significant differences did exist between the chemistries. 5-methyl cytidine and pseudouridine modified mRNA resulted in low but detectable levels of IFN-alpha and TNF-alpha production, while 5-methyl cytidine and N1-methyl-pseudouridine modified mRNA resulted in no detectable IFN-alpha and TNF-alpha production.

[0001358] Consequently, it has been determined that, in addition to the need to review more than one cytokine marker of the activation of the innate immune response, it has surprisingly been found that combinations of modifications provide differing levels of cellular response (protein production and immune activation). The modification, N1-methyl-pseudouridine, in this study has been shown to convey added protection over the standard combination of 5-methylcytidine/pseudouridine explored by others resulting in twice as much protein and almost 150 fold reduction in immune activation (TNF-alpha).

[0001359] Given that PBMC contain a large array of innate immune RNA recognition sensors and are also capable of protein translation, it offers a useful system to test the interdependency of these two pathways. It is known that mRNA translation can be negatively affected by activation of such innate immune pathways (Kariko et al. Immunity (2005) 23:165-175; Warren et al. Cell Stem Cell (2010) 7:618-630). Using PBMC as an in vitro assay system it is possible to establish a correlation between translation (in this case G-CSF protein production) and cytokine production (in this case exemplified by IFN-alpha and TNF-alpha protein production). Better protein production is correlated with lower induction of innate immune activation pathway, and new chemistries can be judged favorably based on this ratio (Table 92).

[0001360] In this study, the PC Ratio for the two chemical modifications, pseudouridine and N1-methyl-pseudouridine, both with 5-methy cytosine was 4742/141=34 as compared to 9944/1=9944 for the cytokine IFN-alpha. For the cytokine, TNF-alpha, the two chemistries had PC Ratios of 153 and 1243, respectively suggesting that for either cytokine, the N1-methyl-pseudouridine is the superior modification. In Tables 90 and 91, "NT" means not tested.

Table 90. G-CSF

G-CSF: 3 Donor Average (pg/ml)	
G-CSF 5-methylcytosine/ pseudouridine	4742
G-CSF 5-methylcytosine/ N1-methyl-pseudouridine	9944
Luciferase	18
LF2000	16

Table 91. IFN-alpha and TNF-alpha

	IFN-alpha: 3 Donor Average (pg/ml)	TNF-alpha: 3 Donor Average (pg/ml)
G-CSF 5-methylcytosine/pseudouridine	141	31
G-CSF 5-methylcytosine/ N1-methyl-pseudouridine	1	8
P(I)P(C)	1104	NT
R-848	NT	1477
LF2000	17	25

Table 92. G-CSF to Cytokine Ratios

	G-CSF/ IFN-alpha (ratio)		G-CSF/TNF-alpha (ratio)	
	5-methyl cytosine/ pseudouridine	5-methylcytosine/ N1-methyl-pseudouridine	5-methyl cytosine/ pseudouridine	5-methylcytosine/ N1-methyl-pseudouridine
PC Ratio	34	9944	153	1243

Example 63. *In Vitro* PBMC Studies: Percent modification

[0001361] 480 ng of G-CSF mRNA modified with 5-methylcytosine (5mC) and pseudouridine (pseudoU) or unmodified G-CSF mRNA was transfected with 0.4 uL of Lipofectamine 2000 into peripheral blood mononuclear cells (PBMC) from three normal blood donors (D1, D2, and D3). The G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was completely modified with 5mC and pseudoU (100% modification), not modified with 5mC and pseudoU (0% modification) or was partially modified with 5mC and pseudoU so the mRNA would contain 75% modification, 50% modification or 25% modification. A control sample of Luciferase (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified 5meC and pseudoU) was also analyzed for G-CSF expression. For TNF-alpha and IFN-alpha control samples of Lipofectamine2000, LPS, R-848, Luciferase (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified 5mC and pseudo), and P(I)P(C) were also analyzed. The supernatant was harvested and run by ELISA 22 hours

after transfection to determine the protein expression. The expression of G-CSF is shown in Table 93 and the expression of IFN-alpha and TNF-alpha is shown in Table 94. The expression of IFN-alpha and TNF-alpha may be a secondary effect from the transfection of the G-CSF mRNA. Tables 93 and 94 show that the amount of chemical modification of G-CSF, interferon alpha (IFN-alpha) and tumor necrosis factor-alpha (TNF-alpha) is titratable when the mRNA is not fully modified and the titratable trend is not the same for each target.

[0001362] By using PBMC as an *in vitro* assay system it is possible to establish a correlation between translation (in this case G-CSF protein production) and cytokine production (in this case exemplified by IFN-alpha protein production). Better protein production is correlated with lower induction of innate immune activation pathway, and the percentage modification of a chemistry can be judged favorably based on this ratio (Table 95). As calculated from Tables 93 and 94 and shown in Table 95, full modification with 5-methylcytidine and pseudouridine shows a much better ratio of protein/cytokine production than without any modification (natural G-CSF mRNA) (100-fold for IFN-alpha and 27-fold for TNF-alpha). Partial modification shows a linear relationship with increasingly less modification resulting in a lower protein/cytokine ratio.

Table 93. G-CSF Expression

	G-CSF Expression (pg/ml)		
	D1	**D2**	**D3**
100% modification	1968.9	2595.6	2835.7
75% modification	566.7	631.4	659.5
50% modification	188.9	187.2	191.9
25% modification	139.3	126.9	102.0
0% modification	194.8	182.0	183.3
Luciferase	90.2	0.0	22.1

Table 94. IFN-alpha and TNF-alpha Expression

	IFN-alpha Expression (pg/ml)			TNF-alpha Expression (pg/ml)		
	D1	**D2**	**D3**	**D1**	**D2**	**D3**
100% modification	336.5	78.0	46.4	115.0	15.0	11.1
75% modification	339.6	107.6	160.9	107.4	21.7	11.8
50% modification	478.9	261.1	389.7	49.6	24.1	10.4
25% modification	564.3	400.4	670.7	85.6	26.6	19.8
0% modification	1421.6	810.5	1260.5	154.6	96.8	45.9
LPS	0.0	0.6	0.0	0.0	12.6	4.3

R-848	0.5	3.0	14.1	655.2	989.9	420.4
P(I)P(C)	130.8	297.1	585.2	765.8	2362.7	1874.4
Lipid only	1952.2	866.6	855.8	248.5	82.0	60.7

Table 95. PC Ratio and Effect of Percentage of Modification

% Modification	Average G-CSF (pg/ml)	Average IFN-a (pg/ml)	Average TNF-a (pg/ml)	G-CSF/ IFN-alpha (PC ratio)	G-CSF/TNF-alpha (PC ratio)
100	2466	153	47	16	52
75	619	202	47	3.1	13
50	189	376	28	0.5	6.8
25	122	545	44	0.2	2.8
0	186	1164	99	0.16	1.9

Example 64. Modified RNA transfected in PBMC

[0001363] 500 ng of G-CSF mRNA modified with 5-methylcytosine (5mC) and pseudouridine (pseudoU) or unmodified G-CSF mRNA was transfected with 0.4 uL of Lipofectamine 2000 into peripheral blood mononuclear cells (PBMC) from three normal blood donors (D1, D2, and D3). The G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was completely modified with 5mC and pseudoU (100% modification), not modified with 5mC and pseudoU (0% modification) or was partially modified with 5mC and pseudoU so the mRNA would contain 50% modification, 25% modification, 10% modification, %5 modification, 1% modification or 0.1% modification. A control sample of mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified 5meC and pseudouridine), G-CSF fully modified with 5-methylcytosine and pseudouridine (Control G-CSF) and an untreated control was also analyzed for expression of G-CSF, tumor necrosis factor-alpha (TNF-alpha) and interferon-alpha (IFN-alpha). The supernatant was harvested 6 hours and 18 hours after transfection and run by ELISA to determine the protein expression. The expression of G-CSF, IFN-alpha, and TNF-alpha for Donor 1 is shown in Table 96, Donor 2 is shown in Table 97 and Donor 3 is shown in Table 98.

[0001364] Full 100% modification with 5-methylcytidine and pseudouridine resulted in the most protein translation (G-CSF) and the least amount of cytokine produced across all three human PBMC donors. Decreasing amounts of modification results in more cytokine

production (IFN-alpha and TNF-alpha), thus further highlighting the importance of fully modification to reduce cytokines and to improve protein translation (as evidenced here by G-CSF production).

Table 96. Donor 1

	G-CSF (pg/mL)		IFN-alpha (pg/mL)		TNF-alpha (pg/mL)	
	6 hours	18 hours	6 hours	18 hours	6 hours	18 hours
100% Mod	1815	2224	1	13	0	0
75% Mod	591	614	0	89	0	0
50% Mod	172	147	0	193	0	0
25% Mod	111	92	2	219	0	0
10% Mod	138	138	7	536	18	0
1% Mod	199	214	9	660	18	3
0.1% Mod	222	208	10	597	0	6
0 % Mod	273	299	10	501	10	0
Control G-CSF	957	1274	3	123	18633	1620
mCherry	0	0	0	10	0	0
Untreated	N/A	N/A	0	0	1	1

Table 97. Donor 2

	G-CSF (pg/mL)		IFN-alpha (pg/mL)		TNF-alpha (pg/mL)	
	6 hours	18 hours	6 hours	18 hours	6 hours	18 hours
100% Mod	2184	2432	0	7	0	11
75% Mod	935	958	3	130	0	0
50% Mod	192	253	2	625	7	23
25% Mod	153	158	7	464	6	6
10% Mod	203	223	25	700	22	39
1% Mod	288	275	27	962	51	66
0.1% Mod	318	288	33	635	28	5
0 % Mod	389	413	26	748	1	253
Control G-CSF	1461	1634	1	59	481	814
mCherry	0	7	0	1	0	0
Untreated	N/A	N/A	1	0	0	0

Table 98. Donor 3

	G-CSF (pg/mL)		IFN-alpha (pg/mL)		TNF-alpha (pg/mL)	
	6 hours	18 hours	6 hours	18 hours	6 hours	18 hours
100% Mod	6086	7549	7	658	11	11
75% Mod	2479	2378	23	752	4	35
50% Mod	667	774	24	896	22	18
25% Mod	480	541	57	1557	43	115
10% Mod	838	956	159	2755	144	123
1% Mod	1108	1197	235	3415	88	270
0.1% Mod	1338	1177	191	2873	37	363

0 % Mod	1463	1666	215	3793	74	429
Control G-CSF	3272	3603	16	1557	731	9066
mCherry	0	0	2	645	0	0
Untreated	N/A	N/A	1	1	0	8

Example 65. Innate Immune Response Study in BJ Fibroblasts

A. Single Transfection

[0001365] Human primary foreskin fibroblasts (BJ fibroblasts) were obtained from American Type Culture Collection (ATCC) (catalog # CRL-2522) and grown in Eagle's Minimum Essential Medium (ATCC, catalog # 30-2003) supplemented with 10% fetal bovine serum at 37°C, under 5% CO_2. BJ fibroblasts were seeded on a 24-well plate at a density of 300,000 cells per well in 0.5 ml of culture medium. 250 ng of modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (Gen1) or fully modified with 5-methylcytosine and N1-methyl-pseudouridine (Gen2) having Cap0, Cap1 or no cap was transfected using Lipofectamine 2000 (Invitrogen, catalog # 11668-019), following manufacturer's protocol. Control samples of poly I:C (PIC), Lipofectamine 2000 (Lipo), natural luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and natural G-CSF mRNA were also transfected. The cells were harvested after 18 hours, the total RNA was isolated and DNASE® treated using the RNeasy micro kit (catalog #74004) following the manufacturer's protocol. 100 ng of total RNA was used for cDNA synthesis using High Capacity cDNA Reverse Transcription kit (catalog #4368814) following the manufacturer's protocol. The cDNA was then analyzed for the expression of innate immune response genes by quantitative real time PCR using SybrGreen in a Biorad CFX 384 instrument following manufacturer's protocol. Table 99 shows the expression level of innate immune response transcripts relative to house-keeping gene HPRT (hypoxanthine phosphoribosytransferase) and is expressed as fold-induction relative to HPRT. In the table, the panel of standard metrics includes: RIG-I is retinoic acid inducible gene 1, IL6 is interleukin-6, OAS-1 is oligoadenylate synthetase 1, IFNb is interferon-beta, AIM2 is absent in melanoma-2, IFIT-1 is interferon-induced protein with

tetratricopeptide repeats 1, PKR is protein kinase R, TNFa is tumor necrosis factor alpha and IFNa is interferon alpha.

Table 99. Innate Immune Response Transcript Levels

Formulation	RIG-I	IL6	OAS-1	IFNb	AIM2	IFIT-1	PKR	TNFa	IFNa
Natural Luciferase	71.5	20.6	20.778	11.404	0.251	151.218	16.001	0.526	0.067
Natural G-CSF	73.3	47.1	19.359	13.615	0.264	142.011	11.667	1.185	0.153
PIC	30.0	2.8	8.628	1.523	0.100	71.914	10.326	0.264	0.063
G-CSF Gen1-UC	0.81	0.22	0.080	0.009	0.008	2.220	1.592	0.090	0.027
G-CSF Gen1-Cap0	0.54	0.26	0.042	0.005	0.008	1.314	1.568	0.088	0.038
G-CSF Gen1-Cap1	0.58	0.30	0.035	0.007	0.006	1.510	1.371	0.090	0.040
G-CSF Gen2-UC	0.21	0.20	0.002	0.007	0.007	0.603	0.969	0.129	0.005
G-CSF Gen2-Cap0	0.23	0.21	0.002	0.0014	0.007	0.648	1.547	0.121	0.035
G-CSF Gen2-Cap1	0.27	0.26	0.011	0.004	0.005	0.678	1.557	0.099	0.037
Lipo	0.27	0.53	0.001	0	0.007	0.954	1.536	0.158	0.064

B. Repeat Transfection

[0001366] Human primary foreskin fibroblasts (BJ fibroblasts) were obtained from American Type Culture Collection (ATCC) (catalog # CRL-2522) and grown in Eagle's Minimum Essential Medium (ATCC, catalog # 30-2003) supplemented with 10% fetal bovine serum at 37°C, under 5% CO_2. BJ fibroblasts were seeded on a 24-well plate at a density of 300,000 cells per well in 0.5 ml of culture medium. 250 ng of modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) unmodified, fully modified with 5-methylcytosine and pseudouridine (Gen1) or fully modified with 5-methylcytosine and N1-methyl-pseudouridine (Gen2) was transfected daily for 5 days following manufacturer's protocol. Control samples of Lipofectamine 2000 (L2000) and mCherry mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with

5-methylcytidine and pseudouridine) were also transfected daily for 5 days. The results are shown in Table 100.

[0001367] Unmodified mRNA showed a cytokine response in interferon-beta (IFN-beta) and interleukin-6 (IL-6) after one day. mRNA modified with at least pseudouridine showed a cytokine response after 2-3 days whereas mRNA modified with 5-methylcytosine and N1-methyl-pseudouridine showed a reduced response after 3-5 days.

Table 100. Cytokine Response

Formulation	Transfection	IFN-beta (pg/ml)	IL-6 (pg/ml)
G-CSF unmodified	6 hours	0	3596
	Day 1	1363	15207
	Day 2	238	12415
	Day 3	225	5017
	Day 4	363	4267
	Day 5	225	3094
G-CSF Gen 1	6 hours	0	3396
	Day 1	38	3870
	Day 2	1125	16341
	Day 3	100	25983
	Day 4	75	18922
	Day 5	213	15928
G-CSF Gen 2	6 hours	0	3337
	Day 1	0	3733
	Day 2	150	974
	Day 3	213	4972
	Day 4	1400	4122
	Day 5	350	2906
mCherry	6 hours	0	3278
	Day 1	238	3893
	Day 2	113	1833
	Day 3	413	25539
	Day 4	413	29233
	Day 5	213	20178
L2000	6 hours	0	3270
	Day 1	13	3933
	Day 2	388	567
	Day 3	338	1517
	Day 4	475	1594
	Day 5	263	1561

Example 66. *In vivo* detection of Innate Immune Response

[0001368] In an effort to distringuish the importance of different chemical modification of mRNA on *in vivo* protein production and cytokine response *in vivo*, female BALB/C mice (n=5) are injected intramuscularly with G-CSF mRNA (G-CSF mRNA unmod) (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160

nucleotides not shown in sequence;) with a 5'cap of Cap1 , G-CSF mRNA fully modified with 5-methylcytosine and pseudouridine (G-CSF mRNA 5mc/pU), G-CSF mRNA fully modified with 5-methylcytosine and N1-methyl-pseudouridine with (G-CSF mRNA 5mc/N1pU) or without a 5' cap (G-CSF mRNA 5mc/N1 pU no cap) or a control of either R848 or 5% sucrose as described in Table 101.

Table 101. Dosing Chart

Formulation	Route	Dose (ug/mouse)	Dose (ul)
G-CSF mRNA unmod	I.M.	200	50
G-CSF mRNA 5mc/pU	I.M.	200	50
G-CSF mRNA 5mc/N1pU	I.M.	200	50
G-CSF mRNA 5mc/N1pU no cap	I.M.	200	50
R848	I.M.	75	50
5% sucrose	I.M.	-	50
Untreated	I.M.	-	-

[0001369] Blood is collected at 8 hours after dosing. Using ELISA the protein levels of G-CSF, TNF-alpha and IFN-alpha is determined by ELISA. 8 hours after dosing, muscle is collected from the injection site and quantitative real time polymerase chain reaction (QPCR) is used to determine the mRNA levels of RIG-I, PKR, AIM-2, IFIT-1, OAS-2, MDA-5, IFN-beta, TNF-alpha, IL-6, G-CSF, CD45 in the muscle.

Example 67. *In vivo* detection of Innate Immune Response Study

[0001370] Female BALB/C mice (n=5) were injected intramuscularly with G-CSF mRNA (G-CSF mRNA unmod) (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence;) with a 5'cap of Cap1 , G-CSF mRNA fully modified with 5-methylcytosine and pseudouridine (G-CSF mRNA 5mc/pU), G-CSF mRNA fully modified with 5-methylcytosine and N1-methyl-pseudouridine with (G-CSF mRNA 5mc/N1pU) or without a 5' cap (G-CSF mRNA 5mc/N1 pU no cap) or a control of either R848 or 5% sucrose as described in Table 102. Blood is collected at 8 hours after dosing and using ELISA the protein levels of G-CSF and interferon-alpha (IFN-alpha) is determined by ELISA and are shown in Table 102.

[0001371] As shown in Table 102, unmodified, 5mc/pU, and 5mc/N1pU modified G-CSF mRNA resulted in human G-CSF expression in mouse serum. The uncapped

5mC/N1pU modified G-CSF mRNA showed no human G-CSF expression in serum, highlighting the importance of having a 5' cap structure for protein translation.

[0001372] As expected, no human G-CSF protein was expressed in the R848, 5% sucrose only, and untreated groups. Importantly, significant differences were seen in cytokine production as measured by mouse IFN-alpha in the serum. As expected, unmodified G-CSF mRNA demonstrated a robust cytokine response *in vivo* (greater than the R848 positive control). The 5mc/pU modified G-CSF mRNA did show a low but detectable cytokine response *in vivo*, while the 5mc/N1pU modified mRNA showed no detectable IFN-alpha in the serum (and same as vehicle or untreated animals).

[0001373] Also, the response of 5mc/N1pU modified mRNA was the same regardless of whether it was capped or not. These *in vivo* results reinforce the conclusion that 1) that unmodified mRNA produce a robust innate immune response, 2) that this is reduced, but not abolished, through 100% incorporation of 5mc/pU modification, and 3) that incorporation of 5mc/N1pU modifications results in no detectable cytokine response.

[0001374] Lastly, given that these injections are in 5% sucrose (which has no effect by itself), these result should accurately reflect the immunostimulatory potential of these modifications.

[0001375] From the data it is evident that N1pU modified molecules produce more protein while concomitantly having little or no effect on IFN-alpha expression. It is also evident that capping is required for protein production for this chemical modification. The Protein: Cytokine Ratio of 748 as compared to the PC Ratio for the unmodified mRNA (PC=9) means that this chemical modification is far superior as related to the effects or biological implications associated with IFN-alpha.

Table 102. Human G-CSF and Mouse IFN-alpha in serum

Formulation	Route	Dose (ug/mouse)	Dose (ul)	G-CSF protein (pg/ml)	IFN-alpha expression (pg/ml)	PC Ratio
G-CSF mRNA unmod	I.M.	200	50	605.6	67.01	9
G-CSF mRNA 5mc/pU	I.M.	200	50	356.5	8.87	40
G-CSF mRNA5mc/N1pU	I.M.	200	50	748.1	0	748
G-CSF mRNA5mc/N1pU no cap	I.M.	200	50	6.5	0	6.5
R848	I.M.	75	50	3.4	40.97	.08
5% sucrose	I.M.	-	50	0	1.49	0
Untreated	I.M.	-	-	0	0	0

Example 68: *In Vivo* Delivery of Modified RNA

[0001376] Protein production of modified mRNA was evaluated by delivering modified G-CSF mRNA or modified Factor IX mRNA to female Sprague Dawley rats (n=6). Rats were injected with 400 ug in 100 ul of G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (G-CSF Gen1), G-CSF mRNA fully modified with 5-methylcytosine and N1-methyl-pseudouridine (G-CSF Gen2) or Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (Factor IX Gen1) reconstituted from the lyophilized form in 5% sucrose. Blood was collected 8 hours after injection and the G-CSF protein level in serum was measured by ELISA. Table 103 shows the G-CSF protein levels in serum after 8 hours.

[0001377] These results demonstrate that both G-CSF Gen 1 and G-CSF Gen 2 modified mRNA can produce human G-CSF protein in a rat following a single intramuscular injection, and that human G-CSF protein production is improved when using Gen 2 chemistry over Gen 1 chemistry.

Table 103. G-CSF Protein in Rat Serum (I.M. Injection Route)

Formulation	G-CSF protein (pg/ml)
G-CSF Gen1	19.37
G-CSF Gen2	64.72
Factor IX Gen 1	2.25

Example 69. Chemical Modification: *In vitro* studies

A. *In vitro* Screening in PBMC

[0001378] 500 ng of G-CSF (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) mRNA fully modified with the chemical modification outlined Tables 104 and 105 was transfected with 0.4 uL Lipofectamine 2000 into peripheral blood mononuclear cells (PBMC) from three normal blood donors. Control samples of LPS, R848, P(I)P(C) and mCherry (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence, 5'cap, Cap1; fully modified with 5-methylcytosine

and pseudouridine) were also analyzed. The supernatant was harvested and stored frozen until analyzed by ELISA to determine the G-CSF protein expression, and the induction of the cytokines interferon-alpha (IFN-α) and tumor necrosis factor alpha (TNF-α). The protein expression of G-CSF is shown in Table 104, the expression of IFN-α and TNF-α is shown in Table 105.

[0001379] The data in Table 104 demonstrates that many, but not all, chemical modifications can be used to productively produce human G-CSF in PBMC. Of note, 100% N1-methyl-pseudouridine substitution demonstrates the highest level of human G-CSF production (almost 10-fold higher than pseudouridine itself). When N1-methyl-pseudouridine is used in combination with 5-methylcytidine a high level of human G-CSF protein is also produced (this is also higher than when pseudouridine is used in combination with 5 methylcytidine).

[0001380] Given the inverse relationship between protein production and cytokine production in PBMC, a similar trend is also seen in Table 105, where 100% substitution with N1-methyl-pseudouridine results no cytokine induction (similar to transfection only controls) and pseudouridine shows detectable cytokine induction which is above background.

[0001381] Other modifications such as N6-methyladenosine and alpha-thiocytidine appear to increase cytokine stimulation.

Table 104. Chemical Modifications and G-CSF Protein Expression

Chemical Modifications	G-CSF Protein Expression (pg/ml)		
	Donor 1	Donor 2	Donor 3
Pseudouridine	2477	1,909	1,498
5-methyluridine	318	359	345
N1-methyl-pseudouridine	21,495	16,550	12,441
2-thiouridine	932	1,000	600
4-thiouridine	5	391	218
5-methoxyuridine	2,964	1,832	1,800
5-methylcytosine and pseudouridine (1st set)	2,632	1,955	1,373
5-methylcytosine and N1-methyl-pseudouridine (1st set)	10,232	7,245	6,214
2'Fluoroguanosine	59	186	177
2'Fluorouridine	118	209	191
5-methylcytosine and pseudouridine (2nd set)	1,682	1,382	1,036
5-methylcytosine and N1-methyl-pseudouridine (2nd set)	9,564	8,509	7,141
5-bromouridine	314	482	291

5-(2-carbomethoxyvinyl)uridine	77	286	177
5-[3(1-E-propenylamino)uridine	541	491	550
α-thiocytidine	105	264	245
5-methylcytosine and pseudouridine (3rd set)	1,595	1,432	955
N1-methyladenosine	182	177	191
N6-methyladenosine	100	168	200
5-methylcytidine	291	277	359
N4-acetylcytidine	50	136	36
5-formylcytidine	18	205	23
5-methylcytosine and pseudouridine (4th set)	264	350	182
5-methylcytosine and N1-methyl-pseudouridine (4th set)	9,505	6,927	5,405
LPS	1,209	786	636
mCherry	5	168	164
R848	709	732	636
P(I)P(C)	5	186	182

Table 105. Chemical Modifications and Cytokine Expression

Chemical Modifications	IFN-α Expression (pg/ml)			TNF-α Expression (pg/ml)		
	Donor 1	Donor 2	Donor 3	Donor 1	Donor 2	Donor 3
Pseudouridine	120	77	171	36	81	126
5-methyluridine	245	135	334	94	100	157
N1-methyl-pseudouridine	26	75	138	101	106	134
2-thiouridine	100	108	154	133	133	141
4-thiouridine	463	258	659	169	126	254
5-methoxyuridine	0	64	133	39	74	111
5-methylcytosine and pseudouridine (1st set)	88	94	148	64	89	121
5-methylcytosine and N1-methyl-pseudouridine (1st set)	0	60	136	54	79	126
2'Fluoroguanosine	107	97	194	91	94	141
2'Fluorouridine	158	103	178	164	121	156
5-methylcytosine and pseudouridine (2nd set)	133	92	167	99	111	150
5-methylcytosine and N1-methyl-pseudouridine (2nd set)	0	66	140	54	97	149
5-bromouridine	95	86	181	87	106	157
5-(2-carbomethoxyvinyl)uridine	0	61	130	40	81	116
5-[3(1-E-propenylamino)uridine	0	58	132	71	90	119
α-thiocytidine	1,138	565	695	300	273	277
5-methylcytosine and pseudouridine (3rd set)	88	75	150	84	89	130

N1-methyladenosine	322	255	377	256	157	294
N6-methyladenosine	1,935	1,065	1,492	1,080	630	857
5-methylcytidine	643	359	529	176	136	193
N4-acetylcytidine	789	593	431	263	67	207
5-formylcytidine	180	93	88	136	30	40
5-methylcytosine and pseudouridine (4^{th} set)	131	28	18	53	24	29
5-methylcytosine and N1-methyl-pseudouridine (4^{th} set)	0	0	0	36	14	13
LPS	0	67	146	7,004	3,974	4,020
mCherry	100	75	143	67	100	133
R848	674	619	562	11,179	8,546	9,907
P(I)P(C)	470	117	362	249	177	197

B. *In vitro* Screening in HeLa Cells

[0001382] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37oG in 5% CO_2 atmosphere overnight. Next day, 83 ng of Luciferase modified RNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 106, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY).

[0001383] Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul were diluted in 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature.

[0001384] After 18 to 22 hours of incubation cells expressing luciferase were lysed with 100 ul of Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100 ul complete luciferase assay solution (Promega, Madison, WI). The lysate volumes were adjusted or diluted until no

more than 2 mio relative light units (RLU) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 106. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).The background signal of the plates without reagent was about 200 relative light units per well.

[0001385] These results demonstrate that many, but not all, chemical modifications can be used to productively produce human G-CSF in HeLa cells. Of note, 100% N1-methyl-pseudouridine substitution demonstrates the highest level of human G-CSF production.

Table 106. Relative Light Units of Luciferase

Chemical Modification	RLU
N6-methyladenosine (m6a)	534
5-methylcytidine (m5c)	138,428
N4-acetylcytidine (ac4c)	235,412
5-formylcytidine (f5c)	436
5-methylcytosine/pseudouridine, test A1	48,659
5-methylcytosine/N1-methyl-pseudouridine, test A1	190,924
Pseudouridine	655,632
1-methylpseudouridine (m1u)	1,517,998
2-thiouridine (s2u)	3387
5-methoxyuridine (mo5u)	253,719
5-methylcytosine/pseudouridine, test B1	317,744
5-methylcytosine/N1-methyl-pseudouridine, test B1	265,871
5-Bromo-uridine	43,276
5 (2 carbovinyl) uridine	531
5 (3-1E propenyl Amino) uridine	446
5-methylcytosine/pseudouridine, test A2	295,824
5-methylcytosine/N1-methyl-pseudouridine, test A2	233,921
5-methyluridine	50,932
α-Thio-cytidine	26,358
5-methylcytosine/pseudouridine, test B2	481,477
5-methylcytosine/N1-methyl-pseudouridine, test B2	271,989
5-methylcytosine/pseudouridine, test A3	438,831
5-methylcytosine/N1-methyl-pseudouridine, test A3	277,499
Unmodified Luciferase	234,802

C. *In vitro* Screening in Rabbit Reticulocyte Lysates

[0001386] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was modified with the chemical modification listed in Table 107 and were diluted in sterile nuclease-free water to a final amount of 250 ng in 10 ul. The diluted luciferase was added to 40 ul of freshly prepared Rabbit Reticulocyte Lysate and the *in vitro* translation reaction was done in a standard 1.5 mL polypropylene reaction tube (Thermo Fisher Scientific, Waltham, MA) at 30°C in a dry heating block. The translation assay was done with the Rabbit Reticulocyte Lysate (nuclease-treated) kit (Promega, Madison, WI) according to the manufacturer's instructions. The reaction buffer was supplemented with a one-to-one blend of provided amino acid stock solutions devoid of either Leucine or Methionine resulting in a reaction mix containing sufficient amounts of both amino acids to allow effective *in vitro* translation.

[0001387] After 60 minutes of incubation, the reaction was stopped by placing the reaction tubes on ice. Aliquots of the *in vitro* translation reaction containing luciferase modified RNA were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100ul complete luciferase assay solution (Promega, Madison, WI). The volumes of the *in vitro* translation reactions were adjusted or diluted until no more than 2 mio relative light units (RLUs) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 107. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).The background signal of the plates without reagent was about 200 relative light units per well.

[0001388] These cell-free translation results very nicely correlate with the protein production results in HeLa, with the same modifications generally working or not working in both systems. One notable exception is 5-formylcytidine modified luciferase mRNA which worked in the cell-free translation system, but not in the HeLa cell-based transfection system. A similar difference between the two assays was also seen with 5-formylcytidine modified G-CSF mRNA.

Table 107. Relative Light Units of Luciferase

Chemical Modification	RLU
N6-methyladenosine (m6a)	398

5-methylcytidine (m5c)	152,989
N4-acetylcytidine (ac4c)	60,879
5-formylcytidine (f5c)	55,208
5-methylcytosine/pseudouridine, test A1	349,398
5-methylcytosine/N1-methyl-pseudouridine, test A1	205,465
Pseudouridine	587,795
1-methylpseudouridine (m1u)	589,758
2-thiouridine (s2u)	708
5-methoxyuridine (mo5u)	288,647
5-methylcytosine/pseudouridine, test B1	454,662
5-methylcytosine/N1-methyl-pseudouridine, test B1	223,732
5-Bromo-uridine	221,879
5 (2 carbovinyl) uridine	225
5 (3-1E propenyl Amino) uridine	211
5-methylcytosine/pseudouridine, test A2	558,779
5-methylcytosine/N1-methyl-pseudouridine, test A2	333,082
5-methyluridine	214,680
α-Thio-cytidine	123,878
5-methylcytosine/pseudouridine, test B2	487,805
5-methylcytosine/N1-methyl-pseudouridine, test B2	154,096
5-methylcytosine/pseudouridine, test A3	413,535
5-methylcytosine/N1-methyl-pseudouridine, test A3	292,954
Unmodified Luciferase	225,986

Example 70. Chemical Modification: *In vivo* studies

A. *In vivo* Screening of G-CSF Modified mRNA

[0001389] Balb-C mice (n=4) are intramuscularly injected in each leg with modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), fully modified with the chemical modifications outlined in Table 108, is formulated in 1xPBS. A control of luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with pseudouridine and 5-methylcytosine) and a control of PBS are also tested. After 8 hours serum is collected to determine G-CSF protein levels cytokine levels by ELISA.

Table 108. G-CSF

mRNA	Chemical Modifications

G-CSF	Pseudouridine
G-CSF	5-methyluridine
G-CSF	2-thiouridine
G-CSF	4-thiouridine
G-CSF	5-methoxyuridine
G-CSF	2'-fluorouridine
G-CSF	5-bromouridine
G-CSF	5-[3(1-E-propenylamino)uridine)
G-CSF	alpha-thio-cytidine
G-CSF	5-methylcytidine
G-CSF	N4-acetylcytidine
G-CSF	Pseudouridine and 5-methylcytosine
G-CSF	N1-methyl-pseudouridine and 5-methylcytosine
Luciferase	Pseudouridine and 5-methylcytosine
PBS	None

B. *In vivo* Screening of Luciferase Modified mRNA

[0001390] Balb-C mice (n=4) were subcutaneously injected with 200ul containing 42 to 103 ug of modified luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), fully modified with the chemical modifications outlined in Table 109, was formulated in 1xPBS. A control of PBS was also tested. The dosages of the modified luciferase mRNA is also outlined in Table 109. 8 hours after dosing the mice were imaged to determine luciferase expression. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse.

[0001391] As demonstrated in Table 109, all luciferase mRNA modified chemistries demonstrated *in vivo* activity, with the exception of 2'-fluorouridine. In addition 1-methylpseudouridine modified mRNA demonstrated very high expression of luciferase (5-fold greater expression than pseudouridine containing mRNA).

Table 109. Luciferase Screening

mRNA	**Chemical Modifications**	**Dose (ug) of mRNA**	**Dose volume (ml)**	**Luciferase expression (photon/second)**
Luciferase	5-methylcytidine	83	0.72	1.94E+07
Luciferase	N4-acetylcytidine	76	0.72	1.11E07

Luciferase	Pseudouridine	95	1.20	1.36E+07
Luciferase	1-methylpseudouridine	103	0.72	7.40E+07
Luciferase	5-methoxyuridine	95	1.22	3.32+07
Luciferase	5-methyluridine	94	0.86	7.42E+06
Luciferase	5-bromouridine	89	1.49	3.75E+07
Luciferase	2'-fluoroguanosine	42	0.72	5.88E+05
Luciferase	2'-fluorocytidine	47	0.72	4.21E+05
Luciferase	2'-flurorouridine	59	0.72	3.47E+05
PBS	None	-	0.72	3.16E+05

Example 71. *In vivo* Screening of Combination Luciferase Modified mRNA

[0001392] Balb-C mice (n=4) were subcutaneously injected with 200ul of 100 ug of modified luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), fully modified with the chemical modifications outlined in Table 110, was formulated in 1x PBS. A control of PBS was also tested. 8 hours after dosing the mice were imaged to determine luciferase expression. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse.

[0001393] As demonstrated in Table 110, all luciferase mRNA modified chemistries (in combination) demonstrated *in vivo* activity. In addition the presence of N1-methyl-pseudouridine in the modified mRNA (with N4-acetylcytidine or 5 methylcytidine) demonstrated higher expression than when the same combinations where tested using with pseudouridine. Taken together, these data demonstrate that N1-methyl-pseudouridine containing luciferase mRNA results in improved protein expression in vivo whether used alone (Table 109) or when used in combination with other modified nulceotides (Table 110).

Table 110. Luciferase Screening Combinations

mRNA	Chemical Modifications	Luciferase expression (photon/second)
Luciferase	N4-acetylcytidine/pseudouridine	4.18E+06
Luciferase	N4-acetylcytidine/N1-methyl-pseudouridine	2.88E+07

Luciferase	5-methylcytidine/5-methoxyuridine	3.48E+07
Luciferase	5-methylcytidine/5-methyluridine	1.44E+07
Luciferase	5-methylcytidine/where 50% of the uridine is replaced with 2-thiouridine	2.39E+06
Luciferase	5-methylcytidine/pseudouridine	2.36E+07
Luciferase	5-methylcytidine/N1-methyl-pseudouridine	4.15E+07
PBS	None	3.59E+05

Example 72. Innate Immune Response in BJ Fibroblasts

[0001394] Human primary foreskin fibroblasts (BJ fibroblasts) are obtained from American Type Culture Collection (ATCC) (catalog #CRL-2522) and grown in Eagle's Minimum Essential Medium (ATCC, cat# 30-2003) supplemented with 10% fetal bovine serum at 37°C, under 5% CO2. BJ fibroblasts are seeded on a 24-well plate at a density of 130,000 cells per well in 0.5 ml of culture medium. 250 ng of modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (Gen1) or fully modified with 5-methylcytosine and N1-methyl-pseudouridine (Gen2) is transfected using Lipofectamine 2000 (Invitrogen, cat# 11668-019), following manufacturer's protocol. Control samples of Lipofectamine 2000 and unmodified G-CSF mRNA (natural G-CSF) are also transfected. The cells are transfected for five consecutive days. The transfection complexes are removed four hours after each round of transfection.

[0001395] The culture supernatant is assayed for secreted G-CSF (R&D Systems, catalog #DCS50), tumor necrosis factor-alpha (TNF-alpha) and interferon alpha (IFN-alpha by ELISA every day after transfection following manufacturer's protocols. The cells are analyzed for viability using CELL TITER GLO® (Promega, catalog #G7570) 6 hrs and 18 hrs after the first round of transfection and every alternate day following that. At the same time from the harvested cells, total RNA is isolated and treated with DNASE® using the RNAEASY micro kit (catalog #74004) following the manufacturer's protocol. 100 ng of total RNA is used for cDNA synthesis using the High Capacity cDNA Reverse Transcription kit (Applied Biosystems, cat #4368814) following the manufacturer's protocol. The cDNA is then analyzed for the expression of innate immune response genes by quantitative real time PCR using SybrGreen in a Biorad CFX 384 instrument following the manufacturer's protocol.

Example 73. *In vitro* Transcription with wild-type T7 polymerase

[0001396] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were fully modified with different chemistries and chemistry combinations listed in Tables 111-114 using wild-type T7 polymerase as previously described.

[0001397] The yield of the translation reactions was determined by spectrophometric measurement (OD260) and the yield for Luciferase is shown in Table 111 and G-CSF is shown in Table 113.

[0001398] The luciferase and G-CSF modified mRNA were also subjected to an enzymatic capping reaction and each modified mRNA capping reaction was evaluated for yield by spectrophometic measurement (OD260) and correct size assessed using bioanalyzer. The yield from the capping reaction for luciferase is shown in Table 112 and G-CSF is shown in Table 114.

Table 111. *In vitro* transcription chemistry for Luciferase

Chemical Modification	Yield (mg)
N6-methyladenosine	0.99
5-methylcytidine	1.29
N4-acetylcytidine	1.0
5-formylcytidine	0.55
Pseudouridine	2.0
N1-methyl-pseudouridine	1.43
2-thiouridine	1.56
5-methoxyuridine	2.35
5-methyluridine	1.01
α-Thio-cytidine	0.83
5-Br-uridine (5Bru)	1.96
5 (2 carbomethoxyvinyl) uridine	0.89
5 (3-1E propenyl Amino) uridine	2.01
N4-acetylcytidine/pseudouridine	1.34
N4-acetylcytidine/N1-methyl-pseudouridine	1.26
5-methylcytidine/5-methoxyuridine	1.38
5-methylcytidine/5-bromouridine	0.12
5-methylcytidine/5-methyluridine	2.97
5-methylcytidine/ half of the uridines are modified with 2-thiouridine	1.59
5-methylcytidine/2-thiouridine	0.90

5-methylcytidine/pseudouridine	1.83
5-methylcytidine/N1-methyl-pseudouridine	1.33

Table 112. Capping chemistry and yield for Luciferase modified mRNA

Chemical Modification	Yield (mg)
5-methylcytidine	1.02
N4-acetylcytidine	0.93
5-formylcytidine	0.55
Pseudouridine	2.07
N1-methyl-pseudouridine	1.27
2-thiouridine	1.44
5-methoxyuridine	2
5-methyluridine	0.8
α-Thio-cytidine	0.74
5-Br-uridine (5Bru)	1.29
5 (2 carbomethoxyvinyl) uridine	0.54
5 (3-1E propenyl Amino) uridine	1.39
N4-acetylcytidine/pseudouridine	0.99
N4-acetylcytidine/N1-methyl-pseudouridine	1.08
5-methylcytidine/5-methoxyuridine	1.13
5-methylcytidine/5-methyluridine	1.08
5-methylcytidine/ half of the uridines are modified with 2-thiouridine	1.2
5-methylcytidine/2-thiouridine	1.27
5-methylcytidine/pseudouridine	1.19
5-methylcytidine/N1-methyl-pseudouridine	1.04

Table 113. *In vitro* transcription chemistry and yield for G-CSF modified mRNA

Chemical Modification	Yield (mg)
N6-methyladenosine	1.57
5-methylcytidine	2.05
N4-acetylcytidine	3.13
5-formylcytidine	1.41
Pseudouridine	4.1
N1-methyl-pseudouridine	3.24
2-thiouridine	3.46
5-methoxyuridine	2.57
5-methyluridine	4.27
4-thiouridine	1.45
2'-F-uridine	0.96
α-Thio-cytidine	2.29
2'-F-guanosine	0.6

N-1-methyladenosine	0.63
5-Br-uridine (5Bru)	1.08
5 (2 carbomethoxyvinyl) uridine	1.8
5 (3-1E propenyl Amino) uridine	2.09
N4-acetylcytidine/pseudouridine	1.72
N4-acetylcytidine/N1-methyl-pseudouridine	1.37
5-methylcytidine/5-methoxyuridine	1.85
5-methylcytidine/5-methyluridine	1.56
5-methylcytidine/ half of the uridines are modified with 2-thiouridine	1.84
5-methylcytidine/2-thiouridine	2.53
5-methylcytidine/pseudouridine	0.63
N4-acetylcytidine/2-thiouridine	1.3
N4-acetylcytidine/5-bromouridine	1.37
5-methylcytidine/N1-methyl-pseudouridine	1.25
N4-acetylcytidine/pseudouridine	2.24

Table 114. Capping chemistry and yield for G-CSF modified mRNA

Chemical Modification	Yield (mg)
N6-methyladenosine	1.04
5-methylcytidine	1.08
N4-acetylcytidine	2.73
5-formylcytidine	0.95
Pseudouridine	3.88
N1-methyl-pseudouridine	2.58
2-thiouridine	2.57
5-methoxyuridine	2.05
5-methyluridine	3.56
4-thiouridine	0.91
2'-F-uridine	0.54
α-Thio-cytidine	1.79
2'-F-guanosine	0.14
5-Br-uridine (5Bru)	0.79
5 (2 carbomethoxyvinyl) uridine	1.28
5 (3-1E propenyl Amino) uridine	1.78
N4-acetylcytidine/pseudouridine	0.29
N4-acetylcytidine/N1-methyl-pseudouridine	0.33
5-methylcytidine/5-methoxyuridine	0.91
5-methylcytidine/5-methyluridine	0.61
5-methylcytidine/ half of the uridines are modified with 2-thiouridine	1.24
5-methylcytidine/pseudouridine	1.08
N4-acetylcytidine/2-thiouridine	1.34
N4-acetylcytidine/5-bromouridine	1.22
5-methylcytidine/N1-methyl-pseudouridine	1.56

Example 74. *In vitro* Transcription with mutant T7 polymerase

[0001399] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were fully modified with different chemistries and chemistry combinations listed in Tables 115-118 using a mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI).

[0001400] The yield of the translation reactions was determined by spectrophometric measurement (OD260) and the yield for Luciferase is shown in Tables 115 and G-CSF is shown in Tables 117.

[0001401] The luciferase and G-CSF modified mRNA were also subjected to an enzymatic capping reaction and each modified mRNA capping reaction was evaluated for yield by spectrophometic measurement (OD260) and correct size assessed using bioanalyzer. The yield from the capping reaction for luciferase is shown in Table 116 and G-CSF is shown in Table 118.

Table 115. *In vitro* transcription chemistry and yield for Luciferase modified mRNA

Chemical Modification	Yield (ug)
2'Fluorocytosine	71.4
2'Fluorouridine	57.5
5-methylcytosine/pseudouridine, test A	26.4
5-methylcytosine/N1-methyl-pseudouridine, test A	73.3
N1-acetylcytidine/2-fluorouridine	202.2
5-methylcytidine/2-fluorouridine	131.9
2-fluorocytosine/pseudouridine	119.3
2-fluorocytosine/N1-methyl-pseudouridine	107.0
2-fluorocytosine/2-thiouridine	34.7
2-fluorocytosine/5-bromouridine	81.0
2-fluorocytosine/2-fluorouridine	80.4
2-fluoroguanine/5-methylcytosine	61.2
2-fluoroguanine/5-methylcytosine/pseudouridine	65.0
2-fluoroguanine/5-methylcytidine/N1-methyl-pseudouridine	41.2
2-fluoroguanine/pseudouridine	79.1
2-fluoroguanine/N1-methyl-pseudouridine	74.6
5-methylcytidine/pseudouridine, test B	91.8
5-methylcytidine/N1-methyl-pseudouridine, test B	72.4
2'fluoroadenosine	190.98

Table 116. Capping chemistry and yield for Luciferase modified mRNA

Chemical Modification	Yield (ug)
2'Fluorocytosine	19.2
2'Fluorouridine	16.7
5-methylcytosine/pseudouridine, test A	7.0
5-methylcytosine/N1-methyl-pseudouridine, test A	21.5
N1-acetylcytidine/2-fluorouridine	47.5
5-methylcytidine/2-fluorouridine	53.2
2-fluorocytosine/pseudouridine	58.4
2-fluorocytosine/N1-methyl-pseudouridine	26.2
2-fluorocytosine/2-thiouridine	12.9
2-fluorocytosine/5-bromouridine	26.5
2-fluorocytosine/2-fluorouridine	35.7
2-fluoroguanine/5-methylcytosine	24.7
2-fluoroguanine/5-methylcytosine/pseudouridine	32.3
2-fluoroguanine/5-methylcytidine/N1-methyl-pseudouridine	31.3
2-fluoroguanine/pseudouridine	20.9
2-fluoroguanine/N1-methyl-pseudouridine	29.8
5-methylcytidine/pseudouridine, test B	58.2
5-methylcytidine/N1-methyl-pseudouridine, test B	44.4

Table 117. *In vitro* transcription chemistry and yield for G-CSF modified mRNA

Chemical Modification	Yield (ug)
2'Fluorocytosine	56.5
2'Fluorouridine	79.4
5-methylcytosine/pseudouridine, test A	21.2
5-methylcytosine/N1-methyl-pseudouridine, test A	77.1
N1-acetylcytidine/2-fluorouridine	168.6
5-methylcytidine/2-fluorouridine	134.7
2-fluorocytosine/pseudouridine	97.8
2-fluorocytosine/N1-methyl-pseudouridine	103.1
2-fluorocytosine/2-thiouridine	58.8
2-fluorocytosine/5-bromouridine	88.8
2-fluorocytosine/2-fluorouridine	93.9
2-fluoroguanine/5-methylcytosine	97.3
2-fluoroguanine/5-methylcytosine/pseudouridine	96.0
2-fluoroguanine/5-methylcytidine/N1-methyl-pseudouridine	82.0
2-fluoroguanine/pseudouridine	68.0
2-fluoroguanine/N1-methyl-pseudouridine	59.3
5-methylcytidine/pseudouridine, test B	58,7
5-methylcytidine/N1-methyl-pseudouridine, test B	78.0

Table 118. Capping chemistry and yield for G-CSF modified mRNA

Chemical Modification	Yield (ug)
2'Fluorocytosine	16.9
2'Fluorouridine	17.0
5-methylcytosine/pseudouridine, test A	10.6
5-methylcytosine/N1-methyl-pseudouridine, test A	22.7
N1-acetylcytidine/2-fluorouridine	19.9
5-methylcytidine/2-fluorouridine	21.3
2-fluorocytosine/pseudouridine	65.2
2-fluorocytosine/N1-methyl-pseudouridine	58.9
2-fluorocytosine/2-thiouridine	41.2
2-fluorocytosine/5-bromouridine	35.8
2-fluorocytosine/2-fluorouridine	36.7
2-fluoroguanine/5-methylcytosine	36.6
2-fluoroguanine/5-methylcytosine/pseudouridine	37.3
2-fluoroguanine/5-methylcytidine/N1-methyl-pseudouridine	30.7
2-fluoroguanine/pseudouridine	29.0
2-fluoroguanine/N1-methyl-pseudouridine	22.7
5-methylcytidine/pseudouridine, test B	60.4
5-methylcytidine/N1-methyl-pseudouridine, test B	33.0

Example 75. 2'O-methyl and 2'Fluoro compounds

[0001402] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were produced as fully modified versions with the chemistries in Table 119 and transcribed using mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI). 2' fluoro-containing mRNA were made using Durascribe T7, however, 2'Omethyl-containing mRNA could not be transcribed using Durascribe T7.

[0001403] Incorporation of 2'Omethyl modified mRNA might possibly be accomplished using other mutant T7 polymerases (Nat Biotechnol. (2004) 22:1155-1160; Nucleic Acids Res. (2002) 30:e138) or US Patent 7,309,570, the contents of each of which are incorporated herein by reference in their entirety. Alternatively, 2'OMe modifications could be introduced post-transcriptionally using enzymatic means.

[0001404] Introduction of modifications on the 2' group of the sugar has many potential advantages. 2'OMe substitutions, like 2' fluoro substitutions are known to protect against nucleases and also have been shown to abolish innate immune recognition when incorporated into other nucleic acids such as siRNA and anti-sense (incorporated in its entirety, Crooke, ed. Antisense Drug Technology, 2nd edition; Boca Raton: CRC press).

[0001405] The 2'Fluoro-modified mRNA were then transfected into HeLa cells to assess protein production in a cell context and the same mRNA were also assessed in a cell-free rabbit reticulocyte system. A control of unmodified luciferase (natural luciferase) was used for both transcription experiments, a control of untreated and mock transfected (Lipofectamine 2000 alone) were also analyzed for the HeLa transfection and a control of no RNA was analyzed for the rabbit reticulysates.

[0001406] For the HeLa transfection experiments, the day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37oG in 5% CO_2 atmosphere overnight. Next day, 83 ng of the 2'fluoro-containing luciferase modified RNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 119, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul were diluted in 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature. After 18 to 22 hours of incubation cells expressing luciferase were lysed with 100 ul of Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100 ul complete luciferase assay solution (Promega, Madison, WI). The lysate volumes were adjusted or diluted until no more than 2 mio relative light units (RLU) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 119. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).The background signal of the plates without reagent was about 200 relative light units per well.

[0001407] For the rabbit reticulocyte lysate assay, 2'-fluoro-containing luciferase mRNA were diluted in sterile nuclease-free water to a final amount of 250 ng in 10 ul and added to 40 ul of freshly prepared Rabbit Reticulocyte Lysate and the *in vitro* translation reaction was done in a standard 1.5 mL polypropylene reaction tube (Thermo Fisher Scientific, Waltham, MA) at 30°C in a dry heating block. The translation assay was done with the Rabbit Reticulocyte Lysate (nuclease-treated) kit (Promega, Madison, WI) according to the manufacturer's instructions. The reaction buffer was supplemented with a one-to-one blend of provided amino acid stock solutions devoid of either Leucine or Methionine resulting in a reaction mix containing sufficient amounts of both amino acids to allow effective *in vitro* translation. After 60 minutes of incubation, the reaction was stopped by placing the reaction tubes on ice.

[0001408] Aliquots of the *in vitro* translation reaction containing luciferase modified RNA were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100ul complete luciferase assay solution (Promega, Madison, WI). The volumes of the *in vitro* translation reactions were adjusted or diluted until no more than 2 mio relative light units (RLUs) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 120. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT). The background signal of the plates without reagent was about 160 relative light units per well.

[0001409] As can be seen in Table 119 and 120, multiple 2'Fluoro-containing compounds are active in vitro and produce luciferase protein.

Table 119. HeLa Cells

Chemical Modification	Concentration (ug/ml)	Volume (ul)	Yield (ug)	RLU
2'Fluoroadenosine	381.96	500	190.98	388.5
2'Fluorocytosine	654.56	500	327.28	2420
2'Fluoroguanine	541,795	500	270.90	11,705.5
2'Flurorouridine	944.005	500	472.00	6767.5
Natural luciferase	N/A	N/A	N/A	133,853.5
Mock	N/A	N/A	N/A	340
Untreated	N/A	N/A	N/A	238

Table 120. Rabbit Reticulysates

Chemical Modification	RLU
2'Fluoroadenosine	162

2'Fluorocytosine	208
2'Fluoroguanine	371,509
2'Flurorouridine	258
Natural luciferase	2,159,968
No RNA	156

Example 76. Luciferase in HeLa Cells using a combination of modifications

[0001410] To evaluate using of 2'fluoro-modified mRNA in combination with other modification a series of mRNA were transcribed using either wild-type T7 polymerase (non-fluoro-containing compounds) or using mutant T7 polymerases (fluyoro-containing compounds) as described in Example 75. All modified mRNA were tested by in vitro transfection in HeLa cells.

[0001411] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37oG in 5% CO_2 atmosphere overnight. Next day, 83 ng of Luciferase modified RNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 121, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul were diluted in 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature.

[0001412] After 18 to 22 hours of incubation cells expressing luciferase were lysed with 100 ul of Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100 ul complete luciferase assay solution (Promega, Madison, WI). The lysate volumes were adjusted or diluted until no more than 2 mio relative light units (RLU) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 121. The

plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).The background signal of the plates without reagent was about 200 relative light units per well.

[0001413] As evidenced in Table 121, most combinations of modifications resulted in mRNA which produced functional luciferase protein, including all the non-flouro containing compounds and many of the combinations containing 2'fluro modifications.

Table 121. Luciferase

Chemical Modification	RLU
N4-acetylcytidine/pseudouridine	113,796
N4-acetylcytidine/N1-methyl-pseudouridine	316,326
5-methylcytidine/5-methoxyuridine	24,948
5-methylcytidine/5-methyluridine	43,675
5-methylcytidine/half of the uridines modified with 50% 2-thiouridine	41,601
5-methylcytidine/2-thiouridine	1,102
5-methylcytidine/pseudouridine	51,035
5-methylcytidine/N1-methyl-pseudouridine	152,151
N4-acetylcytidine/2'Fluorouridine triphosphate	288
5-methylcytidine/2'Fluorouridine triphosphate	269
2'Fluorocytosine triphosphate /pseudouridine	260
2'Fluorocytosine triphosphate /N1-methyl-pseudouridine	412
2'Fluorocytosine triphosphate/2-thiouridine	427
2'Fluorocytosine triphosphate/5-bromouridine	253
2'Fluorocytosine triphosphate /2'Fluorouridine triphosphate	184
2'Fluoroguanine triphosphate/5-methylcytidine	321
2'Fluoroguanine triphosphate/5-methylcytidine/Pseudouridine	207
2'Fluoroguanine /5-methylcytidine/N1-methyl-psuedouridine	235
2'Fluoroguanine/pseudouridine	218
2'Fluoroguanine/N1-methyl-psuedouridine	247
5-methylcytidine/pseudouridine, test A	13,833
5-methylcytidine/N1-methyl-pseudouridine, test A	598
2'Fluorocytosine triphosphate	201
2'F luorouridine triphosphate	305
5-methylcytidine/pseudouridine, test B	115,401
5-methylcytidine/N1-methyl-pseudouridine, test B	21,034
Natural luciferase	30,801
Untreated	344
Mock	262

Example 77. G-CSF *In Vitro* Transcription

[0001414] To assess the activity of all our different chemical modifications in the context of a second open reading frame, we replicated experiments previously conducted using luciferase mRNA, with human G-CSF mRNA. G-CSF mRNA (mRNA sequence shown

in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were fully modified with the chemistries in Tables 122 and 123 using wild-type T7 polymerase (for all non-fluoro-containing compounds) or mutant T7 polymerase (for all fluoro-containing compounds). The mutant T7 polymerase was obtained commercially (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI).

[0001415] The modified RNA in Tables 122 and 123 were transfected *in vitro* in HeLa cells or added to rabbit reticulysates (250ng of modified mRNA) as indicated. A control of untreated, mock transfected (transfection reagent alone), G-CSF fully modified with 5-methylcytosine and N1-methyl-pseudouridine or luciferase control (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine were also analyzed. The expression of G-CSF protein was determined by ELISA and the values are shown in Tables 122 and 123. In Table 122, "NT" means not tested.

[0001416] As shown in Table 123, many, but not all, chemical modifications resulted in human G-CSF protein production. These results from cell-based and cell-free translation systems correlate very nicely with the same modifications generally working or not working in both systems. One notable exception is 5-formylcytidine modified G-CSF mRNA which worked in the cell-free translation system, but not in the HeLa cell-based transfection system. A similar difference between the two assays was also seen with 5-formylcytidine modified luciferase mRNA.

[0001417] As demonstrated in Table 123, many, but not all, G-CSF mRNA modified chemistries (when used in combination) demonstrated *in vivo* activity. In addition the presence of N1-methyl-pseudouridine in the modified mRNA (with N4-acetylcytidine or 5 methylcytidine) demonstrated higher expression than when the same combinations where tested using with pseudouridine. Taken together, these data demonstrate that N1-methyl-pseudouridine containing G-CSF mRNA results in improved protein expression *in vitro*.

Table 122. G-CSF Expression

Chemical Modification	G-CSF protein	G-CSF protein

	(pg/ml) HeLa cells	(pg/ml) Rabbit reticulysates cells
Pseudouridine	1,150,909	147,875
5-methyluridine	347,045	147,250
2-thiouridine	417,273	18,375
N1-methyl-pseudouridine	NT	230,000
4-thiouridine	107,273	52,375
5-methoxyuridine	1,715,909	201,750
5-methylcytosine/pseudouridine, Test A	609,545	119,750
5-methylcytosine/N1-methyl-pseudouridine , Test A	1,534,318	110,500
2'-Fluoro-guanosine	11,818	0
2'-Fluoro-uridine	60,455	0
5-methylcytosine/pseudouridine, Test B	358,182	57,875
5-methylcytosine/N1-methyl-pseudouridine , Test B	1,568,636	76,750
5-Bromo-uridine	186,591	72,000
5-(2carbomethoxyvinyl) uridine	1,364	0
5-[3(1-E-propenylamino) uridine	27,955	32,625
α-thio-cytidine	120,455	42,625
5-methylcytosine/pseudouridine, Test C	882,500	49,250
N1-methyl-adenosine	4,773	0
N6-methyl-adenosine	1,591	0
5-methyl-cytidine	646,591	79,375
N4-acetylcytidine	39,545	8,000
5-formyl-cytidine	0	24,000
5-methylcytosine/pseudouridine, Test D	87,045	47,750
5-methylcytosine/N1-methyl-pseudouridine , Test D	1,168,864	97,125
Mock	909	682
Untreated	0	0
5-methylcytosine/N1-methyl-pseudouridine , Control	1,106,591	NT
Luciferase control	NT	0

Table 123. Combination Chemistries in HeLa cells

Chemical Modification	G-CSF protein (pg/ml) HeLa cells
N4-acetylcytidine/pseudouridine	537,273
N4-acetylcytidine/N1-methyl-pseudouridine	1,091,818
5-methylcytidine/5-methoxyuridine	516,136
5-methylcytidine/5-bromouridine	48,864
5-methylcytidine/5-methyluridine	207,500
5-methylcytidine/2-thiouridine	33,409
N4-acetylcytidine/5-bromouridine	211,591
N4-acetylcytidine/2-thiouridine	46,136
5-methylcytosine/pseudouridine	301,364

5-methylcytosine/N1-methyl-pseudouridine	1,017,727
N4-acetylcytidine/2'Fluorouridine triphosphate	62,273
5-methylcytidine/2'Fluorouridine triphosphate	49,318
2'Fluorocytosine triphosphate/pseudouridine	7,955
2'Fluorocytosine triphosphate/N1-methyl-pseudouridine	1,364
2'Fluorocytosine triphosphate/2-thiouridine	0
2'Fluorocytosine triphosphate/5-bromouridine	1,818
2'Fluorocytosine triphosphate/2'Fluorouridine triphosphate	909
2'Fluoroguanine triphosphate/5-methylcytidine	0
2'Fluoroguanine triphosphate/5-methylcytidine/pseudouridine	0
2'Fluoroguanine triphosphate /5-methylcytidine/N1 methylpseudouridine	1,818
2'Fluoroguanine triphosphate/pseudouridine	1,136
2'Fluoroguanine triphosphate/2'Fluorocytosine triphosphate/N1-methyl-pseudouridine	0
5-methylcytidine/pseudouridine	617,727
5-methylcytidine/N1-methyl-pseudouridine	747,045
5-methylcytidine/pseudouridine	475,455
5-methylcytidine/N1-methyl-pseudouridine	689,091
5-methylcytosine/N1-methyl-pseudouridine, Control 1	848,409
5-methylcytosine/N1-methyl-pseudouridine, Control 2	581,818
Mock	682
Untreated	0
Luciferase 2'Fluorocytosine triphosphate	0
Luciferase 2'Fluorouridine triphosphate	0

Example 78. Screening of Chemistries

[0001418] The tables listed in below (Tables 124-126) summarize much of the *in vitro* and *in vitro* screening data with the different compounds presented in the previous examples. A good correlation exists between cell-based and cell-free translation assays. The same chemistry substitutions generally show good concordance whether tested in the context of luciferase or G-CSF mRNA. Lastly, N1-methyl-pseudouridine containing mRNA show a very high level of protein expression with little to no detectable cytokine stimulation in vitro and in vivo, and is superior to mRNA containing pseudouridine both *in vitro* and *in vivo*.

[0001419] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) were modified with naturally and non-

naturally occurring chemistries described in Tables 124 and 125 or combination chemistries described in Table 126 and tested using methods described herein.

[0001420] In Tables 125 and 126, "*" refers to *in vitro* transcription reaction using a mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI); "**" refers to the second result *in vitro* transcription reaction using a mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI); "***" refers to production seen in cell free translations (rabbit reticulocyte lysates); the protein production of HeLa is judged by "+," "+/-" and "-"; when referring to G-CSF PBMC "++++" means greater than 6,000 pg/ml G-CSF, "+++" means greater than 3,000 pg/ml G-CSF, "++" means greater than 1,500 pg/ml G-CSF, "+" means greater than 300 pg/ml G-CSF, "+/-" means 150-300 pg/ml G-CSF and the background was about 110 pg/ml; when referring to cytokine PBMC "++++" means greater than 1,000 pg/ml interferon-alpha (IFN-alpha), "+++" means greater than 600 pg/ml IFN-alpha, "++" means greater than 300 pg/ml IFN-alpha, "+" means greater than 100 pg/ml IFN-alpha, "-" means less than 100 pg/ml and the background was about 70 pg/ml; and "NT" means not tested. In Table 125, the protein production was evaluated using a mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI).

Table 124. Naturally Occurring

Common Name (symbol)	IVT (Luc)	IVT (G-CSF)	Protein (Luc; HeLa)	Protein (G-CSF; HeLa)	Protein (G-CSF; PBMC)	Cytokines (G-CSF; PBMC)	In Vivo Protein (Luc)	In Vivo Protein (G-CSF)
1-methyladenosine (m^1A)	Fail	Pass	NT	-	+/-	++	NT	NT
N^6-methyladenosine (m^6A)	Pass	Pass	-	-	+/-	++++	NT	NT
2'-O-methyladenosine (Am)	Fail*	Not Done	NT	NT	NT	NT	NT	NT
5-methylcytidine (m^5C)	Pass	Pass	+	+	+	++	+	NT
2'-O-methylcytidine (Cm)	Fail*	Not Done	NT	NT	NT	NT	NT	NT
2-thiocytidine (s^2C)	Fail	Fail	NT	NT	NT	NT	NT	NT
N^4-acetylcytidine (ac^4C)	Pass	Pass	+	+	+/-	+++	+	NT
5-formylcytidine	Pass	Pass	-***	-***	-	+	NT	NT

(f^5C)								
2'-O-methylguanosine (Gm)	Fail*	Not Done	NT	NT	NT	NT	NT	NT
inosine (I)	Fail	Fail	NT	NT	NT	NT	NT	NT
pseudouridine (Y)	Pass	Pass	+	+	++	+	+	NT
5-methyluridine (m^5U)	Pass	Pass	+	+	+/-	+	NT	NT
2'-O-methyluridine (Um)	Fail*	Not Done	NT	NT	NT	NT	NT	NT
1-methylpseudouridine (m^1Y)	Pass	Pass	+	Not Done	++++	-	+	NT
2-thiouridine (s^2U)	Pass	Pass	-	+	+	+	NT	NT
4-thiouridine (s^4U)	Fail	Pass		+	+/-	++	NT	NT
5-methoxyuridine (mo^5U)	Pass	Pass	+	+	++	-	+	NT
3-methyluridine (m^3U)	Fail	Fail	NT	NT	NT	NT	NT	NT

Table 125. Non-Naturally Occurring

Common Name	IVT (Luc)	IVT (G-CSF)	Protein (Luc; HeLa)	Protein (G-CSF; HeLa)	Protein (G-CSF; PBMC)	Cytokines (G-CSF; PBMC)	In Vivo Protein (Luc)	In Vivo Protein (G-CSF)
2'-F-ara-guanosine	Fail	Fail	NT	NT	NT	NT	NT	NT
2'-F-ara-adenosine	Fail	Fail	NT	NT	NT	NT	NT	NT
2'-F-ara-cytidine	Fail	Fail	NT	NT	NT	NT	NT	NT
2'-F-ara-uridine	Fail	Fail	NT	NT	NT	NT	NT	NT
2'-F-guanosine	Fail/Pass**	Pass/Fail**	+**	+/-	-	+	+	NT
2'-F-adenosine	Fail/Pass**	Fail/Fail**	-**	NT	NT	NT	NT	NT
2'-F-cytidine	Fail/Pass**	Fail/Pass**	+**	NT	NT	NT	+	NT
2'-F-uridine	Fail/Pass**	Pass/Pass**	+**	+	+/-	+	-	NT
2'-OH-ara-guanosine	Fail	Fail	NT	NT	NT	NT	NT	NT

2'-OH-ara-adenosine	Not Done	Not Done	NT	NT	NT	NT	NT	NT
2'-OH-ara-cytidine	Fail	Fail	NT	NT	NT	NT	NT	NT
2'-OH-ara-uridine	Fail	Fail	NT	NT	NT	NT	NT	NT
5-Br-Uridine	Pass	Pass	+	+	+	+	+	
5-(2-carbomethoxy vinyl) Uridine	Pass	Pass	-	-	+/-	-		
5-[3-(1-E-Propenylamino) Uridine (aka Chem 5)	Pass	Pass	-	+	+	-		
N6-(19-Amino-pentaoxanonadecyl) A	Fail	Fail	NT	NT	NT	NT	NT	NT
2-Dimethylamino guanosine	Fail	Fail	NT	NT	NT	NT	NT	NT
6-Aza-cytidine	Fail	Fail	NT	NT	NT	NT	NT	NT
a-Thio-cytidine	Pass	Pass	+	+	+/-	+++	NT	NT
Pseudo-isocytidine	NT	NT	NT	NT	NT	NT	NT	NT
5-Iodo-uridine	NT	NT	NT	NT	NT	NT	NT	NT
a-Thio-uridine	NT	NT	NT	NT	NT	NT	NT	NT
6-Aza-uridine	NT	NT	NT	NT	NT	NT	NT	NT
Deoxy-thymidine	NT	NT	NT	NT	NT	NT	NT	NT
a-Thio guanosine	NT	NT	NT	NT	NT	NT	NT	NT
8-Oxo-guanosine	NT	NT	NT	NT	NT	NT	NT	NT
O6-Methyl-guanosine	NT	NT	NT	NT	NT	NT	NT	NT
7-Deaza-guanosine	NT	NT	NT	NT	NT	NT	NT	NT
6-Chloro-purine	NT	NT	NT	NT	NT	NT	NT	NT
a-Thio-adenosine	NT	NT	NT	NT	NT	NT	NT	NT
7-Deaza-adenosine	NT	NT	NT	NT	NT	NT	NT	NT
5-iodo-cytidine	NT	NT	NT	NT	NT	NT	NT	NT

[0001421] In Table 126, the protein production of HeLa is judged by "+," "+/-" and "-"; when referring to G-CSF PBMC "++++" means greater than 6,000 pg/ml G-CSF, "+++" means greater than 3,000 pg/ml G-CSF, "++" means greater than 1,500 pg/ml G-CSF, "+" means greater than 300 pg/ml G-CSF, "+/-" means 150-300 pg/ml G-CSF and the background was about 110 pg/ml; when referring to cytokine PBMC "++++" means greater than 1,000 pg/ml interferon-alpha (IFN-alpha), "+++" means greater than 600 pg/ml IFN-alpha, "++" means greater than 300 pg/ml IFN-alpha, "+" means greater than 100 pg/ml IFN-alpha, "-" means less than 100 pg/ml and the background was about 70 pg/ml; "WT" refers to the wild type T7 polymerase, "MT" refers to mutant T7 polymerase (Durascribe® T7 Transcription kit (Cat. No. DS010925) (Epicentre®, Madison, WI) and "NT" means not tested.

Table 126. Combination Chemistry

Cytidine analog	Uridine analog	Purine	IVT Luc	IVT (G-CSF)	Protein (Luc; HeLa)	Protein (G-CSF; HeLa)	Protein (G-CSF; PBMC)	Cytokines (G-CSF; PBMC)	In Vivo Protein (Luc)
N4-acetylcytidine	pseudouridine	A,G	Pass WT	Pass WT	+	+	NT	NT	+
N4-acetylcytidine	N1-methyl-pseudouridine	A,G	Pass WT	Pass WT	+	+	NT	NT	+
5-methylcytidine	5-methoxyuridine	A,G	Pass WT	Pass WT	+	+	NT	NT	+
5-methylcytidine	5-bromouridine	A,G	Pass WT	Pass WT	Not Done	+	NT	NT	
5-methylcytidine	5-methyluridine	A,G	Pass WT	Pass WT	+	+	NT	NT	+
5-methylcytidine	50% 2-thiouridine; 50% uridine	A,G	Pass WT	Pass WT	+	NT	NT	NT	+
5-methylcytidine	100% 2-thiouridine	A,G	Pass WT	Pass WT	-	+	NT	NT	
5-methylcytid	pseudouridine	A,G	Pass WT	Pass WT	+	+	++	+	+

ine									
5-methylcytidine	N1-methyl-pseudouridine	A,G	Pass WT	Pass WT	+	+	++++	-	+
N4-acetylcytidine	2-thiouridine	A,G	Not Done	Pass WT	Not Done	+	NT	NT	NT
N4-acetylcytidine	5-bromouridine	A, G	Not Done	Pass WT	Not Done	+	NT	NT	NT
N4-acetylcytidine	2 Fluorouridine triphosphate	A,G	Pass	Pass	-	+	NT	NT	NT
5-methylcytidine	2 Fluorouridine triphosphate	A,G	Pass	Pass	-	+	NT	NT	NT
2 Fluorocytosine triphosphate	pseudouridine	A,G	Pass	Pass	-	+	NT	NT	NT
2 Fluorocytosine triphosphate	N1-methyl-pseudouridine	A,G	Pass	Pass	-	+/-	NT	NT	NT
2 Fluorocytosine triphosphate	2-thiouridine	A,G	Pass	Pass	-	-	NT	NT	NT
2 Fluorocytosine triphosphate	5-bromouridine	A,G	Pass	Pass	-	+/-	NT	NT	NT
2 Fluorocytosine triphosphate	2 Fluorouridine triphosphate	A,G	Pass	Pass	-	+/-	NT	NT	NT
5-methylcytidine	uridine	A,2 Fluoro GTP	Pass	Pass	-	-	NT	NT	NT
5-methylcytidine	pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	-	NT	NT	NT
5-methylcytidine	N1-methyl-pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	+/-	NT	NT	NT
2 Fluorocytosine	pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	+/-	NT	NT	NT

triphosphate									
2 Fluorocytosine triphosphate	N1-methyl-pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	-	NT	NT	NT

Example 79. 2'Fluoro Chemistries in PBMC

[0001422] The ability of G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) to trigger innate an immune response was determined by measuring interferon-alpha (IFN-alpha) and tumor necrosis factor-alpha (TNF-alpha) production. Use of *in vitro* PBMC cultures is an accepted way to measure the immunostimulatory potential of oligonucleotides (Robbins et al., Oligonucleotides 2009 19:89-102) and transfection methods are described herein. Shown in Table 127 are the average from 2 or 3 separate PBMC donors of the interferon-alpha (IFN-alpha) and tumor necrosis factor alpha (TNF-alpha) production over time as measured by specific ELISA. Controls of R848, P(I)P(C), LPS and Lipofectamine 2000 (L2000) were also analyzed.

[0001423] With regards to innate immune recognition, while both modified mRNA chemistries largely prevented IFN-alpha and TNF-alpha production relative to positive controls (R848, P(I)P(C)), 2'fluoro compounds reduce IFN-alpha and TNF-alpha production even lower than other combinations and N4-acetylcytidine combinations raised the cytokine profile.

Table 127. IFN-alpha and TNF-alpha

	IFN-alpha: 3 Donor Average (pg/ml)	**TNF-alpha: 2 Donor Average (pg/ml)**
L2000	1	361
P(I)P(C)	482	544
R848	45	8,235
LPS	0	6,889
N4-acetylcytidine/pseudouridine	694	528
N4-acetylcytidine/N1-methyl-pseudouridine	307	283
5-methylcytidine/5-methoxyuridine	0	411
5-methylcytidine/5-bromouridine	0	270
5-methylcytidine/5-methyluridine	456	428
5-methylcytidine/2-thiouridine	274	277
N4-acetylcytidine/2-thiouridine	0	285
N4-acetylcytidine/5-bromouridine	44	403

5-methylcytidine/pseudouridine	73	332
5-methylcytidine/N1-methyl-pseudouridine	31	280
N4-acetylcytidine/2'fluorouridine triphosphate	35	32
5-methylcytodine /2'fluorouridine triphosphate	24	0
2'fluorocytidine triphosphate/N1-methyl-pseudouridine	0	11
2'fluorocytidine triphosphate/2-thiouridine	0	0
2'fluorocytidine/ triphosphate5-bromouridine	12	2
2'fluorocytidine triphosphate/2'fluorouridine triphosphate	11	0
2'fluorocytidine triphosphate/5-methylcytidine	14	23
2'fluorocytidine triphosphate/5-methylcytidine/pseudouridine	6	21
2'fluorocytidine triphosphate/5-methylcytidine/N1-methyl-pseudouridine	3	15
2'fluorocytidine triphosphate/pseudouridine	0	4
2'fluorocytidine triphosphate/N1-methyl-pseudouridine	6	20
5-methylcytidine/pseudouridine	82	18
5-methylcytidine/N1-methyl-pseudouridine	35	3

Example 80. Modified mRNA with a Tobacco Etch Virus 5'UTR

[0001424] A 5′ untranslated region (UTR) may be provided as a flanking region. Multiple 5′ UTRs may be included in the flanking region and may be the same or of different sequences. Any portion of the flanking regions, including none, may be codon optimized and any may independently contain one or more different structural or chemical modifications, before and/or after codon optimization.

[0001425] The 5' UTR may comprise the 5'UTR from the tobacco etch virus (TEV). Variants of 5' UTRs may be utilized wherein one or more nucleotides are added or removed to the termini, including A, T, C or G.

Example 81. Expression of PLGA Formulated mRNA

A. Synthesis and Characterization of Luciferase PLGA Microspheres

[0001426] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine, modified with 25% of uridine replaced with 2-thiouridine and 25% of cytosine replaced with 5-methylcytosine, fully modified with N1-methyl-pseudouridine, or fully modified with pseudouridine was reconstituted in 1x TE buffer and then formulated in PLGA microspheres. PLGA microspheres were synthesized using the water/oil/water double emulsification methods

known in the art using PLGA-ester cap (Lactel, Cat# B6010-2, inherent viscosity 0.55-0.75, 50:50 LA:GA), polyvinylalcohol (PVA) (Sigma, Cat# 348406-25G, MW 13-23k) dichloromethane and water. Briefly, 0.4 ml of mRNA in TE buffer at 4 mg/ml (W1) was added to 2 ml of PLGA dissolved in dichloromethane (DCM) (O1) at a concentration of 200 mg/ml of PLGA. The W1/O1 emulsion was homogenized (IKA Ultra-Turrax Homogenizer, T18) for 30 seconds at speed 5 (~19,000 rpm). The W1/O1 emulsion was then added to 250 ml 1% PVA (W2) and homogenized for 1 minute at speed 5 (~19,000 rpm). Formulations were left to stir for 3 hours, then passed through a 100 μm nylon mesh strainer (Fisherbrand Cell Strainer, Cat # 22-363-549) to remove larger aggregates, and finally washed by centrifugation (10 min, 9,250 rpm, 4°C). The supernatant was discarded and the PLGA pellets were resuspended in 5-10 ml of water, which was repeated 2x. After washing and resuspension with water, 100-200 μl of a PLGA microspheres sample was used to measure particle size of the formulations by laser diffraction (Malvern Mastersizer2000). The washed formulations were frozen in liquid nitrogen and then lyophilized for 2-3 days.

[0001427] After lyophilization, ~10 mg of PLGA MS were weighed out in 2 ml eppendorf tubes and deformulated by adding 1 ml of DCM and letting the samples shake for 2-6 hrs. The mRNA was extracted from the deformulated PLGA micropsheres by adding 0.5 ml of water and shaking the sample overnight. Unformulated luciferase mRNA in TE buffer (unformulated control) was spiked into DCM and went through the deformulation process (deformulation control) to be used as controls in the transfection assay. The encapsulation efficiency, weight percent loading and particle size are shown in Table 128. Encapsulation efficiency was calculated as mg of mRNA from deformulation of PLGA microspheres divided by the initial amount of mRNA added to the formulation. Weight percent loading in the formulation was calculated as mg of mRNA from deformulation of PLGA microspheres divided by the initial amount of PLGA added to the formulation.

Table 128. PLGA Characteristics

Chemical Modifications	Sample ID	Encapsulation Efficiency (%)	Theoretical mRNA Loading (wt %)	Actual mRNA Loading (wt %)	Particle Size (D50, um)
Fully modified with	43-66A	45.8	0.4	0.18	33.4

5-methylcytosine and N1-methyl-pseudouridine	43-66B	29.6		0.12	27.7
	43-66C	25.5		0.10	27.1
25% of uridine replaced with 2-thiouridine and 25% of cytosine replaced with 5-methylcytosine	43-67A	34.6	0.4	0.14	29.9
	43-67B	22.8		0.09	30.2
	43-67C	23.9		0.10	25.1
Fully modified with N1-methyl-pseudouridine	43-69A	55.8	0.4	0.22	40.5
	43-69B	31.2		0.12	41.1
	43-69C	24.9		0.10	46.1
Fully modified with pseudouridine	43-68-1	49.3	0.4	0.20	34.8
	43-68-2	37.4		0.15	35.9
	43-68-3	45.0		0.18	36.5

B. Protein Expression of modified mRNA Encapsulated in PLGA Microspheres

[0001428] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37oC in a 5% CO2 atmosphere overnight. The next day, 83 ng of the deformulated luciferase mRNA PLGA microsphere samples, deformulated luciferase mRNA control (Deform control), or unformulated luciferase mRNA control (Unfomul control) was diluted in a 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as a transfection reagent and 0.2ul was diluted in a 10ul final volume of OPTI-MEM. After 5min of incubation at room temperature, both solutions were combined and incubated an additional 15min at room temperature. Then 20ul of the combined solution was added to 100ul of cell culture medium containing the HeLa cells. The plates were then incubated as described before.

[0001429] After an 18 to 22 hour incubation, cells expressing luciferase were lysed with 100ul Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100ul complete luciferase assay solution (Promega, Madison, WI). The background signal of the plates without reagent

was about 200 relative light units per well. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).

[0001430] Cells were harvested and the bioluminescence (in relative light units, RLU) for each sample is shown in Table 129. Transfection of these samples confirmed that the varied chemistries of luciferase mRNA is still able to express luciferase protein after PLGA microsphere formulation.

Table 129. Chemical Modifications

Chemical Modifications	Sample ID	Biolum. (RLU)
Fully modified with 5-methylcytosine and N1-methyl-pseudouridine	Deform contol	164266.5
	Unformul control	113714
	43-66A	25174
	43-66B	25359
	43-66C	20060
25% of uridine replaced with 2-thiouridine and 25% of cytosine replaced with 5-methylcytosine	Deform contol	90816.5
	Unformul control	129806
	43-67A	38329.5
	43-67B	8471.5
	43-67C	10991.5
Fully modified with N1-methyl-pseudouridine	Deform contol	928093.5
	Unformul control	1512273.5
	43-69A	1240299.5
	43-69B	748667.5
	43-69C	1193314
Fully modified with pseudouridine	Deform contol	154168
	Unformul control	151581
	43-68-1	120974.5
	43-68-2	107669
	43-68-3	97226

Example 82. *In vitro* studies of Factor IX

A. Serum-Free Media

[0001431] Human Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was transfected in serum-free media. The cell culture supernatant was collected and subjected to trypsin digestion before undergoing 2-dimensional HPLC separation of the peptides. Matrix-assisted laser

desorption/ionization was used to detect the peptides. 8 peptides were detected and 7 of the detected peptides are unique to Factor IX. These results indicate that the mRNA transfected in the serum-free media was able to express full-length Factor IX protein.

B. Human Embryonic Kidney (HEK) 293A Cells

[0001432] 250 ng of codon optimized Human Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 61652; fully modified with 5-methylcytosine and pseudouridine; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) was transfected into HEK 293A cells (150, 000 cells/well) using Lipofectamine 2000 in DMEM in presence of 10% FBS. The transfection complexes were removed 3 hours after transfection. Cells were harvested at 3, 6, 9, 12, 24, 48 and 72 hours after transfection. Total RNA was isolated and used for cDNA synthesis. The cDNA was subjected to analysis by quantitative Real-Time PCR using codon optimized Factor IX specific primer set. Human hypoxanthine phosphoribosyltransfersase 1 (HPRT) level was used for normalization. The data is plotted as a percent of detectable mRNA considering the mRNA level as 100% at the 3 hour time point. The half-life of Factor IX modified mRNA fully modified with 5-methylcytosine and pseudouridine in human embryonic kidney 293 (HEK293) cells is about 8-10 hours.

Example 83. Saline formulation: Subcutaneous Administration

[0001433] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) and human EPO modified mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine), were formulated in saline and delivered to mice via intramuscular (IM) injection at a dose of 100 ug.

[0001434] Controls included Luciferase (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine)) or the formulation buffer (F.Buffer). The mice were bled at 13 hours after the injection to determine the concentration of the human polypeptide in serum in pg/mL. (G-CSF groups measured human G-CSF in

mouse serum and EPO groups measured human EPO in mouse serum). The data are shown in Table 130.

[0001435] mRNA degrades rapidly in serum in the absence of formulation suggesting the best method to deliver mRNA to last longer in the system is by formulating the mRNA. As shown in Table 130, mRNA can be delivered subcutaneously using only a buffer formulation.

Table 130. Dosing Regimen

Group	Treatment	Dose Vol. (µl/mouse)	Dosing Vehicle	Average Protein Product pg/mL, serum
G-CSF	G-CSF	100	F. buffer	45
G-CSF	Luciferase	100	F. buffer	0
G-CSF	F. buffer	100	F. buffer	2.2
EPO	EPO	100	F. buffer	72.03
EPO	Luciferase	100	F. buffer	26.7
EPO	F. buffer	100	F. buffer	13.05

Example 84. Intravitreal Delivery

[0001436] mCherry modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) and luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) formulated in saline was delivered intravitreally in rats as described in Table 131. The sample was compared against a control of saline only delivered intravitreally.

Table 131. Dosing Chart

Group No.	Dose Level (µg modified RNA/eye)	Dose volume (µL/eye)	Treatment	
			Right Eye (OD)	Left Eye (OS)
Control	0	5	Delivery buffer only	Delivery buffer only
Modified RNA in delivery buffer	10	5	mCherry	Luciferase

[0001437] The formulation will be administered to the left or right eye of each animal on day 1 while the animal is anesthetized. On the day prior to administration gentamicin ophthalmic ointment or solution was applied to both eyes twice. The gentamicin ophthalmic ointment or solution was also applied immediately following the injection and on the day following the injection.Prior to dosing, mydriatic drops (1% tropicamide and/or 2.5% phenylephrine) are applied to each eye.

[0001438] 18 hours post dosing the eyes receiving the dose of mCherry and delivery buffer are enucleated and each eye was separately placed in a tube containing 10 mL 4% paraformaldehyde at room temperature for overnight tissue fixation. The following day, eyes will be separately transferred to tubes containing 10 mL of 30% sucurose and stored at 21°C until they were processed and sectioned. The slides prepared from different sections were evaluated under F-microscopy. Postive expression was seen in the slides prepared with the eyes administered mCherry modified mRNA and the control showed no expression.

Example 85. *In Vivo* Cytokine Expression Study

[0001439] Mice were injected intramuscularly with 200 ug of G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence) which was unmodified with a 5'cap, Cap1 (unmodified), fully modified with 5-methylcytosine and pseudouridine and a 5'cap, Cap1 (Gen1) or fully modified with 5-methylcytosine and N1-methyl-pseudouridine and a 5'cap, Cap1 (Gen2 cap) or no cap (Gen2 uncapped). Controls of R-848, 5% sucrose and untreated mice were also analyzed. After 8 hours serum was collected from the mice and analyzed for interferon-alpha (IFN-alpha) expression. The results are shown in Table 132.

Table 132. IFN-alpha Expression

Formulation	IFN-alpha (pg/ml)
G-CSF unmodified	67.012
G-CSF Gen1	8.867
G-CSF Gen2 cap	0
G-CSF Gen2 uncapped	0
R-848	40.971
5% sucrose	1.493
Untreated	0

Example 86. *In vitro* expression of VEGF modified mRNA

[0001440] HEK293 cells were transfected with modified mRNA (mmRNA) VEGF-A (mRNA sequence shown in SEQ ID NO: 61661; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) which had been complexed with Lipofectamine2000 from Invitrogen (Carlsbad, CA) at the concentration shown in Table 133. The protein expression was detected by ELISA and the protein (pg/ml) is shown in Table 133 and Figure 7.

Table 134. Protein Expression

Amount Transfected	10 ng	2.5 ng	625 pg	156 pg	39 pg	10 pg	2 pg	610 fg
Protein (pg/ml)	10495	10038	2321.23	189.6	0	0	0	0

Example 87. *In vitro* Screening in HeLa Cells of GFP

[0001441] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37°C in 5% CO_2 atmosphere overnight. Next day, 37.5 ng or 75 ng of Green Fluroescent protein (GFP) modified RNA (mRNA sequence shown in SEQ ID NO: 61660; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 134, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul were diluted in 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature.

[0001442] After an 18 to 22 hour incubation cells expressing luciferase were lysed with 100 ul of Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100 ul complete luciferase assay

solution (Promega, Madison, WI). The median fluorescence intensity (MFI) was determined for each chemistry and is shown in Table 134.

[0001443] These results demonstrate that GFP fully modified with N1-methyl-pseudouridine and 5-methylcytosine produces more protein in HeLa cells compared to the other chemistry. Additionally the higher dose of GFP administered to the cells resulted in the highest MFI value.

Table 134. Mean Fluorescence Intensity

Chemistry	37.5 ng	75 ng
	MFI	MFI
No modifications	97400	89500
5-methylcytosine/pseudouridine	324000	715000
5-methylcytosine/N1-methyl-pseudouridine	643000	1990000

Example 88. Homogenization

[0001444] Different luciferase mRNA solutions (as described in Table 135 where "X" refers to the solution containing that component) (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were evaluated to test the percent yield of the different solutions, the integrity of the mRNA by bioanalyzer, and the protein expression of the mRNA by in vitro transfection. The mRNA solutions were prepared in water, 1x TE buffer at 4 mg/ml as indicated in Table 135, and added to either dichloromethane (DCM) or DCM containing 200 mg/ml of poly(lactic-co-glycolic acid) (PLGA) (Lactel, Cat# B6010-2, inherent viscosity 0.55-0.75, 50:50 LA:GA) to achieve a final mRNA concentration of 0.8 mg/ml. The solutions requiring homogenization were homogenized for 30 seconds at speed 5 (approximately 19,000 rpm) (IKA Ultra-Turrax Homogenizer, T18). The mRNA samples in water, dicloromethane and poly(lactic-co-glycolic acid) (PLGA) were not recoverable (NR). All samples, except the NR samples, maintained integrity of the mRNA as determined by bioanalyzer (Bio-rad Experion).

[0001445] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas,

VA). The cells were grown at 37oC in a 5% CO2 atmosphere overnight. The next day, 250 ng of luciferase mRNA from the recoverable samples was diluted in a 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as a transfection reagent and 0.2ul was diluted in a 10ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minutes at room temperature. Then 20ul of the combined solution was added to 100ul of cell culture medium containing the HeLa cells. The plates were then incubated as described before. Controls luciferase mRNA (luciferase mRNA formulated in saline) (Control) and untreated cells (Untreat.) were also evaluated. Cells were harvested and the bioluminescence average (in photons/second) (biolum. (p/s)) for each signal is also shown in Table 135. The recoverable samples all showed activity of luciferase mRNA when analyzed.

[0001446] After an 18 to 22 hour incubation, cells expressing luciferase were lysed with 100ul Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100ul complete luciferase assay solution (Promega, Madison, WI). The background signal of the plates without reagent was about 200 relative light units per well. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).

[0001447] Cells were harvested and the bioluminescence average (in relative light units, RLU) (biolum. (RLU)) for each signal is also shown in Table 135. The recoverable samples all showed activity of luciferase mRNA when analyzed.

Table 135. Solutions

Solution No.	Water	1x TE Buffer	DCM	DCM/PLGA	Homogenizer	Yield (%)	Biolum. (RLU)
1	X					96	5423780
2		X			X	95	4911950
3	X				X	92	2367230
4		X			X	90	4349410
5	X		X		X	66	4145340
6		X	X		X	71	3834440
7	X			X	X	NR	n/a
8		X		X	X	24	3182080
9	X			X		NR	n/a
10		X		X		79	3276800

11	X		X			79	5563550
12		X	X			79	4919100
Control							2158060
Untreat.							3530

Example 89. TE Buffer and Water Evaluation

[0001448] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was reconstituted in water or TE buffer as outlined in Table 136 and then formulated in PLGA microspheres. PLGA microspheres were synthesized using the water/oil/water double emulsification methods known in the art using PLGA (Lactel, Cat# B6010-2, inherent viscosity 0.55-0.75, 50:50 LA:GA), polyvinylalcohol (PVA) (Sigma, Cat# 348406-25G, MW 13-23k) dichloromethane and water. Briefly, 0.2 to 0.6 ml of mRNA in water or TE buffer at a concentration of 2 to 6 mg/ml (W1) was added to 2 ml of PLGA dissolved in dichloromethane (DCM) (O1) at a concentration of 100 mg/ml of PLGA. The W1/O1 emulsion was homogenized (IKA Ultra-Turrax Homogenizer, T18) for 30 seconds at speed 5 (~19,000 rpm). The W1/O1 emulsion was then added to 250 ml 1% PVA (W2) and homogenized for 1 minute at speed 5 (~19,000 rpm).

[0001449] Formulations were left to stir for 3 hours, then passed through a 100 μm nylon mesh strainer (Fisherbrand Cell Strainer, Cat # 22-363-549) to remove larger aggregates, and finally washed by centrifugation (10 min, 9,250 rpm, 4°C). The supernatant was discarded and the PLGA pellets were resuspended in 5-10 ml of water, which was repeated 2x. The washed formulations were frozen in liquid nitrogen and then lyophilized for 2-3 days. After lyophilization, ~10 mg of PLGA MS were weighed out in 2 ml eppendorf tubes and deformulated by adding 1 ml of DCM and letting the samples shake for 2-6 hrs. mRNA was extracted from the deformulated PLGA micropsheres by adding 0.5 ml of water and shaking the sample overnight. Unformulated luciferase mRNA in water or TE buffer (deformulation controls) was spiked into DCM and went through the deformulation process to be used as controls in the transfection assay.

[0001450] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with

10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37oC in a 5% CO2 atmosphere overnight. The next day, 100 ng of the deformulated luciferase mRNA samples was diluted in a 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as a transfection reagent and 0.2ul was diluted in a 10ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minutes at room temperature. Then 20ul of the combined solution was added to 100ul of cell culture medium containing the HeLa cells. The plates were then incubated as described before.

[0001451] After 18 to 22 hour incubation, cells expressing luciferase were lysed with 100ul Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100ul complete luciferase assay solution (Promega, Madison, WI). The background signal of the plates without reagent was about 200 relative light units per well. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT). To determine the activity of the luciferase mRNA from each formulation, the relative light units (RLU) for each formulation was divided by the RLU of the appropriate mRNA deformulation control (mRNA in water or TE buffer). Table 136 shows the activity of the luciferase mRNA. The activity of the luciferase mRNA in the PLGA microsphere formulations (Form.) was substantitally improved by formulating in TE buffer versus water.

Table 136. Formulations

Form.	mRNA conc. (mg/ml)	W1 Solvent volume (ul)	Total mRNA (ug)	Theoretical mRNA Loading (wt%)	Actual mRNA Loading (wt%)	W1 Solvent	Activity (% of deformulation control)
PLGA A	4	400	1600	0.80	0.14	Water	12.5%
PLGA B	4	200	800	0.40	0.13	Water	1.3%
PLGA C	4	600	2400	1.20	0.13	Water	12.1%
PLGA D	2	400	800	0.40	0.07	Water	1.3%
PLGA E	6	400	2400	1.20	0.18	TE Buffer	38.9%
PLGA F	4	400	1600	0.80	0.16	TE Buffer	39.7%
PLGA G	4	400	1600	0.80	0.10	TE Buffer	26.6%

Example 90. Chemical Modifications on mRNA

[0001452] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (Life Technologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37°C in 5% CO_2 atmosphere overnight. The next day, 83 ng of Luciferase modified RNA (mRNA sequence shown SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 137, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul were diluted in 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature.

[0001453] After 18 to 22 hours of incubation cells expressing luciferase were lysed with 100 ul of Passive Lysis Buffer (Promega, Madison, WI) according to manufacturer instructions. Aliquots of the lysates were transferred to white opaque polystyrene 96-well plates (Corning, Manassas, VA) and combined with 100 ul complete luciferase assay solution (Promega, Madison, WI). The lysate volumes were adjusted or diluted until no more than 2 mio relative light units (RLU) per well were detected for the strongest signal producing samples and the RLUs for each chemistry tested are shown in Table 137. The plate reader was a BioTek Synergy H1 (BioTek, Winooski, VT).The background signal of the plates without reagent was about 200 relative light units per well.

Table 137. Chemical Modifications

Sample	RLU
Untreated	336
Unmodified Luciferase	33980
5-methylcytosine and pseudouridine	1601234
5-methylcytosine and N1-methyl-pseudouridine	421189
25% cytosines replaced with 5-methylcytosine and 25% of uridines replaced with 2-thiouridine	222114
N1-methyl-pseudouridine	3068261

Pseudouridine	140234
N4-Acetylcytidine	1073251
5-methoxyuridine	219657
5-Bromouridine	6787
N4-Acetylcytidineand N1-methyl-pseudouridine	976219
5-methylcytosine and 5-methoxyuridine	66621
5-methylcytosine and 2'fluorouridine	11333

Example 91. Intramuscular and Subcutaneous Administration of Modified mRNA

[0001454] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (5mC/pU), fully modified with 5-methylcytosine and N1-methyl-pseudouridine (5mC/N1mpU), fully modified with pseudouridine (pU), fully modified with N1-methyl-pseudouridine (N1mpU) or modified where 25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-thiouridine (5mC/s2U) formulated in PBS (pH 7.4) was administered to Balb-C mice intramuscularly or subcutaneously at a dose of 2.5 mg/kg. The mice were imaged at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours, 96 hours, 120 hours and 144 hours for intramuscular delivery and 2 hours, 8 hours, 24 hours, 48 hours, 72 hours, 96 hours and 120 hours for subcutaneous delivery. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The average total flux (photons/second) for intramuscular administration is shown in Table 138 and the average total flux (photons/second) for subcutaneous administration is shown in Table 139. The background signal was 3.79E+05 (p/s). The peak expression for intramuscular administration was seen between 24 and 48 hours for all chemistry and expression was still detected at 144 hours. For subcutaneous delivery the peak expression was seen at 2-8 hours and expression was detected at 72 hours.

Table 138. Intramuscular Administration

	5mC/pU	5mC/N1mpU	5mC/s2U	pU	N1mpU
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
2 hours	1.98E+07	4.65E+06	4.68E+06	2.33E+06	3.66E+07
8 hours	1.42E+07	3.64E+06	3.78E+06	8.07E+06	7.21E+07

24 hours	2.92E+07	1.22E+07	3.35E+07	1.01E+07	1.75E+08
48 hours	2.64E+07	1.01E+07	5.06E+07	7.46E+06	3.42E+08
72 hours	2.18E+07	8.59E+06	3.42E+07	4.08E+06	5.83E+07
96 hours	2.75E+07	2.70E+06	2.38E+07	4.35E+06	7.15E+07
120 hours	2.19E+07	1.60E+06	1.54E+07	1.25E+06	3.87E+07
144 hours	9.17E+06	2.19E+06	1.14E+07	1.86E+06	5.04E+07

Table 139. Subcutaneous Administration

	5mC/pU	5mC/N1mpU	5mC/s2U	pU	N1mpU
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
2 hours	5.26E+06	4.54E+06	9.34E+06	2.43E+06	2.80E+07
8 hours	2.32E+06	8.75E+05	8.15E+06	2.12E+06	3.09E+07
24 hours	2.67E+06	5.49E+06	3.80E+06	2.24E+06	1.48E+07
48 hours	1.22E+06	1.77E+06	3.07E+06	1.58E+06	1.24E+07
72 hours	1.12E+06	8.00E+05	8.53E+05	4.80E+05	2.29E+06
96 hours	5.16E+05	5.33E+05	4.30E+05	4.30E+05	6.62E+05
120 hours	3.80E+05	4.09E+05	3.21E+05	6.82E+05	5.05E+05

Example 92. Osmotic Pump Study

[0001455] Prior to implantation, an osmotic pump (ALZET® Osmotic Pump 2001D, DURECT Corp. Cupertino, CA) is loaded with the 0.2 ml of 1X PBS (pH 7.4) (PBS loaded pump) or 0.2 ml of luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) at 1 mg/ml in 1x PBS (pH 7.4) (Luciferase loaded pump) and incubated overnight in 1x PBS (pH 7.4) at 37°C.

[0001456] Balb-C mice (n=3) are implanted subcutaneously with either the PBS loaded pump or the luciferase loaded pump and imaged at 2 hours, 8 hours and 24 hours. As a control a PBS loaded pump is implanted subcutaneously and the mice are injected subcutaneously with luciferase modified mRNA in 1x PBS (PBS loaded pump; SC Luciferase) or an osmotic pump is not implanted and the mice are injected subcutaneously with luciferase modified mRNA in 1x PBS (SC Luciferase). The luciferase formulations are outlined in Table 140.

Table 140. Luciferase Formulations

Group	Vehicle	Conc	Inj. Vol.	Amt	Dose

		(mg/ml)	(ul)	(ug)	(mg/kg)
PBS loaded pump; SC Luciferase	PBS	1.00	50	50	2.5
Luciferase loaded pump	PBS	1.00	-	200	10.0
PBS loaded pump	PBS	-	-	-	-
SC Luciferase	PBS	1.00	50	50	2.5

Example 93. External Osmotic Pump Study

[0001457] An external osmotic pump (ALZET® Osmotic Pump 2001D, DURECT Corp. Cupertino, CA) is loaded with the 0.2 ml of 1X PBS (pH 7.4) (PBS loaded pump) or 0.2 ml of luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) at 1 mg/ml in 1x PBS (pH 7.4) (luciferase loaded pump) and incubated overnight in 1x PBS (pH 7.4) at 37°C.

[0001458] Using a catheter connected to the external PBS loaded pump or the luciferase loaded pump Balb-C mice (n=3) are administered the formulation. The mice are imaged at 2 hours, 8 hours and 24 hours. As a control an external PBS loaded pump is used and the mice are injected subcutaneously with luciferase modified mRNA in 1x PBS (PBS loaded pump; SC Luciferase) or the external pump is not used and the mice are only injected subcutaneously with luciferase modified mRNA in 1x PBS (SC Luciferase). Twenty minutes prior to imaging, mice are injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals are then anesthetized and images are acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence is measured as total flux (photons/second) of the entire mouse. The luciferase formulations are outlined in Table 141 and the average total flux (photons/second).

Table 141. Luciferase Formulations

Group	Vehicle	Conc (mg/ml)	Inj. Vol. (ul)	Amt (ug)	Dose (mg/kg)
PBS loaded pump; SC Luciferase	PBS	1.00	50	50	2.5
Luciferase loaded pump	PBS	1.00	-	200	10.0
PBS loaded pump	PBS	-	-	-	-
SC Luciferase	PBS	1.00	50	50	2.5

Example 94. Fibrin Sealant Study

[0001459] Fibrin sealant, such as Tisseel (Baxter Healthcare Corp., Deerfield, IL), is composed of fibrinogen and thrombin in a dual-barreled syringe. Upon mixing, fibrinogen is converted to fibrin to form a fibrin clot in about 10 to 30 seconds. This clot can mimic the natural clotting mechanism of the body. Additionally a fibrin hydrogel is a three dimensional structure that can potentially be used in sustained release delivery. Currently, fibrin sealant is approved for application in hemostasis and sealing to replace conventional surgical techniques such as suture, ligature and cautery.

[0001460] The thrombin and fibrinogen components were loaded separately into a dual barreled syringe. Balb-C mice (n=3) were injected subcutaneously with 50 ul of fibrinogen, 50 ul of thrombin and they were also injected at the same site with modified luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) (Tisseel+Luciferase), 50 ul of fibrinogen and 50 ul thrombin (Tisseel) or modified luciferase mRNA (Luciferase). The injection of fibrinogen and thrombin was done simultaneously using the dual-barreled syringe. The SC injection of luciferase was done 15 minutes after the fibrinogen/thrombin injection to allow the fibrin hydrogel to polymerize (Tisseel + Luciferase group). A control group of untreated mice were also evaluated. The mice were imaged at 5 hours and 24 hours. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The luciferase formulations are outlined in Table 142 and the average total flux (photons/second) is shown in Table 143. The fibrin sealant was found to not interfere with imaging and the injection of luciferase and Tisseel showed expression of luciferase.

Table 142. Luciferase Formulations

Group	Vehicle	Conc (mg/ml)	Inj. Vol. (ul)	Amt (ug)	Dose (mg/kg)
Tisseel+Luciferase	PBS	1.00	50	50	2.5
Tisseel	-	-	-	-	-
Luciferase	PBS	1.00	50	50	2.5
Untreated	-	-	-	-	-

Table 143. Total Flux

Group	5 Hours	24 Hours
	Flux (p/s)	Flux (p/s)
Tisseel+Luciferase	4.59E+05	3.39E+05
Tisseel	1.99E+06	1.06E+06
Luciferase	9.94E+05	7.44E+05
Untreated	3.90E+05	3.79E+05

Example 95. Fibrin Containing mRNA Sealant Study

A. Modified mRNA and Calcium Chloride

[0001461] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is added to calcium chloride. The calcium chloride is then used to reconstitute thrombin. Fibrinogen is reconstituted with fibrinolysis inhibitor solution per the manufacturer's instructions. The reconstituted thrombin containing modified mRNA and fibrinogen is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of fibrinogen and50 ul of thrombin containing modified mRNA or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

B. Lipid Nanoparticle Formulated Modified mRNA and Calcium Chloride

[0001462] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is formulated in a lipid nanoparticle is added to calcium chloride. The calcium chloride is then used to reconstitute thrombin. Fibrinogen is reconstituted with fibrinolysis inhibitor solution per the manufacturer's instructions. The reconstituted thrombin containing modified mRNA and fibrinogen is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of fibrinogen and50 ul of thrombin containing modified mRNA or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of

untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

C. Modified mRNA and Fibrinogen

[0001463] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is added to the fibrinolysis inhibitor solution. The fibrinolysis inhibitor solution is then used to reconstitute fibrinogen. Thrombin is reconstituted with the calcium chloride solution per the manufacturer's instructions. The reconstituted fibrinogen containing modified mRNA and thrombin is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of thrombin and 50 ul of fibrinogen containing modified mRNA or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

D. Lipid Nanoparticle Formualted Modified mRNA and Fibrinogen

[0001464] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is formulated in a lipid nanoparticle is added to the fibrinolysis inhibitor solution. The fibrinolysis inhibitor solution is then used to reconstitute fibrinogen. Thrombin is reconstituted with the calcium chloride solution per the manufacturer's instructions. The reconstituted fibrinogen containing modified mRNA and thrombin is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of thrombin and 50 ul of fibrinogen containing modified mRNA or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

E. Modified mRNA and Thrombin

[0001465] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap,

Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is added to the reconstituted thrombin after it is reconstituted with the calcium chloride per the manufactuer's instructions. The fibrinolysis inhibitor solution is then used to reconstitute fibrinogen per the manufacturer's instructions. The reconstituted fibrinogen and thrombin containing modified mRNA is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of thrombin containing modified mRNA and 50 ul of fibrinogen or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

F. Lipid Nanoparticle Formualted Modified mRNA and Thrombin

[0001466] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine or fully modified with N1-methyl-pseudouridine is formulated in a lipid nanoparticle is added to the reconstituted thrombin after it is reconstituted with the calcium chloride per the manufactuer's instructions. The fibrinolysis inhibitor solution is then used to reconstitute fibrinogen per the manufacturer's instructions. The reconstituted fibrinogen and thrombin containing modified mRNA is loaded into a dual barreled syringe. Mice are injected subcutaneously with 50 ul of thrombin containing modified mRNA and 50 ul of fibrinogen or they were injected with 50 ul of PBS containing an equivalent dose of modified luciferase mRNA. A control group of untreated mice is also evaluated. The mice are imaged at predetermined intervals to determine the average total flux (photons/second).

Example 96. Cationic Lipid Formulation of 5-Methylcytosine and N1-Methyl-pseudouridine Modified mRNA

[0001467] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine was formulated in the cationic

lipids described in Table 144. The formulations were administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg.

Table 144. Cationic Lipid Formulations

Formulation	NPA-126-1	NPA-127-1	NPA-128-1	NPA-129-1	111612-B
Lipid	DLin-MC3-DMA	DLin-KC2-DMA	C12-200	DLinDMA	DODMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1	20:1	20:1	20:1
Mean Size	122 nm PDI: 0.13	114 nm PDI: 0.10	153 nm PDI: 0.17	137 nm PDI: 0.09	223.2 nm PDI: 0.142
Zeta at pH 7.4	-1.4 mV	-0.5 mV	-1.4 mV	2.0 mV	-3.09 mV
Encaps. (RiboGr)	95%	77%	69%	80%	64%

[0001468] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 4.17E+05 p/s. The results of the imaging are shown in Table 145. In Table 145, "NT" means not tested.

Table 145. Flux

Route	**Time Point**	**DLin-MC3-DMA**	**DLin-KC2-DMA**	**C12-200**	**DLinDMA**	**DODMA**
		Flux (p/s)	**Flux (p/s)**	**Flux (p/s)**	**Flux (p/s)**	**Flux (p/s)**
I.V.	2 hrs	1.92E+08	2.91E+08	1.08E+08	2.53E+07	8.40E+06
I.V.	8 hrs	1.47E+08	2.13E+08	3.72E+07	3.82E+07	5.62E+06
I.V.	24 hrs	1.32E+07	2.41E+07	5.35E+06	4.20E+06	8.97E+05
I.M.	2 hrs	8.29E+06	2.37E+07	1.80E+07	1.51E+06	NT
I.M.	8 hrs	5.83E+07	2.12E+08	2.60E+07	1.99E+07	NT
I.M.	24 hrs	4.30E+06	2.64E+07	3.01E+06	9.46E+05	NT
S.C.	2 hrs	1.90E+07	5.16E+07	8.91E+07	4.66E+06	9.61E+06
S.C.	8 hrs	7.74E+07	2.00E+08	4.58E+07	9.67E+07	1.90E+07
S.C.	24 hrs	7.49E+07	2.47E+07	6.96E+06	6.50E+06	1.28E+06

Example 97. Lipid Nanoparticle Intravenous Study

[0001469] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was formulated in a lipid nanoparticle containing 50% DLin-MC3-DMA OR DLin-KC2-DMA as described in Table 146, 38.5% cholesterol, 10% DSPC and 1.5% PEG. The formulation was administered intravenously (I.V.) to Balb-C mice at a dose of 0.5 mg/kg, 0.05 mg/kg, 0.005 mg/kg or 0.0005 mg/kg. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse.

Table 146. Formulations

Formulation	NPA-098-1	NPA-100-1
Lipid	DLin-KC2-DMA	DLin-MC3-DMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1
Mean Size	135 nm PDI: 0.08	152 nm PDI: 0.08
Zeta at pH 7.4	-0.6 mV	-1.2 mV
Encaps. (RiboGr)	91%	94%

[0001470] For DLin-KC2-DMA the mice were imaged at 2 hours, 8 hours, 24 hours, 72 hours, 96 hours and 168 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 3.66E+05 p/s. The results of the imaging are shown in Table 147. Organs were imaged at 8 hours and the average total flux (photons/second) was measured for the liver, spleen, lung and kidney. A control for each organ was also analyzed. The results are shown in Table 149. The peak signal for all dose levels was at 8 hours after administration. Also, distribution to the various organs (liver, spleen, lung, and kidney) may be able to be controlled by increasing or decreasing the LNP dose.

Table 147. Flux

Time Point	0.5 mg/kg	0.05 mg/kg	0.005 mg/kg	0.0005 mg/kg
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
2 hrs	3.54E+08	1.75E+07	2.30E+06	4.09E+05
8 hrs	1.67E+09	1.71E+08	9.81E+06	7.84E+05
24 hrs	2.05E+08	2.67E+07	2.49E+06	5.51E+05

72 hrs	8.17E+07	1.43E+07	1.01E+06	3.75E+05
96 hrs	4.10E+07	9.15E+06	9.58E+05	4.29E+05
168 hrs	3.42E+07	9.15E+06	1.47E+06	5.29E+05

Table 148. Organ Flux

	Liver	Spleen	Lung	Kidney
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
0.5 mg/kg	1.42E+08	4.86E+07	1.90E+05	3.20E+05
0.05 mg/kg	7.45E+06	4.62E+05	6.86E+04	9.11E+04
0.005 mg/kg	3.32E+05	2.97E+04	1.42E+04	1.15E+04
0.0005 mg/kg	2.34E+04	1.08E+04	1.87E+04	9.78E+03
Untreated	1.88E+04	1.02E+04	1.41E+04	9.20E+03

[0001471] For DLin-MC3-DMA the mice were imaged at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours and 144 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 4.51E+05 p/s. The results of the imaging are shown in Table 149. Organs were imaged at 8 hours and the average total flux (photons/second) was measured for the liver, spleen, lung and kidney. A control for each organ was also analyzed. The results are shown in Table 150. The peak signal for all dose levels was at 8 hours after administration. Also, distribution to the various organs (liver, spleen, lung, and kidney) may be able to be controlled by increasing or decreasing the LNP dose.

Table 149. Flux

Time Point	0.5 mg/kg	0.05 mg/kg	0.005 mg/kg	0.0005 mg/kg
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
2 hrs	1.23E+08	7.76E+06	7.66E+05	4.88E+05
8 hrs	1.05E+09	6.79E+07	2.75E+06	5.61E+05
24 hrs	4.44E+07	1.00E+07	1.06E+06	5.71E+05
48 hrs	2.12E+07	4.27E+06	7.42E+05	4.84E+05
72 hrs	1.34E+07	5.84E+06	6.90E+05	4.38E+05
144 hrs	4.26E+06	2.25E+06	4.58E+05	3.99E+05

Table 150. Organ Flux

	Liver	Spleen	Lung	Kidney
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
0.5 mg/kg	1.19E+08	9.66E+07	1.19E+06	1.85E+05
0.05 mg/kg	1.10E+07	1.79E+06	7.23E+04	5.82E+04
0.005 mg/kg	3.58E+05	6.04E+04	1.33E+04	1.33E+04
0.0005 mg/kg	2.25E+04	1.88E+04	2.05E+04	1.65E+04
Untreated	1.91E+04	1.66E+04	2.63E+04	2.14E+04

Example 98. Lipid Nanoparticle Subcutaneous Study

[0001472] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) was formulated in a lipid nanoparticle containing 50% DLin-KC2-DMA as described in Table 151, 385% cholesterol, 10% DSPC and 1.5% PEG. The formulation was administered subcutaneously (S.C.) to Balb-C mice at a dose of 0.5 mg/kg, 0.05 mg/kg or 0.005 mg/kg.

Table 151. DLin-KC2-DMA Formulation

Formulation	NPA-098-1
Lipid	DLin-KC2-DMA
Lipid/mRNA ratio (wt/wt)	20:1
Mean Size	135 nm PDI: 0.08
Zeta at pH 7.4	-0.6 mV
Encaps. (RiboGr)	91%

[0001473] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours and 144 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The lower limit of detection was about 3E+05 p/s. The results of the imaging are shown in Table 152. Organs were imaged at 8 hours and the average total flux (photons/second) was measured for the liver, spleen, lung and kidney. A control for each organ was also analyzed. The results are shown in Table 153. The peak signal for all dose levels was at 8 hours after administration. Also, distribution to the various organs (liver, spleen, lung, and kidney) may be able to be controlled by increasing or decreasing the LNP dose. At high doses, the LNP formulations migrates outside of the subcutaneous injection site, as high levels of luciferase expression are detected in the liver, spleen, lung, and kidney.

Table 152. Flux

Time Point	0.5 mg/kg	0.05 mg/kg	0.005 mg/kg
	Flux (p/s)	Flux (p/s)	Flux (p/s)
2 hrs	3.18E+07	7.46E+06	8.94E+05
8 hrs	5.15E+08	2.18E+08	1.34E+07
24 hrs	1.56E+08	5.30E+07	7.16E+06
48 hrs	5.22E+07	8.75E+06	9.06E+05
72 hrs	8.87E+06	1.50E+06	2.98E+05
144 hrs	4.55E+05	3.51E+05	2.87E+05

Table 153. Organ Flux

	Liver	Spleen	Lung	Kidney
	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
0.5 mg/kg	1.01E+07	7.43E+05	9.75E+04	1.75E+05
0.05 mg/kg	1.61E+05	3.94E+04	4.04E+04	3.29E+04
0.005 mg/kg	2.84E+04	2.94E+04	2.42E+04	9.79E+04
Untreated	1.88E+04	1.02E+04	1.41E+04	9.20E+03

Example 99. Cationic Lipid Nanoparticle Subcutaneous Study

[0001474] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) is formulated in a lipid nanoparticle containing 50% DLin-MC3-DMA, 38.5% cholesterol, 10% DSPC and 1.5% PEG. The formulation is administered subcutaneously (S.C.) to Balb-C mice at a dose of 0.5 mg/kg, 0.05 mg/kg or 0.005 mg/kg.

[0001475] The mice are imaged at 2 hours, 8 hours, 24 hours, 48 hours, 72 hours and 144 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. Organs are imaged at 8 hours and the average total flux (photons/second) is measured for the liver, spleen, lung and kidney. A control for each organ is also analyzed.

Example 100. Luciferase Lipoplex Study

[0001476] Lipoplexed luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (5mC/pU), fully modified with 5-methylcytosine and N1-methyl-pseudouridine (5mC/N1mpU) or modified where 25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-

thiouridine (5mC/s2U). The formulation was administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.10 mg/kg.

[0001477] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 8 hours, 24 hours and 48 hours after dosing and the average total flux (photons/second) was measured for each route of administration and chemical modification. The background signal was about 3.91E+05 p/s. The results of the imaging are shown in Table 154. Organs were imaged at 6 hours and the average total flux (photons/second) was measured for the liver, spleen, lung and kidney. A control for each organ was also analyzed. The results are shown in Table 155.

Table 154. Flux

Route	Time Point	5mC/pU	5mC/N1mpU	5mC/s2U
		Flux (p/s)	Flux (p/s)	Flux (p/s)
I.V.	8 hrs	5.76E+06	1.78E+06	1.88E+06
I.V.	24 hrs	1.02E+06	7.13E+05	5.28E+05
I.V.	48 hrs	4.53E+05	3.76E+05	4.14E+05
I.M.	8 hrs	1.90E+06	2.53E+06	1.29E+06
I.M.	24 hrs	9.33E+05	7.84E+05	6.48E+05
I.M.	48 hrs	8.51E+05	6.59E+05	5.49E+05
S.C.	8 hrs	2.85E+06	6.48E+06	1.14E+06
S.C.	24 hrs	6.66E+05	7.15E+06	3.93E+05
S.C.	48 hrs	3.24E+05	3.20E+06	5.45E+05

Table 155. Organ Flux

Route	Chemistry	Liver	Spleen	Lung	Kidney	Inj. Site
		Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
I.V.	5mC/pU	5.26E+05	2.04E+07	4.28E+06	1.77E+04	n/a
I.V.	5mC/N1mpU	1.48E+05	5.00E+06	1.93E+06	1.77E+04	n/a
I.V.	5mC/s2U	2.14E+04	3.29E+06	5.48E+05	2.16E+04	n/a
I.M.	5mC/pU	2.46E+04	1.38E+04	1.50E+04	1.44E+04	1.15E+06
I.M.	5mC/N1mpU	1.72E+04	1.76E+04	1.99E+04	1.56E+04	1.20E+06
I.M.	5mC/s2U	1.28E+04	1.36E+04	1.33E+04	1.07E+04	7.60E+05
S.C.	5mC/pU	1.55E+04	1.67E+04	1.45E+04	1.69E+04	4.46E+04
S.C.	5mC/N1mpU	1.20E+04	1.46E+04	1.38E+04	1.14E+04	8.29E+04
S.C.	5mC/s2U	1.22E+04	1.31E+04	1.45E+04	1.08E+04	5.62E+04
	Untreated	2.59E+04	1.34E+04	1.26E+04	1.22E+04	n/a

Example 101. Cationic Lipid Formulation of Modified mRNA

[0001478] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) modified where 25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-thiouridine (5mC/s2U) was formulated in the cationic lipids described in Table 156. The formulations were administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg.

Table 156. Cationic Lipid Formulations

Formulation	NPA-130-1	NPA-131-1	NPA-132-1	NPA-133-1	111612-C
Lipid	DLin-MC3-DMA	DLin-KC2-DMA	C12-200	DLinDMA	DODMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1	20:1	20:1	20:1
Mean Size	120 nm PDI: 0.10	105 nm PDI: 0.11	122 nm PDI: 0.13	105 nm PDI: 0.14	221.3 nm PDI: 0.063
Zeta at pH 7.4	0.2 mV	-0.6 mV	-0.5 mV	-0.3 mV	-3.10 mV
Encaps. (RiboGr)	100%	100%	93%	93%	60%

[0001479] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 3.31E+05 p/s. The results of the imaging are shown in Table 157. In Table 157, "NT" means not tested. Untreated mice showed an average flux of 3.14E+05 at 2 hours, 3.33E+05 at 8 hours and 3.46E+05 at 24 hours. Peak expression was seen for all three routes tested at 8 hours. DLin-KC2-DMA has better expression than DLin-MC3-DMA and DODMA showed expression for all routes evaluated.

Table 157. Flux

Route	**Time Point**	**DLin-MC3-**	**DLin-KC2-**	**C12-200**	**DLinDMA**	**DODMA**

		DMA	DMA			
		Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
I.V.	2 hrs	9.88E+06	6.98E+07	9.18E+06	3.98E+06	5.79E+06
I.V.	8 hrs	1.21E+07	1.23E+08	1.02E+07	5.98E+06	6.14E+06
I.V.	24 hrs	2.02E+06	1.05E+07	1.25E+06	1.35E+06	5.72E+05
I.M.	2 hrs	6.72E+05	3.66E+06	3.25E+06	7.34E+05	4.42E+05
I.M.	8 hrs	7.78E+06	2.85E+07	4.29E+06	2.22E+06	1.38E+05
I.M.	24 hrs	4.22E+05	8.79E+05	5.95E+05	8.48E+05	4.80E+05
S.C.	2 hrs	2.37E+06	4.77E+06	4.44E+06	1.07E+06	1.05E+06
S.C.	8 hrs	3.65E+07	1.17E+08	3.71E+06	9.33E+06	2.57E+06
S.C.	24 hrs	4.47E+06	1.28E+07	6.39E+05	8.89E+05	4.27E+05

Example 102. Formulation of 5-Methylcytosine and N1-Methyl-pseudouridine Modified mRNA

[0001480] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and N1-methyl-pseudouridine was formulated in PBS (pH of 7.4). The formulations were administered intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 2.5 mg/kg.

[0001481] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 5 minutes, 30 minutes, 60 minutes and 120 minutes after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 3.78E+05 p/s. The results of the imaging are shown in Table 158. Expression of luciferase was already seen at 30 minutes with both routes of delivery. Peak expression from subcutaneous administration appears between 30 to 60 minutes. Intramuscular expression was still increasing at 120 minutes.

Table 158. Flux

Route	Time Point	PBS (pH 7.4)
		Flux (p/s)
I.M.	5 min	4.38E+05
I.M.	30 min	1.09E+06
I.M.	60 min	1.18E+06
I.M.	120 min	2.86E+06
S.C.	5 min	4.19E+05
S.C.	30 min	6.38E+06

S.C.	60 min	5.61E+06
S.C.	120 min	2.66E+06

Example 103. Intramuscular and Subcutaneous Administration of Chemically Modified mRNA

[0001482] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with N4-acetylcytidine, fully modified with 5-methoxyuridine, fully modified with N4-acetylcytidine and N1-methyl-pseudouridine or fully modified 5-methylcytosine and 5-methoxyuridine formulated in PBS (pH 7.4) was administered to Balb-C mice intramuscularly or subcutaneously at a dose of 2.5 mg/kg. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours. The average total flux (photons/second) for intramuscular administration is shown in Table 159 and the average total flux (photons/second) for subcutaneous administration is shown in Table 160. The background signal was 3.84E+05 (p/s). The peak expression for intramuscular administration was seen between 24 and 48 hours for all chemistry and expression was still detected at 120 hours. For subcutaneous delivery the peak expression was seen at 2-8 hours and expression was detected at 72 hours.

Table 159. Intramuscular Administration

	2 hours	8 hours	24 hours
	Flux (p/s)	Flux (p/s)	Flux (p/s)
N4-acetylcytidine	1.32E+07	2.15E+07	4.01E+07
5-methoxyuridine	4.93E+06	1.80E+07	4.53E+07
N4-acetylcytidine/ N1-methyl-pseudouridine	2.02E+07	1.93E+07	1.63E+08
5-methylcytosine/5-methoxyuridine	6.79E+06	4.55E+07	3.44E+07

Table 160. Subcutaneous Administration

	2 hours	8 hours	24 hours
	Flux (p/s)	Flux (p/s)	Flux (p/s)
N4-acetylcytidine	3.07E+07	1.23E+07	1.28E+07
5-methoxyuridine	7.10E+06	9.38E+06	1.32E+07

N4-acetylcytidine/ N1-methyl-pseudouridine	7.12E+06	3.07E+06	1.03E+07
5-methylcytosine/5-methoxyuridine	7.15E+06	1.25E+07	1.11E+07

Example 104. *In vivo* study

[0001483] Luciferase modified mRNA containing at least one chemical modification is formulated as a lipid nanoparticle (LNP) using the syringe pump method and characterized by particle size, zeta potential, and encapsulation.

[0001484] As outlined in Table 161, the luciferase LNP formulation is administered to Balb-C mice intramuscularly (I.M.), intravenously (I.V.) and subcutaneously (S.C.). As a control luciferase modified RNA formulated in PBS is administered intravenously to mice.

Table 161. Luciferase Formulations

Formulation	Vehicle	Route	Concentration (mg/ml)	Injection Volume (ul)	Amount of modified RNA (ug)	Dose (mg/kg)
Luc-LNP	PBS	S.C.	0.2000	50	10	0.5000
Luc-LNP	PBS	S.C.	0.0200	50	1	0.0500
Luc-LNP	PBS	S.C.	0.0020	50	0.1	0.0050
Luc-LNP	PBS	S.C.	0.0002	50	0.01	0.0005
Luc-LNP	PBS	I.V.	0.2000	50	10	0.5000
Luc-LNP	PBS	I.V.	0.0200	50	1	0.0500
Luc-LNP	PBS	I.V.	0.0020	50	0.1	0.0050
Luc-LNP	PBS	I.V.	0.0002	50	0.01	0.0005
Luc-LNP	PBS	I.M.	0.2000	50	10	0.5000
Luc-LNP	PBS	I.M.	0.0200	50	1	0.0500
Luc-LNP	PBS	I.M.	0.0020	50	0.1	0.0050
Luc-LNP	PBS	I.M.	0.0002	50	0.01	0.0005
Luc-PBS	PBS	I.V.	0.20	50	10	0.50

[0001485] The mice are imaged at 2, 8, 24, 48, 120 and 192 hours to determine the bioluminescence (measured as total flux (photons/second) of the entire mouse). At 8 hours or 192 hours the liver, spleen, kidney and injection site for subcutaneous and intramuscular administration are imaged to determine the bioluminescence.

Example 105. Cationic Lipid Formulation Studies of Chemically Modified mRNA

[0001486] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (5mC/pU), pseudouridine (pU) or N1-methyl-

pseudouridine (N1mpU) was formulated in the cationic lipids described in Table 162. The formulations were administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg.

Table 162. Cationic Lipid Formulations

Formulation	NPA-137-1	NPA-134-1	NPA-135-1	NPA-136-1	111612-A
Lipid	DLin-MC3-DMA	DLin-MC3-DMA	DLin-KC2-DMA	C12-200	DODMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1	20:1	20:1	20:1
Mean Size	111 nm PDI: 0.15	104 nm PDI: 0.13	95 nm PDI: 0.11	143 nm PDI: 0.12	223.2 nm PDI: 0.142
Zeta at pH 7.4	-4.1 mV	-1.9 mV	-1.0 mV	0.2 mV	-3.09 mV
Encaps. (RiboGr)	97%	100%	100%	78%	64%
Chemistry	pU	N1mpU	N1mpU	N1mpU	5mC/pU

[0001487] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 4.11E+05 p/s. The results of the imaging are shown in Table 163. Peak expression was seen for all three routes tested at 8 hours.

Table 163. Flux

Route	Time Point	DLin-MC3-DMA (pU)	DLin-MC3-DMA (N1mpU)	DLin-KC2-DMA (N1mpU)	C12-200 (N1mpU)	DODMA (5mC/pU)
		Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
I.V.	2 hrs	3.21E+08	1.24E+09	1.01E+09	9.00E+08	3.90E+07
I.V.	8 hrs	1.60E+09	3.22E+09	2.38E+09	1.11E+09	1.17E+07
I.V.	24 hrs	1.41E+08	3.68E+08	3.93E+08	8.06E+07	1.11E+07
I.M.	2 hrs	2.09E+07	3.29E+07	8.32E+07	9.43E+07	4.66E+06
I.M.	8 hrs	2.16E+08	6.14E+08	1.00E+09	8.77E+07	7.05E+06
I.M.	24 hrs	1.23E+07	1.40E+08	5.09E+08	1.36E+07	1.14E+06
S.C.	2 hrs	2.32E+07	3.60E+07	2.14E+08	1.01E+08	3.11E+07
S.C.	8 hrs	5.55E+08	9.80E+08	4.93E+09	1.01E+09	8.04E+07

S.C.	24 hrs	1.81E+08	2.74E+08	2.12E+09	4.74E+07	1.34E+07

Example 106. Studies of Chemical Modified mRNA

[0001488] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with N4-acetylcytidine (N4-acetyl), fully modified with 5-methoxyuridine (5meth), fully modified with N4-acetylcytidine and N1-methyl-pseudouridine (N4-acetyl/N1mpU) or fully modified with 5-methylcytosine and 5-methoxyuridine (5mC/5-meth) was formulated in DLin-MC3-DMA as described in Table 164.

[0001489] The formulations were administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg.

Table 164. Cationic Lipid Formulations

Formulation	NPA-141-1	NPA-142-1	NPA-143-1	NPA-144-1
Lipid	DLin-MC3-DMA	DLin-MC3-DMA	DLin-MC3-DMA	DLin-MC3-DMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1	20:1	20:1
Mean Size	138 nm PDI: 0.16	116 nm PDI: 0.15	144 nm PDI: 0.15	131 nm PDI: 0.15
Zeta at pH 7.4	-2.8 mV	-2.8 mV	-4.3 mV	-5.0 mV
Encaps. (RiboGr)	97%	100%	75%	72%
Chemistry	N4-acetyl	5meth	N4-acetyl/ N1mpU	5mC/5-meth

[0001490] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 6 hours and 24 hours after dosing and the average total flux (photons/second) was measured for each route of administration and cationic lipid formulation. The background flux was about 2.70E+05 p/s. The results of the imaging are shown in Table 165.

Table 165. Flux

Route	Time Point	N4-acetyl	5meth	N4-acetyl/ N1mpU	5mC/5-meth
		Flux (p/s)	Flux (p/s)	Flux (p/s)	Flux (p/s)
I.V.	2 hrs	9.17E+07	3.19E+06	4.21E+07	1.88E+06
I.V.	6 hrs	7.70E+08	9.28E+06	2.34E+08	7.75E+06
I.V.	24 hrs	6.84E+07	1.04E+06	3.55E+07	3.21E+06
I.M.	2 hrs	8.59E+06	7.86E+05	5.30E+06	5.11E+05
I.M.	6 hrs	1.27E+08	8.88E+06	3.82E+07	3.17E+06
I.M.	24 hrs	4.46E+07	1.38E+06	2.00E+07	1.39E+06
S.C.	2 hrs	1.83E+07	9.67E+05	4.45E+06	1.01E+06
S.C.	6 hrs	2.89E+08	1.78E+07	8.91E+07	1.29E+07
S.C.	24 hrs	6.09E+07	6.40E+06	2.08E+08	6.63E+06

Example 107. Lipid Nanoparticle Containing A Plurality of Modified mRNAs

[0001491] EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine), G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) and Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine), is formulated in DLin-MC3-DMA as described in Table 166. The formulations are administered intravenously (I.V.), intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg. Control LNP formulations containing only one mRNA are also admininistered at an equivalent dose.

Table 166. DLin-MC3-DMA Formulation

Formulation	NPA-157-1
Lipid	DLin-MC3- DMA
Lipid/mRNA ratio (wt/wt)	20:1
Mean Size	89 nm PDI: 0.08
Zeta at pH 7.4	1.1 mV
Encaps. (RiboGr)	97%

[0001492] Serum is collected from the mice at 8 hours, 24 hours, 72 hours and/or 7 days after administration of the formulation. The serum is analyzed by ELISA to determine the protein expression of EPO, G-CSF, and Factor IX.

Example 108. Cationic Lipid Formulation Studies of of 5-Methylcytosine and N1-Methyl-pseudouridine Modified mRNA

[0001493] EPO mRNA (mRNA sequence shown in SEQ ID NO: 61651; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) or G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) is formulated in DLin-MC3-DMA and DLin-KC2-DMA as described in Table 167. The formulations are administered intravenously (I.V) , intramuscularly (I.M.) or subcutaneously (S.C.) to Balb-C mice at a dose of 0.05 mg/kg.

Table 167. DLin-MC3-DMA and DLin-KC2-DMA Formulations

Formulation	NPA-147-1	NPA-148-1	NPA-150-1	NPA-151-1
mRNA	EPO	EPO	G-CSF	G-CSF
Lipid	DLin-MC3-DMA	DLin-KC2-DMA	DLin-MC3-DMA	DLin-KC2-DMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1	20:1	20:1
Mean Size	117 nm PDI: 0.14	82 nm PDI: 0.08	119 nm PDI: 0.13	88 nm PDI: 0.08
Zeta at pH 7.4	-1.7 mV	0.6 mV	3.6 mV	2.2 mV
Encaps. (RiboGr)	100%	96%	100%	100%

[0001494] Serum is collected from the mice at 8 hours, 24 hours, 72 hours and/or 7 days after administration of the formulation. The serum is analyzed by ELISA to determine the protein expression of EPO and G-CSF.

Example 109. *In Vitro* VEGF PBMC Study

[0001495] 500 ng of VEGF mRNA (mRNA sequence shown in SEQ ID NO: 61661 polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) fully

modified with 5-methylcytosine and pseudouridine (VEGF 5mC/pU), fully modified with 5-methylcytosine and N1-methyl-pseudouridine (VEGF 5mC/N1mpU) or unmodified (VEGF unmod) was transfected with 0.4 uL of Lipofectamine 2000 into peripheral blood mononuclear cells (PBMC) from three normal blood donors (D1, D2, and D3). Cells were also untreated for each donor as a control. The supernatant was harvested and run by ELISA 22 hours after transfection to determine the protein expression and cytokine induction. The expression of VEGF and IFN-alpha induction is shown in Table 168 and Figures 8A and 8B.

Table 168. Protein and Cytokine levels

	VEGF Expression (pg/ml)			IFN-alpha Induction (pg/ml)		
	D1	**D2**	**D3**	**D1**	**D2**	**D3**
VEGF unmod	2	0	0	5400	3537	4946
VEGF 5mC/pU	424	871	429	145	294	106
VEGF 5mC/N1mpU	5088	10331	6183	205	165	6

Example 110. *In vitro* expression of modified mRNA

[0001496] HEK293 cells were transfected EPO modified mRNA (mRNA sequence shown in SEQ ID NO:61651; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine), HeLa cells were forward transfected with Transforming growth factor beta (TGF-beta) modified mRNA (mRNA sequence shown in SEQ ID NO: 61662; poly A tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) and HepG2 cells were transfected with bactericidal/permeability-increasing protein (rBPI-21) modified mRNA (mRNA sequence shown in SEQ ID NO: 61663; poly A tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) which had been complexed with Lipofectamine2000 from Invitrogen (Carlsbad, CA) at the concentrations shown in Table 169, 170 and 171 using the procedures described herein. The protein expression was detected by ELISA and the protein (pg/ml) is also shown in Table 169, 170 and 171. In Table 169, ">" means greater than. For TGF-beta a control of untreated cells and a mock transfection of Lipofectamine2000 was also tested.

Table 169. EPO Protein Expression

Amount Transfected	5 ng	1 ng	200 pg	40 pg	8 pg	1.6 pg	320 fg	64 fg
Protein (pg/ml)	>2000	609.486	114.676	0	0	0	0	0

Table 170. TGF-beta Protein Expression

Amount Transfected	750 ng	250 ng	83 ng	Mock	Untreated
Protein (pg/ml)	5058	4325	3210	2	0

Table 171. rBPI-21 Protein Expression

Amount Transfected	2 ug	400 ng	80 ng	16 ng	3.2 ng	640 pg	128 pg	26 pg
Protein (pg/ml)	20.683	9.269	4.768	0	0	0	0	0

Example 111. Bicistronic modified mRNA

[0001497] Human embryonic kidney epithelial (HEK293) were seeded on 96-well plates (Greiner Bio-one GmbH, Frickenhausen, Germany) HEK293 were seeded at a density of 30,000 in 100 µl cell culture medium (DMEM, 10% FCS, adding 2mM L-Glutamine, 1 mM Sodiumpyruvate and 1x non-essential amino acids (Biochrom AG, Berlin, Germany) and 1.2 mg/ml Sodiumbicarbonate (Sigma-Aldrich, Munich, Germany)) 75 ng of the bi-cistronic modified mRNA (mCherry-2A-GFP) (SEQ ID NO: 61664; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine), mCherry modified mRNA (mRNA SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) or green fluorescent protein (GFP) modified mRNA (mRNA sequence shown in SEQ ID NO: 61660; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and pseudouridine) were added after seeding the cells and incubated. A control of untreated cells was also evaluated. mCherry-2A-GFP refers to a modified mRNA sequence comprising the coding region of mCherry, the 2A peptide and the coding region of GFP.

[0001498] Cells were harvested by transferring the culture media supernatants to a 96-well Pro-Bind U-bottom plate (Beckton Dickinson GmbH, Heidelberg, Germany). Cells were trypsinized with ½ volume Trypsin/EDTA (Biochrom AG, Berlin, Germany), pooled with respective supernatants and fixed by adding one volume PBS/2%FCS (both Biochrom AG, Berlin, Germany)/0.5% formaldehyde (Merck, Darmstadt, Germany). Samples then were submitted to a flow cytometer measurement with a 532nm excitation laser and the 610/20 filter for PE-Texas Red in a LSRII cytometer (Beckton Dickinson GmbH, Heidelberg, Germany). The mean fluorescence intensity (MFI) of all events is shown in Table 172. Cells transfected with the bi-cistronic modified mRNA were able to express both mCherry and GFP.

Table 172. MFI of Modified mRNA

Modified mRNA	mCherry MFI	GFP MFI
mCherry	17746	427
GFP	427	20019
mCherry-2A-GFP	5742	6783
Untreated	427	219

Example 112. Cationic Lipid Formulation Studies of of 5-Methylcytosine and N1-Methyl-pseudouridine Modified mRNA to Produce an Antibody

[0001499] Herceptin heavy chain (HC) mRNA (mRNA sequence shown in SEQ ID NO: 61665; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) and Herceptin light chain (LC) (mRNA sequence shown in SEQ ID NO: 61666; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1; fully modified with 5-methylcytosine and N1-methyl-pseudouridine) are formulated in DLin-MC3-DMA and DLin-KC2-DMA as described in Table 173. The formulations are administered intravenously (I.V) to Balb-C mice at a dose of 0.500, 0.050, and 0.005 mg/kg.

Table 173. DLin-MC3-DMA and DLin-KC2-DMA Formulations

Formulation	NPA-158-1	NPA-159-1
Herceptin HC:LC Ratio (wt/wt)	2:1	2:1

Lipid	DLin-MC3-DMA	DLin-KC2-DMA
Lipid/Total mRNA ratio (wt/wt)	20:1	20:1
Mean Size	129 nm PDI: 0.14	100 nm PDI: 0.10
Zeta at pH 7.4	0.9 mV	1.9 mV
Encaps. (RiboGr)	100%	100%

[0001500] Serum was collected from the mice at 8 hours, 24 hours, 72 hours and/or 7 days after administration of the formulation. The serum was analyzed by ELISA to determine the protein expression of Herceptin.

Example 113. Directed SAR of Pseudouridine and N1-methyl-Pseudouridine

[0001501] With the recent focus on the pyrimidine nucleoside pseudouridine, a series of structure-activity studies were designed to investigate mRNA containing modifications to pseudouridine or N1-methyl-pseudourdine.

[0001502] The study was designed to explore the effect of chain length, increased lipophilicity, presence of ring structures, and alteration of hydrophobic or hydrophilic interactions when modifications were made at the N1 position, C6 position, the 2-position, the 4-position and on the phosphate backbone. Stability is also investigated.

[0001503] To this end, modifications involving alkylation, cycloalkylation, alkyl-cycloalkylation, arylation, alkyl-arylation, alkylation moieties with amino groups, alkylation moieties with carboxylic acid groups, and alkylation moieties containing amino acid charged moieties are investigated. The degree of alkylation is generally C_1-C_6. Examples of the chemistry modifications include those listed in Table 174 and Table 175.

Table 174. Pseudouridine and N1-methylPseudouridine SAR

Chemistry Modification	**Compound #**	**Naturally occuring**
N1-Modifications		
N1-Ethyl-pseudo-UTP	1	N
N1-Propyl-pseudo-UTP	2	N
N1-*iso*-propyl-pseudo-UTP	3	N
N1-(2,2,2-Trifluoroethyl)-pseudo-UTP	4	N
N1-Cyclopropyl-pseudo-UTP	5	N

N1-Cyclopropylmethyl-pseudo-UTP	6	N
N1-Phenyl-pseudo-UTP	7	N
N1-Benzyl-pseudo-UTP	8	N
N1-Aminomethyl-pseudo-UTP	9	N
P seudo-UTP-N1-2-ethanoic acid	10	N
N 1-(3-Amino-3-carboxypropyl)pseudo-UTP	11	N
N1-Methyl-3-(3-amino-3-carboxypropyl)pseudo-UTP	12	Y
C-6 Modifications		
6-Methyl-pseudo-UTP	13	N
6-Trifluoromethyl-pseudo-UTP	14	N
6-Methoxy-pseudo-UTP	15	N
6-Phenyl-pseudo-UTP	16	N
6-Iodo-pseudo-UTP	17	N
6-Bromo-pseudo-UTP	18	N
6-Chloro-pseudo-UTP	19	N
6-Fluoro-pseudo-UTP	20	N
2- or 4-position Modifications		
4-Thio-pseudo-UTP	21	N
2-Thio-pseudo-UTP	22	N
Phosphate backbone Modifications		
Alpha-thio-pseudo-UTP	23	N
N1-Me-alpha-thio-pseudo-UTP	24	N

Table 175. Pseudouridine and N1-methyl-Pseudouridine SAR

Chemistry Modification	Compound #	Naturally occurring
N1-Methyl-pseudo-UTP	1	Y
N1-Butyl-pseudo-UTP	2	N
N1-*tert*-Butyl-pseudo-UTP	3	N
N1-Pentyl-pseudo-UTP	4	N
N1-Hexyl-pseudo-UTP	5	N
N1-Trifluoromethyl-pseudo-UTP	6	Y
N1-Cyclobutyl-pseudo-UTP	7	N
N1-Cyclopentyl-pseudo-UTP	8	N
N1-Cyclohexyl-pseudo-UTP	9	N
N1-Cycloheptyl-pseudo-UTP	10	N
N1-Cyclooctyl-pseudo-UTP	11	N
N1-Cyclobutylmethyl-pseudo-UTP	12	N
N1-Cyclopentylmethyl-pseudo-UTP	13	N
N1-Cyclohexylmethyl-pseudo-UTP	14	N
N1-Cycloheptylmethyl-pseudo-UTP	15	N

N1-Cyclooctylmethyl-pseudo-UTP	16	N
N1-*p*-tolyl-pseudo-UTP	17	N
N1-(2,4,6-Trimethyl-phenyl)pseudo-UTP	18	N
N1-(4-Methoxy-phenyl)pseudo-UTP	19	N
N1-(4-Amino-phenyl)pseudo-UTP	20	N
N1(4-Nitro-phenyl)pseudo-UTP	21	N
Pseudo-UTP-N1-*p*-benzoic acid	22	N
N1-(4-Methyl-benzyl)pseudo-UTP	24	N
N1-(2,4,6-Trimethyl-benzyl)pseudo-UTP	23	N
N1-(4-Methoxy-benzyl)pseudo-UTP	25	N
N1-(4-Amino-benzyl)pseudo-UTP	26	N
N1-(4-Nitro-benzyl)pseudo-UTP	27	N
Pseudo-UTP-N1-methyl-p-benzoic acid	28	N
N1-(2-Amino-ethyl)pseudo-UTP	29	N
N1-(3-Amino-propyl)pseudo-UTP	30	N
N1-(4-Amino-butyl)pseudo-UTP	31	N
N1-(5-Amino-pentyl)pseudo-UTP	32	N
N1-(6-Amino-hexyl)pseudo-UTP	33	N
Pseudo-UTP-N1-3-propionic acid	34	N
Pseudo-UTP-N1-4-butanoic acid	35	N
Pseudo-UTP-N1-5-pentanoic acid	36	N
Pseudo-UTP-N1-6-hexanoic acid	37	N
Pseudo-UTP-N1-7-heptanoic acid	38	N
N1-(2-Amino-2-carboxyethyl)pseudo-UTP	39	N
N1-(4-Amino-4-carboxybutyl)pseudo-UTP	40	N
N3-Alkyl-pseudo-UTP	41	N
6-Ethyl-pseudo-UTP	42	N
6-Propyl-pseudo-UTP	43	N
6-iso-Propyl-pseudo-UTP	44	N
6-Butyl-pseudo-UTP	45	N
6-tert-Butyl-pseudo-UTP	46	N
6-(2,2,2-Trifluoroethyl)-pseudo-UTP	47	N
6-Ethoxy-pseudo-UTP	48	N
6-Trifluoromethoxy-pseudo-UTP	49	N
6-Phenyl-pseudo-UTP	50	N
6-(Substituted-Phenyl)-pseudo-UTP	51	N
6-Cyano-pseudo-UTP	52	N
6-Azido-pseudo-UTP	53	N
6-Amino-pseudo-UTP	54	N
6-Ethylcarboxylate-pseudo-UTP	54b	N
6-Hydroxy-pseudo-UTP	55	N
6-Methylamino-pseudo-UTP	55b	N
6-Dimethylamino-pseudo-UTP	57	N

6-Hydroxyamino-pseudo-UTP	59	N
6-Formyl-pseudo-UTP	60	N
6-(4-Morpholino)-pseudo-UTP	61	N
6-(4-Thiomorpholino)-pseudo-UTP	62	N
N1-Me-4-thio-pseudo-UTP	63	N
N1-Me-2-thio-pseudo-UTP	64	N
1,6-Dimethyl-pseudo-UTP	65	N
1-Methyl-6-trifluoromethyl-pseudo-UTP	66	N
1-Methyl-6-ethyl-pseudo-UTP	67	N
1-Methyl-6-propyl-pseudo-UTP	68	N
1-Methyl-6-iso-propyl-pseudo-UTP	69	N
1-Methyl-6-butyl-pseudo-UTP	70	N
1-Methyl-6-tert-butyl-pseudo-UTP	71	N
1-Methyl-6-(2,2,2-Trifluoroethyl)pseudo-UTP	72	N
1-Methyl-6-iodo-pseudo-UTP	73	N
1-Methyl-6-bromo-pseudo-UTP	74	N
1-Methyl-6-chloro-pseudo-UTP	75	N
1-Methyl-6-fluoro-pseudo-UTP	76	N
1-Methyl-6-methoxy-pseudo-UTP	77	N
1-Methyl-6-ethoxy-pseudo-UTP	78	N
1-Methyl-6-trifluoromethoxy-pseudo-UTP	79	N
1-Methyl-6-phenyl-pseudo-UTP	80	N
1-Methyl-6-(substituted phenyl)pseudo-UTP	81	N
1-Methyl-6-cyano-pseudo-UTP	82	N
1-Methyl-6-azido-pseudo-UTP	83	N
1-Methyl-6-amino-pseudo-UTP	84	N
1-Methyl-6-ethylcarboxylate-pseudo-UTP	85	N
1-Methyl-6-hydroxy-pseudo-UTP	86	N
1-Methyl-6-methylamino-pseudo-UTP	87	N
1-Methyl-6-dimethylamino-pseudo-UTP	88	N
1-Methyl-6-hydroxyamino-pseudo-UTP	89	N
1-Methyl-6-formyl-pseudo-UTP	90	N
1-Methyl-6-(4-morpholino)-pseudo-UTP	91	N
1-Methyl-6-(4-thiomorpholino)-pseudo-UTP	92	N
1-Alkyl-6-vinyl-pseudo-UTP	93	N
1-Alkyl-6-allyl-pseudo-UTP	94	N
1-Alkyl-6-homoallyl-pseudo-UTP	95	N
1-Alkyl-6-ethynyl-pseudo-UTP	96	N
1-Alkyl-6-(2-propynyl)-pseudo-UTP	97	N
1-Alkyl-6-(1-propynyl)-pseudo-UTP	98	N

Example 114. Incorporation of naturally and non-naturally occuring nucleosides

[0001504] Naturally and non-naturally occurring nucleosides are incorporated into mRNA encoding a polypeptide of interest. Examples of these are given in Tables 176 and 177. Certain commercially available nucleoside triphosphates (NTPs) are investigated in the polynucleotides of the invention. A selection of these are given in Table 176. The resultant mRNA are then examined for their ability to produce protein, induce cytokines, and/or produce a therapeutic outcome.

Table 176. Naturally and non-naturally occurring nucleosides

Chemistry Modification	Compound #	Naturally occuring
N4-Methyl-Cytosine	1	Y
N4,N4-Dimethyl-2'-OMe-Cytosine	2	Y
5-Oxyacetic acid-methyl ester-Uridine	3	Y
N3-Methyl-pseudo-Uridine	4	Y
5-Hydroxymethyl-Cytosine	5	Y
5-Trifluoromethyl-Cytosine	6	N
5-Trifluoromethyl-Uridine	7	N
5-Methyl-amino-methyl-Uridine	8	Y
5-Carboxy-methyl-amino-methyl-Uridine	9	Y
5-Carboxymethylaminomethyl-2'-OMe-Uridine	10	Y
5-Carboxymethylaminomethyl-2-thio-Uridine	11	Y
5-Methylaminomethyl-2-thio-Uridine	12	Y
5-Methoxy-carbonyl-methyl-Uridine	13	Y
5-Methoxy-carbonyl-methyl-2'-OMe-Uridine	14	Y
5-Oxyacetic acid- Uridine	15	Y
3-(3-Amino-3-carboxypropyl)-Uridine	16	Y
5-(carboxyhydroxymethyl)uridine methyl ester	17	Y
5-(carboxyhydroxymethyl)uridine	18	Y

Table 177. Non-naturally occurring nucleoside triphosphates

Chemistry Modification	Compound #	Naturally occuring
N1-Me-GTP	1	N
2'-OMe-2-Amino-ATP	2	N
2'-OMe-pseudo-UTP	3	Y
2'-OMe-6-Me-UTP	4	N
2'-Azido-2'-deoxy-ATP	5	N
2'-Azido-2'-deoxy-GTP	6	N
2'-Azido-2'-deoxy-UTP	7	N
2'-Azido-2'-deoxy-CTP	8	N

2'-Amino-2'-deoxy-ATP	9	N
2'-Amino-2'-deoxy-GTP	10	N
2'-Amino-2'-deoxy-UTP	11	N
2'-Amino-2'-deoxy-CTP	12	N
2-Amino-ATP	13	N
8-Aza-ATP	14	N
Xanthosine-5'-TP	15	N
5-Bromo-CTP	16	N
2'-F-5-Methyl-2'-deoxy-UTP	17	N
5-Aminoallyl-CTP	18	N
2-Amino-riboside-TP	19	N

Example 115. Incorporation of modifications to the nucleobase and carbohydrate (sugar)

[0001505] Naturally and non-naturally occurring nucleosides are incorporated into mRNA encoding a polypeptide of interest. Commercially available nucleosides and NTPs having modifications to both the nucleobase and carbohydrate (sugar) are examined for their ability to be incorporated into mRNA and to produce protein, induce cytokines, and/or produce a therapeutic outcome. Examples of these nucleosides are given in Tables 178 and 179.

Table 178. Combination modifications

Chemistry Modification	Compound #
5-iodo-2'-fluoro-deoxyuridine	1
5-iodo-cytidine	6
2'-bromo-deoxyuridine	7
8-bromo-adenosine	8
8-bromo-guanosine	9
2,2'-anhydro-cytidine hydrochloride	10
2,2'-anhydro-uridine	11
2'-Azido-deoxyuridine	12
2-amino-adenosine	13
N4-Benzoyl-cytidine	14
N4-Amino-cytidine	15
2'-O-Methyl-N4-Acetyl-cytidine	16
2'Fluoro-N4-Acetyl-cytidine	17
2'Fluor-N4-Bz-cytidine	18
2'O-methyl-N4-Bz-cytidine	19
2'O-methyl-N6-Bz-deoxyadenosine	20

2'Fluoro-N6-Bz-deoxyadenosine	21
N2-isobutyl-guanosine	22
2'Fluro-N2-isobutyl-guanosine	23
2'O-methyl-N2-isobutyl-guanosine	24

Table 179. Naturally occuring combinations

Name	Compound #	Naturally occurring
5-Methoxycarbonylmethyl-2-thiouridine TP	1	Y
5-Methylaminomethyl-2-thiouridine TP	2	Y
5-Crbamoylmethyluridine TP	3	Y
5-Carbamoylmethyl-2'-O-methyluridine TP	4	Y
1-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine TP	5	Y
5-Methylaminomethyl-2-selenouridine TP	6	Y
5-Carboxymethyluridine TP	7	Y
5-Methyldihydrouridine TP	8	Y
lysidine TP	9	Y
5-Taurinomethyluridine TP	10	Y
5-Taurinomethyl-2-thiouridine TP	11	Y
5-(*iso*-Pentenylaminomethyl)uridine TP	12	Y
5-(*iso*-Pentenylaminomethyl)- 2-thiouridine TP	13	Y
5-(*iso*-Pentenylaminomethyl)-2'-O-methyluridine TP	14	Y
N4-Acetyl-2'-O-methylcytidine TP	15	Y
N4,2'-O-Dimethylcytidine TP	16	Y
5-Formyl-2'-O-methylcytidine TP	17	Y
2'-O-Methylpseudouridine TP	18	Y
2-Thio-2'-O-methyluridine TP	19	Y
3,2'-O-Dimethyluridine TP	20	Y

[0001506] In the tables "UTP" stands for uridine triphosphate, "GTP" stands for guanosine triphosphate, "ATP" stands for adenosine triphosphate, "CTP" stands for cytosine triphosphate, "TP" stands for triphosphate and "Bz" stands for benzyl.

Example 116. Protein Production of Vascular Endothelial Growth Factor in HeLa Cells

[0001507] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas,

VA). The cells were grown at 37°C in 5% CO_2 atmosphere overnight. The next day, 250 ng of vascular endothelial growth factor (VEGF) modified RNA (mRNA sequence shown in SEQ ID NO: 61661; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 180, was diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul of lipofectamine 2000 was diluted to 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature. A second set of HeLa cells was also evaluated with the VEGF mRNA according to the procedure set out above. A control of untreated cells and cells treated with just lipofecatamine 2000 was also analyzed for the first set of HeLa cells.

[0001508] After an 18 to 22 hour incubation cell culture supernatants of cells expressing VEGF were collected and centrifuged at 10.000rcf for 2 minutes. The cleared supernatants were then analyzed with a VEGF-specific ELISA kit (R & D Systems, Minneapolis, MN) according to the manufacturer instructions. All samples were diluted until the determined values were within the linear range of the ELISA standard curve. The amount of protein produced is shown in Table 180.

[0001509] These results demonstrate that VEGF fully modified with 1-methylpseudouridine produced more protein in HeLa cells compared to the other chemistry.

Table 180. Protein Production

Sample	VEGF set 1 (pg/ml)	VEGF set 2 (pg/ml)
5-methylcytosine and pseudouridine (5mC and pU)	25,455	50,341
5-methylcytosine and 1-methylpsudouridine (5mC and 1mpU)	5,795	8,523
25% of uridine modified with 2-thiouridine and 25% of cytosine modified with 5-methylcytosine (s2U and 5mC)	27,045	27,045

Pseudouridine (pU)	216,023	345,114
1-methylpseudouridine (1mpU)	32,614	38,523
Unmodified	409,318	447,273
Lipofectamine 2000 (L2000)	0	N/A
Untreated	0	N/A

Example 117. Comparison of Protein Production of Chemically Modified Vascular Endothelial Growth Factor in HeLa Cells

[0001510] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37°C in 5% CO_2 atmosphere overnight. Next day, 250 ng of vascular endothelial growth factor (VEGF) modified RNA (mRNA sequence shown in SEQ ID NO: 61661; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 181, were diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul of lipofectamine 2000 was diluted to 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature. A control of untreated cells was also analyzed.

[0001511] After an 18 to 22 hour incubation cell culture supernatants of cells expressing VEGF were collected and centrifuged at 10.000rcf for 2 minutes. The cleared supernatants were then analyzed with a VEGF-specific ELISA kit (R & D Systems, Minneapolis, MN) according to the manufacturer instructions. All samples were diluted until the determined values were within the linear range of the ELISA standard curve. The amount of protein produced is shown in Table 181 and Figure 9.

[0001512] These results demonstrate that VEGF fully modified with 1-methylpseudouridine produced more protein in HeLa cells compared to the other chemistry.

Table 181. Protein Production

Sample	VEGF (pg/ml)
Unmodified	121,176
5-methylcytosine and 1-methylpsudouridine (5mC and 1mpU)	760,000
1-methylpseudouridine (1mpU)	1,393,824
Untreated	0

Example 118. Production of Vascular Endothelial Growth Factor Protein in Mammals

[0001513] Lipoplexed vascular endothelial growth factor (VEGF) mRNA (mRNA sequence shown in SEQ ID NO: 61661; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) unmodified, fully modified with 5-methylcytosine and pseudouridine (5mC/pU), fully modified with 5-methylcytosine and 1-methylpseudouridine (5mC/1mpU), modified where 25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-thiouridine (5mC/s2U), fully modified with 1-methylpseudouridine (1mpU) or fully modified with pseudouridine (pU). The formulation was administered intravenously to mice at a dose of 2 ug of mRNA per mouse. As a control, a group of mice were untreated. Serum from the mice is measured by specific VEGF ELISA 3 hours after administration for VEGF protein expression. The results are shown in Table 182 and Figure 10.

Table 182. Protein Production

Sample	VEGF (pg/ml)
Unmodified	34
5-methylcytosine and pseudouridine (5mC and pU)	40
5-methylcytosine and 1-methylpsudouridine (5mC and 1mpU)	11
25% of uridine modified with 2-thiouridine and 25% of cytosine modified with 5-methylcytosine (s2U and 5mC)	53
Pseudouridine (pU)	86
1-methyl-pseudouridine (1mpU)	51
Untreated	0

Example 119. Protein Production of Granulocyte Colony Stimulating Factor in HeLa Cells

[0001514] The day before transfection, 20,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin-EDTA solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul EMEM medium (supplemented with 10%FCS and 1x Glutamax) per well in a 96-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37ºC in 5% CO_2 atmosphere overnight. The next day, 250 ng of granulocyte colony stimulating factor (G-CSF) modified RNA (mRNA sequence shown in SEQ ID NO: 61649; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) with the chemical modification described in Table 183, was diluted in 10ul final volume of OPTI-MEM (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul of lipofectamine 2000 was diluted to 10 ul final volume of OPTI-MEM. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature. A control of untreated cells and cells treated with just lipofecatamine 2000 was also analyzed.

[0001515] After an 18 to 22 hour incubation cell culture supernatants of cells expressing G-CSF were collected and centrifuged at 10.000rcf for 2 minutes. The cleared supernatants were then analyzed with a G-CSF-specific ELISA kit (R & D Systems, Minneapolis, MN) according to the manufacturer instructions. All samples were diluted until the determined values were within the linear range of the ELISA standard curve. The amount of protein produced is shown in Table 183 and Figure 11.

Table 183. Protein Production

Sample	G-CSF (pg/ml)
5-methylcytosine and pseudouridine (5mC and pU)	704,250
5-methylcytosine and 1-methylpsudouridine (5mC and 1mpU)	1,523,750
25% of uridine modified with 2-thiouridine and 25% of cytosine modified with 5-methylcytosine (s2U and 5mC)	89,000
Pseudouridine (pU)	408,250
1-methylpseudouridine (1mpU)	1,391,250
Lipofectamine 2000 (L2000)	0
Untreated	0

Example 120. Protein Production of Chemically Modified Factor IX in HeLa Cell Supernatant

[0001516] The day before transfection, 15,000 HeLa cells (ATCC no. CCL-2; Manassas, VA) were harvested by treatment with Trypsin- Ethylenediaminetetraacetic acid (EDTA) solution (LifeTechnologies, Grand Island, NY) and seeded in a total volume of 100ul Eagle's minimal essential medium (EMEM) (supplemented with 10% fetal calf serum (FCS) and 1x Glutamax) per well in a 24-well cell culture plate (Corning, Manassas, VA). The cells were grown at 37°C in 5% CO_2 atmosphere overnight. Next day, 250 ng of factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 61652; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 5-methylcytosine and pseudouridine (5mC/pU), fully modified with 5-methylcytosine and 1-methylpseudouridine (5mC/1mpU), modified where 25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-thiouridine (s2U/5mC), fully modified with 1-methylpseudouridine (1mpU) or fully modified with pseudouridine (pU) were diluted in 10 ul final volume of OPTI-MEM® (LifeTechnologies, Grand Island, NY). Lipofectamine 2000 (LifeTechnologies, Grand Island, NY) was used as transfection reagent and 0.2 ul of lipofectamine 2000 was diluted to 10 ul final volume of OPTI-MEM®. After 5 minutes of incubation at room temperature, both solutions were combined and incubated an additional 15 minute at room temperature. Then the 20ul combined solution was added to the 100ul cell culture medium containing the HeLa cells and incubated at room temperature. A control of untreated was also analyzed.

[0001517] After an 18 hour incubation cell culture supernatants of cells expressing factor IX were collected by lysing cells with immuno-precipitation (IP) buffer from Pierce Biotechnology (Thermo Scientific, Rockford, IL) and centrifuged at 10.000rcf for 2 minutes. The cleared supernatants were diluted 1:2 (1 ml lysate/2 wells/24 well plate) or 1:5 (1 ml lysate/5 wells/24 well plate) then analyzed with a factor IX-specific ELISA kit according to the manufacturer instructions. All samples were diluted until the determined values were within the linear range of the ELISA standard curve. The amount of protein produced in both studies is shown in Table 184 and Figure 12.

Table 184. Protein Production

Sample	Factor IX (ng/ml)
5-methylcytosine and pseudouridine (5mC/pU)	45.8
5-methylcytosine and 1-methylpseudouridine (5mC/1mpU)	147.1
25% of the cytosines replaced with 5-methylcytosine and 25% of the uridines replaced with 2-thiouridine (s2U/5mC)	7.4
Pseudouridine (pU)	17.0
1-methylpseudouridine (1mpU)	32.0
Untreated	0

Example 121. Intranasal Lung Delivery of 1-methylpseudouridine or 5-methylcytosine and 1-methylpseudouridine Modified Luciferase mRNA Formulated in Cationic Lipid Nanoparticle

[0001518] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 1-methylpseudouridine (Luc-G5-LNP-KC2) or fully modified with 1-methylpseudouridine and 5-methylcytosine (Luc-G2-LNP-KC2) were formulated in the cationic Lipid Nanoparticle (LNP-KC2) as described in Table 185.

Table 185. Formulation

Formulation	NPA-127-1	NPA-135-1
Lipid	DLin-KC2-DMA	DLin-KC2-DMA
Lipid/mRNA ratio (wt/wt)	20:1	20:1
Mean Size	114 nm PDI: 0.10	95 nm PDI: 0.11
Zeta at pH 7.4	-0.5 mV	-1.0 mV
Encaps. (RiboGr)	77%	100%

[0001519] The formulations were administered intranasally (I.N.) to Balb-C mice at a dose of 0.3 mg/kg. Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours, 48, and 72 hours after dosing and the average total flux (photons/second) was measured. The background flux was about 6.3+05 p/s. The results

of the imaging of Luc-G5-LNP-KC2 or Luc-G5-LNP-KC2 vs. Vehicle are shown in the Table 185, "NT" means not tested.

Table 185. Luciferase expression after intranasal dosing

Route	Time Point	Luc-G5-LNP-KC2	Luc-G2-LNP-KC2	Vehicle (PBS)
		Flux (p/s)	Flux (p/s)	Flux (p/s)
I.N.	2 hrs	1.53E+06	5.81E+05	3.87E+05
I.N.	8 hrs	1.09E+07	9.35E+05	5.57E+05
I.N.	24 hrs	5.93E+06	5.33E+05	4.89E+05
I.N.	28 hrs	1.22E+06	7.63E+05	8.81E+05
I.N.	72 hrs	8.43E+05	NT	8.17E+05

Example 122. Intranasal Lung Delivery of 1-methylpseudouridine or 5-methylcytosine and 1-methylpseudouridine Modified Luciferase mRNA lipoplexed in Lipofectamine 2000

[0001520] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 1-methylpseudouridine (Luc-G5-Lipoplex) or fully modified with 1-methylpseudouridine and 5-methylcytosine (Luc-G2-Lipoplex) were lipoplexed in two steps, first step was the dilution of 16.6ul from 3mg/ml of 1-methylpseudouridine or 1-methylpseudouridine and 5-methylcytosine modified luciferase mRNA in 108.5 ul DMEM and the second step was the dilution of 100ul LF2000 in 25ul DMEM then both mixed together gently to make 250ul total mixer which incubated 5-10 min at RT to form a Lipid-mRNA complex before injection. The lipoplex from both Luciferase mRNA fully modified with 1-methylpseudouridine or 1-methylpseudouridine and 5-methylcytosine were administered intranasally (I.N.) to Balb-C mice at a dose of 0.5 mg/kg.

[0001521] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours after dosing and the average total flux (photons/second) was

measured. The background signal was about 4.8+05 p/s. The background flux was about 6.3+05 p/s. The results of the imaging of Luc-G5-Lipoplex or Luc-G2-Lipoplex vs. Vehicle are shown in the Table 186.

Table 186. Luciferase expression after intranasal dosing

Route	Time Point	Luc-G5-Lipoplex	Luc-G2-Lipoplex	Vehicle (PBS)
		Flux (p/s)	Flux (p/s)	Flux (p/s)
I.N.	2 hrs	8.37E+05	9.58E+05	3.87E+05
I.N.	8 hrs	8.42E+05	7.11E+05	5.57E+05
I.N.	24 hrs	5.74E+05	5.53E+05	4.89E+05

Example 123. Intranasal Lung Delivery of 1-methylpseudouridine or 5-methylcytosine and 1-methylpseudouridine Modified Luciferase mRNA formulated in PBS

[0001522] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 61658; polyA tail of approximately 140 nucleotides not shown in sequence; 5'cap, Cap1) fully modified with 1-methylpseudouridine (Luc-G5-Buffer(PBS)) or fully modified with 1-methylpseudouridine and 5-methylcytosine (Luc-G2-Buffer(PBS)) formulated in PBS (pH 7.4) were administered intranasally (I.N.) to Balb-C mice at a dose of 7.5 mg/kg.

[0001523] Twenty minutes prior to imaging, mice were injected intraperitoneally with a D-luciferin solution at 150 mg/kg. Animals were then anesthetized and images were acquired with an IVIS Lumina II imaging system (Perkin Elmer). Bioluminescence was measured as total flux (photons/second) of the entire mouse. The mice were imaged at 2 hours, 8 hours and 24 hours after dosing and the average total flux (photons/second) was measured. The background flux was about 4.8+05 p/s. The background flux was about 6.3+05 p/s. The results of the imaging of Luc-G5-in Buffer vs. Vehicle are shown in the Table 187.

Table 187. Luciferase expression after intranasal dosing

Route	Time Point	Luc-G5-in Buffer (PBS)	Luc-G2-in Buffer (PBS)	Vehicle (PBS)
		Flux [p/s]	Flux [p/s]	Flux (p/s)
I.N.	2 hrs	4.50E+05	9.58E+05	3.87E+05
I.N.	8 hrs	7.12E+05	7.11E+05	5.57E+05

I.N.	24 hrs	4.47E+05	5.53E+05	4.89E+05

[0001524] It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit of the invention in its broader aspects.

[0001525] While the present invention has been described at some length and with some particularity with respect to the several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope of the invention.

[0001526] All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, section headings, the materials, methods, and examples are illustrative only and not intended to be limiting.

Claims

We claim:

1. An isolated polynucleotide comprising;

(a) a first region of linked nucleosides, said first region encoding a polypeptide of interest, said polypeptide of interest selected from the group consisting of SEQ ID NOs 8922-17687;

(b) a first flanking region located at the 5′ terminus of said first region comprising;

(i) a sequence of linked nucleosides selected from the group consisting of the native 5′ UTR of any of the nucleic acids that encode any of SEQ ID NOs 8922-17687, SEQ ID NOs: 1-4 and functional variants thereof; and

(ii) at least one 5′ terminal cap;

(c) a second flanking region located at the 3′ terminus of said first region comprising;

(i') a sequence of linked nucleosides selected from the group consisting of the native 3′ UTR of any of the nucleic acids that encode any of SEQ ID NOs 8922-17687, SEQ ID NOs 5-21 and functional variants thereof; and

(ii') a 3′ tailing sequence of linked nucleosides.

2. The isolated polynucleotide of claim 1 wherein the first region of linked nucleosides comprises at least an open reading frame of a nucleic acid sequence, wherein the nucleic acid sequence selected from the group consisting of SEQ ID NOs: 17688-61633.

3. The isolated polynucleotide of claim 1, wherein the 3′tailing sequence of linked nucleosides is selected from the group consisting of a poly-A tail of approximately 160 nucleotides and a polyA-G quartet.

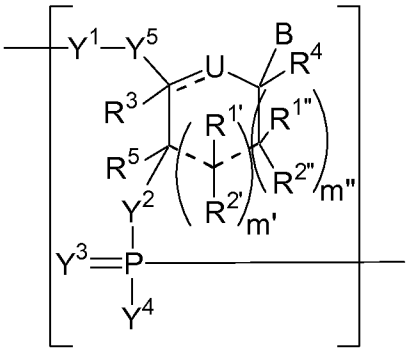
4. The isolated polynucleotide of any one of claims 1-3 which is purified.

5. The isolated polynucleotide of any one of claims 1-4, wherein the at least one 5′ terminal cap is selected from the group consisting of Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2′fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, and 2-azido-guanosine.

6. The isolated polynucleotide of any preceding claim, wherein at least one of said linked nucleosides comprises at least one modification as compared to the chemical structure of an A, G, U or C ribonucleotide.

7. The isolated polynucleotide of claim 6, wherein at least one said modification is located in a nucleoside base and/or sugar portion.

8. The isolated polynucleotide of any one of claims 1-7, wherein said first region comprises n number of linked nucleosides having Formula (Ia):



(Ia), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

U is O, S, $N(R^U)_{nu}$, or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

is a single or double bond;

--- is a single bond or absent;

each of $R^{1'}$, $R^{2'}$, $R^{1''}$, $R^{2''}$, R^3, R^4, and R^5 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally

substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, or absent; wherein the combination of R^3 with one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, $R^{2''}$, or R^5 can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl; wherein the combination of R^5 with one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, or $R^{2''}$ can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl; and wherein the combination of R^4 and one or more of $R^{1'}$, $R^{1''}$, $R^{2'}$, $R^{2''}$, R^3, or R^5 can join together to form optionally substituted alkylene or optionally substituted heteroalkylene and, taken together with the carbons to which they are attached, provide an optionally substituted heterocyclyl;

each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, or absent;

each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

each Y^5 is, independently, O, S, optionally substituted alkylene, or optionally substituted heteroalkylene;

n is an integer from 1 to 100,000; and

B is a nucleobase, wherein the combination of B and $R^{1'}$, the combination of B and $R^{2'}$, the combination of B and $R^{1''}$, or the combination of B and $R^{2''}$ can, taken together with the carbons to which they are attached, optionally form a bicyclic group or wherein the combination of B, $R^{1''}$, and R^3 or the combination of B, $R^{2''}$, and R^3 can optionally form a tricyclic or tetracyclic group.

9. The isolated polynucleotide of claim 8, wherein B is not pseudouridine (ψ) or 5-methyl-cytidine (m^5C).

10. The isolated polynucleotide of any one of claims 8-9, wherein

U is O or $C(R^U)_{nu}$, wherein nu is an integer from 1 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

each of R^1, $R^{1'}$, $R^{1''}$, R^2, $R^{2'}$, and $R^{2''}$, if present, is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, or optionally substituted aminoalkyl;

each of R^3 and R^4 is, independently, H, halo, hydroxy, optionally substituted alkyl, or optionally substituted alkoxyalkoxy;

each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, or optionally substituted amino;

each Y^5 is, independently, O or optionally substituted alkylene; and

n is an integer from 10 to 10,000.

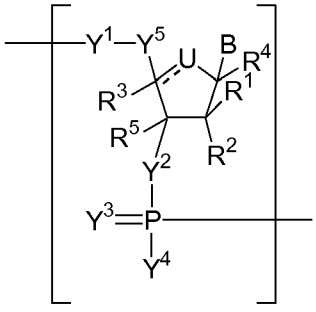
11. The isolated polynucleotide of claim 10, wherein each of R^1, $R^{1'}$, and $R^{1''}$, if present, is H.

12. The isolated polynucleotide of claim 11, wherein each of R^2, $R^{2'}$, and $R^{2''}$, if present, is, independently, H, halo, hydroxy, optionally substituted alkoxy, or optionally substituted alkoxyalkoxy.

13. The isolated polynucleotide of claim 10, wherein each of R^2, $R^{2'}$, and $R^{2''}$, if present, is H.

14. The isolated polynucleotide of claim 13, wherein each of R^1, $R^{1'}$, and $R^{1''}$, if present, is, independently, H, halo, hydroxy, optionally substituted alkoxy, or optionally substituted alkoxyalkoxy.

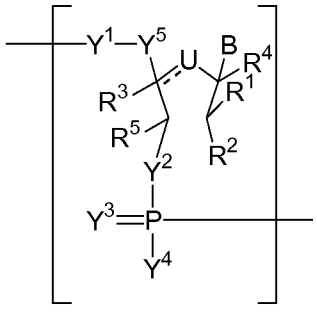
15. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleotides having Formula (IIa):



(IIa), or a pharmaceutically acceptable salt or stereoisomer thereof.

16. isolated The polypeptide of claim 15, wherein said first region comprises n number of linked nucleosides having Formula (IIb) or (IIc), or a pharmaceutically acceptable salt thereof.

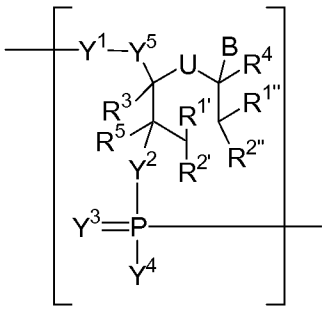
17. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleosides having Formula (IId):



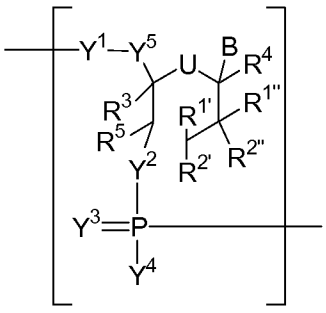
(IId), or a pharmaceutically acceptable salt or stereoisomer thereof.

18. The isolated polypeptide of claim 17, wherein said first region comprises n number of linked nucleosides having Formula (IIe) or (IIf), or a pharmaceutically acceptable salt thereof.

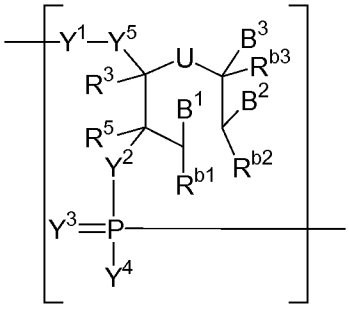
19. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleotides, each of said linked nucleotides independently having one of Formulas (IIg)-(IIj):



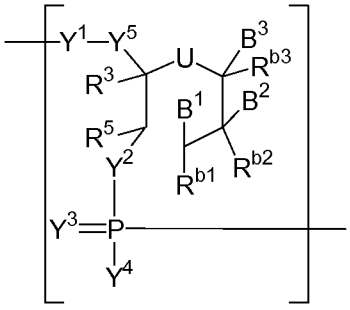
(IIg),



(IIh),

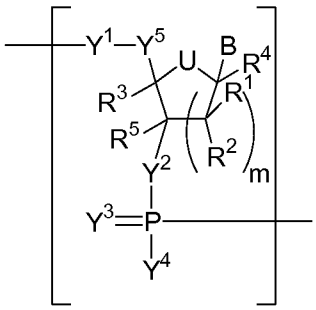


(IIi), or



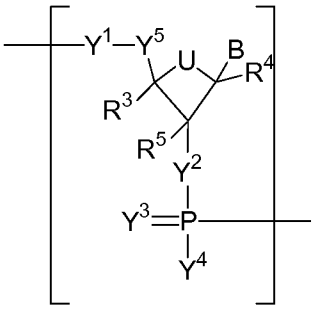
(IIj), or a pharmaceutically acceptable salt or stereoisomer thereof.

20. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleosides having Formula (IIk):



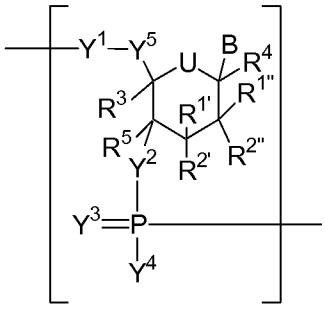
(IIk) , or a pharmaceutically acceptable salt or stereoisomer thereof.

21. The isolated polynucleotide of claim 20, wherein said first region comprises n number of linked nucleosides having Formula (III):



(III), or a pharmaceutically acceptable salt or stereoisomer thereof.

22. The isolated polynucleotide of claim 20, wherein said first region comprises n number of linked nucleosides having Formula (IIm):



(IIm), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

each of $R^{1'}$, $R^{1''}$, $R^{2'}$, and $R^{2''}$ is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, or absent; and wherein the combination of $R^{2'}$ and R^3 or the combination of $R^{2''}$ and R^3 can be taken together to form optionally substituted alkylene or optionally substituted heteroalkylene.

23. The isolated polynucleotide of any one of claims 11-22, wherein

U is O or $C(R^U)_{nu}$, wherein nu is an integer from 1 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

each of R^1 and R^2 is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted

alkoxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, or optionally substituted aminoalkyl;

each of R^3 and R^4 is, independently, H or optionally substituted alkyl;

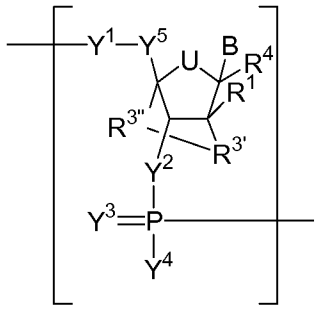
each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, or optionally substituted amino;

each Y^5 is, independently, O or optionally substituted alkylene; and

n is an integer from 10 to 10,000.

24. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleosides having Formula (IIn):



(IIn), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

U is O or $C(R^U)_{nu}$, wherein nu is an integer from 1 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl;

each of R^1 and R^4 is, independently, H, halo, hydroxy, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, or optionally substituted aminoalkyl;

$R^{3'}$ is O, S, or $-NR^{N1}-$, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl;

$R^{3"}$ is optionally substituted alkylene or optionally substituted heteroalkylene;

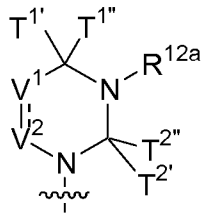
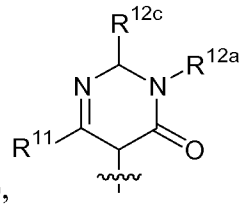
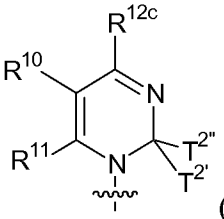
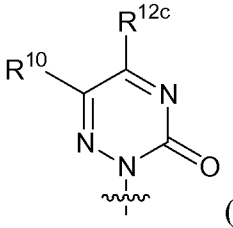
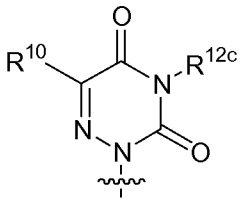
each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

each Y^4 is, independently, H, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, or optionally substituted amino;

each Y^5 is, independently, O, S, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene; and

n is an integer from 10 to 10,000.

25. The isolated polynucleotide of any one of claims 8-24, wherein in said n number of B has, each B independently has a formula selected from Formula (b1)-(b5):


(b1),

(b2),

(b3),

(b4),

or (b5), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

≈ connecting V^1 and V^2 in formula (b1) is a single or double bond;

each of $T^{1'}$, $T^{1"}$, $T^{2'}$, and $T^{2"}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of

$T^{1'}$ and $T^{1''}$ or the combination of $T^{2'}$ and $T^{2''}$ join together to form O (oxo), S (thio), or Se (seleno);

each of V^1 and V^2 is, independently, O, S, $N(R^{Vb})_{nv}$, or $C(R^{Vb})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vb} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy;

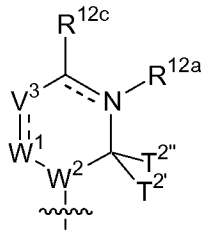
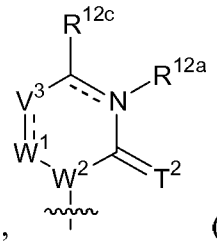
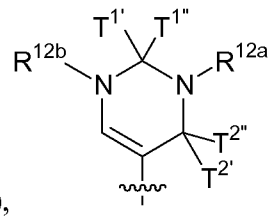
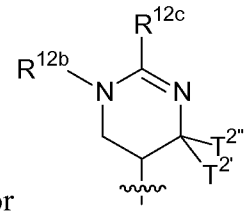
R^{10} is H, halo, optionally substituted amino acid, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aminoalkyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl;

R^{11} is H or optionally substituted alkyl;

R^{12a} is H, optionally substituted alkyl, or optionally substituted aminoalkyl; and

R^{12c} is H, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted amino, or optionally substituted aminoalkyl.

26. The isolated polynucleotide of any one of claims 8-25, wherein n number of B has Formula (b6)-(b9):


(b6),

(b7),

(b8), or


(b9), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

≈ is a single or double bond;

each of $T^{1'}$, $T^{1''}$, $T^{2'}$, and $T^{2''}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of

$T^{1'}$ and $T^{1''}$ or the combination of $T^{2'}$ and $T^{2''}$ join together to form O (oxo), S (thio), or Se (seleno);

each of W^1 and W^2 is, independently, $N(R^{Wa})_{nw}$ or $C(R^{Wa})_{nw}$, wherein nw is an integer from 0 to 2 and each R^{Wa} is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy;

each V^3 is, independently, O, S, $N(R^{Va})_{nv}$, or $C(R^{Va})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Va} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy, and wherein R^{Va} and R^{12c} taken together with the carbon atoms to which they are attached can form optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heterocyclyl;

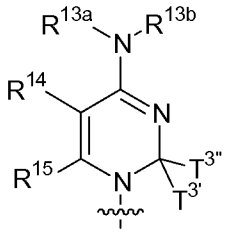
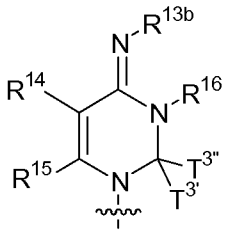
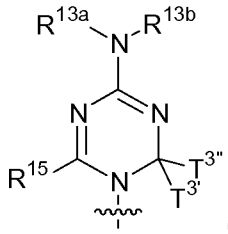
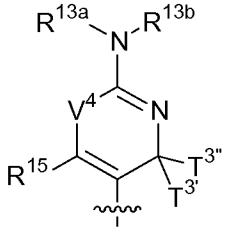
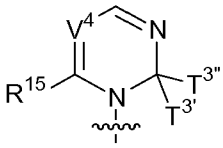
R^{12a} is H, optionally substituted alkyl, optionally substituted aminoalkyl, or absent;

R^{12b} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkaryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted amino acid, wherein the combination of R^{12b} and $T^{1'}$ or the combination of R^{12b} and R^{12c} can join together to form optionally substituted heterocyclyl; and

R^{12c} is H, halo, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted thioalkoxy, optionally substituted amino, or optionally substituted aminoalkyl.

27. The isolated polynucleotide of claim 26, wherein R^{12a}, R^{12b}, R^{12c}, or R^{Va} is substituted with $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10, each of s2 and s3, independently, is an integer from 0 to 10, and R' is H or C_{1-20} alkyl); or $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10, each of s2 and s3, independently, is an integer from 0 to 10, and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl.

28. The isolated polynucleotide of any one of claims 8-27, wherein n number of B has Formula (b10)-(b14):


(b10),

(b11),

(b12),

(b13), or

(b14), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

each of $T^{3'}$ and $T^{3''}$ is, independently, H, optionally substituted alkyl, optionally substituted alkoxy, or optionally substituted thioalkoxy, or the combination of $T^{3'}$ and $T^{3''}$ join together to form O (oxo), S (thio), or Se (seleno);

each V^4 is, independently, O, S, $N(R^{Vc})_{nv}$, or $C(R^{Vc})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vc} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted alkynyloxy, wherein the combination of R^{13b} and R^{Vc} can be taken together to form optionally substituted heterocyclyl;

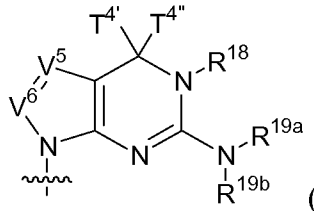
each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted alkyl, or optionally substituted alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

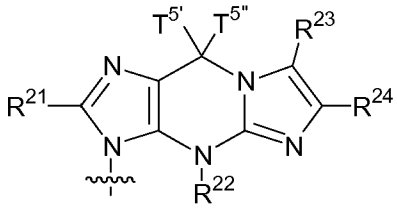
each R^{14} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy,

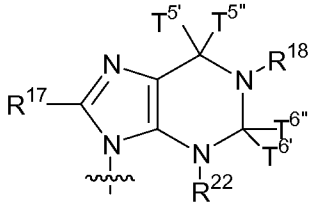
optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted aminoalkyl; and

each of R^{15} and R^{16} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

29. The isolated polynucleotide of any one of claims 7-27, wherein n number of B has Formula (b15)-(b17):


(b15),


(b16), or


(b17), or a pharmaceutically acceptable salt or stereoisomer thereof,

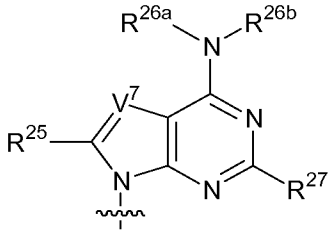
wherein

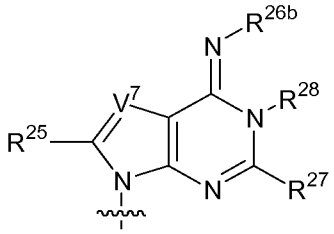
each of $T^{4'}$, $T^{4''}$, $T^{5'}$, $T^{5''}$, $T^{6'}$, and $T^{6''}$ is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy, and wherein the combination of $T^{4'}$ and $T^{4''}$ or the combination of $T^{5'}$ and $T^{5''}$ or the combination of $T^{6'}$ and $T^{6''}$ together form O, S, or Se;

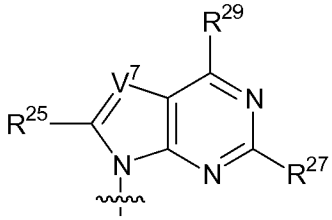
each of V^5 and V^6 is, independently, O, S, $N(R^{Vd})_{nv}$, or $C(R^{Vd})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vd} is, independently, H, halo, optionally substituted amino acid, cyano, amidine, optionally substituted aminoalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy; and

each of R^{17}, R^{18}, R^{19a}, R^{19b}, R^{21}, R^{22}, R^{23}, and R^{24} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted amino acid.

30. The polynucleotide of any one of claims 8-29, wherein n number of B has Formula (b18)-(b20):


(b18),


(b19), or


(b20), or a pharmaceutically acceptable salt or stereoisomer thereof,

wherein

each V^7 is, independently, O, S, $N(R^{Ve})_{nv}$, or $C(R^{Ve})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Ve} is, independently, H, halo, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, or optionally substituted alkynyloxy;

each R^{25} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

each of R^{26a} and R^{26b} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, or optionally substituted alkoxy;

each R^{27} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, or optionally substituted amino;

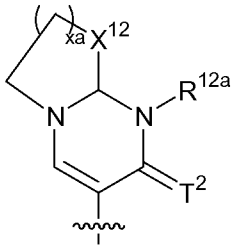
each R^{28} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

each R^{29} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally

substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted alkoxy, or optionally substituted amino.

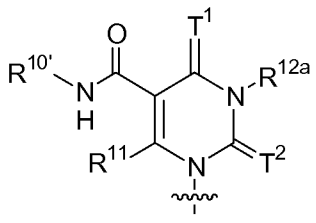
31. The isolated polynucleotide of claim 30, wherein R^{26a}, R^{26b}, or R^{29} is substituted with $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10, each of s2 and s3, independently, is an integer from 0 to 10, and R' is H or C_{1-20} alkyl); or $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, wherein s1 is an integer from 1 to 10, each of s2 and s3, independently, is an integer from 0 to 10, and each R^{N1} is, independently, hydrogen or optionally substituted C_{1-6} alkyl.

32. The isolated polynucleotide of any one of claims 8-31, wherein n number of B has Formula (b21):



(b21), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein X^{12} is, independently, O, S, optionally substituted alkylene, or optionally substituted heteroalkylene; xa is an integer from 0 to 3; R^{12a} is H, optionally substituted alkyl, optionally substituted aminoalkyl, or absent; and T^2 is O, S, or Se.

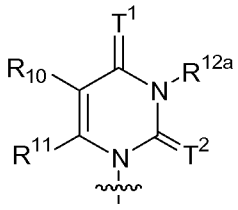
33. The isolated polynucleotide of any one of claims 8-32, wherein n number of B has Formula (b22):



(b22), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{10'}$ is, independently, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted aminoalkyl, optionally

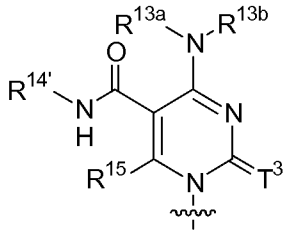
substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl; R^{11} is H or optionally substituted alkyl; R^{12a} is H, optionally substituted alkyl, optionally substituted aminoalkyl, or absent; and each of T^1 and T^2 is, independently, O, S, or Se.

34. The isolated polynucleotide of any one of claims 8-33, wherein n number of B has Formula (b23):



(b23), wherein R^{10} is optionally substituted heterocyclyl or optionally substituted aryl; R^{11} is H or optionally substituted alkyl; R^{12a} is H, optionally substituted alkyl, optionally substituted aminoalkyl, or absent; and each of T^1 and T^2 is, independently, O, S, or Se.

35. The isolated polynucleotide of any one of claims 8-34, wherein n number of B has Formula (b24):



(b24), wherein

T^3 is O, S, or Se;

each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted alkyl, or optionally substituted alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

$R^{14'}$ is, independently, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, optionally substituted alkaryl,

optionally substituted aminoalkyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl; and

each R^{15} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

36. The isolated polynucleotide of any one of claims 1-35, further comprising a targeting moiety, wherein said targeting moiety is covalently bound to said polynucleotide.

37. The isolated polynucleotide of claim 36, wherein said targeting moiety is an antibody, thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-gulucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, an RGD peptide, an RGD peptide mimetic, or an aptamer.

38. A pharmaceutical composition comprising the isolated polynucleotide of any one of claims 1-37.

39. A pharmaceutical composition comprising the isolated polynucleotide of any one of claims 1-37 and a pharmaceutically acceptable excipient.

40. The pharmaceutical composition of claim 39, wherein the excipient is selected from a solvent, aqueous solvent, non-aqueous solvent, dispersion media, diluent, dispersion, suspension aid, surface active agent, isotonic agent, thickening or emulsifying agent, preservative, lipid, lipidoids liposome, lipid nanoparticle, core-shell nanoparticles, polymer, lipoplexe peptide, protein, cell, hyaluronidase, and mixtures thereof.

41. The pharmaceutical composition of claim 40, where the pharmaceutical composition comprises a lipid and wherein said lipid is selected from DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DODMA, DSDMA, DLenDMA, reLNPs, PLGA and PEGylated lipids and mixtures thereof.

42. A method of producing a polypeptide of interest in a mammalian cell, tissue or organism comprising administering to said cell, tissue or organism the isolated polynucleotide of any one of claims 1-37 or the pharmaceutical composition of any of claims 38-41.

43. The method of claim 42, wherein the isolated polynucleotide is formulated.

44. The method of claim 43, wherein the formulation comprises a lipid which is selected from one of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DODMA, DSDMA, DLenDMA, reLNPs, PLGA, PEGylated lipids and mixtures or combinations thereof.

45. The method of claim 44, wherein the isolated polynucleotide is administered at a total daily dose of between 1 ug and 150 ug.

46. The method of claim 45, wheriein administration is by injection.

47. The method of claim 46, wherein administration is intradermal or subcutaneous or intramuscular or intravitreal.

48. The method of claim 45, wherein levels of the polypeptide of interest in the serum of the mammal are at least 50 pg/mL at least two hours after administration.

49. The method of claim 45, wherein the levels of the polypeptide of interest in the serum of the mammal remain above 50 pg/mL for at least 72 hours after administration.

50. The method of claim 49, wherein the levels of the polypeptide of interest in the serum of the mammal remain above 60 pg/mL for at least 72 hours after administration.

51. The method of claim 44, wherein the resulting polynucleotide formulation has a mean particle size of 80 nm-160 nm, a PDI of between 0.02 and 0.20 and a lipid to polnucleotide ratio (wt/wt) of between 10-20.

52. A method for producing an increased level of a polypeptide of interest selected from the group consisting of SEQ ID NOs 8922-17687 in a mammalian cell, tissue or organism, comprising administering to said cell, tissue or organism a total daily dose of the isolated polynucleotide of any one of claims 4-37 or the pharmaceutical composition of any one of claims 38-41 in two or more equal or unequal split doses.

53. The method of claim 52, wherein the level of the polypeptide produced in response to said administration is greater than the levels produced by administering the same total daily dose of the isolated polynucleotide or pharmaceutical composition as a single administration.

54. The method of claim 52, wherein the mammalian organism is a human patient in need of an increased level of the polypeptide of interest.

55. The method of claim 54, wherein the increased level of the polypeptide of interest is detectable in a bodily fluid of said patient.

56. The method of claim 55, wherein the bodily fluid is selected from the group consisting of peripheral blood, serum, plasma, ascites, urine, cerebrospinal fluid (CSF), sputum, saliva, bone marrow, synovial fluid, aqueous humor, amniotic fluid, cerumen, breast milk, broncheoalveolar lavage fluid, semen, prostatic fluid, cowper's fluid or pre-ejaculatory fluid, sweat, fecal matter, hair, tears, cyst fluid, pleural and peritoneal fluid, pericardial fluid, lymph, chyme, chyle, bile, interstitial fluid, menses, pus, sebum, vomit, vaginal secretions, mucosal secretion, stool water, pancreatic juice, lavage fluids from

sinus cavities, bronchopulmonary aspirates, blastocyl cavity fluid, and umbilical cord blood.

57. The method of claim 56, wherein the bodily fluid is serum and the polpeptide per unit drug (PUD) is greater than 1.

58. The method of claim 57, wherein the dose splitting factor (DSF) is greater than 4.

59. The method of claim 55, wherein administration is transdermal.

60. The method of claim 59, wherein transdermal administration comprises utilization of one or more members selected from the group consisting of a patch, cream, ointment, mechanical device, needle, sponge, depot and fabric.

61. The method of claim 59, wherein administration is according to a dosing regimen which occurs over the course of hours, days, weeks, months, or years.

62. The method of claim 52, wherein said two or more split doses comprise a first dose of the polynucleotide or pharmaceutical composition administered at a time T1 followed by a second dose of the polynucleotide or pharmaceutical composition administered at a time T2, wherein said time T1 and said time T2 are separated by no more than 1 minute and wherein said first dose and said second dose are administered in amounts that result in higher levels of the polypeptide of interest in said subject than if the amounts of polynucleotide or pharmaceutical composition were administered together in a single unit dose.

63. The method of claim 62, further comprising administering a plurality of doses of said polynucleotide or pharmaceutical composition, Nx at times Tn, wherein x and n are independently selected from 3 to about 1000 and where the time between Tn and Tn+1 is separated by increments of no more than 10 seconds.

64. The method of claim 63, wherein administration occurs by direct injection.

65. The method of claim 64, wherein direct injection is selected from the group consisting of intravenous, intradermal, subcutaneous, intramuscular and intravitreal.

66. The method of claim 64, wherein said first dose is administered proximal to said second or plurality of doses.

67. The method of claim 64, wherein said first dose is administered distal to said second or plurality of doses.

68. The method of claim 64, wherein the distance between the site of injection of said first dose and the site of injection of any second or plurality of doses is from about 1mm to about 10 cm.

69. The method of claim 64, wherein injection is made at a depth of from 0.1mm to about 1cm.

70. The method of claim 65, wherein direct injection is achieved by using one or more devices selected from multineedle injection systems, catheter or lumen systems, and ultrasound, electrical or radiation based systems.

71. The method of claim 63, wherein the amount polynucleotide or pharmaceutical composition administered in any dose is substantially equal.

72. The method of claim 63, wherein time T1 and time T2 are separated by no more than 30 seconds.

73. The method of claim 63, wherein time T1 and time T2 are separated by no more than 10 seconds.

74. The method of claim 63, wherein the first dose, the second dose and any of a plurality of doses are administered at substantially the same time.

75. The method of claim 63, wherein the single unit dose is between about 10 mg/kg and about 500 mg/kg.

76. The method of claim 63, wherein the single unit dose is between about 1.0 mg/kg and about 10 mg/kg.

77. The method of claim 63, wherein the single unit dose is between about 0.001 mg/kg and about 1.0 mg/kg.

78. A method of preparing a lipid nanopartical formulation of a polynucleotide encoding a polypeptide of interest comprising rapidly injecting a first ethanolic solution into a second aqueous solution wherein,

(a) said first ethanolic solution comprises a mixture of lipid:DSPC: Cholesterol: PEG-c-DOMG to yield a molar ratio of 50:10:38.5:1.5 and having a final lipid concentration of approximately 25mM, and

(b) said second aqueous solution comprises a sodium citrate buffered solution of the polynucleotide encoding the polypeptide of interest having a concentration of 1-2 mg/mL and a pH of approximately 3,

wherein the rapid injection results in a suspension containing 33% ethanol and a total lipid to polynucleotide weight ratio of at least 10:1.

79. The method of claim 78, wherein the rapid injection is performed either manually (MI) or by the aid of a syringe pump (SP).

80. The method of claim 79, further comprising dialyzing the resultant suspension against phosphate buffered saline (PBS) at pH 7.4.

81. The method of claim 80, wherein dialysis is performed more than once.

82. The method of claim 81, further comprising filtering the dialyzed suspension through a 0.2 μm sterile filter.

83. The method of any of claims 78-82, wherein the lipid is selected from the group consisting of DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, 98N12-5, C12-200, DLin-MC3-DMA, DODMA, DSDMA, DLenDMA, reLNPs, PLGA and PEGylated lipids.

84. The method of any of claims 78-83, wherein the polynucleotide is selected from the polynucleotide of any of claims 1-37.

85. A lipid nanopartical formulation of a polynucleotide encoding a polypeptide of interest produced by the method of any of claims 78-84 and having a particle size of 80 nm-160 nm, a PDI of between 0.02 and 0.20 and a lipid to polnucleotide ratio (wt/wt) of between 10-30.

86. A lipid nanopartical formulation of claim 85, wherein the polynucleotide is selected from the polynucleotide of any of claims 1-37.

87. A reLNP formulation of a polynucleotide said polynucleotide encoding a polypeptide of interest.

88. A reLNP formulation of claim 87, wherein the polynucleotide is selected from the polynucleotide of any of claims 1-36.

89. A sustained release formulation of a polynucleotide said polynucleotide encoding a polypeptide of interest.

90. A sustained release formulation of claim 89, wherein the polynucleotide is selected from the polynucleotide of any of claims 1-36.

91. A polynucleotide encoding a fusion protein said fusion protein comprising a first polypeptide and a second polypeptide.

92. The polynucleotide of claim 91 where the first polypeptide is selected from the group consisting of Fc receptor, Fab fragment, Fab' fragment, $F(ab')_2$ fragment, Fv fragment, IgA domain, IgD domain, IgE domain, IgD domain, IgM domain, IgV domain, IgC1 domain, IgC2 domain and IgI domain and the second polypeptide is a polypeptide of interest.

FIGURE 1

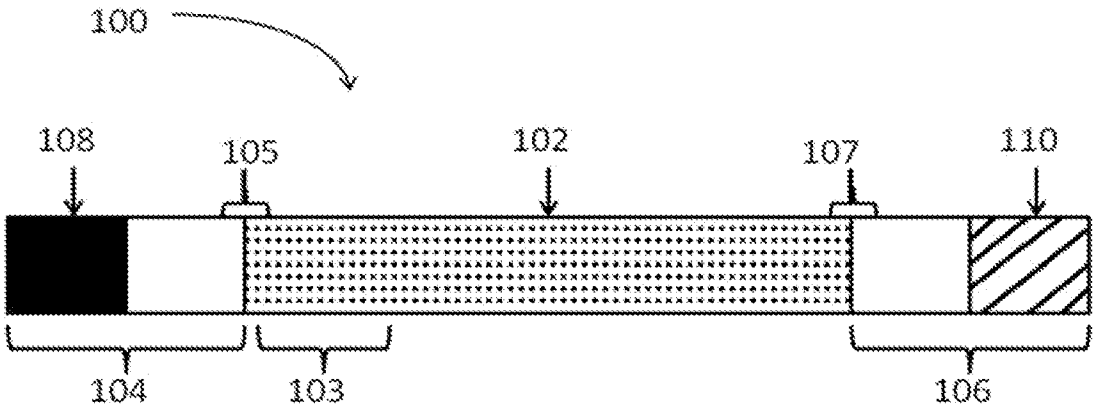
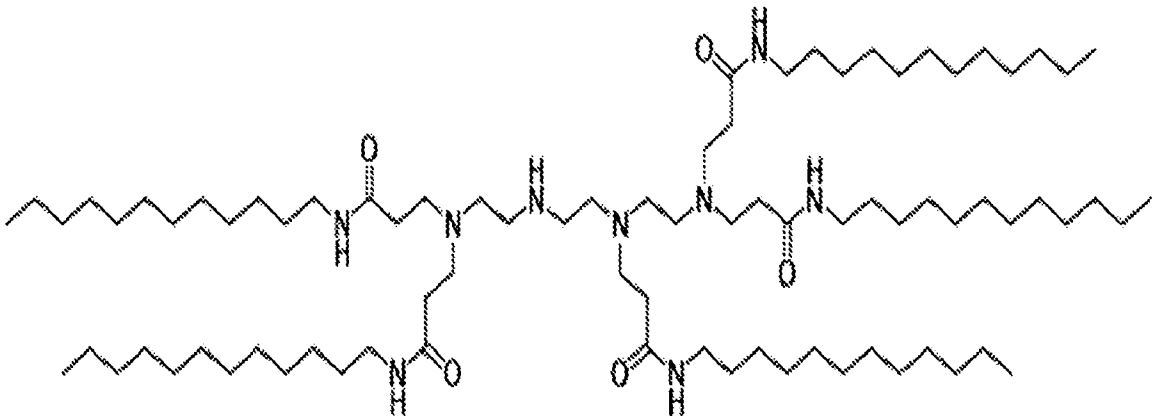
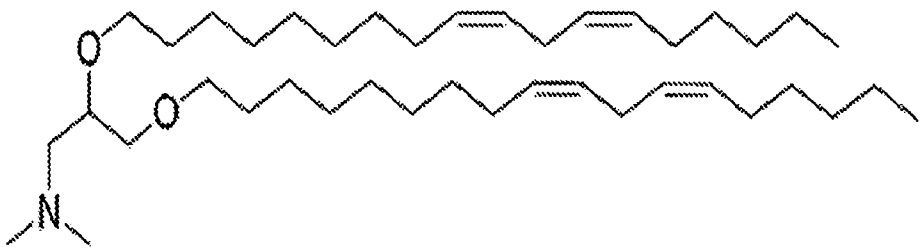


FIGURE 2

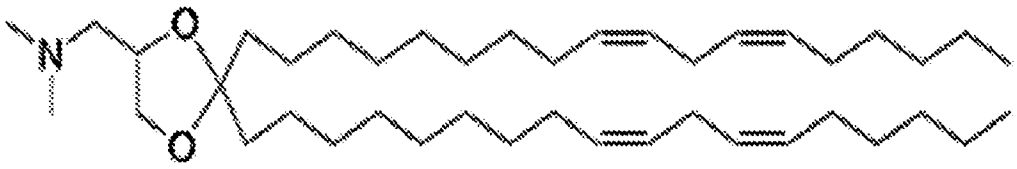
98N12-5 (TETA5-LAP)



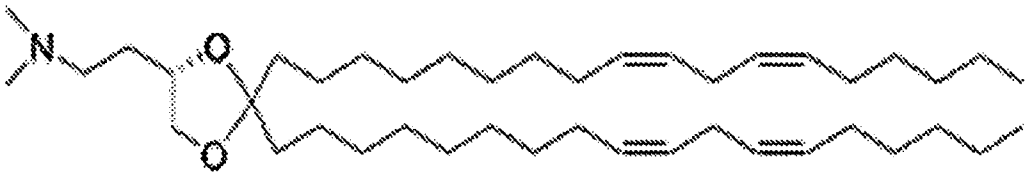
DLin-DMA



DLin-K-DMA (2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane)



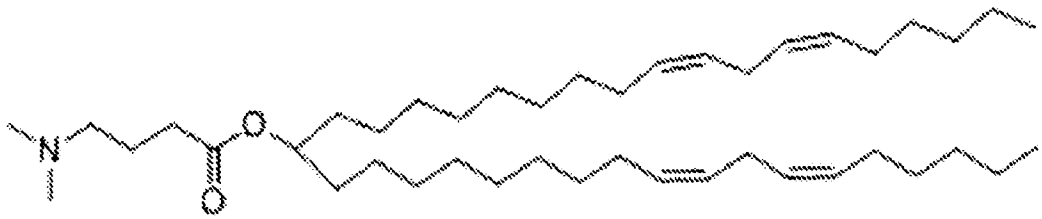
DLin-KC2-DMA



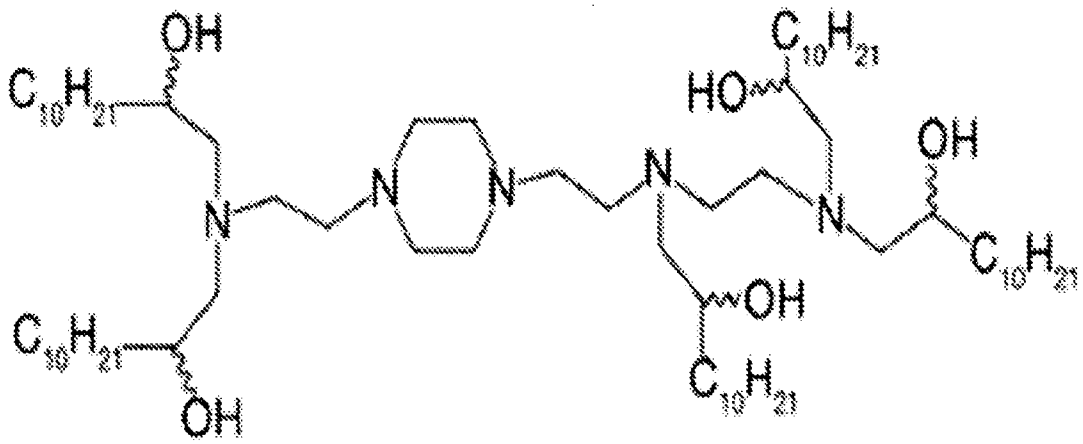
PRIOR ART

FIGURE 2 CONT.

DLin-MC3-DMA

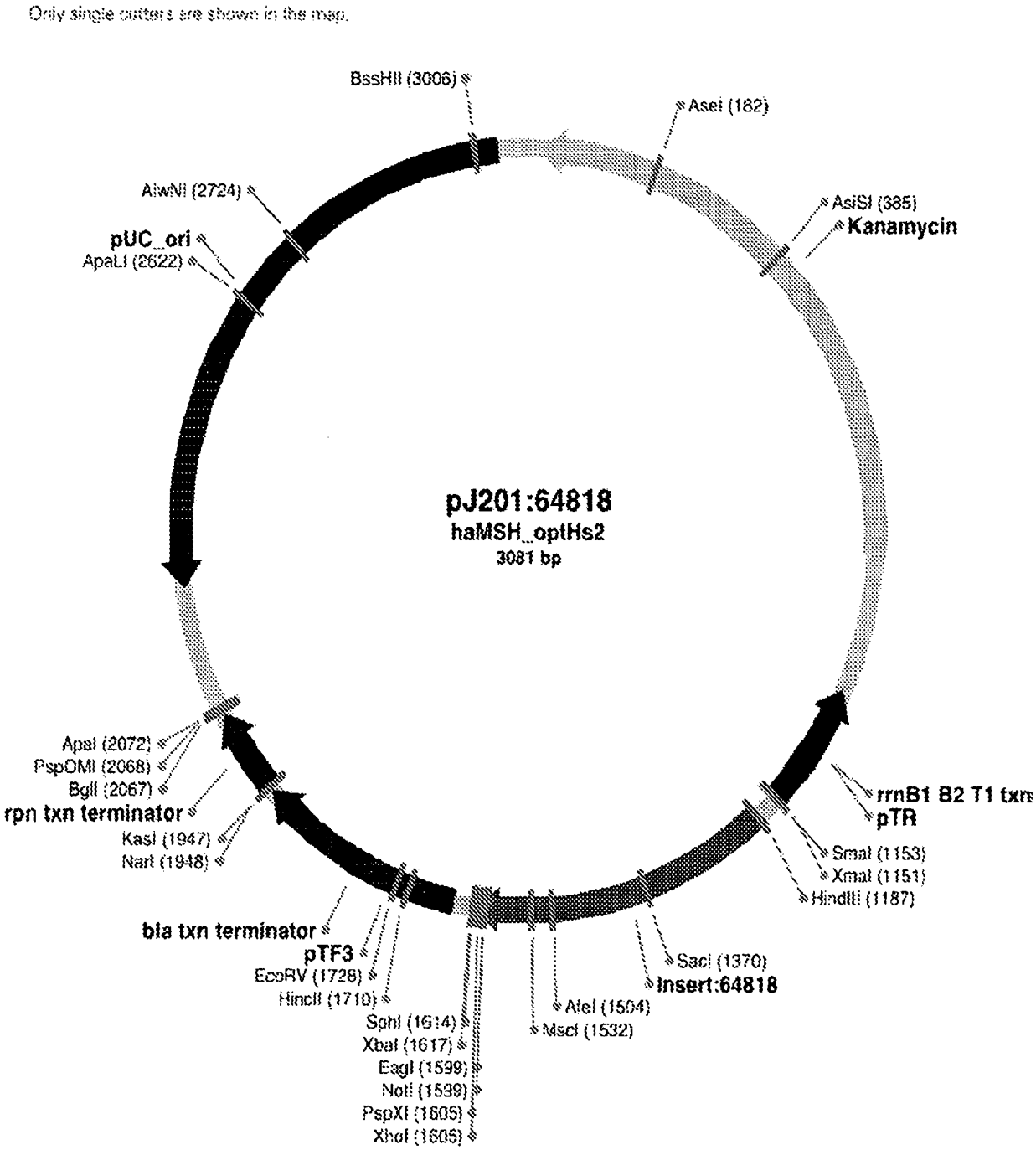


C12-200



PRIOR ART

FIGURE 3



PRIOR ART

FIGURE 4

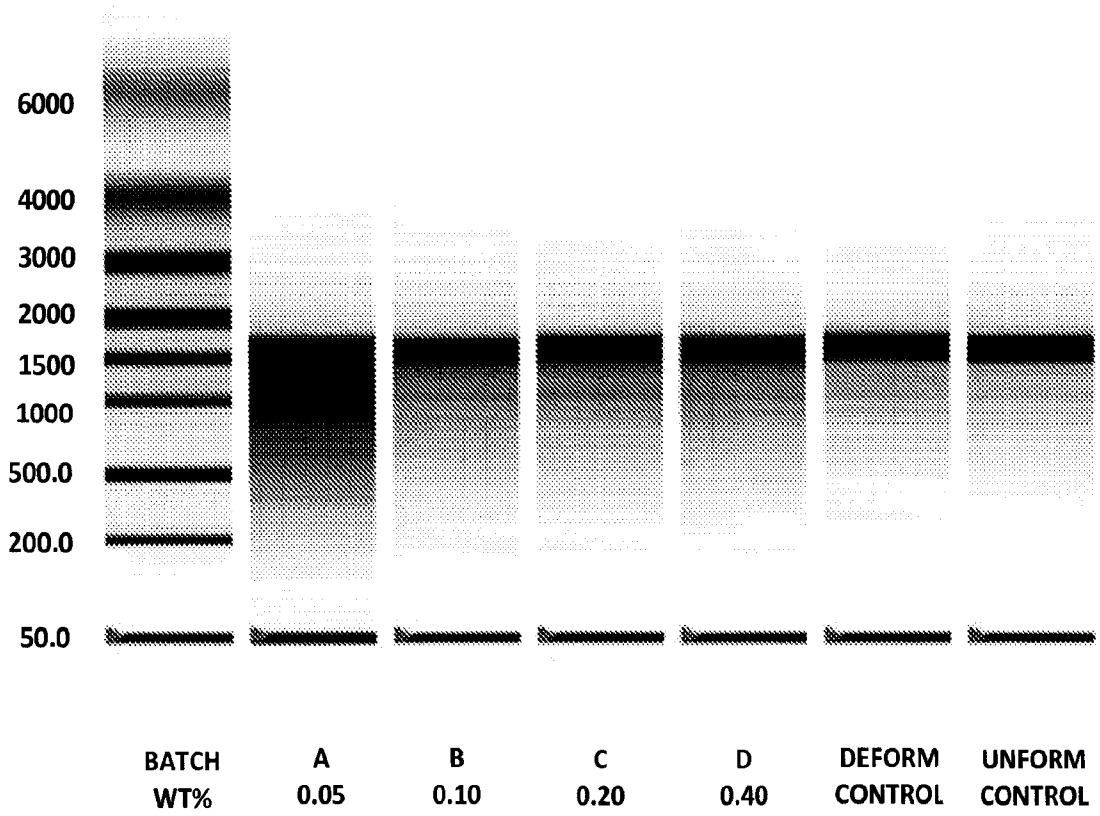

6000
4000
3000
2000
1500
1000
500.0
200.0
50.0
BATCH
WT%
A
0.05
B
0.10
C
0.20
D
0.40
DEFORM
CONTROL
UNFORM
CONTROL

FIGURE 5

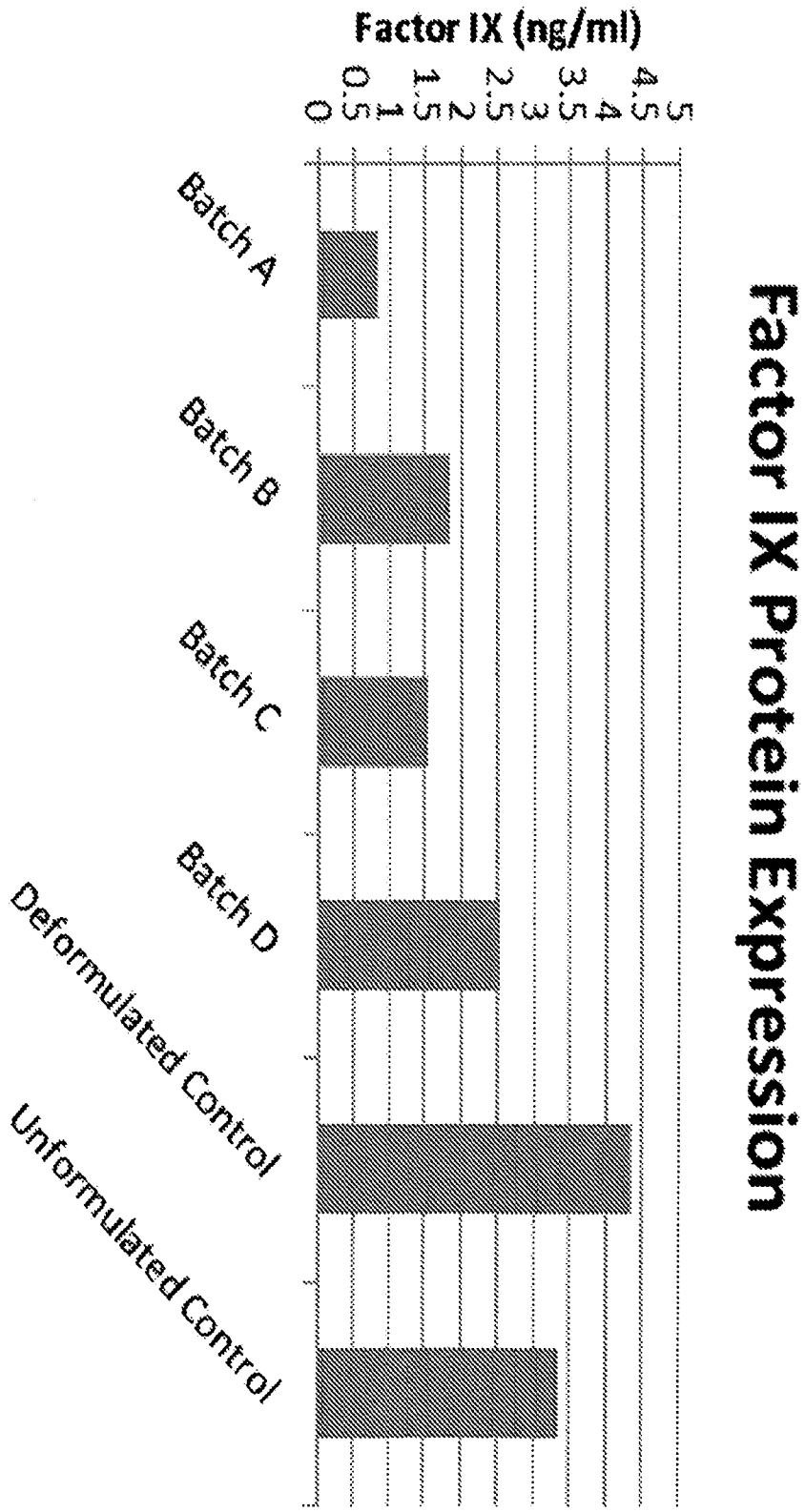

Factor IX (ng/ml)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Batch A
Batch B
Batch C
Batch D
Deformulated Control
Unformulated Control
Factor IX Protein Expression

FIGURE 6

A.

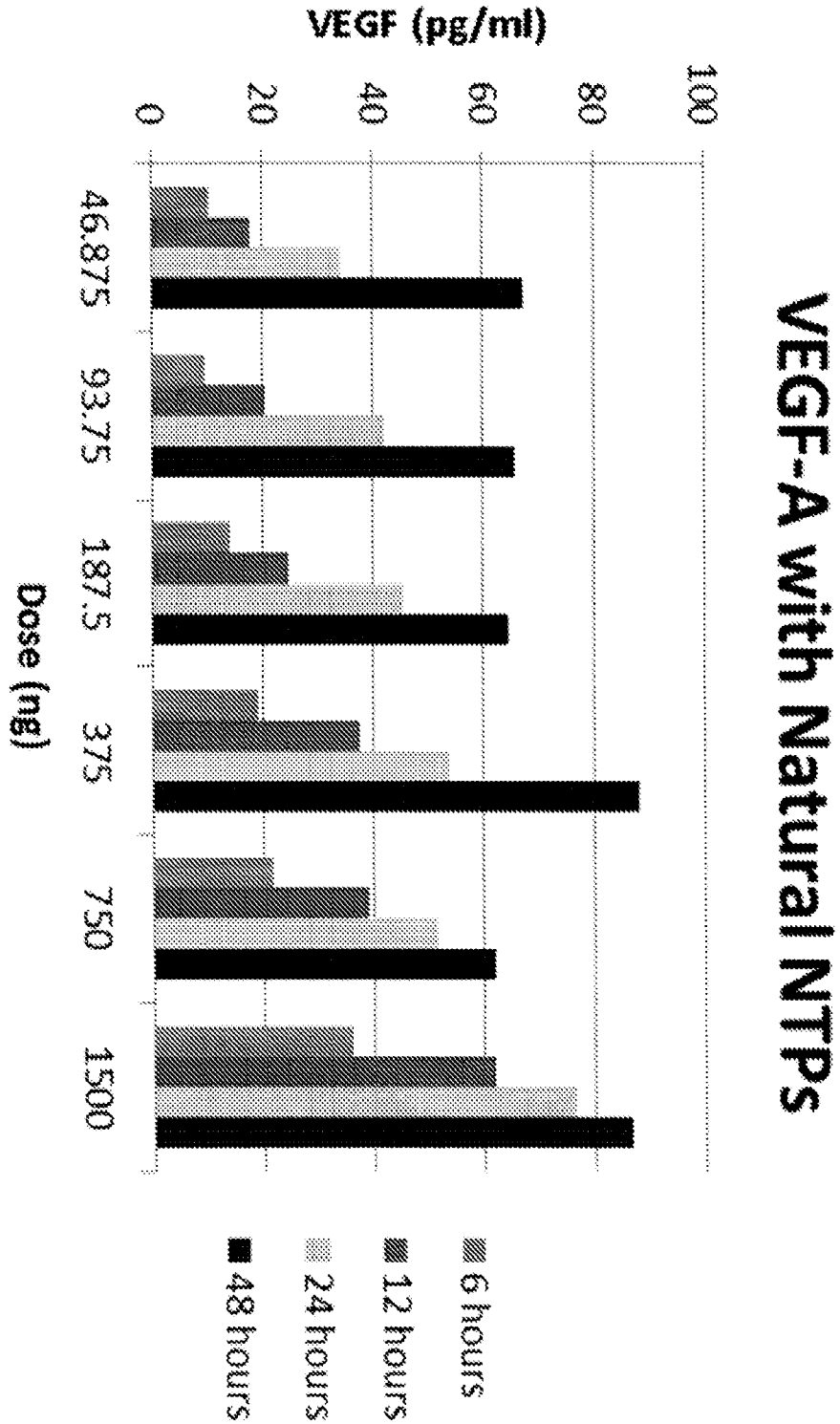

VEGF-A with Natural NTPs
VEGF (pg/ml)
0
20
40
60
80
100
Dose (ng)
46.875
93.75
187.5
375
750
1500
6 hours
12 hours
24 hours
48 hours

FIGURE 6 CONT.

B.

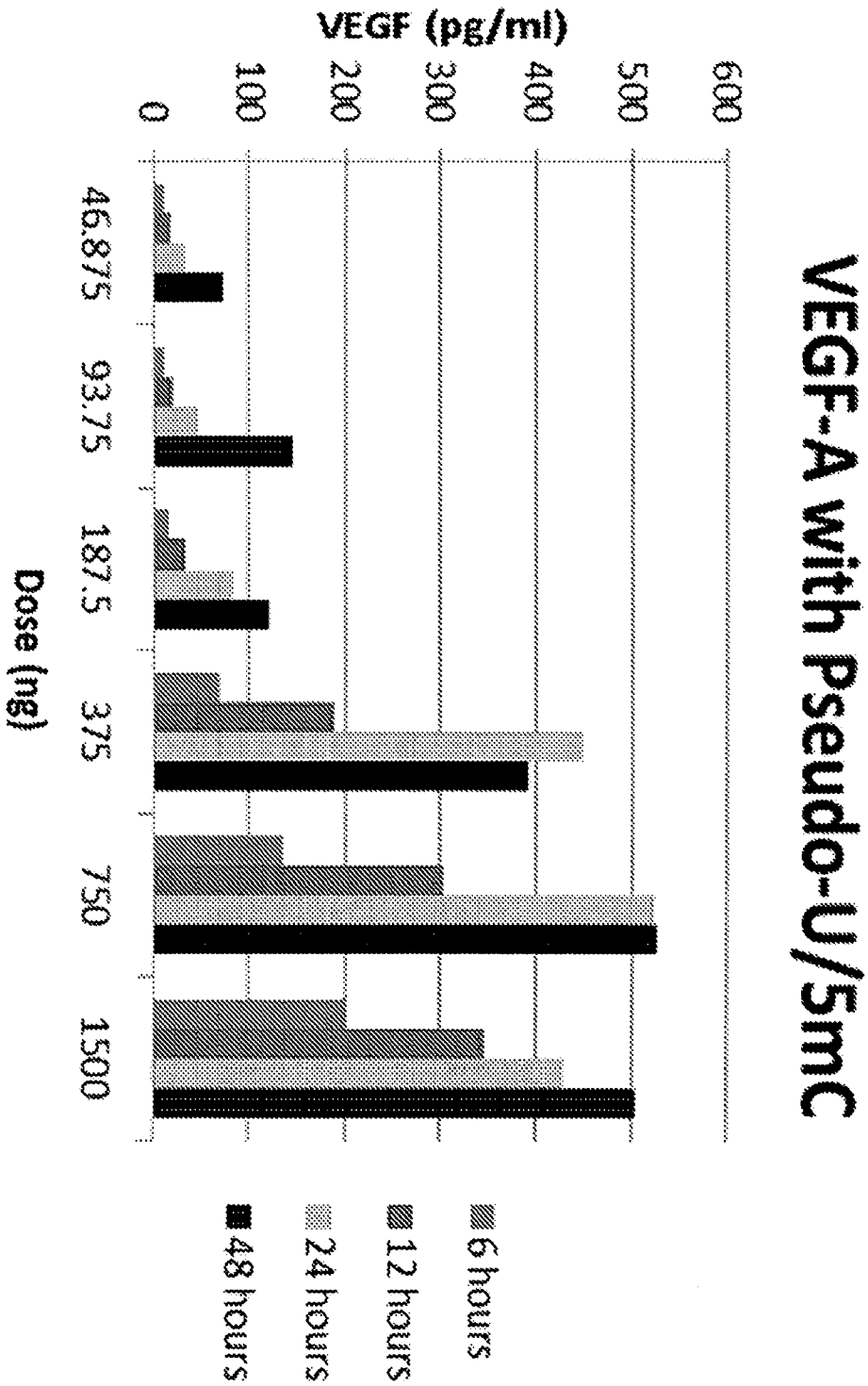


FIGURE 6 CONT.

C.

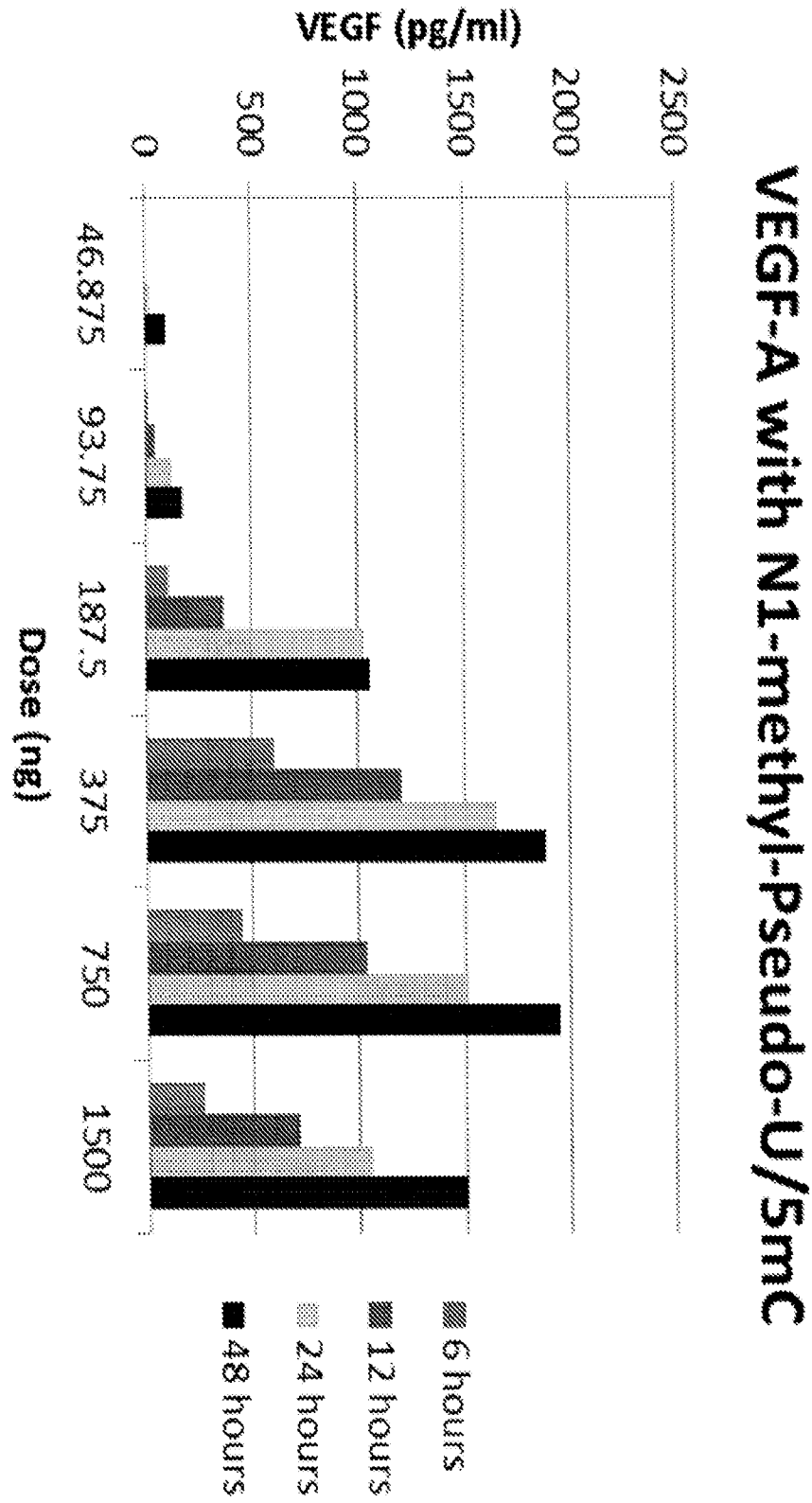


FIGURE 7

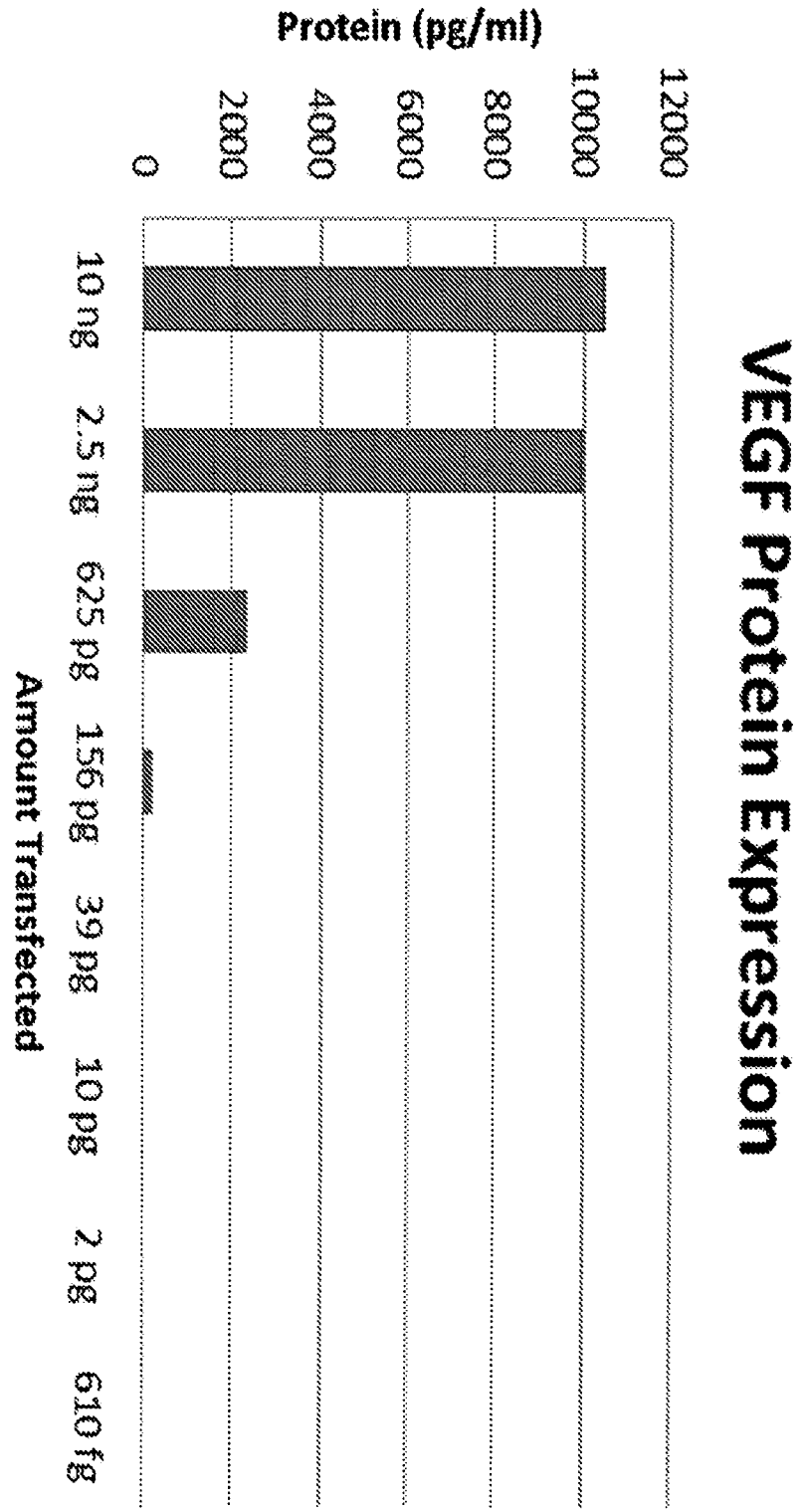

VEGF Protein Expression
Protein (pg/ml)
0
2000
4000
6000
8000
10000
12000
Amount Transfected
10 ng
2.5 ng
625 pg
156 pg
39 pg
10 pg
2 pg
610 fg

FIGURE 8

A.

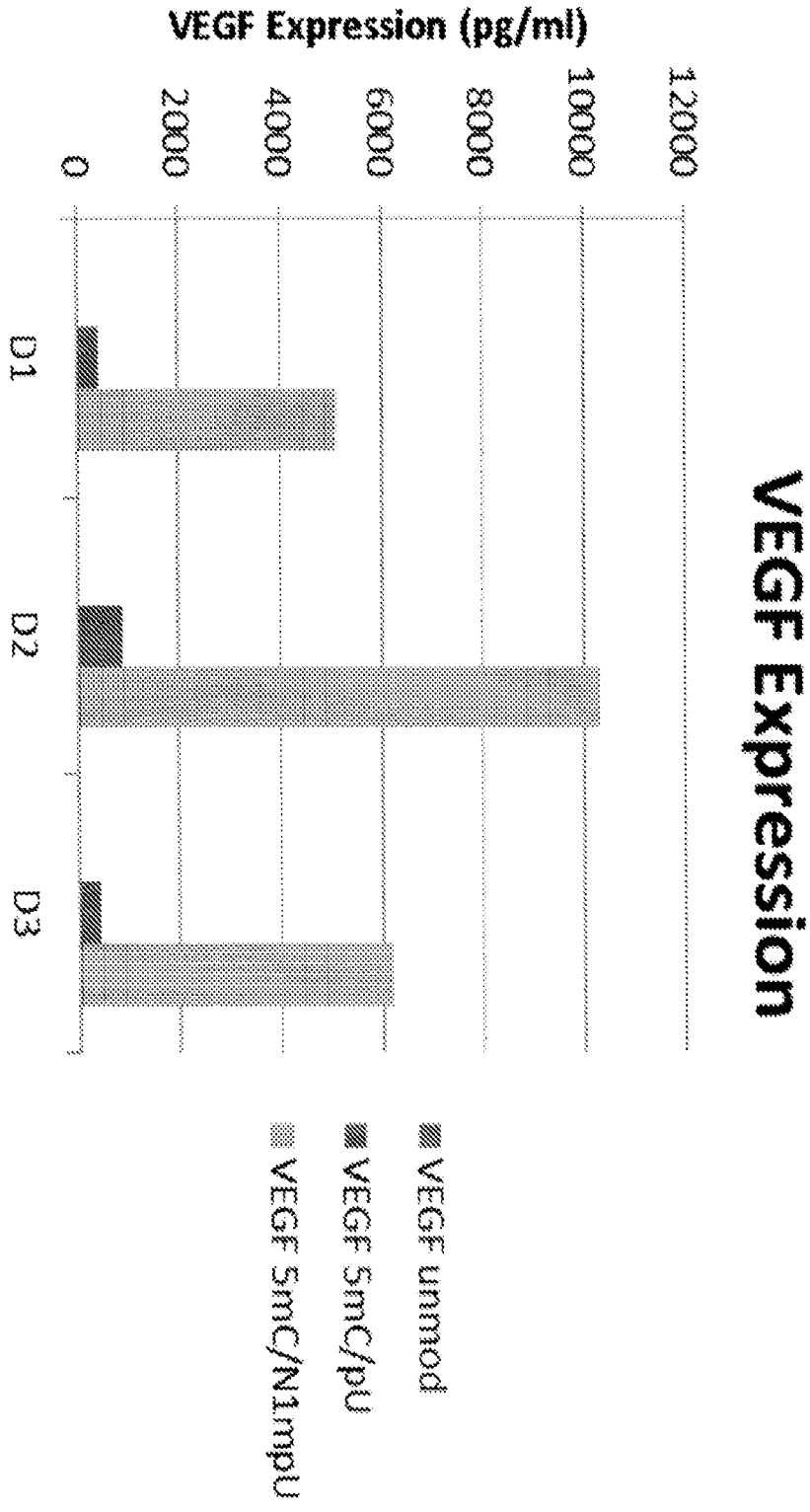

VEGF Expression (pg/ml)
0
2000
4000
6000
8000
10000
12000
D1
D2
D3
VEGF unmod
VEGF 5mC/pU
VEGF 5mC/N1mpU
VEGF Expression

FIGURE 8 CONT.

B.

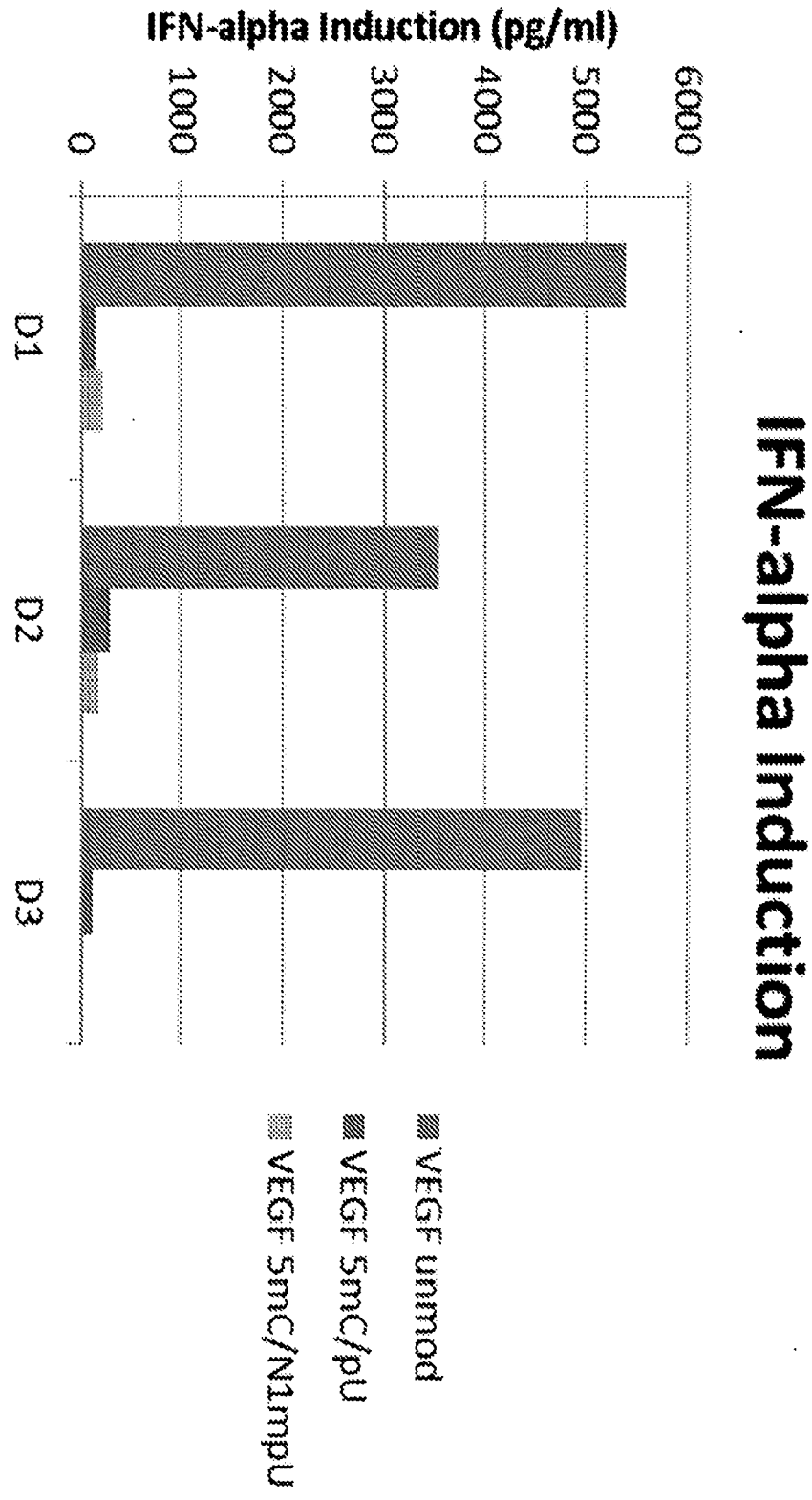


FIGURE 9

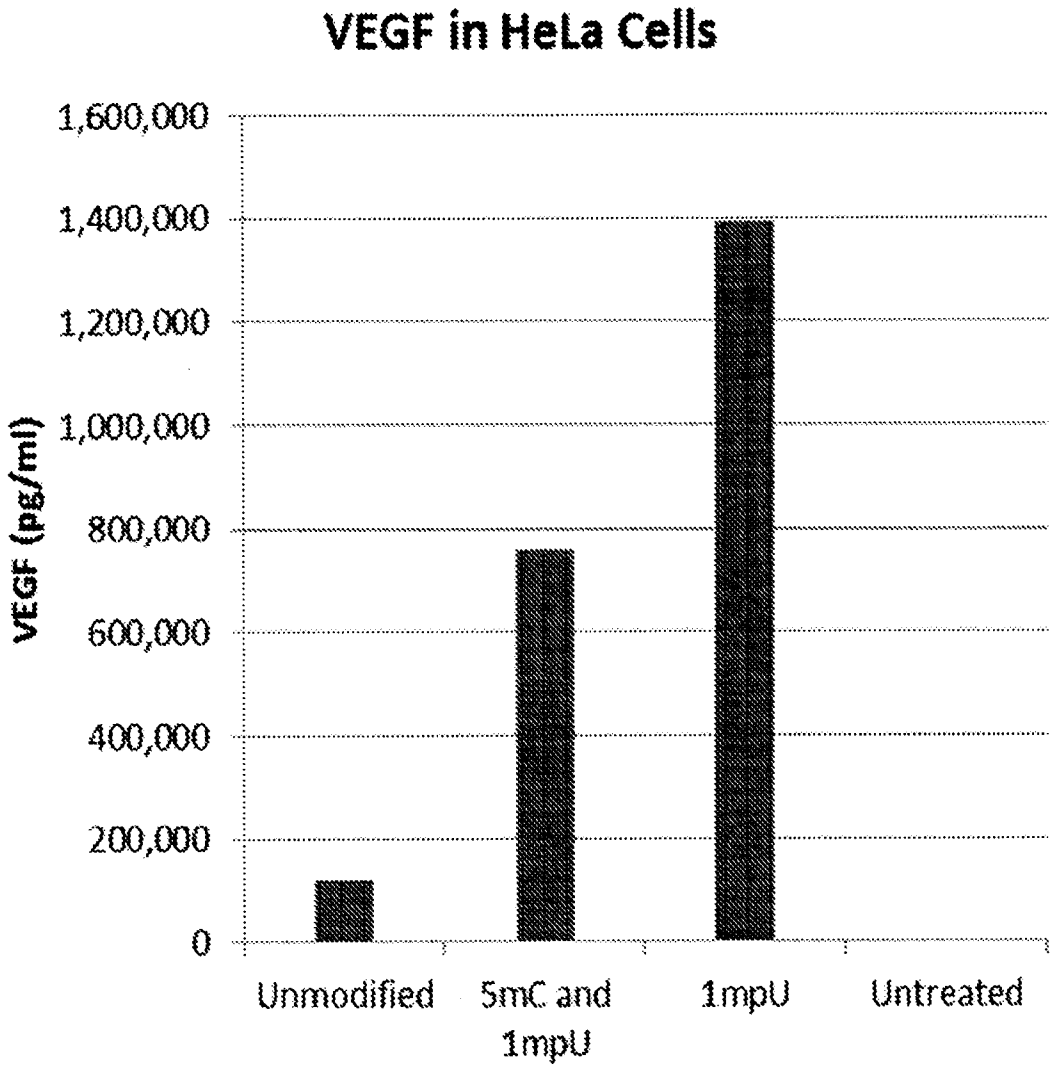

VEGF in HeLa Cells
VEGF (pg/ml)
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
Unmodified
5mC and 1mpU
1mpU
Untreated

FIGURE 10

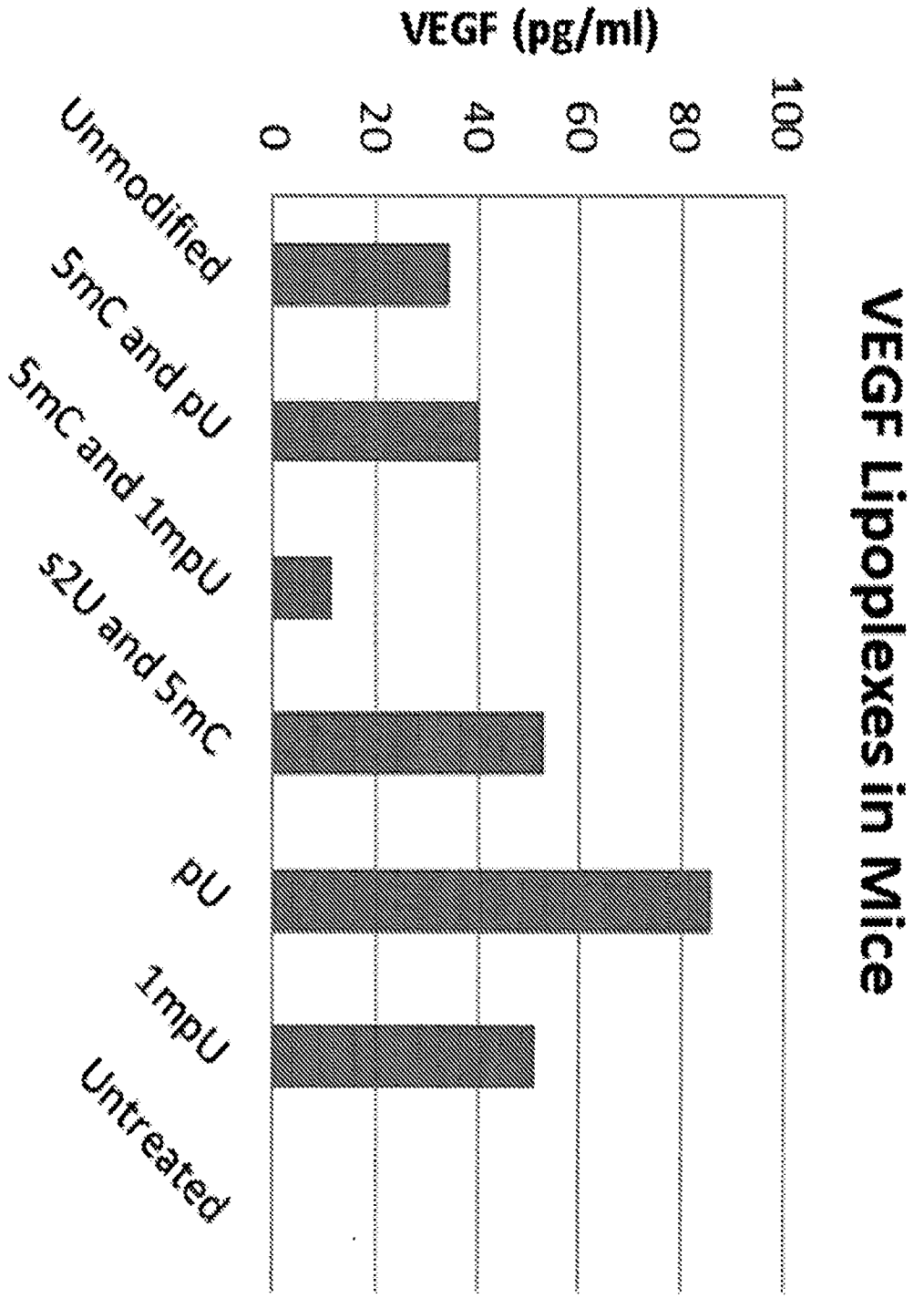

VEGF (pg/ml)
0
20
40
60
80
100
Unmodified
5mC and pU
5mC and 1mpU
s2U and 5mC
pU
1mpU
Untreated
VEGF Lipoplexes in Mice

FIGURE 11

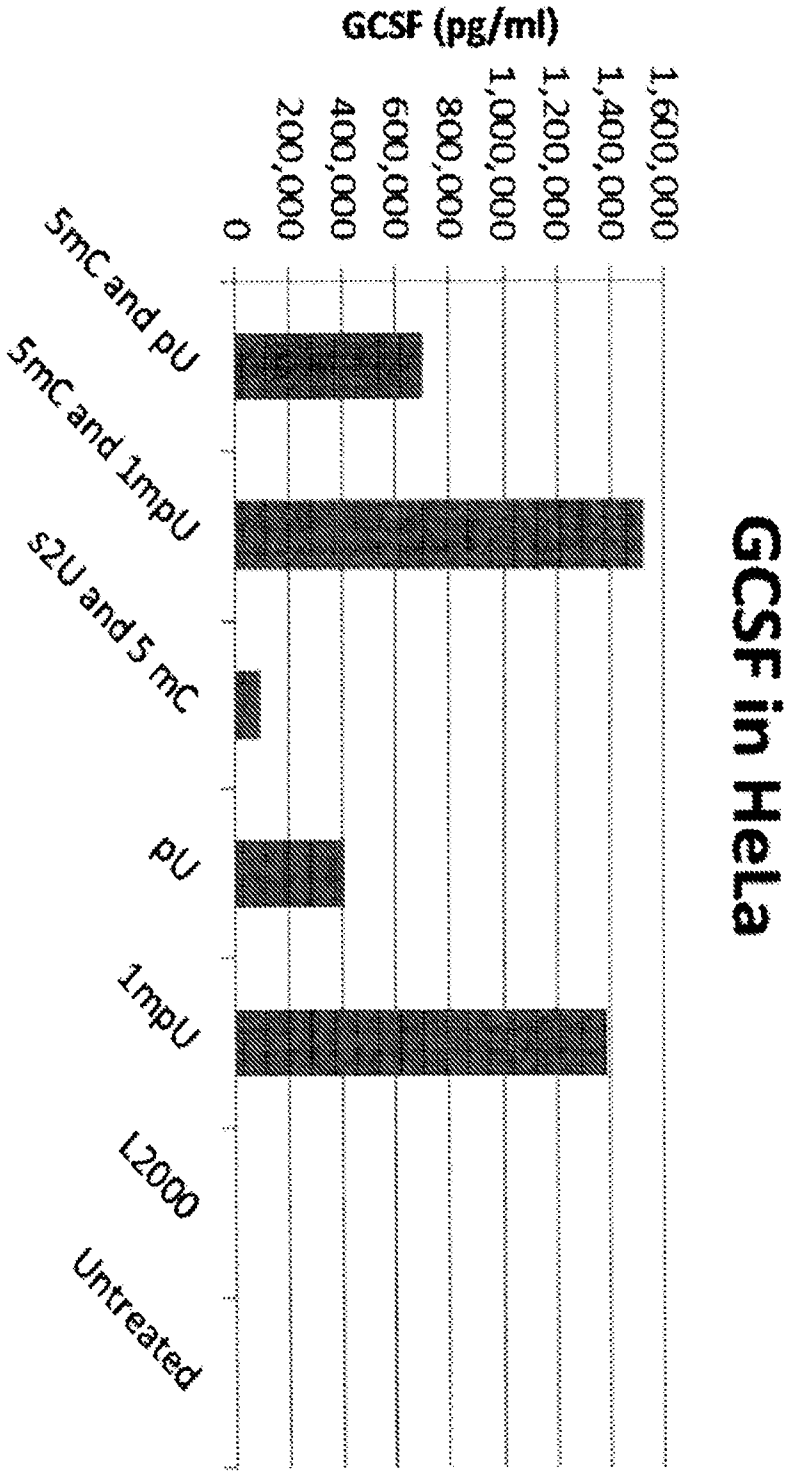
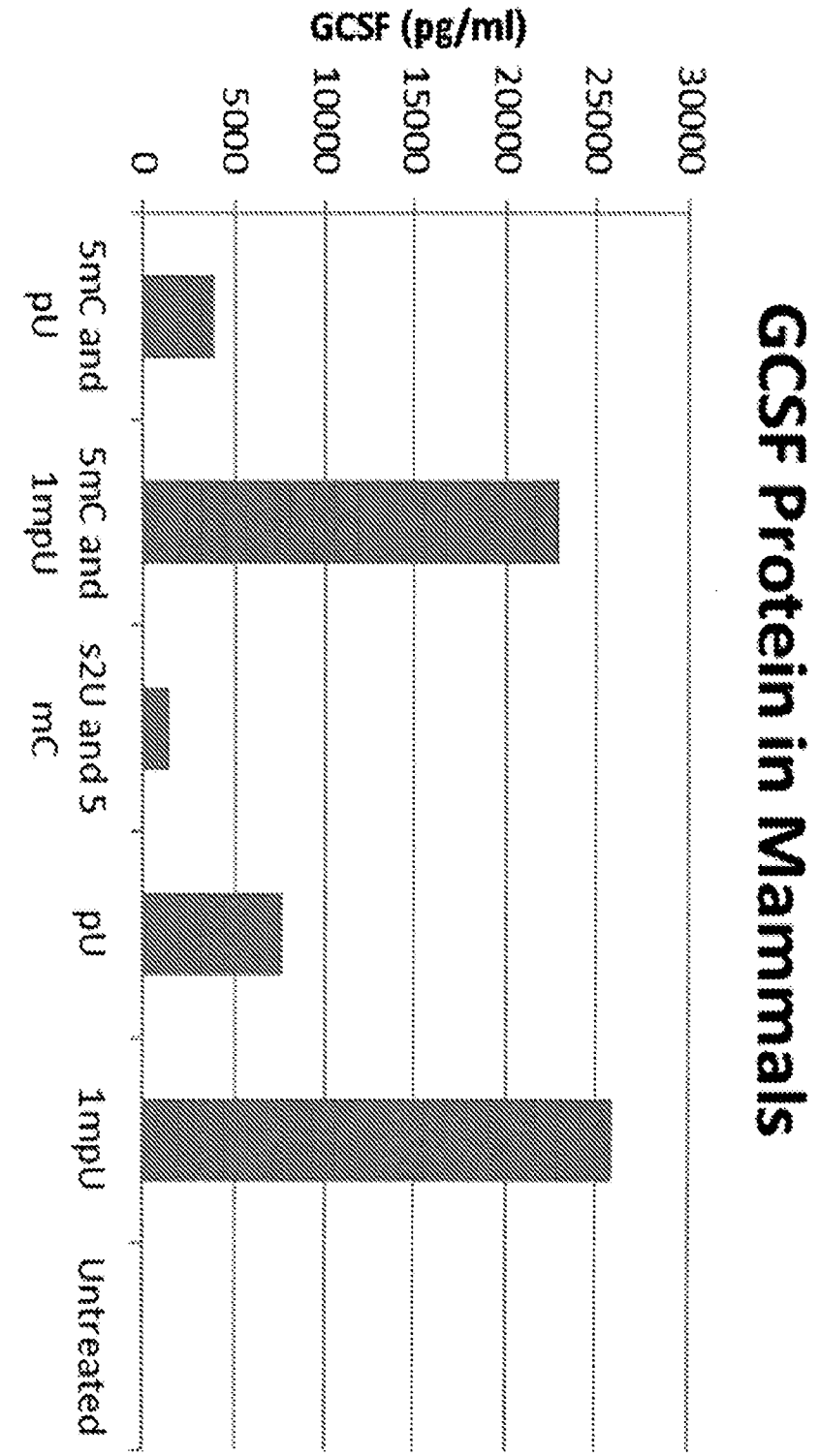

GCSF (pg/ml)
0
200,000
400,000
600,000
800,000
1,000,000
1,200,000
1,400,000
1,600,000
5mC and pU
5mC and 1mpU
s2U and 5 mC
pU
1mpU
L2000
Untreated
GCSF in HeLa

FIGURE 12


GCSF Protein in Mammals
GCSF (pg/ml)
0
5000
10000
15000
20000
25000
30000
Untreated
1mpU
pU
5mC and s2U and 5 mC
1mpU
5mC and pU

EDITORIAL NOTE

2013243947

Gene sequence for this application has 52151 pages. A copy can be obtained from WIPO Patenscope