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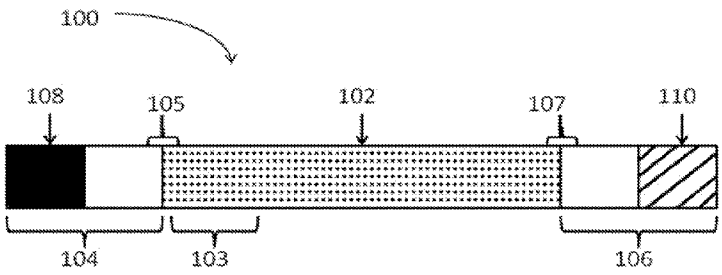
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61/737,160	14 December 2012 (14.12.2012)	US
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[Continued on next page]

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

FIGURE 1



(57) Abstract: The disclosure relates to compositions and methods for the preparation, manufacture and therapeutic use of polynucleotides. More specifically, the disclosure provides compositions, methods, processes, kits and devices for the design, preparation, manufacture and/or formulation of modified mRNA (mmRNA) molecules from primary transcripts. Methods of using mmRNA for treating conditions or diseases are also disclosed.

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MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF MEMBRANE 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: M305.20-2030.1305PCT_SL.txt; File size: 129,495,040 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 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 M301.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of 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 M309.20 (PCT/US13/XXXXX), entitled Modified Polynucleotides for the Production of Proteins; 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: 8144-16131 as disclosed herein, e.g., any of SEQ ID NOs 8144, 8145, 8146, 8147, 8148, 8149, 8150, 8151, 8152, 8153, 8154, 8155, 8156, 8157, 8158, 8159, 8160, 8161, 8162, 8163, 8164, 8165, 8166, 8167, 8168, 8169, 8170, 8171, 8172, 8173, 8174, 8175, 8176, 8177, 8178, 8179, 8180, 8181, 8182, 8183, 8184, 8185, 8186, 8187, 8188, 8189, 8190, 8191, 8192, 8193, 8194, 8195, 8196, 8197, 8198, 8199, 8200, 8201, 8202, 8203, 8204, 8205, 8206, 8207, 8208, 8209, 8210, 8211, 8212, 8213, 8214, 8215, 8216, 8217, 8218, 8219, 8220, 8221, 8222, 8223, 8224, 8225, 8226, 8227, 8228, 8229, 8230, 8231, 8232, 8233, 8234, 8235, 8236, 8237, 8238, 8239, 8240, 8241, 8242, 8243, 8244, 8245, 8246, 8247, 8248, 8249, 8250, 8251, 8252, 8253, 8254, 8255, 8256, 8257, 8258, 8259, 8260, 8261, 8262, 8263, 8264, 8265, 8266, 8267, 8268, 8269, 8270, 8271, 8272, 8273, 8274, 8275, 8276, 8277, 8278, 8279, 8280, 8281, 8282, 8283, 8284, 8285, 8286, 8287, 8288, 8289, 8290, 8291, 8292, 8293, 8294, 8295, 8296, 8297, 8298, 8299, 8300, 8301, 8302, 8303, 8304, 8305, 8306, 8307, 8308, 8309, 8310, 8311, 8312, 8313, 8314, 8315, 8316, 8317, 8318, 8319, 8320, 8321, 8322, 8323, 8324, 8325, 8326, 8327, 8328, 8329, 8330, 8331, 8332, 8333, 8334, 8335, 8336, 8337, 8338, 8339, 8340, 8341, 8342, 8343, 8344, 8345, 8346, 8347, 8348, 8349, 8350, 8351, 8352, 8353, 8354, 8355, 8356, 8357, 8358, 8359, 8360, 8361, 8362, 8363, 8364, 8365, 8366, 8367, 8368, 8369, 8370, 8371, 8372, 8373, 8374, 8375, 8376, 8377, 8378, 8379, 8380, 8381, 8382, 8383, 8384, 8385, 8386, 8387, 8388, 8389, 8390, 8391, 8392, 8393, 8394, 8395, 8396, 8397, 8398, 8399, 8400, 8401, 8402, 8403, 8404, 8405, 8406, 8407, 8408, 8409, 8410, 8411, 8412, 8413, 8414, 8415, 8416, 8417, 8418, 8419, 8420, 8421, 8422, 8423,

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[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	GGGAAATAAGAGAGAAAAGAAGAGTAAG AAGAAATATAAGAGCCACC	1
5UTR-002	Upstream UTR	GGGAGATCAGAGAGAAAAGAAGAGTAAG AAGAAATATAAGAGCCACC	2
5UTR-003	Upstream UTR	GGAATAAAAGTCTCAACACAACATATACA AAACAAACGAATCTCAAGCAATCAAGCAT TCTACTTCTATTGCAGCAATTTAAATCATT TCTTTTAAAGCAAAAGCAATTTTCTGAAA ATTTTCACCATTTACGAACGATAGCAAC	3
5UTR-004	Upstream UTR	GGGAGACAAGCUUGGCAUUCCGGUACUG UUGGUAAAGCCACC	4

[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	GCGCCTGCCCACCTGCCACCGACTGCTGG AACCCAGCCAGTGGGAGGGCCTGGCCCAC CAGAGTCCTGCTCCCTCACTCCTCGCCCCG CCCCCTGTCCCAGAGTCCCACCTGGGGGC TCTCTCCACCCTTCTCAGAGTTCCAGTTTC AACCAGAGTTCCAACCAATGGGCTCCATC CTCTGGATTCTGGCCAATGAAATATCTCCC	5

		TGGCAGGGTCCTCTTCTTTTCCCAGAGCTC CACCCCAACCAGGAGCTCTAGTTAATGGA GAGCTCCCAGCACACTCGGAGCTTGTGCT TTGTCTCCACGCAAAGCGATAAATAAAAG CATTGGTGGCCTTTGGTCTTTGAATAAAGC CTGAGTAGGAAGTCTAGA	
3UTR-002	Myoglobin	GCCCCTGCCGCTCCCACCCCCACCCATCTG GGCCCCGGGTTCAAGAGAGAGCGGGGTCT GATCTCGTGTAGCCATATAGAGTTTGCTTC TGAGTGTCTGCTTTGTTTAGTAGAGGTGG GCAGGAGGAGCTGAGGGGCTGGGGCTGG GGTGTTGAAGTTGGCTTTGCATGCCCAGC GATGCGCCTCCCTGTGGGATGTCATCACC CTGGGAACCGGGAGTGGCCCTTGGCTCAC TGTGTTCTGCATGGTTTGGATCTGAATTAA TTGTCCTTTCTTCTAAATCCCAACCGAACT TCTTCCAACCTCCAAACTGGCTGTAACCCC AAATCCAAGCCATTAACTACACCTGACAG TAGCAATTGTCTGATTAATCACTGGCCCCT TGAAGACAGCAGAATGTCCCTTTGCAATG AGGAGGAGATCTGGGCTGGGCGGGCCAG CTGGGGAAGCATTTGACTATCTGGAACTT GTGTGTGCCTCCTCAGGTATGGCAGTGAC TCACCTGGTTTTAATAAAACAACCTGCAA CATCTCATGGTCTTTGAATAAAGCCTGAG TAGGAAGTCTAGA	6
3UTR-003	α-actin	ACACACTCCACCTCCAGCACGCGACTTCT CAGGACGACGAATCTTCTCAATGGGGGGG CGGCTGAGCTCCAGCCACCCCGCAGTCAC TTTCTTTGTAACAACTTCCGTTGCTGCCAT CGTAAACTGACACAGTGTTTATAACGTGT ACATACATTAACTTATTACCTCATTTTGTT ATTTTTCGAAACAAAGCCCTGTGGAAGAA AATGGAAAACTTGAAGAAGCATTAAAGTC ATTCTGTTAAGCTGCGTAAATGGTCTTTGA ATAAAGCCTGAGTAGGAAGTCTAGA	7
3UTR-004	Albumin	CATCACATTTAAAAGCATCTCAGCCTACC ATGAGAATAAGAGAAAGAAAATGAAGAT CAAAAGCTTATTCATCTGTTTTTCTTTTTC GTTGGTGTAAAGCCAACACCCTGTCTAAA AAACATAAATTTCTTTAATCATTTTGCCTC TTTTCTCTGTGCTTCAATTAATAAAAAATG GAAAGAATCTAATAGAGTGGTACAGCACT GTTATTTTTCAAAGATGTGTTGCTATCCTG AAAATTCTGTAGGTTCTGTGGAAGTTCCA GTGTTCTCTCTTATTCCACTTCGGTAGAGG ATTTCTAGTTTCTTGTGGGCTAATTAAATA AATCATTAATACTCTTCTAATGGTCTTTGA ATAAAGCCTGAGTAGGAAGTCTAGA	8
3UTR-005	α-globin	GCTGCCTTCTGCGGGGCTTGCCTTCTGGCC	9

		ATGCCCTTCTTCTCTCCCTTGCACCTGTAC CTCTTGGTCTTTGAATAAAGCCTGAGTAG GAAGGCGGCCGCTCGAGCATGCATCTAGA	
3UTR-006	G-CSF	GCCAAGCCCTCCCCATCCCATGTATTTATC TCTATTTAATATTTATGTCTATTTAAGCCT CATATTTAAAGACAGGGAAGAGCAGAAC GGAGCCCCAGGCCTCTGTGTCCTTCCCTGC ATTTCTGAGTTTCATTCTCCTGCCTGTAGC AGTGAGAAAAAGCTCCTGTCCTCCCATCC CCTGGACTGGGAGGTAGATAGGTAAATAC CAAGTATTTATTACTATGACTGCTCCCCAG CCCTGGCTCTGCAATGGGCACTGGGATGA GCCGCTGTGAGCCCCTGGTCCTGAGGGTC CCCACCTGGGACCCTTGAGAGTATCAGGT CTCCCACGTGGGAGACAAGAAATCCCTGT TTAATATTTAAACAGCAGTGTTCCCCATCT GGGTCCTTGCACCCCTCACTCTGGCCTCAG CCGACTGCACAGCGGCCCCTGCATCCCCT TGGCTGTGAGGCCCCTGGACAAGCAGAGG TGGCCAGAGCTGGGAGGCATGGCCCTGGG GTCCCACGAATTTGCTGGGGAATCTCGTTT TTCTTCTTAAGACTTTTGGGACATGGTTTG ACTCCCGAACATCACCGACGCGTCTCCTG TTTTTCTGGGTGGCCTCGGGACACCTGCCC TGCCCCCACGAGGGTCAGGACTGTGACTC TTTTTAGGGCCAGGCAGGTGCCTGGACAT TTGCCTTGCTGGACGGGGACTGGGGATGT GGGAGGGAGCAGACAGGAGGAATCATGT CAGGCCTGTGTGTGAAAGGAAGCTCCACT GTCACCCTCCACCTCTTCACCCCCCACTCA CCAGTGTCCCCTCCACTGTCACATTGTAAC TGAACTTCAGGATAATAAAGTGTTTGCCT CCATGGTCTTTGAATAAAGCCTGAGTAGG AAGGCGGCCGCTCGAGCATGCATCTAGA	10
3UTR-007	Col1a2; collagen, type I, alpha 2	ACTCAATCTAAATTAAAAAAGAAAGAAAT TTGAAAAAACTTTCTCTTTGCCATTTCTTC TTCTTCTTTTTTAACTGAAAGCTGAATCCT TCCATTTCTTCTGCACATCTACTTGCTTAA ATTGTGGGCAAAAGAGAAAAAGAAGGAT TGATCAGAGCATTGTGCAATACAGTTTCA TTAACTCCTTCCCCCGCTCCCCCAAAAATT TGAATTTTTTTTTCAACACTCTTACACCTG TTATGGAAAATGTCAACCTTTGTAAGAAA ACCAAAATAAAAATTGAAAAATAAAAAC CATAAACATTTGCACCACTTGTGGCTTTTG AATATCTTCCACAGAGGGAAGTTTAAAAC CCAAACTTCCAAAGGTTTAAACTACCTCA AAACACTTTCCCATGAGTGTGATCCACAT TGTTAGGTGCTGACCTAGACAGAGATGAA CTGAGGTCCTTGTTTTGTTTTGTTCATAAT ACAAAGGTGCTAATTAATAGTATTTCAGA	11

		TACTTGAAGAATGTTGATGGTGCTAGAAG AATTTGAGAAGAAATACTCCTGTATTGAG TTGTATCGTGTGGTGTATTTTTTAAAAAAT TTGATTTAGCATTCATATTTTCCATCTTAT TCCCAATTAAAAGTATGCAGATTATTTGC CCAAATCTTCTTCAGATTCAGCATTTGTTC TTTGCCAGTCTCATTTTCATCTTCTTCCAT GGTTCCACAGAAGCTTTGTTTCTTGGGCA AGCAGAAAAATTAAATTGTACCTATTTTG TATATGTGAGATGTTTAAATAAATTGTGA AAAAAATGAAATAAAGCATGTTTGGTTTT CCAAAAGAACATAT	
3UTR-008	Col6a2; collagen, type VI, alpha 2	CGCCGCCGCCCGGGCCCCGCAGTCGAGGG TCGTGAGCCCACCCCGTCCATGGTGCTAA GCGGGCCCGGGTCCCACACGGCCAGCACC GCTGCTCACTCGGACGACGCCCTGGGCCT GCACCTCTCCAGCTCCTCCCACGGGGTCC CCGTAGCCCCGGCCCCCGCCCAGCCCCAG GTCTCCCCAGGCCCTCCGCAGGCTGCCCG GCCTCCCTCCCCCTGCAGCCATCCCAAGG CTCCTGACCTACCTGGCCCCTGAGCTCTGG AGCAAGCCCTGACCCAATAAAGGCTTTGA ACCCAT	12
3UTR-009	RPN1; ribophorin I	GGGGCTAGAGCCCTCTCCGCACAGCGTGG AGACGGGGCAAGGAGGGGGGTTATTAGG ATTGGTGGTTTTGTTTTGCTTTGTTTAAAG CCGTGGGAAAATGGCACAACTTTACCTCT GTGGGAGATGCAACACTGAGAGCCAAGG GGTGGGAGTTGGGATAATTTTTATATAAA AGAAGTTTTTCCACTTTGAATTGCTAAAA GTGGCATTTTTCCTATGTGCAGTCACTCCT CTCATTTCTAAAATAGGGACGTGGCCAGG CACGGTGGCTCATGCCTGTAATCCCAGCA CTTTGGGAGGCCGAGGCAGGCGGCTCACG AGGTCAGGAGATCGAGACTATCCTGGCTA ACACGGTAAAACCCTGTCTCTACTAAAAG TACAAAAAATTAGCTGGGCGTGGTGGTGG GCACCTGTAGTCCCAGCTACTCGGGAGGC TGAGGCAGGAGAAAGGCATGAATCCAAG AGGCAGAGCTTGCAGTGAGCTGAGATCAC GCCATTGCACTCCAGCCTGGGCAACAGTG TTAAGACTCTGTCTCAAATATAAATAAAT AAATAAATAAATAAATAAATAAATAAAA ATAAAGCGAGATGTTGCCCTCAAA	13
3UTR-010	LRP1; low density lipoprotein receptor-related protein 1	GGCCCTGCCCCGTCGGACTGCCCCCAGAA AGCCTCCTGCCCCCTGCCAGTGAAGTCCTT CAGTGAGCCCCTCCCCAGCCAGCCCTTCC CTGGCCCCGCCGGATGTATAAATGTAAAA ATGAAGGAATTACATTTTATATGTGAGCG AGCAAGCCGGCAAGCGAGCACAGTATTAT	14

		TTCTCCATCCCCTCCCTGCCTGCTCCTTGG CACCCCCATGCTGCCTTCAGGGAGACAGG CAGGGAGGGCTTGGGGCTGCACCTCCTAC CCTCCCACCAGAACGCACCCCACTGGGAG AGCTGGTGGTGCAGCCTTCCCCTCCCTGTA TAAGACACTTTGCCAAGGCTCTCCCCTCTC GCCCCATCCCTGCTTGCCCGCTCCCACAGC TTCCTGAGGGCTAATTCTGGGAAGGGAGA GTTCTTTGCTGCCCCTGTCTGGAAGACGTG GCTCTGGGTGAGGTAGGCGGGAAAGGAT GGAGTGTTTTAGTTCTTGGGGGAGGCCAC CCCAAACCCCAGCCCCAACTCCAGGGGCA CCTATGAGATGGCCATGCTCAACCCCCCT CCCAGACAGGCCCTCCCTGTCTCCAGGGC CCCCACCGAGGTTCCCAGGGCTGGAGACT TCCTCTGGTAAACATTCCTCCAGCCTCCCC TCCCCTGGGGACGCCAAGGAGGTGGGCCA CACCCAGGAAGGGAAAGCGGGCAGCCCC GTTTTGGGGACGTGAACGTTTTAATAATTT TTGCTGAATTCCTTTACAACTAAATAACAC AGATATTGTTATAAATAAAATTGT	
3UTR-011	Nnt1; cardiotrophin-like cytokine factor 1	ATATTAAGGATCAAGCTGTTAGCTAATAA TGCCACCTCTGCAGTTTTGGGAACAGGCA AATAAAGTATCAGTATACATGGTGATGTA CATCTGTAGCAAAGCTCTTGGAGAAAATG AAGACTGAAGAAAGCAAAGCAAAAACTG TATAGAGAGATTTTTCAAAAGCAGTAATC CCTCAATTTTAAAAAAGGATTGAAAATTC TAAATGTCTTTCTGTGCATATTTTTTGTGT TAGGAATCAAAAGTATTTTATAAAAGGAG AAAGAACAGCCTCATTTTAGATGTAGTCC TGTTGGATTTTTTATGCCTCCTCAGTAACC AGAAATGTTTTAAAAAACTAAGTGTTTAG GATTTCAAGACAACATTATACATGGCTCT GAAATATCTGACACAATGTAAACATTGCA GGCACCTGCATTTTATGTTTTTTTTTTCAA CAAATGTGACTAATTTGAAACTTTTATGA ACTTCTGAGCTGTCCCCTTGCAATTCAACC GCAGTTTGAATTAATCATATCAAATCAGT TTTAATTTTTTAAATTGTACTTCAGAGTCT ATATTTCAAGGGCACATTTTCTCACTACTA TTTTAATACATTAAAGGACTAAATAATCTT TCAGAGATGCTGGAAACAAATCATTTGCT TTATATGTTTCATTAGAATACCAATGAAA CATACAACTTGAAAATTAGTAATAGTATT TTTGAAGATCCCATTTCTAATTGGAGATCT CTTTAATTTCGATCAACTTATAATGTGTAG TACTATATTAAGTGCACTTGAGTGGAATT CAACATTTGACTAATAAAATGAGTTCATC ATGTTGGCAAGTGATGTGGCAATTATCTC TGGTGACAAAAGAGTAAAATCAAATATTT	15

		CTGCCTGTTACAAATATCAAGGAAGACCT GCTACTATGAAATAGATGACATTAATCTG TCTTCACTGTTTATAATACGGATGGATTTT TTTTCAAATCAGTGTGTGTTTTGAGGTCTT ATGTAATTGATGACATTTGAGAGAAATGG TGGCTTTTTTTAGCTACCTCTTTGTTCATTT AAGCACCAGTAAAGATCATGTCTTTTTAT AGAAGTGTAGATTTTCTTTGTGACTTTGCT ATCGTGCCTAAAGCTCTAAATATAGGTGA ATGTGTGATGAATACTCAGATTATTTGTCT CTCTATATAATTAGTTTGGTACTAAGTTTC TCAAAAAATTATTAACACATGAAAGACAA TCTCTAAACCAGAAAAAGAAGTAGTACAA ATTTTGTTACTGTAATGCTCGCGTTTAGTG AGTTTAAAACACACAGTATCTTTTGGTTTT ATAATCAGTTTCTATTTTGCTGTGCCTGAG ATTAAGATCTGTGTATGTGTGTGTGTGTGT GTGTGCGTTTGTGTGTTAAAGCAGAAAAG ACTTTTTTAAAAGTTTTAAGTGATAAATGC AATTTGTTAATTGATCTTAGATCACTAGTA AACTCAGGGCTGAATTATACCATGTATAT TCTATTAGAAGAAAGTAAACACCATCTTT ATTCCTGCCCTTTTTCTTCTCTCAAAGTAG TTGTAGTTATATCTAGAAAGAAGCAATTT TGATTTCTTGAAAAGGTAGTTCCTGCACTC AGTTTAAACTAAAAATAATCATACTTGGA TTTTATTTATTTTTGTCATAGTAAAAATTT TAATTTATATATATTTTTATTTAGTATTAT CTTATTCTTTGCTATTTGCCAATCCTTTGTC ATCAATTGTGTTAAATGAATTGAAAATTC ATGCCCTGTTCATTTTATTTTACTTTATTG GTTAGGATATTTAAAGGATTTTTGTATATA TAATTTCTTAAATTAATATTCCAAAAGGTT AGTGGACTTAGATTATAAATTATGGCAAA AATCTAAAAACAACAAAAATGATTTTTAT ACATTCTATTTCATTATTCCTCTTTTTCCAA TAAGTCATACAATTGGTAGATATGACTTA TTTTATTTTTGTATTATTCACTATATCTTTA TGATATTTAAGTATAAATAATTAAAAAAA TTTATTGTACCTTATAGTCTGTCACCAAAA AAAAAAAATTATCTGTAGGTAGTGAAATG CTAATGTTGATTTGTCTTTAAGGGCTTGTT AACTATCCTTTATTTTCTCATTTGTCTTAA ATTAGGAGTTTGTGTTTAAATTACTCATCT AAGCAAAAAATGTATATAAATCCCATTAC TGGGTATATACCCAAAGGATTATAAATCA TGCTGCTATAAAGACACATGCACACGTAT GTTTATTGCAGCACTATTCACAATAGCAA AGACTTGGAACCAACCCAAATGTCCATCA ATGATAGACTTGATTAAGAAAATGTGCAC ATATACACCATGGAATACTATGCAGCCAT	

		AAAAAAGGATGAGTTCATGTCCTTTGTAG GGACATGGATAAAGCTGGAAACCATCATT CTGAGCAAACTATTGCAAGGACAGAAAAC CAAACACTGCATGTTCTCACTCATAGGTG GGAATTGAACAATGAGAACACTTGGACAC AAGGTGGGGAACACCACACACCAGGGCC TGTCATGGGGTGGGGGGAGTGGGGAGGG ATAGCATTAGGAGATATACCTAATGTAAA TGATGAGTTAATGGGTGCAGCACACCAAC ATGGCACATGTATACATATGTAGCAAACC TGCACGTTGTGCACATGTACCCTAGAACT TAAAGTATAATTAAAAAAAAAAAGAAAA CAGAAGCTATTTATAAAGAAGTTATTTGC TGAAATAAATGTGATCTTTCCCATTAAAA AAATAAAGAAATTTTGGGGTAAAAAAAC ACAATATATTGTATTCTTGAAAAATTCTAA GAGAGTGGATGTGAAGTGTTCTCACCACA AAAGTGATAACTAATTGAGGTAATGCACA TATTAATTAGAAAGATTTTGTCATTCCACA ATGTATATATACTTAAAAATATGTTATAC ACAATAAATACATACATTAAAAAATAAGT AAATGTA	
3UTR-012	Col6a1; collagen, type VI, alpha 1	CCCACCCTGCACGCCGGCACCAAACCCTG TCCTCCCACCCCTCCCCACTCATCACTAAA CAGAGTAAAATGTGATGCGAATTTTCCCG ACCAACCTGATTCGCTAGATTTTTTTTAAG GAAAAGCTTGGAAAGCCAGGACACAACG CTGCTGCCTGCTTTGTGCAGGGTCCTCCGG GGCTCAGCCCTGAGTTGGCATCACCTGCG CAGGGCCCTCTGGGGCTCAGCCCTGAGCT AGTGTCACCTGCACAGGGCCCTCTGAGGC TCAGCCCTGAGCTGGCGTCACCTGTGCAG GGCCCTCTGGGGCTCAGCCCTGAGCTGGC CTCACCTGGGTTCCCCACCCCGGGCTCTCC TGCCCTGCCCTCCTGCCCGCCCTCCCTCCT GCCTGCGCAGCTCCTTCCCTAGGCACCTCT GTGCTGCATCCCACCAGCCTGAGCAAGAC GCCCTCTCGGGGCCTGTGCCGCACTAGCC TCCCTCTCCTCTGTCCCCATAGCTGGTTTT TCCCACCAATCCTCACCTAACAGTTACTTT ACAATTAAACTCAAAGCAAGCTCTTCTCC TCAGCTTGGGGCAGCCATTGGCCTCTGTCT CGTTTTGGGAAACCAAGGTCAGGAGGCCG TTGCAGACATAAATCTCGGCGACTCGGCC CCGTCTCCTGAGGGTCCTGCTGGTGACCG GCCTGGACCTTGGCCCTACAGCCCTGGAG GCCGCTGCTGACCAGCACTGACCCCGACC TCAGAGAGTACTCGCAGGGGCGCTGGCTG CACTCAAGACCCTCGAGATTAACGGTGCT AACCCCGTCTGCTCCTCCCTCCCGCAGAG ACTGGGGCCTGGACTGGACATGAGAGCCC	16

		CTTGGTGCCACAGAGGGCTGTGTCTTACT AGAAACAACGCAAACCTCTCCTTCCTCAG AATAGTGATGTGTTCGACGTTTTATCAAA GGCCCCCTTTCTATGTTCATGTTAGTTTTG CTCCTTCTGTGTTTTTTTCTGAACCATATC CATGTTGCTGACTTTTCCAAATAAAGGTTT TCACTCCTCTC	
3UTR-013	Calr; calreticulin	AGAGGCCTGCCTCCAGGGCTGGACTGAGG CCTGAGCGCTCCTGCCGCAGAGCTGGCCG CGCCAAATAATGTCTCTGTGAGACTCGAG AACTTTCATTTTTTTCCAGGCTGGTTCGGA TTTGGGGTGGATTTTGGTTTTGTTCCCCTC CTCCACTCTCCCCCACCCCCTCCCCGCCCT TTTTTTTTTTTTTTTTTAAACTGGTATTTTA TCTTTGATTCTCCTTCAGCCCTCACCCCTG GTTCTCATCTTTCTTGATCAACATCTTTTCT TGCCTCTGTCCCCTTCTCTCATCTCTTAGC TCCCCTCCAACCTGGGGGGCAGTGGTGTG GAGAAGCCACAGGCCTGAGATTTCATCTG CTCTCCTTCCTGGAGCCCAGAGGAGGGCA GCAGAAGGGGGTGGTGTCTCCAACCCCCC AGCACTGAGGAAGAACGGGGCTCTTCTCA TTTCACCCCTCCCTTTCTCCCCTGCCCCCA GGACTGGGCCACTTCTGGGTGGGGCAGTG GGTCCCAGATTGGCTCACACTGAGAATGT AAGAACTACAAACAAAATTTCTATTAAAT TAAATTTTGTGTCTCC	17
3UTR-014	Col1a1; collagen, type I, alpha 1	CTCCCTCCATCCCAACCTGGCTCCCTCCCA CCCAACCAACTTTCCCCCCAACCCGGAAA CAGACAAGCAACCCAAACTGAACCCCCTC AAAAGCCAAAAAATGGGAGACAATTTCA CATGGACTTTGGAAAATATTTTTTTCCTTT GCATTCATCTCTCAAACTTAGTTTTTATCT TTGACCAACCGAACATGACCAAAAACCAA AAGTGCATTCAACCTTACCAAAAAAAAAA AAAAAAAAAGAATAAATAAATAACTTTTT AAAAAAGGAAGCTTGGTCCACTTGCTTGA AGACCCATGCGGGGGTAAGTCCCTTTCTG CCCGTTGGGCTTATGAAACCCCAATGCTG CCCTTTCTGCTCCTTTCTCCACACCCCCCT TGGGGCCTCCCCTCCACTCCTTCCCAAATC TGTCTCCCCAGAAGACACAGGAAACAATG TATTGTCTGCCCAGCAATCAAAGGCAATG CTCAAACACCCAAGTGGCCCCCACCCTCA GCCCGCTCCTGCCCGCCCAGCACCCCCAG GCCCTGGGGGACCTGGGGTTCTCAGACTG CCAAAGAAGCCTTGCCATCTGGCGCTCCC ATGGCTCTTGCAACATCTCCCCTTCGTTTT TGAGGGGGTCATGCCGGGGGAGCCACCA GCCCCTCACTGGGTTCGGAGGAGAGTCAG GAAGGGCCACGACAAAGCAGAAACATCG	18

		GATTTGGGGAACGCGTGTCAATCCCTTGT GCCGCAGGGCTGGGCGGGAGAGACTGTTC TGTTCCTTGTGTAACTGTGTTGCTGAAAGA CTACCTCGTTCTTGTCTTGATGTGTCACCG GGGCAACTGCCTGGGGGCGGGGATGGGG GCAGGGTGGAAGCGGCTCCCCATTTTATA CCAAAGGTGCTACATCTATGTGATGGGTG GGGTGGGGAGGGAATCACTGGTGCTATAG AAATTGAGATGCCCCCCCAGGCCAGCAAA TGTTCCTTTTTGTTCAAAGTCTATTTTTATT CCTTGATATTTTTCTTTTTTTTTTTTTTTTT TGTGGATGGGGACTTGTGAATTTTTCTAA AGGTGCTATTTAACATGGGAGGAGAGCGT GTGCGGCTCCAGCCCAGCCCGCTGCTCAC TTTCCACCCTCTCTCCACCTGCCTCTGGCT TCTCAGGCCTCTGCTCTCCGACCTCTCTCC TCTGAAACCCTCCTCCACAGCTGCAGCCC ATCCTCCCGGCTCCCTCCTAGTCTGTCCTG CGTCCTCTGTCCCCGGGTTTCAGAGACAA CTTCCCAAAGCACAAAGCAGTTTTTCCCC CTAGGGGTGGGAGGAAGCAAAAGACTCT GTACCTATTTTGTATGTGTATAATAATTTG AGATGTTTTTAATTATTTTGATTGCTGGAA TAAAGCATGTGGAAATGACCCAAACATAA TCCGCAGTGGCCTCCTAATTTCCTTCTTTG GAGTTGGGGGAGGGGTAGACATGGGGAA GGGGCTTTGGGGTGATGGGCTTGCCTTCC ATTCCTGCCCTTTCCCTCCCCACTATTCTC TTCTAGATCCCTCCATAACCCCACTCCCCT TTCTCTCACCCTTCTTATACCGCAAACCTT TCTACTTCCTCTTTCATTTTCTATTCTTGCA ATTTCCTTGCACCTTTTCCAAATCCTCTTC TCCCCTGCAATACCATACAGGCAATCCAC GTGCACAACACACACACACACTCTTCACA TCTGGGGTTGTCCAAACCTCATACCCACTC CCCTTCAAGCCCATCCACTCTCCACCCCCT GGATGCCCTGCACTTGGTGGCGGTGGGAT GCTCATGGATACTGGGAGGGTGAGGGGA GTGGAACCCGTGAGGAGGACCTGGGGGC CTCTCCTTGAACTGACATGAAGGGTCATC TGGCCTCTGCTCCCTTCTCACCCACGCTGA CCTCCTGCCGAAGGAGCAACGCAACAGGA GAGGGGTCTGCTGAGCCTGGCGAGGGTCT GGGAGGGACCAGGAGGAAGGCGTGCTCC CTGCTCGCTGTCCTGGCCCTGGGGGAGTG AGGGAGACAGACACCTGGGAGAGCTGTG GGGAAGGCACTCGCACCGTGCTCTTGGGA AGGAAGGAGACCTGGCCCTGCTCACCACG GACTGGGTGCCTCGACCTCCTGAATCCCC AGAACACAACCCCCCTGGGCTGGGGTGGT CTGGGGAACCATCGTGCCCCCGCCTCCCG	

		CCTACTCCTTTTTAAGCTT	
3UTR-015	Plod1; procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	TTGGCCAGGCCTGACCCTCTTGGACCTTTC TTCTTTGCCGACAACCACTGCCCAGCAGC CTCTGGGACCTCGGGGTCCCAGGGAACCC AGTCCAGCCTCCTGGCTGTTGACTTCCCAT TGCTCTTGGAGCCACCAATCAAAGAGATT CAAAGAGATTCCTGCAGGCCAGAGGCGG AACACACCTTTATGGCTGGGGCTCTCCGT GGTGTTCTGGACCCAGCCCCTGGAGACAC CATTCACTTTTACTGCTTTGTAGTGACTCG TGCTCTCCAACCTGTCTTCCTGAAAAACCA AGGCCCCCTTCCCCCACCTCTTCCATGGGG TGAGACTTGAGCAGAACAGGGGCTTCCCC AAGTTGCCCAGAAAGACTGTCTGGGTGAG AAGCCATGGCCAGAGCTTCTCCCAGGCAC AGGTGTTGCACCAGGGACTTCTGCTTCAA GTTTTGGGGTAAAGACACCTGGATCAGAC TCCAAGGGCTGCCCTGAGTCTGGGACTTC TGCCTCCATGGCTGGTCATGAGAGCAAAC CGTAGTCCCCTGGAGACAGCGACTCCAGA GAACCTCTTGGGAGACAGAAGAGGCATCT GTGCACAGCTCGATCTTCTACTTGCCTGTG GGGAGGGGAGTGACAGGTCCACACACCA CACTGGGTCACCCTGTCCTGGATGCCTCTG AAGAGAGGGACAGACCGTCAGAAACTGG AGAGTTTCTATTAAAGGTCATTTAAACCA	19
3UTR-016	Nucb1; nucleobindin 1	TCCTCCGGGACCCCAGCCCTCAGGATTCC TGATGCTCCAAGGCGACTGATGGGCGCTG GATGAAGTGGCACAGTCAGCTTCCCTGGG GGCTGGTGTCATGTTGGGCTCCTGGGGCG GGGGCACGGCCTGGCATTTCACGCATTGC TGCCACCCCAGGTCCACCTGTCTCCACTTT CACAGCCTCCAAGTCTGTGGCTCTTCCCTT CTGTCCTCCGAGGGGCTTGCCTTCTCTCGT GTCCAGTGAGGTGCTCAGTGATCGGCTTA ACTTAGAGAAGCCCGCCCCCTCCCCTTCTC CGTCTGTCCCAAGAGGGTCTGCTCTGAGC CTGCGTTCCTAGGTGGCTCGGCCTCAGCT GCCTGGGTTGTGGCCGCCCTAGCATCCTG TATGCCCACAGCTACTGGAATCCCCGCTG CTGCTCCGGGCCAAGCTTCTGGTTGATTA ATGAGGGCATGGGGTGGTCCCTCAAGACC TTCCCCTACCTTTTGTGGAACCAGTGATGC CTCAAAGACAGTGTCCCCTCCACAGCTGG GTGCCAGGGGCAGGGGATCCTCAGTATAG CCGGTGAACCCTGATACCAGGAGCCTGGG CCTCCCTGAACCCCTGGCTTCCAGCCATCT CATCGCCAGCCTCCTCCTGGACCTCTTGGC CCCCAGCCCCTTCCCCACACAGCCCCAGA AGGGTCCCAGAGCTGACCCCACTCCAGGA CCTAGGCCCAGCCCCTCAGCCTCATCTGG	20

		AGCCCCTGAAGACCAGTCCCACCCACCTT TCTGGCCTCATCTGACACTGCTCCGCATCC TGCTGTGTGTCCTGTTCCATGTTCCGGTTC CATCCAAATACACTTTCTGGAACAAA	
3UTR-017	α-globin	GCTGGAGCCTCGGTGGCCATGCTTCTTGC CCCTTGGGCCTCCCCCCAGCCCCTCCTCCC CTTCCTGCACCCGTACCCCCGTGGTCTTTG AATAAAGTCTGAGTGGGCGGC	21

[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	ATGGCCGGACCGGCGAC TCAGTCGCCCATGAAACT CATGGCCCTGCAGTTGTT GCTTTGGCACTCAGCCCT CTGGACCGTCCAAGAGG CG	33	MAGPATQSP MKLMALQLL LWHSALWTV QEA	95
SS-003	Factor IX	ATGCAGAGAGTGAACAT GATTATGGCCGAGTCCCC ATCGCTCATCACAATCTG CCTGCTTGGTACCTGCTT TCCGCCGAATGCACTGTC TTTCTGGATCACGAGAAT GCGAATAAGATCTTGAAC CGACCCAAACGG	34	MQRVNMIMA ESPSLITICLLG YLLSAECTVF LDHENANKIL NRPKR	96
SS-004	Prolactin	ATGAAAGGATCATTGCTG TTGCTCCTCGTGTCGAAC CTTCTGCTTTGCCAGTCC GTAGCCCCC	35	MKGSLLLLLV SNLLLCQSVA P	97
SS-005	Albumin	ATGAAATGGGTGACGTTC ATCTCACTGTTGTTTTTGT TCTCGTCCGCCTACTCCA GGGGAGTATTCCGCCGA	36	MKWVTFISLL FLFSSAYSRG VFRR	98
SS-006	HMMSP38	ATGTGGTGGCGGCTCTGG TGGCTGCTCCTGTTGCTC CTCTTGCTGTGGCCCATG GTGTGGGCA	37	MWWRLWWL LLLLLLLPMW A	99
MLS-001	ornithine carbamoyltransferase	TGCTCTTTAACCTCCGCA TCCTGTTGAATAACGCTG CGTTCCGAAATGGGCATA ACTTCATGGTACGCAACT TCAGATGCGGCCAGCCAC TCCAG	38	MLFNLRILLN NAAFRNGHN FMVRNFRCG QPLQ	100
MLS-002	Cytochrome C Oxidase subunit 8A	ATGTCCGTCTTGACACCC CTGCTCTTGAGAGGGCTG ACGGGGTCCGCTAGACG CCTGCCGGTACCGCGAGC GAAGATCCACTCCCTG	39	MSVLTPLLLR GLTGSARRLP VPRAKIHSL	101
MLS-003	Cytochrome C Oxidase subunit 8A	ATGAGCGTGCTCACTCCG TTGCTTCTTCGAGGGCTT ACGGGATCGGCTCGGAG GTTGCCCGTCCCGAGAGC GAAGATCCATTCGTTG	40	MSVLTPLLLR GLTGSARRLP VPRAKIHSL	102
SS-007	Type III, bacterial	TGACAAAAATAACTTTAT CTCCCCAGAATTTTAGAA TCCAAAAACAGGAAACC ACACTACTAAAAGAAAA ATCAACCGAGAAAAATT CTTTAGCAAAAAGTATTC TCGCAGTAAAAATCACTT CATCGAATTAAGGTCAAA	41	MVTKITLSPQ NFRIQKQETT LLKEKSTEKN SLAKSILAVK NHFIELRSKLS ERFISHKNT	103

		ATTATCGGAACGTTTTAT TTCGCATAAGAACACT			
SS-008	Viral	ATGCTGAGCTTTGTGGAT ACCCGCACCCTGCTGCTG CTGGCGGTGACCAGCTGC CTGGCGACCTGCCAG	42	MLSFVDTRTL LLLAVTSCLA TCQ	104
SS-009	viral	ATGGGCAGCAGCCAGGC GCCGCGCATGGGCAGCG TGGGCGGCCATGGCCTGA TGGCGCTGCTGATGGCGG GCCTGATTCTGCCGGGCA TTCTGGCG	43	MGSSQAPRM GSVGGHGLM ALLMAGLILP GILA	105
SS-010	Viral	ATGGCGGGCATTTTTTAT TTTCTGTTTAGCTTTCTGT TTGGCATTTGCGAT	44	MAGIFYFLFSF LFGICD	106
SS-011	Viral	ATGGAAAACCGCCTGCTG CGCGTGTTTCTGGTGTGG GCGGCGCTGACCATGGAT GGCGCGAGCGCG	45	MENRLLRVFL VWAALTMDG ASA	107
SS-012	Viral	ATGGCGCGCCAGGGCTG CTTTGGCAGCTATCAGGT GATTAGCCTGTTTACCTT TGCGATTGGCGTGAACCT GTGCCTGGGC	46	MARQGCFGS YQVISLFTFAI GVNLCLG	108
SS-013	*Bacillus*	ATGAGCCGCCTGCCGGTG CTGCTGCTGCTGCAGCTG CTGGTGCGCCCGGGCCTG CAG	47	MSRLPVLLLL QLLVRPGLQ	109
SS-014	*Bacillus*	ATGAAACAGCAGAAACG CCTGTATGCGCGCCTGCT GACCCTGCTGTTTGCGCT GATTTTTCTGCTGCCGCA TAGCAGCGCGAGCGCG	48	MKQQKRLYA RLLTLLFALIF LLPHSSASA	110
SS-015	Secretion signal	ATGGCGACGCCGCTGCCT CCGCCCTCCCCGCGGCAC CTGCGGCTGCTGCGGCTG CTGCTCTCCGCCCTCGTC CTCGGC	49	MATPLPPPSP RHLRLLRLLL SG	111
SS-016	Secretion signal	ATGAAGGCTCCGGGTCG GCTCGTGCTCATCATCCT GTGCTCCGTGGTCTTCTC T	50	MKAPGRLVLI ILCSVVFS	112
SS-017	Secretion signal	ATGCTTCAGCTTTGGAAA CTTGTTCTCCTGTGCGGC GTGCTCACT	51	MLQLWKLLC GVLT	113
SS-018	Secretion signal	ATGCTTTATCTCCAGGGT TGGAGCATGCCTGCTGTG GCA	52	MLYLQGWSM PAVA	114
SS-019	Secretion signal	ATGGATAACGTGCAGCC GAAAATAAAACATCGCC	53	MDNVQPKIK HRPFCFSVKG	115

		CCTTCTGCTTCAGTGTGA AAGGCCACGTGAAGATG CTGCGGCTGGATATTATC AACTCACTGGTAACAACA GTATTCATGCTCATCGTA TCTGTGTTGGCACTGATA CCA		HVKMLRLDII NSLVTTVFML IVSVLALIP	
SS-020	Secretion signal	ATGCCCTGCCTAGACCAA CAGCTCACTGTTCATGCC CTACCCTGCCCTGCCCAG CCCTCCTCTCTGGCCTTCT GCCAAGTGGGGTTCTTAA CAGCA	54	MPCLDQQLT VHALPCPAQP SSLAFCQVGF LTA	116
SS-021	Secretion signal	ATGAAAACCTTGTTCAAT CCAGCCCCTGCCATTGCT GACCTGGATCCCCAGTTC TACACCCTCTCAGATGTG TTCTGCTGCAATGAAAGT GAGGCTGAGATTTTAACT GGCCTCACGGTGGGCAG CGCTGCAGATGCT	55	MKTLFNPAPA IADLDPQFYT LSDVFCCNES EAEILTGLTV GSAADA	117
SS-022	Secretion signal	ATGAAGCCTCTCCTTGTT GTGTTTGTCTTTCTTTTCC TTTGGGATCCAGTGCTGG CA	56	MKPLLVVFVF LFLWDPVLA	118
SS-023	Secretion signal	ATGTCCTGTTCCCTAAAG TTTACTTTGATTGTAATTT TTTTTTACTGTTGGCTTTC ATCCAGC	57	MSCSLKFTLI VIFFTCTLSSS	119
SS-024	Secretion signal	ATGGTTCTTACTAAACCT CTTCAAAGAAATGGCAG CATGATGAGCTTTGAAAA TGTGAAAGAAAAGAGCA GAGAAGGAGGGCCCCAT GCACACACACCCGAAGA AGAATTGTGTTTCGTGGT AACACACTACCCTCAGGT TCAGACCACACTCAACCT GTTTTTCCATATATTCAA GGTTCTTACTCAACCACT TTCCCTTCTGTGGGGT	58	MVLTKPLQR NGSMMSFEN VKEKSREGGP HAHTPEEELC FVVTHTPQVQ TTLNLFFHIFK VLTQPLSLLW G	120
SS-025	Secretion signal	ATGGCCACCCCGCCATTC CGGCTGATAAGGAAGAT GTTTTCCTTCAAGGTGAG CAGATGGATGGGGCTTGC CTGCTTCCGGTCCCTGGC GGCATCC	59	MATPPFRLIR KMFSFKVSR WMGLACFRS LAAS	121
SS-026	Secretion signal	ATGAGCTTTTTCCAACTC CTGATGAAAAGGAAGGA ACTCATTCCCTTGGTGGT	60	MSFFQLLMKR KELIPLVVFM TVAAGGASS	122

		GTTCATGACTGTGGCGGC GGGTGGAGCCTCATCT			
SS-027	Secretion signal	ATGGTCTCAGCTCTGCGG GGAGCACCCCTGATCAG GGTGCACTCAAGCCCTGT TTCTTCTCCTTCTGTGAGT GGACCACGGAGGCTGGT GAGCTGCCTGTCATCCCA AAGCTCAGCTCTGAGC	61	MVSALRGAPL IRVHSSPVSSP SVSGPAALVS CLSSQSSALS	123
SS-028	Secretion signal	ATGATGGGGTCCCCAGTG AGTCATCTGCTGGCCGGC TTCTGTGTGTGGGTCGTC TTGGGC	62	MMGSPVSHL LAGFCVWVV LG	124
SS-029	Secretion signal	ATGGCAAGCATGGCTGCC GTGCTCACCTGGGCTCTG GCTCTTCTTTCAGCGTTTT CGGCCACCCAGGCA	63	MASMAAVLT WALALLSAFS ATQA	125
SS-030	Secretion signal	ATGGTGCTCATGTGGACC AGTGGTGACGCCTTCAAG ACGGCCTACTTCCTGCTG AAGGGTGCCCCTCTGCAG TTCTCCGTGTGCGGCCTG CTGCAGGTGCTGGTGGAC CTGGCCATCCTGGGGCAG GCCTACGCC	64	MVLMWTSGD AFKTAYFLLK GAPLQFSVCG LLQVLVDLAI LGQATA	126
SS-031	Secretion signal	ATGGATTTTGTCGCTGGA GCCATCGGAGGCGTCTGC GGTGTTGCTGTGGGCTAC CCCCTGGACACGGTGAA GGTCAGGATCCAGACGG AGCCAAAGTACACAGGC ATCTGGCACTGCGTCCGG GATACGTATCACCGAGA GCGCGTGTGGG GCTTCTACCGGGGCCTCT CGCTGCCCGTGTGCACGG TGTCCCTGGTATCTTCC	65	MDFVAGAIG GVCGVAVGY PLDTVKVRIQ TEPLYTGIWH CVRDTYHRER VWGFYRGLS LPVCTVSLVS S	127
SS-032	Secretion signal	ATGGAGAAGCCCCTCTTC CCATTAGTGCCTTTGCAT TGGTTTGGCTTTGGCTAC ACAGCACTGGTTGTTTCT GGTGGGATCGTTGGCTAT GTAAAAACAGGCAGCGT GCCGTCCCTGGCTGCAGG GCTGCTCTTCGGCAGTCT AGCC	66	MEKPLFPLVP LHWFGFGYT ALVVSGGIVG YVKTGSVPSL AAGLLFGSLA	128
SS-033	Secretion signal	ATGGGTCTGCTCCTTCCC CTGGCACTCTGCATCCTA GTCCTGTGC	67	MGLLLPLALC ILVLC	129

SS-034	Secretion signal	ATGGGGATCCAGACGAG CCCCGTCCTGCTGGCCTC CCTGGGGGTGGGGCTGGT CACTCTGCTCGGCCTGGC TGTGGGC	68	MGIQTSPVLL ASLGVGLVTL LGLAVG	130
SS-035	Secretion signal	ATGTCGGACCTGCTACTA CTGGGCCTGATTGGGGGC CTGACTCTCTTACTGCTG CTGACGCTGCTAGCCTTT GCC	69	MSDLLLLGLI GGLTLLLLLT LLAFA	131
SS-036	Secretion signal	ATGGAGACTGTGGTGATT GTTGCCATAGGTGTGCTG GCCACCATGTTTCTGGCT TCGTTTGCAGCCTTGGTG CTGGTTTGCAGGCAG	70	METVVIVAIG VLATIFLASFA ALVLVCRQ	132
SS-037	Secretion signal	ATGCGCGGCTCTGTGGAG TGCACCTGGGGTTGGGGG CACTGTGCCCCCAGCCCC CTGCTCCTTTGGACTCTA CTTCTGTTTGCAGCCCCA TTTGGCCTGCTGGGG	71	MAGSVECTW GWGHCAPSPL LLWTLLLFAA PFGLLG	133
SS-038	Secretion signal	ATGATGCCGTCCCGTACC AACCTGGCTACTGGAATC CCCAGTAGTAAAGTGAA ATATTCAAGGCTCTCCAG CACAGACGATGGCTACAT TGACCTTCAGTTTAAGAA AACCCCTCCTAAGATCCC TTATAAGGCCATCGCACT TGCCACTGTGCTGTTTTT GATTGGCGCC	72	MMPSRTNLA TGIPSSKVKYS RLSSTDDGYI DLQFKKTPPK IPYKAIALATV LFLIGA	134
SS-039	Secretion signal	ATGGCCCTGCCCCAGATG TGTGACGGGAGCCACTTG GCCTCCACCCTCCGCTAT TGCATGACAGTCAGCGGC ACAGTGGTTCTGGTGGCC GGGACGCTCTGCTTCGCT	73	MALPQMCDG SHLASTLRYC MTVSGTVVL VAGTLCFA	135
SS-041	Vrg-6	TGAAAAAGTGGTTCGTTG CTGCCGGCATCGGCGCTG CCGGACTCATGCTCTCCA GCGCCGCCA	74	MKKWFVAAG IGAGLLMLSS AA	136
SS-042	PhoA	ATGAAACAGAGCACCAT TGCGCTGGCGCTGCTGCC GCTGCTGTTTACCCCGGT GACCAAAGCG	75	MKQSTIALAL LPLLFTPVTK A	137
SS-043	OmpA	ATGAAAAAAACCGCGAT TGCGATTGCGGTGGCGCT GGCGGGCTTTGCGACCGT GGCGCAGGCG	76	MKKTAIAIAV ALAGFATVA QA	138

SS-044	STI	ATGAAAAAACTGATGCTGGCGATTTTTTTTAGCGTGCTGAGCTTTCCGAGCTTTAGCCAGAGC	77	MKKLMLAIFFSVLSFPSFSQS	139
SS-045	STII	ATGAAAAAAAACATTGCGTTTCTGCTGGCGAGCATGTTTGTGTTTAGCATTGCGACCAACGCGTATGCG	78	MKKNIAFLLASMFVFSIATNAYA	140
SS-046	Amylase	ATGTTTGCGAAACGCTTTAAAACCAGCCTGCTGCCGCTGTTTGCGGGCTTTCTGCTGCTGTTTCATCTGGTGCTGGCGGGCCCGGCGGCGGCGAGC	79	MFAKRFKTSLLPLFAGFLLLFHLVLAGPAAAS	141
SS-047	Alpha Factor	ATGCGCTTTCCGAGCATTTTTACCGCGGTGCTGTTTGCGGCGAGCAGCGCGCTGGCG	80	MRFPSIFTAVLFAASSALA	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	ATGGGCGCGGCGGCCGT GCGCTGGCACTTGTGCGT GCTGCTGGCCCTGGGCAC ACGCGGGCGGCTG	89	MGAAAVRW HLCVLLALGT RGRL	151
SS-057	Fungal	ATGAGGAGCTCCCTTGTG CTGTTCTTTGTCTCTGCGT GGACGGCCTTGGCCAG	90	MRSSLVLFFV SAWTALA	152
SS-058	Fibronectin	ATGCTCAGGGGTCCGGG ACCCGGGCGGCTGCTGCT GCTAGCAGTCCTGTGCCT GGGGACATCGGTGCGCT GCACCGAAACCGGGAAG AGCAAGAGG	91	MLRGPGPGRL LLLAVLCLGT SVRCTETGKS KR	153
SS-059	Fibronectin	ATGCTTAGGGGTCCGGGG CCCGGGCTGCTGCTGCTG GCCGTCCAGCTGGGGAC AGCGGTGCCCTCCACG	92	MLRGPGPGLL LLAVQCLGTA VPSTGA	154
SS-060	Fibronectin	ATGCGCCGGGGGGCCCT GACCGGGCTGCTCCTGGT CCTGTGCCTGAGTGTTGT GCTACGTGCAGCCCCCTC TGCAACAAGCAAGAAGC GCAGG	93	MRRGALTGL LLVLCLSVVL RAAPSATSKK RR	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. Membrane Protein Targets

Target No	Target Description	ENST	Trans SEQ ID NO	ENSP	Peptide SEQ ID NO	Optimized ORF SEQ ID
1	1-acylglycerol-3-phosphate O-acyltransferase 3	291572	156	291572	8144	16132, 24120, 32108, 40096, 48084
2	1-acylglycerol-3-phosphate O-acyltransferase 3	327505	157	332989	8145	16133, 24121, 32109, 40097, 48085
3	1-acylglycerol-3-phosphate O-acyltransferase 3	398058	158	381135	8146	16134, 24122, 32110, 40098, 48086
4	1-acylglycerol-3-phosphate O-acyltransferase 3	398061	159	381138	8147	16135, 24123, 32111, 40099, 48087
5	1-acylglycerol-3-phosphate O-acyltransferase 3	398063	160	381140	8148	16136, 24124, 32112, 40100, 48088
6	1-acylglycerol-3-phosphate O-acyltransferase 3	422850	161	414440	8149	16137, 24125, 32113, 40101, 48089
7	1-acylglycerol-3-phosphate O-acyltransferase 3	438598	162	394881	8150	16138, 24126, 32114, 40102, 48090
8	1-acylglycerol-3-phosphate O-acyltransferase 3	445582	163	412079	8151	16139, 24127, 32115, 40103, 48091

9	1-acylglycerol-3-phosphate O-acyltransferase 3	448287	164	389318	8152	16140, 24128, 32116, 40104, 48092
10	1-acylglycerol-3-phosphate O-acyltransferase 3	448845	165	394102	8153	16141, 24129, 32117, 40105, 48093
11	1-acylglycerol-3-phosphate O-acyltransferase 3	457068	166	413906	8154	16142, 24130, 32118, 40106, 48094
12	1-acylglycerol-3-phosphate O-acyltransferase 3	546158	167	443510	8155	16143, 24131, 32119, 40107, 48095
13	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	320285	168	314036	8156	16144, 24132, 32120, 40108, 48096
14	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	366905	169	355872	8157	16145, 24133, 32121, 40109, 48097
15	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	366906	170	355873	8158	16146, 24134, 32122, 40110, 48098
16	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	366908	171	355875	8159	16147, 24135, 32123, 40111, 48099
17	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	366911	172	355878	8160	16148, 24136, 32124, 40112, 48100
18	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	437165	173	400211	8161	16149, 24137, 32125, 40113, 48101
19	1-acylglycerol-3-phosphate O-acyltransferase 4 (lysophosphatidic acid acyltransferase, delta)	457520	174	407007	8162	16150, 24138, 32126, 40114, 48102

20	1-acylglycerol-3-phosphate O-acyltransferase 5 (lysophosphatidic acid acyltransferase, epsilon)	285518	175	285518	8163	16151, 24139, 32127, 40115, 48103
21	2,4-dienoyl CoA reductase 2, peroxisomal	219481	176	219481	8164	16152, 24140, 32128, 40116, 48104
22	2,4-dienoyl CoA reductase 2, peroxisomal	397710	177	380822	8165	16153, 24141, 32129, 40117, 48105
23	2-aminoethanethiol (cysteamine) dioxygenase	373783	178	362888	8166	16154, 24142, 32130, 40118, 48106
24	3-hydroxybutyrate dehydrogenase, type 1	358186	179	350914	8167	16155, 24143, 32131, 40119, 48107
25	3-hydroxybutyrate dehydrogenase, type 1	392378	180	376183	8168	16156, 24144, 32132, 40120, 48108
26	3-hydroxybutyrate dehydrogenase, type 1	392379	181	376184	8169	16157, 24145, 32133, 40121, 48109
27	3-hydroxybutyrate dehydrogenase, type 1	431056	182	396149	8170	16158, 24146, 32134, 40122, 48110
28	3-hydroxybutyrate dehydrogenase, type 1	441275	183	411014	8171	16159, 24147, 32135, 40123, 48111
29	3-hydroxybutyrate dehydrogenase, type 1	445160	184	405462	8172	16160, 24148, 32136, 40124, 48112
30	3-hydroxyisobutyrate dehydrogenase	265395	185	265395	8173	16161, 24149, 32137, 40125, 48113
31	3-oxoacid CoA transferase 2	327582	186	361914	8174	16162, 24150, 32138, 40126, 48114
32	3-oxoacid CoA transferase 2	542949	187	438055	8175	16163, 24151, 32139, 40127, 48115
33	4-hydroxy-2-oxoglutarate aldolase 1	370646	188	359680	8176	16164, 24152, 32140, 40128, 48116
34	4-hydroxy-2-oxoglutarate aldolase 1	370647	189	359681	8177	16165, 24153, 32141, 40129, 48117
35	5,10-methenyltetrahydrofolate synthetase (5-formyltetrahydrofolate cyclo-ligase)	258874	190	258874	8178	16166, 24154, 32142, 40130, 48118

36	5-hydroxytryptamine (serotonin) receptor 3A	299961	191	299961	8179	16167, 24155, 32143, 40131, 48119
37	5-hydroxytryptamine (serotonin) receptor 3A	355556	192	347754	8180	16168, 24156, 32144, 40132, 48120
38	5-hydroxytryptamine (serotonin) receptor 3A	375498	193	364648	8181	16169, 24157, 32145, 40133, 48121
39	5-hydroxytryptamine (serotonin) receptor 3A	504030	194	424189	8182	16170, 24158, 32146, 40134, 48122
40	5-hydroxytryptamine (serotonin) receptor 3A	506841	195	424776	8183	16171, 24159, 32147, 40135, 48123
41	5-hydroxytryptamine (serotonin) receptor 3A	510849	196	423653	8184	16172, 24160, 32148, 40136, 48124
42	5-hydroxytryptamine (serotonin) receptor 3A	535865	197	437776	8185	16173, 24161, 32149, 40137, 48125
43	A kinase (PRKA) anchor protein 12	253332	198	253332	8186	16174, 24162, 32150, 40138, 48126
44	A kinase (PRKA) anchor protein 12	354675	199	346702	8187	16175, 24163, 32151, 40139, 48127
45	A kinase (PRKA) anchor protein 12	359755	200	352794	8188	16176, 24164, 32152, 40140, 48128
46	A kinase (PRKA) anchor protein 12	402676	201	384537	8189	16177, 24165, 32153, 40141, 48129
47	A kinase (PRKA) anchor protein 5	320636	202	315615	8190	16178, 24166, 32154, 40142, 48130
48	A kinase (PRKA) anchor protein 5	394718	203	378207	8191	16179, 24167, 32155, 40143, 48131
49	A kinase (PRKA) anchor protein 6	280979	204	280979	8192	16180, 24168, 32156, 40144, 48132
50	A kinase (PRKA) anchor protein 6	557102	205	451146	8193	16181, 24169, 32157, 40145, 48133
51	A kinase (PRKA) anchor protein 7	342266	206	345149	8194	16182, 24170, 32158, 40146, 48134

52	A kinase (PRKA) anchor protein 7	368123	207	357105	8195	16183, 24171, 32159, 40147, 48135
53	A kinase (PRKA) anchor protein 7	431975	208	405252	8196	16184, 24172, 32160, 40148, 48136
54	A kinase (PRKA) anchor protein 7	474850	209	418208	8197	16185, 24173, 32161, 40149, 48137
55	A kinase (PRKA) anchor protein 8	537303	210	442114	8198	16186, 24174, 32162, 40150, 48138
56	A kinase (PRKA) anchor protein 8	269701	211	269701	8199	16187, 24175, 32163, 40151, 48139
57	aarF domain containing kinase 2	72869	212	72869	8200	16188, 24176, 32164, 40152, 48140, 56072, 56105
58	aarF domain containing kinase 4	243583	213	243583	8201	16189, 24177, 32165, 40153, 48141
59	aarF domain containing kinase 4	324464	214	315118	8202	16190, 24178, 32166, 40154, 48142
60	aarF domain containing kinase 4	450541	215	412839	8203	16191, 24179, 32167, 40155, 48143
61	aarF domain containing kinase 5	308860	216	310547	8204	16192, 24180, 32168, 40156, 48144
62	abhydrolase domain containing 10	273359	217	273359	8205	16193, 24181, 32169, 40157, 48145
63	abhydrolase domain containing 10	534857	218	442932	8206	16194, 24182, 32170, 40158, 48146
64	abhydrolase domain containing 11	222800	219	222800	8207	16195, 24183, 32171, 40159, 48147
65	abhydrolase domain containing 11	322862	220	317293	8208	16196, 24184, 32172, 40160, 48148
66	abhydrolase domain containing 11	395147	221	378579	8209	16197, 24185, 32173, 40161, 48149
67	abhydrolase domain containing 11	437775	222	416970	8210	16198, 24186, 32174, 40162, 48150
68	abhydrolase domain containing 13	375898	223	365063	8211	16199, 24187, 32175, 40163, 48151
69	abhydrolase domain containing 14A	273596	224	273596	8212	16200, 24188, 32176, 40164, 48152

70	abhydrolase domain containing 14A	360889	225	354140	8213	16201, 24189, 32177, 40165, 48153
71	abhydrolase domain containing 14A	452452	226	395914	8214	16202, 24190, 32178, 40166, 48154
72	abhydrolase domain containing 14A	538216	227	439603	8215	16203, 24191, 32179, 40167, 48155
73	abhydrolase domain containing 6	295962	228	295962	8216	16204, 24192, 32180, 40168, 48156
74	abhydrolase domain containing 6	463756	229	420408	8217	16205, 24193, 32181, 40169, 48157
75	abhydrolase domain containing 6	478253	230	420315	8218	16206, 24194, 32182, 40170, 48158
76	abhydrolase domain containing 6	485900	231	418934	8219	16207, 24195, 32183, 40171, 48159
77	abhydrolase domain containing 6	511761	232	442448	8220	16208, 24196, 32184, 40172, 48160
78	acetyl-CoA acyltransferase 2	285093	233	285093	8221	16209, 24197, 32185, 40173, 48161
79	ACN9 homolog (S. cerevisiae)	432641	234	414066	8222	16210, 24198, 32186, 40174, 48162
80	acyl-CoA binding domain containing 5	375888	235	365049	8223	16211, 24199, 32187, 40175, 48163
81	acyl-CoA binding domain containing 5	375889	236	365050	8224	16212, 24200, 32188, 40176, 48164
82	acyl-CoA binding domain containing 5	375897	237	365062	8225	16213, 24201, 32189, 40177, 48165
83	acyl-CoA binding domain containing 5	375901	238	365066	8226	16214, 24202, 32190, 40178, 48166
84	acyl-CoA binding domain containing 5	375905	239	365070	8227	16215, 24203, 32191, 40179, 48167
85	acyl-CoA binding domain containing 5	396271	240	379568	8228	16216, 24204, 32192, 40180, 48168
86	acyl-CoA binding domain containing 5	412279	241	393398	8229	16217, 24205, 32193, 40181, 48169
87	acyl-CoA binding domain containing 5	426079	242	401591	8230	16218, 24206, 32194, 40182, 48170

88	acyl-CoA wax alcohol acyltransferase 1	374521	243	363645	8231	16219, 24207, 32195, 40183, 48171
89	acyl-CoA wax alcohol acyltransferase 2	276101	244	421172	8232	16220, 24208, 32196, 40184, 48172
90	ADAM metallopeptidase domain 18	265707	245	265707	8233	16221, 24209, 32197, 40185, 48173
91	ADAM metallopeptidase domain 18	379866	246	369195	8234	16222, 24210, 32198, 40186, 48174
92	ADAM metallopeptidase domain 18	541111	247	444729	8235	16223, 24211, 32199, 40187, 48175
93	ADAM metallopeptidase domain 18	520772	248	429908	8236	16224, 24212, 32200, 40188, 48176
94	ADAM metallopeptidase domain 32	379907	249	369238	8237	16225, 24213, 32201, 40189, 48177
95	ADAM metallopeptidase domain 32	399826	250	382722	8238	16226, 24214, 32202, 40190, 48178
96	adaptor-related protein complex 1, gamma 2 subunit	308724	251	312442	8239	16227, 24215, 32203, 40191, 48179
97	adaptor-related protein complex 1, gamma 2 subunit	397120	252	380309	8240	16228, 24216, 32204, 40192, 48180
98	adaptor-related protein complex 1, gamma 2 subunit	535852	253	445313	8241	16229, 24217, 32205, 40193, 48181
99	adaptor-related protein complex 1, gamma 2 subunit	545295	254	442716	8242	16230, 24218, 32206, 40194, 48182
100	adaptor-related protein complex 1, gamma 2 subunit	556843	255	451504	8243	16231, 24219, 32207, 40195, 48183
101	adaptor-related protein complex 1, gamma 2 subunit	557189	256	452153	8244	16232, 24220, 32208, 40196, 48184
102	adaptor-related protein complex 1, sigma 3 subunit	396654	257	379891	8245	16233, 24221, 32209, 40197, 48185
103	adaptor-related protein complex 1, sigma 3 subunit	423110	258	406686	8246	16234, 24222, 32210, 40198, 48186
104	adaptor-related protein complex 1, sigma 3 subunit	443700	259	397155	8247	16235, 24223, 32211, 40199, 48187
105	adaptor-related protein complex 1, sigma 3 subunit	446015	260	388738	8248	16236, 24224, 32212, 40200, 48188

106	adaptor-related protein complex 3, beta 2 subunit	261722	261	261722	8249	16237, 24225, 32213, 40201, 48189
107	adaptor-related protein complex 3, beta 2 subunit	535348	262	438721	8250	16238, 24226, 32214, 40202, 48190
108	adaptor-related protein complex 3, beta 2 subunit	535359	263	440984	8251	16239, 24227, 32215, 40203, 48191
109	adaptor-related protein complex 3, delta 1 subunit	343722	264	341579	8252	16240, 24228, 32216, 40204, 48192
110	adaptor-related protein complex 3, delta 1 subunit	345016	265	344055	8253	16241, 24229, 32217, 40205, 48193
111	adaptor-related protein complex 3, delta 1 subunit	350812	266	342321	8254	16242, 24230, 32218, 40206, 48194
112	adaptor-related protein complex 3, delta 1 subunit	355272	267	347416	8255	16243, 24231, 32219, 40207, 48195
113	adaptor-related protein complex 3, delta 1 subunit	356926	268	349398	8256	16244, 24232, 32220, 40208, 48196
114	adaptor-related protein complex 3, mu 1 subunit	355264	269	347408	8257	16245, 24233, 32221, 40209, 48197
115	adaptor-related protein complex 3, mu 1 subunit	372745	270	361831	8258	16246, 24234, 32222, 40210, 48198
116	adaptor-related protein complex 3, mu 2 subunit	174653	271	174653	8259	16247, 24235, 32223, 40211, 48199
117	adaptor-related protein complex 3, mu 2 subunit	396926	272	380132	8260	16248, 24236, 32224, 40212, 48200
118	adaptor-related protein complex 3, mu 2 subunit	517969	273	430538	8261	16249, 24237, 32225, 40213, 48201
119	adaptor-related protein complex 3, mu 2 subunit	518421	274	428787	8262	16250, 24238, 32226, 40214, 48202
120	adaptor-related protein complex 3, mu 2 subunit	522288	275	429515	8263	16251, 24239, 32227, 40215, 48203
121	adaptor-related protein complex 3, mu 2 subunit	530375	276	431918	8264	16252, 24240, 32228, 40216, 48204
122	adaptor-related protein complex 3, sigma 2 subunit	336418	277	338777	8265	16253, 24241, 32229, 40217, 48205
123	adaptor-related protein complex 3, sigma 2 subunit	423566	278	394170	8266	16254, 24242, 32230, 40218, 48206

124	adaptor-related protein complex 3, sigma 2 subunit	560251	279	453288	8267	16255, 24243, 32231, 40219, 48207
125	adenomatosis polyposis coli down-regulated 1-like	371149	280	360191	8268	16256, 24244, 32232, 40220, 48208
126	adenomatosis polyposis coli down-regulated 1-like	439429	281	413261	8269	16257, 24245, 32233, 40221, 48209
127	adenosylhomocysteinase-like 1	359172	282	352092	8270	16258, 24246, 32234, 40222, 48210
128	adenosylhomocysteinase-like 1	369799	283	358814	8271	16259, 24247, 32235, 40223, 48211
129	adenosylhomocysteinase-like 1	393614	284	377238	8272	16260, 24248, 32236, 40224, 48212
130	adenylate cyclase 10 (soluble)	271426	285	271426	8273	16261, 24249, 32237, 40225, 48213
131	adenylate cyclase 10 (soluble)	367848	286	356822	8274	16262, 24250, 32238, 40226, 48214
132	adenylate cyclase 10 (soluble)	367851	287	356825	8275	16263, 24251, 32239, 40227, 48215
133	adenylate cyclase 10 (soluble)	545172	288	441992	8276	16264, 24252, 32240, 40228, 48216
134	adenylate kinase 4	327299	289	322175	8277	16265, 24253, 32241, 40229, 48217
135	adenylate kinase 4	395334	290	378743	8278	16266, 24254, 32242, 40230, 48218
136	adenylate kinase 4	545314	291	445912	8279	16267, 24255, 32243, 40231, 48219
137	adhesion molecule with Ig-like domain 1	369862	292	358878	8280	16268, 24256, 32244, 40232, 48220
138	adhesion molecule with Ig-like domain 1	369864	293	358880	8281	16269, 24257, 32245, 40233, 48221
139	adhesion molecule with Ig-like domain 2	266581	294	266581	8282	16270, 24258, 32246, 40234, 48222
140	adhesion molecule with Ig-like domain 2	321382	295	320848	8283	16271, 24259, 32247, 40235, 48223
141	adhesion molecule with Ig-like domain 2	429635	296	406020	8284	16272, 24260, 32248, 40236, 48224

142	adhesion molecule with Ig-like domain 2	550413	297	449034	8285	16273, 24261, 32249, 40237, 48225
143	adhesion molecule with Ig-like domain 3	320431	298	323096	8286	16274, 24262, 32250, 40238, 48226
144	adhesion molecule with Ig-like domain 3	535833	299	439268	8287	16275, 24263, 32251, 40239, 48227
145	adhesion regulating molecule 1	253003	300	253003	8288	16276, 24264, 32252, 40240, 48228
146	adhesion regulating molecule 1	370744	301	359780	8289	16277, 24265, 32253, 40241, 48229
147	adipogenin	470147	302	434385	8290	16278, 24266, 32254, 40242, 48230
148	adipogenin	537425	303	440331	8291	16279, 24267, 32255, 40243, 48231
149	ADP-ribosylation factor interacting protein 2	254584	304	254584	8292	16280, 24268, 32256, 40244, 48232
150	ADP-ribosylation factor interacting protein 2	396777	305	379998	8293	16281, 24269, 32257, 40245, 48233
151	ADP-ribosylation factor interacting protein 2	423813	306	398375	8294	16282, 24270, 32258, 40246, 48234
152	ADP-ribosylation factor interacting protein 2	445086	307	391427	8295	16283, 24271, 32259, 40247, 48235
153	ADP-ribosylation factor-like 17A	329240	308	331563	8296	16284, 24272, 32260, 40248, 48236
154	ADP-ribosylation factor-like 17A	336125	309	337478	8297	16285, 24273, 32261, 40249, 48237
155	ADP-ribosylation factor-like 17A	337845	310	338611	8298	16286, 24274, 32262, 40250, 48238
156	ADP-ribosylation factor-like 17A	358484	311	351272	8299	16287, 24275, 32263, 40251, 48239
157	ADP-ribosylation factor-like 17A	445552	312	416535	8300	16288, 24276, 32264, 40252, 48240
158	ADP-ribosylation factor-like 17B	434041	313	391751	8301	16289, 24277, 32265, 40253, 48241
159	ADP-ribosylation factor-like 17B	448026	314	395866	8302	16290, 24278, 32266, 40254, 48242

160	ADP-ribosylation factor-like 17B	450673	315	404247	8303	16291, 24279, 32267, 40255, 48243
161	ADP-ribosylation factor-like 17-like isoform a	549665	316	446857	8304	16292, 24280, 32268, 40256, 48244
162	ADP-ribosylation factor-like 17-like isoform a	549904	317	449445	8305	16293, 24281, 32269, 40257, 48245
163	ADP-ribosylation factor-like 17-like isoform a	550273	318	449219	8306	16294, 24282, 32270, 40258, 48246
164	ADP-ribosylation factor-like 17-like isoform a	553155	319	447187	8307	16295, 24283, 32271, 40259, 48247
165	ADP-ribosylation factor-like 4A	356797	320	349250	8308	16296, 24284, 32272, 40260, 48248
166	ADP-ribosylation factor-like 4A	396662	321	379897	8309	16297, 24285, 32273, 40261, 48249
167	ADP-ribosylation factor-like 4A	396663	322	379898	8310	16298, 24286, 32274, 40262, 48250
168	ADP-ribosylation factor-like 4A	396664	323	379899	8311	16299, 24287, 32275, 40263, 48251
169	ADP-ribosylation factor-like 4A	404894	324	385236	8312	16300, 24288, 32276, 40264, 48252
170	ADP-ribosylation factor-like 4A	439721	325	397651	8313	16301, 24289, 32277, 40265, 48253
171	ADP-ribosylation factor-like 4C	339728	326	339754	8314	16302, 24290, 32278, 40266, 48254
172	ADP-ribosylation factor-like 4C	390645	327	375057	8315	16303, 24291, 32279, 40267, 48255
173	ADP-ribosylation factor-like 6 interacting protein 1	304414	328	306788	8316	16304, 24292, 32280, 40268, 48256
174	ADP-ribosylation factor-like 6 interacting protein 1	545430	329	440010	8317	16305, 24293, 32281, 40269, 48257
175	ADP-ribosylation factor-like 6 interacting protein 1	546206	330	440048	8318	16306, 24294, 32282, 40270, 48258
176	ADP-ribosylation factor-like 8A	272217	331	272217	8319	16307, 24295, 32283, 40271, 48259
177	ADP-ribosylation factor-like 8B	256496	332	256496	8320	16308, 24296, 32284, 40272, 48260

178	ADP-ribosylation factor-like 8B	419534	333	402996	8321	16309, 24297, 32285, 40273, 48261
179	ADP-ribosylation factor-like 8B	438743	334	414192	8322	16310, 24298, 32286, 40274, 48262
180	ADP-ribosylation-like factor 6 interacting protein 6	326446	335	315357	8323	16311, 24299, 32287, 40275, 48263
181	AF4/FMR2 family, member 4	265343	336	265343	8324	16312, 24300, 32288, 40276, 48264
182	AF4/FMR2 family, member 4	421773	337	395268	8325	16313, 24301, 32289, 40277, 48265
183	agmatine ureohydrolase (agmatinase)	375826	338	364986	8326	16314, 24302, 32290, 40278, 48266
184	ajuba LIM protein	262713	339	262713	8327	16315, 24303, 32291, 40279, 48267
185	ajuba LIM protein	361265	340	354491	8328	16316, 24304, 32292, 40280, 48268
186	ajuba LIM protein	397388	341	380543	8329	16317, 24305, 32293, 40281, 48269
187	ajuba LIM protein	553592	342	452369	8330	16318, 24306, 32294, 40282, 48270
188	ajuba LIM protein	553911	343	452325	8331	16319, 24307, 32295, 40283, 48271
189	ajuba LIM protein	556731	344	451649	8332	16320, 24308, 32296, 40284, 48272
190	AL138831.1	356722	345	369622	8333	16321, 24309, 32297, 40285, 48273
191	alanine-glyoxylate aminotransferase 2-like 1	296486	346	296486	8334	16322, 24310, 32298, 40286, 48274
192	alanine-glyoxylate aminotransferase 2-like 1	411864	347	392269	8335	16323, 24311, 32299, 40287, 48275
193	alanine-glyoxylate aminotransferase 2-like 1	512646	348	427065	8336	16324, 24312, 32300, 40288, 48276
194	alanine-glyoxylate aminotransferase 2-like 2	308158	349	310978	8337	16325, 24313, 32301, 40289, 48277
195	alkaline ceramidase 3	526597	350	431149	8338	16326, 24314, 32302, 40290, 48278

196	alkaline ceramidase 3	532485	351	434480	8339	16327, 24315, 32303, 40291, 48279
197	alkaline ceramidase 3	533873	352	436252	8340	16328, 24316, 32304, 40292, 48280
198	alkaline ceramidase 3	538157	353	440916	8341	16329, 24317, 32305, 40293, 48281
199	alkaline ceramidase 3	544113	354	440663	8342	16330, 24318, 32306, 40294, 48282
200	allograft inflammatory factor 1-like	247291	355	247291	8343	16331, 24319, 32307, 40295, 48283
201	allograft inflammatory factor 1-like	372300	356	361374	8344	16332, 24320, 32308, 40296, 48284
202	allograft inflammatory factor 1-like	372301	357	361375	8345	16333, 24321, 32309, 40297, 48285
203	allograft inflammatory factor 1-like	372302	358	361376	8346	16334, 24322, 32310, 40298, 48286
204	allograft inflammatory factor 1-like	372309	359	361383	8347	16335, 24323, 32311, 40299, 48287
205	allograft inflammatory factor 1-like	372312	360	361386	8348	16336, 24324, 32312, 40300, 48288
206	alpha-1,4-N-acetylglucosaminyltransferase	236709	361	236709	8349	16337, 24325, 32313, 40301, 48289
207	amiloride-sensitive cation channel 5, intestinal	537611	362	442477	8350	16338, 24326, 32314, 40302, 48290
208	Aminopeptidase Q	357872	363	350541	8351	16339, 24327, 32315, 40303, 48291
209	Aminopeptidase Q	379578	364	368897	8352	16340, 24328, 32316, 40304, 48292
210	Aminopeptidase Q	395528	365	378899	8353	16341, 24329, 32317, 40305, 48293
211	amyloid beta (A4) precursor protein-binding, family B, member 1 interacting protein	356785	366	349237	8354	16342, 24330, 32318, 40306, 48294
212	amyloid beta (A4) precursor protein-binding, family B, member 1 interacting protein	376236	367	365411	8355	16343, 24331, 32319, 40307, 48295

213	amyloid beta (A4) precursor protein-binding, family B, member 1 interacting protein	445780	368	412699	8356	16344, 24332, 32320, 40308, 48296
214	androgen-induced 1	275235	369	275235	8357	16345, 24333, 32321, 40309, 48297
215	androgen-induced 1	344492	370	340090	8358	16346, 24334, 32322, 40310, 48298
216	androgen-induced 1	357847	371	350509	8359	16347, 24335, 32323, 40311, 48299
217	androgen-induced 1	367596	372	356568	8360	16348, 24336, 32324, 40312, 48300
218	androgen-induced 1	367598	373	356570	8361	16349, 24337, 32325, 40313, 48301
219	androgen-induced 1	367601	374	356573	8362	16350, 24338, 32326, 40314, 48302
220	androgen-induced 1	419072	375	398080	8363	16351, 24339, 32327, 40315, 48303
221	androgen-induced 1	447498	376	405048	8364	16352, 24340, 32328, 40316, 48304
222	androgen-induced 1	458219	377	407817	8365	16353, 24341, 32329, 40317, 48305
223	angio-associated, migratory cell protein	248450	378	248450	8366	16354, 24342, 32330, 40318, 48306
224	angiomotin like 1	317829	379	320968	8367	16355, 24343, 32331, 40319, 48307
225	angiomotin like 1	317837	380	323474	8368	16356, 24344, 32332, 40320, 48308
226	angiomotin like 1	433060	381	387739	8369	16357, 24345, 32333, 40321, 48309
227	angiomotin like 1	542840	382	442286	8370	16358, 24346, 32334, 40322, 48310
228	angiomotin like 2	249883	383	249883	8371	16359, 24347, 32335, 40323, 48311
229	angiomotin like 2	422605	384	409999	8372	16360, 24348, 32336, 40324, 48312

230	angiomotin like 2	502491	385	421521	8373	16361, 24349, 32337, 40325, 48313
231	angiomotin like 2	504234	386	424910	8374	16362, 24350, 32338, 40326, 48314
232	angiomotin like 2	505596	387	427292	8375	16363, 24351, 32339, 40327, 48315
233	angiomotin like 2	506107	388	422658	8376	16364, 24352, 32340, 40328, 48316
234	angiomotin like 2	510560	389	427184	8377	16365, 24353, 32341, 40329, 48317
235	angiomotin like 2	513145	390	425475	8378	16366, 24354, 32342, 40330, 48318
236	angiomotin like 2	514516	391	424765	8379	16367, 24355, 32343, 40331, 48319
237	angiomotin like 2	515172	392	427482	8380	16368, 24356, 32344, 40332, 48320
238	angiotensin II receptor-associated protein	314340	393	319713	8381	16369, 24357, 32345, 40333, 48321
239	angiotensin II receptor-associated protein	376629	394	365816	8382	16370, 24358, 32346, 40334, 48322
240	angiotensin II receptor-associated protein	376637	395	365824	8383	16371, 24359, 32347, 40335, 48323
241	angiotensin II receptor-associated protein	400895	396	383688	8384	16372, 24360, 32348, 40336, 48324
242	angiotensin II receptor-associated protein	452018	397	408505	8385	16373, 24361, 32349, 40337, 48325
243	ankyrin and armadillo repeat containing	281412	398	281412	8386	16374, 24362, 32350, 40338, 48326
244	ankyrin and armadillo repeat containing	313581	399	313513	8387	16375, 24363, 32351, 40339, 48327
245	ankyrin and armadillo repeat containing	374838	400	363971	8388	16376, 24364, 32352, 40340, 48328
246	ankyrin and armadillo repeat containing	431575	401	393043	8389	16377, 24365, 32353, 40341, 48329
247	ankyrin and armadillo repeat containing	438402	402	397243	8390	16378, 24366, 32354, 40342, 48330

248	ankyrin and armadillo repeat containing	520309	403	427882	8391	16379, 24367, 32355, 40343, 48331
249	ankyrin repeat and FYVE domain containing 1	341657	404	343362	8392	16380, 24368, 32356, 40344, 48332
250	ankyrin repeat and FYVE domain containing 1	433651	405	416005	8393	16381, 24369, 32357, 40345, 48333
251	ankyrin repeat and FYVE domain containing 1	535427	406	442785	8394	16382, 24370, 32358, 40346, 48334
252	ankyrin repeat and FYVE domain containing 1	574367	407	459775	8395	16383, 24371, 32359, 40347, 48335
253	ankyrin repeat domain 20 family, member A1	377477	408	366697	8396	16384, 24372, 32360, 40348, 48336
254	ankyrin repeat domain 33	301190	409	301190	8397	16385, 24373, 32361, 40349, 48337
255	ankyrin repeat domain 46	335659	410	335287	8398	16386, 24374, 32362, 40350, 48338
256	ankyrin repeat domain 46	358990	411	351881	8399	16387, 24375, 32363, 40351, 48339
257	ankyrin repeat domain 46	519597	412	430056	8400	16388, 24376, 32364, 40352, 48340
258	ankyrin repeat domain 46	520311	413	428388	8401	16389, 24377, 32365, 40353, 48341
259	ankyrin repeat domain 46	520552	414	429015	8402	16390, 24378, 32366, 40354, 48342
260	ankyrin repeat domain 46	521345	415	429647	8403	16391, 24379, 32367, 40355, 48343
261	ankyrin repeat domain 46	523000	416	430800	8404	16392, 24380, 32368, 40356, 48344
262	ankyrin repeat domain 46	524072	417	430357	8405	16393, 24381, 32369, 40357, 48345
263	annexin A13	262219	418	262219	8406	16394, 24382, 32370, 40358, 48346
264	annexin A13	419625	419	390809	8407	16395, 24383, 32371, 40359, 48347
265	anoctamin 3	256737	420	256737	8408	16396, 24384, 32372, 40360, 48348

266	anoctamin 3	525139	421	432576	8409	16397, 24385, 32373, 40361, 48349
267	anoctamin 3	531568	422	432394	8410	16398, 24386, 32374, 40362, 48350
268	anoctamin 3	537978	423	440737	8411	16399, 24387, 32375, 40363, 48351
269	anoctamin 3	538001	424	442241	8412	16400, 24388, 32376, 40364, 48352
270	anoctamin 4	299222	425	299222	8413	16401, 24389, 32377, 40365, 48353
271	anoctamin 4	392977	426	376703	8414	16402, 24390, 32378, 40366, 48354
272	anoctamin 4	392979	427	376705	8415	16403, 24391, 32379, 40367, 48355
273	anoctamin 4	538618	428	443751	8416	16404, 24392, 32380, 40368, 48356
274	anoctamin 4	546991	429	447867	8417	16405, 24393, 32381, 40369, 48357
275	anoctamin 4	550015	430	450192	8418	16406, 24394, 32382, 40370, 48358
276	anoctamin 7	274979	431	274979	8419	16407, 24395, 32383, 40371, 48359
277	anoctamin 7	402430	432	385418	8420	16408, 24396, 32384, 40372, 48360
278	anoctamin 7	402530	433	383985	8421	16409, 24397, 32385, 40373, 48361
279	anoctamin 8	159087	434	159087	8422	16410, 24398, 32386, 40374, 48362, 56073, 56106
280	anoctamin 9	332826	435	332788	8423	16411, 24399, 32387, 40375, 48363
281	AP2 associated kinase 1	406297	436	385181	8424	16412, 24400, 32388, 40376, 48364
282	AP2 associated kinase 1	409085	437	386456	8425	16413, 24401, 32389, 40377, 48365
283	apelin receptor	257254	438	257254	8426	16414, 24402, 32390, 40378, 48366

284	apelin receptor	326830	439	322708	8427	16415, 24403, 32391, 40379, 48367
285	apelin receptor	444275	440	399748	8428	16416, 24404, 32392, 40380, 48368
286	apoptogenic 1	409074	441	386485	8429	16417, 24405, 32393, 40381, 48369
287	apoptosis-inducing factor, mitochondrion-associated, 2	307864	442	312370	8430	16418, 24406, 32394, 40382, 48370
288	apoptosis-inducing factor, mitochondrion-associated, 2	373248	443	362345	8431	16419, 24407, 32395, 40383, 48371
289	apoptosis-inducing factor, mitochondrion-associated, 2	395039	444	378480	8432	16420, 24408, 32396, 40384, 48372
290	aquaporin 10	324978	445	318355	8433	16421, 24409, 32397, 40385, 48373
291	aquaporin 10	484864	446	420341	8434	16422, 24410, 32398, 40386, 48374
292	ArfGAP with dual PH domains 1	265846	447	265846	8435	16423, 24411, 32399, 40387, 48375
293	ArfGAP with dual PH domains 1	449296	448	407267	8436	16424, 24412, 32400, 40388, 48376
294	ArfGAP with dual PH domains 1	449929	449	392174	8437	16425, 24413, 32401, 40389, 48377
295	ArfGAP with dual PH domains 1	538188	450	442254	8438	16426, 24414, 32402, 40390, 48378
296	ArfGAP with dual PH domains 1	539900	451	442682	8439	16427, 24415, 32403, 40391, 48379
297	ArfGAP with dual PH domains 2	330889	452	329468	8440	16428, 24416, 32404, 40392, 48380
298	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	281419	453	281419	8441	16429, 24417, 32405, 40393, 48381
299	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	315273	454	316404	8442	16430, 24418, 32406, 40394, 48382

300	armadillo repeat containing 1	276569	455	276569	8443	16431, 24419, 32407, 40395, 48383
301	armadillo repeat containing 1	458464	456	388572	8444	16432, 24420, 32408, 40396, 48384
302	armadillo repeat containing X-linked 4	423738	457	404304	8445	16433, 24421, 32409, 40397, 48385
303	armadillo repeat containing, X-linked 4	433011	458	424452	8446	16434, 24422, 32410, 40398, 48386
304	armadillo repeat containing, X-linked 4	452188	459	425302	8447	16435, 24423, 32411, 40399, 48387
305	armadillo repeat containing, X-linked 6	361910	460	354708	8448	16436, 24424, 32412, 40400, 48388
306	armadillo repeat containing, X-linked 6	538627	461	440648	8449	16437, 24425, 32413, 40401, 48389
307	armadillo repeat containing, X-linked 6	539247	462	444537	8450	16438, 24426, 32414, 40402, 48390
308	arrestin domain containing 1	371421	463	360475	8451	16439, 24427, 32415, 40403, 48391
309	arrestin domain containing 1	419386	464	406833	8452	16440, 24428, 32416, 40404, 48392
310	arrestin domain containing 1	431925	465	406247	8453	16441, 24429, 32417, 40405, 48393
311	arylacetamide deacetylase-like 4	376221	466	365395	8454	16442, 24430, 32418, 40406, 48394
312	ash1 (absent, small, or homeotic)-like (Drosophila)	368346	467	357330	8455	16443, 24431, 32419, 40407, 48395
313	ash1 (absent, small, or homeotic)-like (Drosophila)	392403	468	376204	8456	16444, 24432, 32420, 40408, 48396
314	asialoglycoprotein receptor 2	254850	469	254850	8457	16445, 24433, 32421, 40409, 48397
315	asialoglycoprotein receptor 2	355035	470	347140	8458	16446, 24434, 32422, 40410, 48398
316	asialoglycoprotein receptor 2	380952	471	370339	8459	16447, 24435, 32423, 40411, 48399
317	asialoglycoprotein receptor 2	446679	472	405844	8460	16448, 24436, 32424, 40412, 48400

318	asialoglycoprotein receptor 2	450034	473	411881	8461	16449, 24437, 32425, 40413, 48401
319	asparagine-linked glycosylation 10, alpha-1,2-glucosyltransferase homolog B (yeast)	308742	474	310120	8462	16450, 24438, 32426, 40414, 48402
320	asparagine-linked glycosylation 3, alpha-1,3-mannosyltransferase homolog (S. cerevisiae)	445626	475	402744	8463	16451, 24439, 32427, 40415, 48403
321	asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (S. cerevisiae)	239891	476	239891	8464	16452, 24440, 32428, 40416, 48404
322	asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (S. cerevisiae)	413537	477	389647	8465	16453, 24441, 32429, 40417, 48405
323	asparagine-linked glycosylation 5, dolichyl-phosphate beta-glucosyltransferase homolog (S. cerevisiae)	443765	478	390533	8466	16454, 24442, 32430, 40418, 48406
324	aspartate beta-hydroxylase domain containing 1	308748	479	311447	8467	16455, 24443, 32431, 40419, 48407
325	aspartate beta-hydroxylase domain containing 1	414952	480	388036	8468	16456, 24444, 32432, 40420, 48408
326	aspartate beta-hydroxylase domain containing 2	215906	481	215906	8469	16457, 24445, 32433, 40421, 48409
327	aspartyl-tRNA synthetase	264161	482	264161	8470	16458, 24446, 32434, 40422, 48410
328	aspartyl-tRNA synthetase	537273	483	444192	8471	16459, 24447, 32435, 40423, 48411
329	ATG12 autophagy related 12 homolog (S. cerevisiae)	274459	484	274459	8472	16460, 24448, 32436, 40424, 48412
330	ATG12 autophagy related 12 homolog	500945	485	425164	8473	16461, 24449, 32437, 40425,

	(S. cerevisiae)					48413
331	ATG12 autophagy related 12 homolog (S. cerevisiae)	509910	486	425107	8474	16462, 24450, 32438, 40426, 48414
332	ATG14 autophagy related 14 homolog (S. cerevisiae)	247178	487	247178	8475	16463, 24451, 32439, 40427, 48415
333	ATG5 autophagy related 5 homolog (S. cerevisiae)	343245	488	343313	8476	16464, 24452, 32440, 40428, 48416
334	ATG5 autophagy related 5 homolog (S. cerevisiae)	360666	489	353884	8477	16465, 24453, 32441, 40429, 48417
335	ATG5 autophagy related 5 homolog (S. cerevisiae)	369070	490	358066	8478	16466, 24454, 32442, 40430, 48418
336	ATG5 autophagy related 5 homolog (S. cerevisiae)	369076	491	358072	8479	16467, 24455, 32443, 40431, 48419
337	ATP synthase H+ transporting mitochondrial Fo complex subunit s (factor B)	245448	492	245448	8480	16468, 24456, 32444, 40432, 48420
338	ATP synthase H+ transporting mitochondrial Fo complex subunit s (factor B)	426751	493	389246	8481	16469, 24457, 32445, 40433, 48421
339	ATP synthase mitochondrial F1 complex assembly factor 1	329231	494	330685	8482	16470, 24458, 32446, 40434, 48422
340	ATP synthase mitochondrial F1 complex assembly factor 1	371937	495	361005	8483	16471, 24459, 32447, 40435, 48423
341	ATP synthase mitochondrial F1 complex assembly factor 1	532925	496	435732	8484	16472, 24460, 32448, 40436, 48424
342	ATP synthase mitochondrial F1 complex assembly factor 1	542495	497	443588	8485	16473, 24461, 32449, 40437, 48425
343	ATP synthase mitochondrial F1 complex assembly factor 1	529214	498	436267	8486	16474, 24462, 32450, 40438, 48426
344	ATP synthase mitochondrial F1 complex assembly factor 1	574428	499	459167	8487	16475, 24463, 32451, 40439, 48427

345	ATP synthase protein 8	361851	500	355265	8488	16476, 24464, 32452, 40440, 48428
346	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	215375	501	215375	8489	16477, 24465, 32453, 40441, 48429
347	ATP synthase, H+ transporting, mitochondrial F1 complex, delta subunit	395633	502	378995	8490	16478, 24466, 32454, 40442, 48430
348	ATP synthase, H+ transporting, mitochondrial F1 complex, epsilon subunit pseudogene 2	381026	503	370414	8491	16479, 24467, 32455, 40443, 48431
349	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	369722	504	358737	8492	16480, 24468, 32456, 40444, 48432
350	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit B1	483994	505	420366	8493	16481, 24469, 32457, 40445, 48433
351	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	301587	506	301587	8494	16482, 24470, 32458, 40446, 48434
352	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	344546	507	344230	8495	16483, 24471, 32459, 40447, 48435
353	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit d	538432	508	437996	8496	16484, 24472, 32460, 40448, 48436
354	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	292475	509	292475	8497	16485, 24473, 32461, 40449, 48437
355	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	359832	510	352890	8498	16486, 24474, 32462, 40450, 48438
356	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	394186	511	377740	8499	16487, 24475, 32463, 40451, 48439
357	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	488775	512	418197	8500	16488, 24476, 32464, 40452, 48440

358	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit F2	544611	513	444922	8501	16489, 24477, 32465, 40453, 48441
359	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G	300688	514	300688	8502	16490, 24478, 32466, 40454, 48442
360	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit G2	505920	515	421076	8503	16491, 24479, 32467, 40455, 48443
361	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit s (factor B)	311459	516	308334	8504	16492, 24480, 32468, 40456, 48444
362	ATP synthase, H+ transporting, mitochondrial Fo complex, subunit s (factor B)	358473	517	351258	8505	16493, 24481, 32469, 40457, 48445
363	ATPase H+ transporting lysosomal 14kDa V1 subunit F	492758	518	417378	8506	16494, 24482, 32470, 40458, 48446
364	ATPase inhibitory factor 1	335514	519	335203	8507	16495, 24483, 32471, 40459, 48447
365	ATPase inhibitory factor 1	465645	520	437337	8508	16496, 24484, 32472, 40460, 48448
366	ATPase inhibitory factor 1	497986	521	435579	8509	16497, 24485, 32473, 40461, 48449
367	ATPase type 13A1	291503	522	291503	8510	16498, 24486, 32474, 40462, 48450
368	ATPase type 13A1	357324	523	349877	8511	16499, 24487, 32475, 40463, 48451
369	ATPase type 13A3	256031	524	256031	8512	16500, 24488, 32476, 40464, 48452
370	ATPase type 13A3	310773	525	311019	8513	16501, 24489, 32477, 40465, 48453
371	ATPase type 13A3	439040	526	416508	8514	16502, 24490, 32478, 40466, 48454
372	ATPase type 13A3	446356	527	410767	8515	16503, 24491, 32479, 40467, 48455

373	ATPase type 13A3	457986	528	406234	8516	16504, 24492, 32480, 40468, 48456
374	ATPase type 13A4	295548	529	295548	8517	16505, 24493, 32481, 40469, 48457
375	ATPase type 13A4	342695	530	339182	8518	16506, 24494, 32482, 40470, 48458
376	ATPase type 13A4	400270	531	383129	8519	16507, 24495, 32483, 40471, 48459
377	ATPase type 13A5	342358	532	341942	8520	16508, 24496, 32484, 40472, 48460
378	ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	264449	533	264449	8521	16509, 24497, 32485, 40473, 48461
379	ATPase, aminophospholipid transporter (APLT), class I, type 8A, member 1	381668	534	371084	8522	16510, 24498, 32486, 40474, 48462
380	ATPase, class I, type 8B, member 4	284509	535	284509	8523	16511, 24499, 32487, 40475, 48463
381	ATPase, class I, type 8B, member 4	558829	536	453539	8524	16512, 24500, 32488, 40476, 48464
382	ATPase, class I, type 8B, member 4	559829	537	453169	8525	16513, 24501, 32489, 40477, 48465
383	ATPase, class II, type 9A	311637	538	309086	8526	16514, 24502, 32490, 40478, 48466
384	ATPase, class II, type 9A	338821	539	342481	8527	16515, 24503, 32491, 40479, 48467
385	ATPase, class II, type 9A	402822	540	385875	8528	16516, 24504, 32492, 40480, 48468
386	ATPase, class V, type 10B	327245	541	313600	8529	16517, 24505, 32493, 40481, 48469
387	ATPase, class V, type 10D	273859	542	273859	8530	16518, 24506, 32494, 40482, 48470
388	ATPase, class V, type 10D	504445	543	420909	8531	16519, 24507, 32495, 40483, 48471
389	ATPase, class VI, type 11C	327569	544	332756	8532	16520, 24508, 32496, 40484, 48472

390	ATPase, class VI, type 11C	359686	545	352715	8533	16521, 24509, 32497, 40485, 48473
391	ATPase, class VI, type 11C	361648	546	355165	8534	16522, 24510, 32498, 40486, 48474
392	ATPase, class VI, type 11C	370543	547	359574	8535	16523, 24511, 32499, 40487, 48475
393	ATPase, class VI, type 11C	370557	548	359588	8536	16524, 24512, 32500, 40488, 48476
394	ATPase, class VI, type 11C	422228	549	394573	8537	16525, 24513, 32501, 40489, 48477
395	ATPase, class VI, type 11C	433868	550	397923	8538	16526, 24514, 32502, 40490, 48478
396	ATPase, class VI, type 11C	450801	551	391259	8539	16527, 24515, 32503, 40491, 48479
397	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G3	281087	552	281087	8540	16528, 24516, 32504, 40492, 48480
398	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G3	309309	553	309574	8541	16529, 24517, 32505, 40493, 48481
399	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G3	367381	554	356351	8542	16530, 24518, 32506, 40494, 48482
400	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G3	367382	555	356352	8543	16531, 24519, 32507, 40495, 48483
401	ATPase, H+ transporting, lysosomal 13kDa, V1 subunit G3	489986	556	417171	8544	16532, 24520, 32508, 40496, 48484
402	ATPase, H+ transporting, lysosomal 14kDa, V1 subunit F	249289	557	249289	8545	16533, 24521, 32509, 40497, 48485
403	ATPase, H+ transporting, lysosomal 31kDa, V1 subunit E2	306448	558	304891	8546	16534, 24522, 32510, 40498, 48486
404	ATPase, H+ transporting, lysosomal 31kDa, V1 subunit E2	522587	559	428141	8547	16535, 24523, 32511, 40499, 48487

405	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D	216442	560	216442	8548	16536, 24524, 32512, 40500, 48488
406	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D	554087	561	451167	8549	16537, 24525, 32513, 40501, 48489
407	ATPase, H+ transporting, lysosomal 34kDa, V1 subunit D	555012	562	451031	8550	16538, 24526, 32514, 40502, 48490
408	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d2	285393	563	285393	8551	16539, 24527, 32515, 40503, 48491
409	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d2	521564	564	429731	8552	16540, 24528, 32516, 40504, 48492
410	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d2	523635	565	428382	8553	16541, 24529, 32517, 40505, 48493
411	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C2	272238	566	272238	8554	16542, 24530, 32518, 40506, 48494
412	ATPase, H+ transporting, lysosomal 42kDa, V1 subunit C2	381661	567	371077	8555	16543, 24531, 32519, 40507, 48495
413	ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H	355221	568	347359	8556	16544, 24532, 32520, 40508, 48496
414	ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H	359530	569	352522	8557	16545, 24533, 32521, 40509, 48497
415	ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H	396774	570	379995	8558	16546, 24534, 32522, 40510, 48498
416	ATPase, H+ transporting, lysosomal 50/57kDa, V1 subunit H	521275	571	429786	8559	16547, 24535, 32523, 40511, 48499
417	ATPase, H+ transporting, lysosomal	524234	572	427835	8560	16548, 24536, 32524, 40512, 48500

	50/57kDa, V1 subunit H					
418	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	234396	573	234396	8561	16549, 24537, 32525, 40513, 48501
419	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	412314	574	388353	8562	16550, 24538, 32526, 40514, 48502
420	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	483246	575	443856	8563	16551, 24539, 32527, 40515, 48503
421	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2	276390	576	276390	8564	16552, 24540, 32528, 40516, 48504
422	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B2	542368	577	439953	8565	16553, 24541, 32529, 40517, 48505
423	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	273398	578	273398	8566	16554, 24542, 32530, 40518, 48506
424	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	475322	579	419294	8567	16555, 24543, 32531, 40519, 48507
425	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	538620	580	439874	8568	16556, 24544, 32532, 40520, 48508
426	ATPase, H+ transporting, lysosomal 70kDa, V1 subunit A	545842	581	441031	8569	16557, 24545, 32533, 40521, 48509
427	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e1	517669	582	427941	8570	16558, 24546, 32534, 40522, 48510
428	ATPase, H+ transporting, lysosomal 9kDa, V0 subunit e1	519374	583	429690	8571	16559, 24547, 32535, 40523, 48511
429	ATPase, H+ transporting, lysosomal accessory protein 1	369762	584	358777	8572	16560, 24548, 32536, 40524, 48512

430	ATPase, H+ transporting, lysosomal accessory protein 1	422890	585	398511	8573	16561, 24549, 32537, 40525, 48513
431	ATPase, H+ transporting, lysosomal accessory protein 1	445849	586	388546	8574	16562, 24550, 32538, 40526, 48514
432	ATPase, H+ transporting, lysosomal accessory protein 1	449556	587	392375	8575	16563, 24551, 32539, 40527, 48515
433	ATPase, H+ transporting, lysosomal accessory protein 1-like	380167	588	369513	8576	16564, 24552, 32540, 40528, 48516
434	ATPase, H+ transporting, lysosomal accessory protein 1-like	439350	589	391381	8577	16565, 24553, 32541, 40529, 48517
435	ATPase, Na+/K+ transporting, beta 4 polypeptide	218008	590	218008	8578	16566, 24554, 32542, 40530, 48518
436	ATPase, Na+/K+ transporting, beta 4 polypeptide	361319	591	355346	8579	16567, 24555, 32543, 40531, 48519
437	ATPase, Na+/K+ transporting, beta 4 polypeptide	539306	592	443334	8580	16568, 24556, 32544, 40532, 48520
438	ATP-binding cassette sub-family B (MDR/TAP) member 5	406935	593	383899	8581	16569, 24557, 32545, 40533, 48521
439	ATP-binding cassette, sub-family B (MDR/TAP), member 5	258738	594	258738	8582	16570, 24558, 32546, 40534, 48522
440	ATP-binding cassette, sub-family B (MDR/TAP), member 5	404938	595	384881	8583	16571, 24559, 32547, 40535, 48523
441	ATP-binding cassette, sub-family B (MDR/TAP), member 5	443026	596	406730	8584	16572, 24560, 32548, 40536, 48524
442	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	302539	597	303960	8585	16573, 24561, 32549, 40537, 48525
443	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	379493	598	368807	8586	16574, 24562, 32550, 40538, 48526

444	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	389817	599	374467	8587	16575, 24563, 32551, 40539, 48527
445	ATP-binding cassette, sub-family C (CFTR/MRP), member 8	527905	600	431653	8588	16576, 24564, 32552, 40540, 48528
446	ATP-binding cassette, sub-family C, member 6 pseudogene 1	546162	601	443361	8589	16577, 24565, 32553, 40541, 48529
447	aurora kinase A interacting protein 1	321751	602	319778	8590	16578, 24566, 32554, 40542, 48530
448	aurora kinase A interacting protein 1	338338	603	340656	8591	16579, 24567, 32555, 40543, 48531
449	aurora kinase A interacting protein 1	338370	604	342676	8592	16580, 24568, 32556, 40544, 48532
450	aurora kinase A interacting protein 1	378853	605	368130	8593	16581, 24569, 32557, 40545, 48533
451	B and T lymphocyte associated	334529	606	333919	8594	16582, 24570, 32558, 40546, 48534
452	B and T lymphocyte associated	383680	607	373178	8595	16583, 24571, 32559, 40547, 48535
453	B7 homolog 6	338965	608	341637	8596	16584, 24572, 32560, 40548, 48536
454	B7 homolog 6	530403	609	434394	8597	16585, 24573, 32561, 40549, 48537
455	BAI1-associated protein 2-like 2	332536	610	328876	8598	16586, 24574, 32562, 40550, 48538
456	BAI1-associated protein 2-like 2	381669	611	371085	8599	16587, 24575, 32563, 40551, 48539
457	BAI1-associated protein 2-like 2	402500	612	384877	8600	16588, 24576, 32564, 40552, 48540
458	B-cell receptor-associated protein 29	5259	613	5259	8601	16589, 24577, 32565, 40553, 48541, 56074, 56107
459	B-cell receptor-associated protein 29	379117	614	368412	8602	16590, 24578, 32566, 40554, 48542
460	B-cell receptor-associated protein 29	379119	615	368414	8603	16591, 24579, 32567, 40555, 48543

461	B-cell receptor-associated protein 29	379121	616	368416	8604	16592, 24580, 32568, 40556, 48544
462	B-cell receptor-associated protein 29	421217	617	395828	8605	16593, 24581, 32569, 40557, 48545
463	B-cell receptor-associated protein 29	436699	618	414164	8606	16594, 24582, 32570, 40558, 48546
464	B-cell receptor-associated protein 29	445771	619	400718	8607	16595, 24583, 32571, 40559, 48547
465	B-cell receptor-associated protein 29	457837	620	409350	8608	16596, 24584, 32572, 40560, 48548
466	B-cell receptor-associated protein 29	465919	621	418993	8609	16597, 24585, 32573, 40561, 48549
467	B-cell receptor-associated protein 29	473124	622	420313	8610	16598, 24586, 32574, 40562, 48550
468	B-cell receptor-associated protein 29	479917	623	418816	8611	16599, 24587, 32575, 40563, 48551
469	B-cell receptor-associated protein 31	345046	624	343458	8612	16600, 24588, 32576, 40564, 48552
470	B-cell receptor-associated protein 31	416815	625	394270	8613	16601, 24589, 32577, 40565, 48553
471	B-cell receptor-associated protein 31	423827	626	389740	8614	16602, 24590, 32578, 40566, 48554
472	B-cell receptor-associated protein 31	426131	627	387751	8615	16603, 24591, 32579, 40567, 48555
473	B-cell receptor-associated protein 31	429550	628	409888	8616	16604, 24592, 32580, 40568, 48556
474	B-cell receptor-associated protein 31	430088	629	402342	8617	16605, 24593, 32581, 40569, 48557
475	B-cell receptor-associated protein 31	441714	630	405417	8618	16606, 24594, 32582, 40570, 48558
476	B-cell receptor-associated protein 31	442093	631	400345	8619	16607, 24595, 32583, 40571, 48559
477	B-cell receptor-associated protein 31	458587	632	392330	8620	16608, 24596, 32584, 40572, 48560
478	BCL2/adenovirus E1B 19kDa interacting protein 1	231668	633	231668	8621	16609, 24597, 32585, 40573, 48561

479	BCL2/adenovirus E1B 19kDa interacting protein 1	351486	634	239215	8622	16610, 24598, 32586, 40574, 48562
480	BCL2/adenovirus E1B 19kDa interacting protein 1	352523	635	239214	8623	16611, 24599, 32587, 40575, 48563
481	BCL2/adenovirus E1B 19kDa interacting protein 1	393770	636	377365	8624	16612, 24600, 32588, 40576, 48564
482	BCL2-like 13 (apoptosis facilitator)	317582	637	318883	8625	16613, 24601, 32589, 40577, 48565
483	BCL2-like 13 (apoptosis facilitator)	337612	638	338932	8626	16614, 24602, 32590, 40578, 48566
484	BCL2-like 13 (apoptosis facilitator)	399782	639	382682	8627	16615, 24603, 32591, 40579, 48567
485	BCL2-like 13 (apoptosis facilitator)	418951	640	410019	8628	16616, 24604, 32592, 40580, 48568
486	BCL2-like 13 (apoptosis facilitator)	493680	641	434764	8629	16617, 24605, 32593, 40581, 48569
487	BCL2-like 13 (apoptosis facilitator)	538149	642	441344	8630	16618, 24606, 32594, 40582, 48570
488	BCL2-like 13 (apoptosis facilitator)	543133	643	437667	8631	16619, 24607, 32595, 40583, 48571
489	BCL2-like 13 (apoptosis facilitator)	355028	644	347133	8632	16620, 24608, 32596, 40584, 48572
490	BEN domain containing 5	294347	645	294347	8633	16621, 24609, 32597, 40585, 48573
491	BEN domain containing 5	371833	646	360899	8634	16622, 24610, 32598, 40586, 48574
492	beta-1,3-glucuronyltransferase 2 (glucuronosyltransferase S)	230053	647	230053	8635	16623, 24611, 32599, 40587, 48575
493	beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)	320474	648	323479	8636	16624, 24612, 32600, 40588, 48576
494	beta-1,3-N-acetylgalactosaminyltransferase 1 (globoside blood group)	392779	649	376530	8637	16625, 24613, 32601, 40589, 48577

495	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	392780	650	376531	8638	16626, 24614, 32602, 40590, 48578
496	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	392781	651	376532	8639	16627, 24615, 32603, 40591, 48579
497	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	417187	652	407027	8640	16628, 24616, 32604, 40592, 48580
498	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	468268	653	419476	8641	16629, 24617, 32605, 40593, 48581
499	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	473142	654	420604	8642	16630, 24618, 32606, 40594, 48582
500	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	473285	655	418226	8643	16631, 24619, 32607, 40595, 48583
501	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	484127	656	420059	8644	16632, 24620, 32608, 40596, 48584
502	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	488170	657	420163	8645	16633, 24621, 32609, 40597, 48585
503	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	492353	658	418567	8646	16634, 24622, 32610, 40598, 48586
504	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	494173	659	419127	8647	16635, 24623, 32611, 40599, 48587
505	beta-1,3-N-acetylgalactosaminyl transferase 1 (globoside blood group)	498216	660	417643	8648	16636, 24624, 32612, 40600, 48588

506	beta-1,3-N-acetylgalactosaminyl transferase 2	313984	661	315678	8649	16637, 24625, 32613, 40601, 48589
507	beta-1,3-N-acetylgalactosaminyl transferase 2	366599	662	355558	8650	16638, 24626, 32614, 40602, 48590
508	beta-1,3-N-acetylgalactosaminyl transferase 2	366600	663	355559	8651	16639, 24627, 32615, 40603, 48591
509	beta-1,4-N-acetyl-galactosaminyl transferase 1	341156	664	341562	8652	16640, 24628, 32616, 40604, 48592
510	beta-1,4-N-acetyl-galactosaminyl transferase 1	548888	665	447945	8653	16641, 24629, 32617, 40605, 48593
511	beta-1,4-N-acetyl-galactosaminyl transferase 1	551220	666	446566	8654	16642, 24630, 32618, 40606, 48594
512	beta-1,4-N-acetyl-galactosaminyl transferase 2	300404	667	300404	8655	16643, 24631, 32619, 40607, 48595
513	beta-1,4-N-acetyl-galactosaminyl transferase 2	393354	668	377022	8656	16644, 24632, 32620, 40608, 48596
514	beta-1,4-N-acetyl-galactosaminyl transferase 2	504681	669	425510	8657	16645, 24633, 32621, 40609, 48597
515	beta-1,4-N-acetyl-galactosaminyl transferase 4	329962	670	328277	8658	16646, 24634, 32622, 40610, 48598
516	blocked early in transport 1 homolog (S. cerevisiae)	222547	671	222547	8659	16647, 24635, 32623, 40611, 48599
517	blocked early in transport 1 homolog (S. cerevisiae)-like	325147	672	339093	8660	16648, 24636, 32624, 40612, 48600
518	blocked early in transport 1 homolog (S. cerevisiae)-like	382762	673	372210	8661	16649, 24637, 32625, 40613, 48601
519	Boc homolog (mouse)	273395	674	273395	8662	16650, 24638, 32626, 40614, 48602
520	Boc homolog (mouse)	355385	675	347546	8663	16651, 24639, 32627, 40615, 48603
521	Boc homolog (mouse)	462425	676	418118	8664	16652, 24640, 32628, 40616, 48604
522	Boc homolog (mouse)	464546	677	417362	8665	16653, 24641, 32629, 40617, 48605
523	Boc homolog (mouse)	484034	678	417337	8666	16654, 24642, 32630, 40618, 48606

524	Boc homolog (mouse)	485230	679	420154	8667	16655, 24643, 32631, 40619, 48607
525	Boc homolog (mouse)	494687	680	418260	8668	16656, 24644, 32632, 40620, 48608
526	Boc homolog (mouse)	495514	681	418663	8669	16657, 24645, 32633, 40621, 48609
527	brain expressed associated with NEDD4 1	561796	682	455212	8670	16658, 24646, 32634, 40622, 48610
528	brain expressed, associated with NEDD4, 1	299694	683	299694	8671	16659, 24647, 32635, 40623, 48611
529	brain expressed, associated with NEDD4, 1	536005	684	442793	8672	16660, 24648, 32636, 40624, 48612
530	brain protein 44	271373	685	271373	8673	16661, 24649, 32637, 40625, 48613
531	brain protein 44	367846	686	356820	8674	16662, 24650, 32638, 40626, 48614
532	brain protein 44	458574	687	392874	8675	16663, 24651, 32639, 40627, 48615
533	brain protein 44-like	341756	688	340784	8676	16664, 24652, 32640, 40628, 48616
534	brain protein 44-like	360961	689	354223	8677	16665, 24653, 32641, 40629, 48617
535	brain protein 44-like	392123	690	375970	8678	16666, 24654, 32642, 40630, 48618
536	branched chain ketoacid dehydrogenase kinase	219794	691	219794	8679	16667, 24655, 32643, 40631, 48619
537	branched chain ketoacid dehydrogenase kinase	287507	692	287507	8680	16668, 24656, 32644, 40632, 48620
538	branched chain ketoacid dehydrogenase kinase	394950	693	378404	8681	16669, 24657, 32645, 40633, 48621
539	branched chain ketoacid dehydrogenase kinase	394951	694	378405	8682	16670, 24658, 32646, 40634, 48622
540	BRI3 binding protein	341446	695	340761	8683	16671, 24659, 32647, 40635, 48623

541	BRO1 domain and CAAX motif containing	340934	696	343742	8684	16672, 24660, 32648, 40636, 48624
542	BRO1 domain and CAAX motif containing	426638	697	398862	8685	16673, 24661, 32649, 40637, 48625
543	BRO1 domain and CAAX motif containing	537020	698	440041	8686	16674, 24662, 32650, 40638, 48626
544	BRO1 domain and CAAX motif containing	539697	699	441080	8687	16675, 24663, 32651, 40639, 48627
545	bromodomain containing 8	230901	700	230901	8688	16676, 24664, 32652, 40640, 48628
546	bromodomain containing 8	239899	701	239899	8689	16677, 24665, 32653, 40641, 48629
547	bromodomain containing 8	254900	702	254900	8690	16678, 24666, 32654, 40642, 48630
548	bromodomain containing 8	411594	703	394330	8691	16679, 24667, 32655, 40643, 48631
549	bromodomain containing 8	418329	704	398873	8692	16680, 24668, 32656, 40644, 48632
550	bromodomain containing 8	454473	705	398067	8693	16681, 24669, 32657, 40645, 48633
551	bromodomain containing 8	455658	706	408396	8694	16682, 24670, 32658, 40646, 48634
552	BTB (POZ) domain containing 11	280758	707	280758	8695	16683, 24671, 32659, 40647, 48635
553	BTB (POZ) domain containing 11	357167	708	349690	8696	16684, 24672, 32660, 40648, 48636
554	BTB (POZ) domain containing 11	420571	709	413889	8697	16685, 24673, 32661, 40649, 48637
555	BTB (POZ) domain containing 11	490090	710	447319	8698	16686, 24674, 32662, 40650, 48638
556	BTB (POZ) domain containing 11	494235	711	448322	8699	16687, 24675, 32663, 40651, 48639
557	butyrophilin-like 8	231229	712	231229	8700	16688, 24676, 32664, 40652, 48640
558	butyrophilin-like 8	340184	713	342197	8701	16689, 24677, 32665, 40653, 48641

559	butyrophilin-like 8	533815	714	435098	8702	16690, 24678, 32666, 40654, 48642
560	butyrophilin-like 8	400707	715	383543	8703	16691, 24679, 32667, 40655, 48643
561	butyrophilin-like 8	508408	716	424585	8704	16692, 24680, 32668, 40656, 48644
562	butyrophilin-like 8	511704	717	425207	8705	16693, 24681, 32669, 40657, 48645
563	butyrophilin-like 9	327705	718	330200	8706	16694, 24682, 32670, 40658, 48646
564	butyrophilin-like 9	376841	719	366037	8707	16695, 24683, 32671, 40659, 48647
565	butyrophilin-like 9	376842	720	366038	8708	16696, 24684, 32672, 40660, 48648
566	butyrophilin-like 9	376850	721	366046	8709	16697, 24685, 32673, 40661, 48649
567	cache domain containing 1	290039	722	290039	8710	16698, 24686, 32674, 40662, 48650
568	cache domain containing 1	371073	723	360113	8711	16699, 24687, 32675, 40663, 48651
569	cadherin 24, type 2	267383	724	267383	8712	16700, 24688, 32676, 40664, 48652
570	cadherin 24, type 2	397359	725	380517	8713	16701, 24689, 32677, 40665, 48653
571	cadherin 24, type 2	422751	726	392742	8714	16702, 24690, 32678, 40666, 48654
572	cadherin 24, type 2	487137	727	434821	8715	16703, 24691, 32679, 40667, 48655
573	cadherin 24, type 2	554034	728	452493	8716	16704, 24692, 32680, 40668, 48656
574	cadherin 26	244047	729	244047	8717	16705, 24693, 32681, 40669, 48657
575	cadherin 26	244049	730	244049	8718	16706, 24694, 32682, 40670, 48658
576	cadherin 26	348616	731	339390	8719	16707, 24695, 32683, 40671, 48659

577	cadherin 26	350849	732	310845	8720	16708, 24696, 32684, 40672, 48660
578	cadherin 26	370991	733	360030	8721	16709, 24697, 32685, 40673, 48661
579	cadherin-related family member 2	261944	734	261944	8722	16710, 24698, 32686, 40674, 48662
580	cadherin-related family member 2	506348	735	421078	8723	16711, 24699, 32687, 40675, 48663
581	cadherin-related family member 2	510636	736	424565	8724	16712, 24700, 32688, 40676, 48664
582	cadherin-related family member 3	317716	737	325954	8725	16713, 24701, 32689, 40677, 48665
583	cadherin-related family member 4	343366	738	341302	8726	16714, 24702, 32690, 40678, 48666
584	cadherin-related family member 4	412678	739	391409	8727	16715, 24703, 32691, 40679, 48667
585	calcium binding protein 1	288616	740	288616	8728	16716, 24704, 32692, 40680, 48668
586	calcium binding protein 1	316803	741	317310	8729	16717, 24705, 32693, 40681, 48669
587	calcium binding protein 1	351200	742	288615	8730	16718, 24706, 32694, 40682, 48670
588	calcium binding protein 7	216144	743	216144	8731	16719, 24707, 32695, 40683, 48671
589	calcium channel, voltage-dependent, alpha 2/delta subunit 1	284088	744	284088	8732	16720, 24708, 32696, 40684, 48672
590	calcium channel, voltage-dependent, alpha 2/delta subunit 1	356253	745	348589	8733	16721, 24709, 32697, 40685, 48673
591	calcium channel, voltage-dependent, alpha 2/delta subunit 1	356860	746	349320	8734	16722, 24710, 32698, 40686, 48674
592	calcium channel, voltage-dependent, alpha 2/delta subunit 1	535308	747	443124	8735	16723, 24711, 32699, 40687, 48675
593	calcium channel, voltage-dependent, gamma subunit 4	262138	748	262138	8736	16724, 24712, 32700, 40688, 48676

594	calcium channel, voltage-dependent, L type, alpha 1C subunit	322367	749	323129	8737	16725, 24713, 32701, 40689, 48677
595	calcium channel, voltage-dependent, L type, alpha 1C subunit	327702	750	329877	8738	16726, 24714, 32702, 40690, 48678
596	calcium channel, voltage-dependent, L type, alpha 1C subunit	335762	751	336982	8739	16727, 24715, 32703, 40691, 48679
597	calcium channel, voltage-dependent, T type, alpha 1G subunit	352832	752	339302	8740	16728, 24716, 32704, 40692, 48680
598	calcium channel, voltage-dependent, T type, alpha 1G subunit	354983	753	347078	8741	16729, 24717, 32705, 40693, 48681
599	calcium channel, voltage-dependent, T type, alpha 1G subunit	358244	754	350979	8742	16730, 24718, 32706, 40694, 48682
600	calcium channel, voltage-dependent, T type, alpha 1G subunit	359106	755	352011	8743	16731, 24719, 32707, 40695, 48683
601	calcium channel, voltage-dependent, T type, alpha 1G subunit	360761	756	353990	8744	16732, 24720, 32708, 40696, 48684
602	calcium channel, voltage-dependent, T type, alpha 1G subunit	416767	757	392390	8745	16733, 24721, 32709, 40697, 48685
603	calcium channel, voltage-dependent, T type, alpha 1G subunit	429973	758	414388	8746	16734, 24722, 32710, 40698, 48686
604	calcium channel, voltage-dependent, T type, alpha 1G subunit	442258	759	409759	8747	16735, 24723, 32711, 40699, 48687
605	calcium channel, voltage-dependent, T type, alpha 1G subunit	502264	760	425522	8748	16736, 24724, 32712, 40700, 48688
606	calcium channel, voltage-dependent, T type, alpha 1G subunit	503436	761	427231	8749	16737, 24725, 32713, 40701, 48689

607	calcium channel, voltage-dependent, T type, alpha 1G subunit	503485	762	427238	8750	16738, 24726, 32714, 40702, 48690
608	calcium channel, voltage-dependent, T type, alpha 1G subunit	503607	763	426558	8751	16739, 24727, 32715, 40703, 48691
609	calcium channel, voltage-dependent, T type, alpha 1G subunit	504076	764	425153	8752	16740, 24728, 32716, 40704, 48692
610	calcium channel, voltage-dependent, T type, alpha 1G subunit	505165	765	422268	8753	16741, 24729, 32717, 40705, 48693
611	calcium channel, voltage-dependent, T type, alpha 1G subunit	506406	766	426313	8754	16742, 24730, 32718, 40706, 48694
612	calcium channel, voltage-dependent, T type, alpha 1G subunit	507336	767	420918	8755	16743, 24731, 32719, 40707, 48695
613	calcium channel, voltage-dependent, T type, alpha 1G subunit	507510	768	423112	8756	16744, 24732, 32720, 40708, 48696
614	calcium channel, voltage-dependent, T type, alpha 1G subunit	507609	769	423045	8757	16745, 24733, 32721, 40709, 48697
615	calcium channel, voltage-dependent, T type, alpha 1G subunit	507896	770	421518	8758	16746, 24734, 32722, 40710, 48698
616	calcium channel, voltage-dependent, T type, alpha 1G subunit	510115	771	427173	8759	16747, 24735, 32723, 40711, 48699
617	calcium channel, voltage-dependent, T type, alpha 1G subunit	510366	772	426814	8760	16748, 24736, 32724, 40712, 48700
618	calcium channel, voltage-dependent, T type, alpha 1G subunit	511765	773	427247	8761	16749, 24737, 32725, 40713, 48701
619	calcium channel, voltage-dependent, T type, alpha 1G subunit	511768	774	424664	8762	16750, 24738, 32726, 40714, 48702

620	calcium channel, voltage-dependent, T type, alpha 1G subunit	512389	775	426261	8763	16751, 24739, 32727, 40715, 48703
621	calcium channel, voltage-dependent, T type, alpha 1G subunit	513689	776	426172	8764	16752, 24740, 32728, 40716, 48704
622	calcium channel, voltage-dependent, T type, alpha 1G subunit	513964	777	425451	8765	16753, 24741, 32729, 40717, 48705
623	calcium channel, voltage-dependent, T type, alpha 1G subunit	514079	778	423317	8766	16754, 24742, 32730, 40718, 48706
624	calcium channel, voltage-dependent, T type, alpha 1G subunit	514181	779	425698	8767	16755, 24743, 32731, 40719, 48707
625	calcium channel, voltage-dependent, T type, alpha 1G subunit	514717	780	422407	8768	16756, 24744, 32732, 40720, 48708
626	calcium channel, voltage-dependent, T type, alpha 1G subunit	515165	781	426098	8769	16757, 24745, 32733, 40721, 48709
627	calcium channel, voltage-dependent, T type, alpha 1G subunit	515411	782	423155	8770	16758, 24746, 32734, 40722, 48710
628	calcium channel, voltage-dependent, T type, alpha 1G subunit	515765	783	426232	8771	16759, 24747, 32735, 40723, 48711
629	calcium homeostasis modulator 3	369783	784	358798	8772	16760, 24748, 32736, 40724, 48712
630	calcium/calmodulin-dependent protein kinase IG	9105	785	9105	8773	16761, 24749, 32737, 40725, 48713, 56075, 56108
631	calcium/calmodulin-dependent protein kinase IG	361322	786	354861	8774	16762, 24750, 32738, 40726, 48714
632	calcyon neuron-specific vesicular protein	252939	787	252939	8775	16763, 24751, 32739, 40727, 48715
633	calcyon neuron-specific vesicular protein	368555	788	357543	8776	16764, 24752, 32740, 40728, 48716
634	calcyon neuron-specific vesicular protein	368556	789	357544	8777	16765, 24753, 32741, 40729, 48717

635	calcyon neuron-specific vesicular protein	368558	790	357546	8778	16766, 24754, 32742, 40730, 48718
636	calmegin	325617	791	326699	8779	16767, 24755, 32743, 40731, 48719
637	calmegin	414773	792	392782	8780	16768, 24756, 32744, 40732, 48720
638	calmegin	509477	793	424593	8781	16769, 24757, 32745, 40733, 48721
639	calmegin	537281	794	439381	8782	16770, 24758, 32746, 40734, 48722
640	calmegin	545667	795	445139	8783	16771, 24759, 32747, 40735, 48723
641	calmodulin regulated spectrin-associated protein family, member 3	160298	796	160298	8784	16772, 24760, 32748, 40736, 48724, 56076, 56109
642	calmodulin regulated spectrin-associated protein family, member 3	446248	797	416797	8785	16773, 24761, 32749, 40737, 48725
643	calneuron 1	329008	798	332498	8786	16774, 24762, 32750, 40738, 48726
644	calneuron 1	395275	799	378690	8787	16775, 24763, 32751, 40739, 48727
645	calneuron 1	395276	800	378691	8788	16776, 24764, 32752, 40740, 48728
646	calneuron 1	405452	801	384354	8789	16777, 24765, 32753, 40741, 48729
647	calneuron 1	412588	802	391882	8790	16778, 24766, 32754, 40742, 48730
648	calneuron 1	431984	803	410704	8791	16779, 24767, 32755, 40743, 48731
649	calneuron 1	446128	804	411806	8792	16780, 24768, 32756, 40744, 48732
650	calpain, small subunit 2	457326	805	400882	8793	16781, 24769, 32757, 40745, 48733
651	calsyntenin 2	458420	806	402460	8794	16782, 24770, 32758, 40746, 48734

652	calsyntenin 3	266546	807	266546	8795	16783, 24771, 32759, 40747, 48735
653	calsyntenin 3	537408	808	440679	8796	16784, 24772, 32760, 40748, 48736
654	calsyntenin 3	541953	809	443959	8797	16785, 24773, 32761, 40749, 48737
655	CaM kinase-like vesicle-associated	296471	810	296471	8798	16786, 24774, 32762, 40750, 48738
656	CaM kinase-like vesicle-associated	477224	811	419195	8799	16787, 24775, 32763, 40751, 48739
657	CaM kinase-like vesicle-associated	488336	812	418809	8800	16788, 24776, 32764, 40752, 48740
658	cAMP responsive element binding protein 3-like 1	288400	813	288400	8801	16789, 24777, 32765, 40753, 48741
659	cAMP responsive element binding protein 3-like 1	446415	814	407420	8802	16790, 24778, 32766, 40754, 48742
660	cAMP responsive element binding protein 3-like 1	529193	815	434939	8803	16791, 24779, 32767, 40755, 48743
661	cAMP responsive element binding protein 3-like 2	330387	816	329140	8804	16792, 24780, 32768, 40756, 48744
662	cAMP responsive element binding protein 3-like 2	417785	817	414123	8805	16793, 24781, 32769, 40757, 48745
663	cAMP responsive element binding protein 3-like 2	452463	818	410314	8806	16794, 24782, 32770, 40758, 48746
664	cAMP responsive element binding protein 3-like 2	456390	819	403550	8807	16795, 24783, 32771, 40759, 48747
665	cAMP responsive element binding protein 3-like 2	544877	820	443915	8808	16796, 24784, 32772, 40760, 48748
666	cancer susceptibility candidate 4	299957	821	299957	8809	16797, 24785, 32773, 40761, 48749
667	cancer susceptibility candidate 4	345795	822	335063	8810	16798, 24786, 32774, 40762, 48750
668	cancer susceptibility candidate 4	360824	823	354067	8811	16799, 24787, 32775, 40763, 48751
669	cancer susceptibility candidate 4	416522	824	411192	8812	16800, 24788, 32776, 40764, 48752

670	cancer susceptibility candidate 4	561305	825	452833	8813	16801, 24789, 32777, 40765, 48753
671	cancer susceptibility candidate 4	561459	826	452807	8814	16802, 24790, 32778, 40766, 48754
672	canopy 2 homolog (zebrafish)	273308	827	273308	8815	16803, 24791, 32779, 40767, 48755
673	canopy 2 homolog (zebrafish)	551475	828	448809	8816	16804, 24792, 32780, 40768, 48756
674	CAP-GLY domain containing linker protein 3	360535	829	353732	8817	16805, 24793, 32781, 40769, 48757
675	CAP-GLY domain containing linker protein 3	534959	830	445491	8818	16806, 24794, 32782, 40770, 48758
676	CAP-GLY domain containing linker protein 3	544037	831	438218	8819	16807, 24795, 32783, 40771, 48759
677	carbohydrate (chondroitin 4) sulfotransferase 11	303694	832	305725	8820	16808, 24796, 32784, 40772, 48760
678	carbohydrate (chondroitin 4) sulfotransferase 11	549260	833	450004	8821	16809, 24797, 32785, 40773, 48761
679	carbohydrate (chondroitin 4) sulfotransferase 12	258711	834	258711	8822	16810, 24798, 32786, 40774, 48762
680	carbohydrate (chondroitin 4) sulfotransferase 12	432336	835	411207	8823	16811, 24799, 32787, 40775, 48763
681	carbohydrate (chondroitin 4) sulfotransferase 13	319340	836	317404	8824	16812, 24800, 32788, 40776, 48764
682	carbohydrate (chondroitin 4) sulfotransferase 13	383575	837	373069	8825	16813, 24801, 32789, 40777, 48765
683	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	338482	838	341206	8826	16814, 24802, 32790, 40778, 48766
684	carbohydrate (N-acetylglucosamine 6-O) sulfotransferase 4	539698	839	441204	8827	16815, 24803, 32791, 40779, 48767
685	carbonic anhydrase VA, mitochondrial	309893	840	309649	8828	16816, 24804, 32792, 40780, 48768
686	carbonyl reductase 4	306193	841	303525	8829	16817, 24805, 32793, 40781, 48769

687	carbonyl reductase 4	504480	842	427615	8830	16818, 24806, 32794, 40782, 48770
688	carboxylesterase 2	317091	843	317842	8831	16819, 24807, 32795, 40783, 48771
689	carboxylesterase 2	417689	844	394452	8832	16820, 24808, 32796, 40784, 48772
690	carcinoembryonic antigen-related cell adhesion molecule 19	403660	845	384887	8833	16821, 24809, 32797, 40785, 48773
691	carcinoembryonic antigen-related cell adhesion molecule 19	358777	846	351627	8834	16822, 24810, 32798, 40786, 48774
692	carcinoembryonic antigen-related cell adhesion molecule 21	187608	847	187608	8835	16823, 24811, 32799, 40787, 48775
693	carcinoembryonic antigen-related cell adhesion molecule 21	401445	848	385739	8836	16824, 24812, 32800, 40788, 48776
694	carcinoembryonic antigen-related cell adhesion molecule 3	221999	849	221999	8837	16825, 24813, 32801, 40789, 48777
695	carcinoembryonic antigen-related cell adhesion molecule 3	344550	850	341725	8838	16826, 24814, 32802, 40790, 48778
696	carcinoembryonic antigen-related cell adhesion molecule 3	357396	851	349971	8839	16827, 24815, 32803, 40791, 48779
697	carcinoembryonic antigen-related cell adhesion molecule 3	389667	852	374318	8840	16828, 24816, 32804, 40792, 48780
698	carcinoembryonic antigen-related cell adhesion molecule 4	221954	853	221954	8841	16829, 24817, 32805, 40793, 48781
699	carcinoembryonic antigen-related cell adhesion molecule 7	6724	854	6724	8842	16830, 24818, 32806, 40794, 48782, 56077, 56110
700	carcinoembryonic antigen-related cell adhesion molecule 7	338196	855	343286	8843	16831, 24819, 32807, 40795, 48783
701	carcinoembryonic antigen-related cell adhesion molecule 7	401731	856	385932	8844	16832, 24820, 32808, 40796, 48784
702	carcinoembryonic antigen-related cell adhesion molecule 7	412062	857	399253	8845	16833, 24821, 32809, 40797, 48785

703	Cas scaffolding protein family member 4	360314	858	353462	8846	16834, 24822, 32810, 40798, 48786
704	Cas scaffolding protein family member 4	371336	859	360387	8847	16835, 24823, 32811, 40799, 48787
705	Cas scaffolding protein family member 4	434344	860	410027	8848	16836, 24824, 32812, 40800, 48788
706	casein kinase 2, beta polypeptide	375880	861	365040	8849	16837, 24825, 32813, 40801, 48789
707	cat eye syndrome chromosome region, candidate 5	155674	862	155674	8850	16838, 24826, 32814, 40802, 48790, 56078, 56111
708	cat eye syndrome chromosome region, candidate 5	336737	863	337358	8851	16839, 24827, 32815, 40803, 48791
709	catechol-O-methyltransferase domain containing 1	372538	864	361616	8852	16840, 24828, 32816, 40804, 48792
710	catechol-O-methyltransferase domain containing 1	536650	865	444168	8853	16841, 24829, 32817, 40805, 48793
711	cathepsin O	433477	866	414904	8854	16842, 24830, 32818, 40806, 48794
712	cation channel, sperm associated 2	299989	867	299989	8855	16843, 24831, 32819, 40807, 48795
713	cation channel, sperm associated 2	321596	868	321463	8856	16844, 24832, 32820, 40808, 48796
714	cation channel, sperm associated 2	354127	869	339137	8857	16845, 24833, 32821, 40809, 48797
715	cation channel, sperm associated 2	355438	870	347613	8858	16846, 24834, 32822, 40810, 48798
716	cation channel, sperm associated 2	396879	871	380088	8859	16847, 24835, 32823, 40811, 48799
717	cation channel, sperm associated 2	409481	872	386595	8860	16848, 24836, 32824, 40812, 48800
718	cation channel, sperm associated 2	419473	873	399035	8861	16849, 24837, 32825, 40813, 48801
719	cation channel, sperm associated 2	432420	874	407694	8862	16850, 24838, 32826, 40814, 48802

720	CCZ1 vacuolar protein trafficking and biogenesis associated homolog (S. cerevisiae)	325974	875	325681	8863	16851, 24839, 32827, 40815, 48803
721	CCZ1 vacuolar protein trafficking and biogenesis associated homolog (S. cerevisiae)	537980	876	444661	8864	16852, 24840, 32828, 40816, 48804
722	CCZ1 vacuolar protein trafficking and biogenesis associated homolog B (S. cerevisiae)	316731	877	314544	8865	16853, 24841, 32829, 40817, 48805
723	CCZ1 vacuolar protein trafficking and biogenesis associated homolog B (S. cerevisiae)	538180	878	444720	8866	16854, 24842, 32830, 40818, 48806
724	CD101 molecule	256652	879	256652	8867	16855, 24843, 32831, 40819, 48807
725	CD101 molecule	369470	880	358482	8868	16856, 24844, 32832, 40820, 48808
726	CD160 molecule	235933	881	235933	8869	16857, 24845, 32833, 40821, 48809
727	CD160 molecule	369288	882	358294	8870	16858, 24846, 32834, 40822, 48810
728	CD160 molecule	369290	883	358296	8871	16859, 24847, 32835, 40823, 48811
729	CD160 molecule	401557	884	385199	8872	16860, 24848, 32836, 40824, 48812
730	CD164 sialomucin-like 2	374025	885	363137	8873	16861, 24849, 32837, 40825, 48813
731	CD164 sialomucin-like 2	374027	886	363139	8874	16862, 24850, 32838, 40826, 48814
732	CD164 sialomucin-like 2	374030	887	363142	8875	16863, 24851, 32839, 40827, 48815
733	CD180 molecule	256447	888	256447	8876	16864, 24852, 32840, 40828, 48816
734	CD200 receptor 1-like	398214	889	381272	8877	16865, 24853, 32841, 40829, 48817

735	CD200 receptor 1-like	448932	890	415132	8878	16866, 24854, 32842, 40830, 48818
736	CD200 receptor 1-like	488794	891	418413	8879	16867, 24855, 32843, 40831, 48819
737	CD274 molecule	381573	892	370985	8880	16868, 24856, 32844, 40832, 48820
738	CD274 molecule	381577	893	370989	8881	16869, 24857, 32845, 40833, 48821
739	CD300 molecule-like family member d	375352	894	364501	8882	16870, 24858, 32846, 40834, 48822
740	CD300 molecule-like family member g	293396	895	293396	8883	16871, 24859, 32847, 40835, 48823
741	CD300 molecule-like family member g	317310	896	321005	8884	16872, 24860, 32848, 40836, 48824
742	CD300 molecule-like family member g	377203	897	366408	8885	16873, 24861, 32849, 40837, 48825
743	CD300 molecule-like family member g	539718	898	442368	8886	16874, 24862, 32850, 40838, 48826
744	CD300a molecule	310828	899	308188	8887	16875, 24863, 32851, 40839, 48827
745	CD300a molecule	360141	900	353259	8888	16876, 24864, 32852, 40840, 48828
746	CD300a molecule	361933	901	354564	8889	16877, 24865, 32853, 40841, 48829
747	CD300a molecule	392625	902	376401	8890	16878, 24866, 32854, 40842, 48830
748	CD300c molecule	330793	903	329507	8891	16879, 24867, 32855, 40843, 48831
749	CD300e molecule	328630	904	329942	8892	16880, 24868, 32856, 40844, 48832
750	CD300e molecule	392619	905	376395	8893	16881, 24869, 32857, 40845, 48833
751	CD300e molecule	412268	906	415488	8894	16882, 24870, 32858, 40846, 48834
752	CD300e molecule	426295	907	416642	8895	16883, 24871, 32859, 40847, 48835

753	CD36 molecule (thrombospondin receptor)	441034	908	396258	8896	16884, 24872, 32860, 40848, 48836
754	CD52 molecule	374213	909	363330	8897	16885, 24873, 32861, 40849, 48837
755	CD84 molecule	311224	910	312367	8898	16886, 24874, 32862, 40850, 48838
756	CD84 molecule	360056	911	353163	8899	16887, 24875, 32863, 40851, 48839
757	CD84 molecule	368047	912	357026	8900	16888, 24876, 32864, 40852, 48840
758	CD84 molecule	368048	913	357027	8901	16889, 24877, 32865, 40853, 48841
759	CD84 molecule	368051	914	357030	8902	16890, 24878, 32866, 40854, 48842
760	CD84 molecule	368054	915	357033	8903	16891, 24879, 32867, 40855, 48843
761	CD84 molecule	534968	916	442845	8904	16892, 24880, 32868, 40856, 48844
762	CD93 molecule	246006	917	246006	8905	16893, 24881, 32869, 40857, 48845
763	CD93 molecule	413585	918	414935	8906	16894, 24882, 32870, 40858, 48846
764	CDC42 effector protein (Rho GTPase binding) 5	301200	919	301200	8907	16895, 24883, 32871, 40859, 48847
765	CDC42 small effector 1	357235	920	349773	8908	16896, 24884, 32872, 40860, 48848
766	CDC42 small effector 1	540998	921	445647	8909	16897, 24885, 32873, 40861, 48849
767	CDC42 small effector 2	360515	922	353706	8910	16898, 24886, 32874, 40862, 48850
768	CDC42 small effector 2	395246	923	378667	8911	16899, 24887, 32875, 40863, 48851
769	CDC42 small effector 2	505065	924	427421	8912	16900, 24888, 32876, 40864, 48852
770	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	219789	925	219789	8913	16901, 24889, 32877, 40865, 48853

771	CDP-diacylglycerol--inositol 3-phosphatidyltransferase	403894	926	386065	8914	16902, 24890, 32878, 40866, 48854
772	cell adhesion molecule 2	383699	927	373200	8915	16903, 24891, 32879, 40867, 48855
773	cell adhesion molecule 2	405615	928	384193	8916	16904, 24892, 32880, 40868, 48856
774	cell adhesion molecule 2	407528	929	384575	8917	16905, 24893, 32881, 40869, 48857
775	cell adhesion molecule 3	368124	930	357106	8918	16906, 24894, 32882, 40870, 48858
776	cell adhesion molecule 3	368125	931	357107	8919	16907, 24895, 32883, 40871, 48859
777	cell adhesion molecule 3	416746	932	387802	8920	16908, 24896, 32884, 40872, 48860
778	cell cycle associated protein 1	341394	933	340329	8921	16909, 24897, 32885, 40873, 48861
779	cell cycle associated protein 1	532820	934	434150	8922	16910, 24898, 32886, 40874, 48862
780	cell cycle associated protein 1	389645	935	374296	8923	16911, 24899, 32887, 40875, 48863
781	cell cycle progression 1	310958	936	311656	8924	16912, 24900, 32888, 40876, 48864
782	cell cycle progression 1	425574	937	415128	8925	16913, 24901, 32889, 40877, 48865
783	cell cycle progression 1	442196	938	403400	8926	16914, 24902, 32890, 40878, 48866
784	cell death-inducing DFFA-like effector c	336832	939	338642	8927	16915, 24903, 32891, 40879, 48867
785	cell death-inducing DFFA-like effector c	383817	940	373328	8928	16916, 24904, 32892, 40880, 48868
786	cell death-inducing DFFA-like effector c	423850	941	400649	8929	16917, 24905, 32893, 40881, 48869
787	cell death-inducing DFFA-like effector c	455015	942	392975	8930	16918, 24906, 32894, 40882, 48870
788	cell death-inducing DFFA-like effector c	430427	943	408631	8931	16919, 24907, 32895, 40883, 48871

789	cell wall biogenesis 43 C-terminal homolog (S. cerevisiae)	226432	944	226432	8932	16920, 24908, 32896, 40884, 48872
790	centrin, EF-hand protein, 3	283122	945	283122	8933	16921, 24909, 32897, 40885, 48873
791	ceramide kinase	216264	946	216264	8934	16922, 24910, 32898, 40886, 48874
792	ceramide kinase	541677	947	438659	8935	16923, 24911, 32899, 40887, 48875
793	ceramide synthase 1	427170	948	402697	8936	16924, 24912, 32900, 40888, 48876
794	ceramide synthase 1	429504	949	389044	8937	16925, 24913, 32901, 40889, 48877
795	ceramide synthase 1	542296	950	437648	8938	16926, 24914, 32902, 40890, 48878
796	ceramide synthase 2	271688	951	271688	8939	16927, 24915, 32903, 40891, 48879
797	ceramide synthase 2	345896	952	337842	8940	16928, 24916, 32904, 40892, 48880
798	ceramide synthase 2	361419	953	355020	8941	16929, 24917, 32905, 40893, 48881
799	ceramide synthase 2	368949	954	357945	8942	16930, 24918, 32906, 40894, 48882
800	ceramide synthase 2	368954	955	357950	8943	16931, 24919, 32907, 40895, 48883
801	ceramide synthase 2	421609	956	393239	8944	16932, 24920, 32908, 40896, 48884
802	ceramide synthase 2	457392	957	394012	8945	16933, 24921, 32909, 40897, 48885
803	ceramide synthase 2	558062	958	452810	8946	16934, 24922, 32910, 40898, 48886
804	ceramide synthase 3	284382	959	284382	8947	16935, 24923, 32911, 40899, 48887
805	ceramide synthase 3	394113	960	377672	8948	16936, 24924, 32912, 40900, 48888
806	ceramide synthase 3	538112	961	437640	8949	16937, 24925, 32913, 40901, 48889

807	ceramide synthase 3	558884	962	453816	8950	16938, 24926, 32914, 40902, 48890
808	ceramide synthase 3	559639	963	453598	8951	16939, 24927, 32915, 40903, 48891
809	ceramide synthase 3	560233	964	452661	8952	16940, 24928, 32916, 40904, 48892
810	ceramide synthase 4	251363	965	251363	8953	16941, 24929, 32917, 40905, 48893
811	ceramide synthase 4	558268	966	453388	8954	16942, 24930, 32918, 40906, 48894
812	ceramide synthase 4	558877	967	454122	8955	16943, 24931, 32919, 40907, 48895
813	ceramide synthase 4	559450	968	453509	8956	16944, 24932, 32920, 40908, 48896
814	ceramide synthase 4	560412	969	452920	8957	16945, 24933, 32921, 40909, 48897
815	ceramide synthase 4	561008	970	453796	8958	16946, 24934, 32922, 40910, 48898
816	ceramide synthase 5	317551	971	325485	8959	16947, 24935, 32923, 40911, 48899
817	ceramide synthase 5	380189	972	369536	8960	16948, 24936, 32924, 40912, 48900
818	ceramide synthase 5	422340	973	389050	8961	16949, 24937, 32925, 40913, 48901
819	ceramide synthase 5	542320	974	442918	8962	16950, 24938, 32926, 40914, 48902
820	ceramide synthase 6	305747	975	306579	8963	16951, 24939, 32927, 40915, 48903
821	ceramide synthase 6	392687	976	376453	8964	16952, 24940, 32928, 40916, 48904
822	cerebellin 2 precursor	269503	977	269503	8965	16953, 24941, 32929, 40917, 48905
823	cerebral endothelial cell adhesion molecule	372838	978	361929	8966	16954, 24942, 32930, 40918, 48906
824	cerebral endothelial cell adhesion molecule	372842	979	361933	8967	16955, 24943, 32931, 40919, 48907

825	cerebral endothelial cell adhesion molecule	411852	980	403766	8968	16956, 24944, 32932, 40920, 48908
826	cerebral endothelial cell adhesion molecule	413863	981	388593	8969	16957, 24945, 32933, 40921, 48909
827	cerebral endothelial cell adhesion molecule	420034	982	402508	8970	16958, 24946, 32934, 40922, 48910
828	cerebral endothelial cell adhesion molecule	420512	983	416676	8971	16959, 24947, 32935, 40923, 48911
829	cerebral endothelial cell adhesion molecule	447915	984	402928	8972	16960, 24948, 32936, 40924, 48912
830	CGRP receptor component	338592	985	340044	8973	16961, 24949, 32937, 40925, 48913
831	CGRP receptor component	395326	986	378736	8974	16962, 24950, 32938, 40926, 48914
832	CGRP receptor component	398684	987	381674	8975	16963, 24951, 32939, 40927, 48915
833	CGRP receptor component	415001	988	398605	8976	16964, 24952, 32940, 40928, 48916
834	CGRP receptor component	431089	989	388653	8977	16965, 24953, 32941, 40929, 48917
835	charged multivesicular body protein 4C	297265	990	297265	8978	16966, 24954, 32942, 40930, 48918
836	chloride channel CLIC-like 1	302500	991	306552	8979	16967, 24955, 32943, 40931, 48919
837	chloride channel CLIC-like 1	348264	992	337243	8980	16968, 24956, 32944, 40932, 48920
838	chloride channel CLIC-like 1	356970	993	349456	8981	16969, 24957, 32945, 40933, 48921
839	chloride channel CLIC-like 1	369968	994	358985	8982	16970, 24958, 32946, 40934, 48922
840	chloride channel CLIC-like 1	369969	995	358986	8983	16971, 24959, 32947, 40935, 48923
841	chloride channel CLIC-like 1	369970	996	358987	8984	16972, 24960, 32948, 40936, 48924
842	chloride channel CLIC-like 1	369971	997	358988	8985	16973, 24961, 32949, 40937, 48925

843	chloride channel CLIC-like 1	369976	998	358993	8986	16974, 24962, 32950, 40938, 48926
844	chloride channel CLIC-like 1	415331	999	411591	8987	16975, 24963, 32951, 40939, 48927
845	chloride intracellular channel 1	375779	1000	364934	8988	16976, 24964, 32952, 40940, 48928
846	chloride intracellular channel 1	375780	1001	364935	8989	16977, 24965, 32953, 40941, 48929
847	chloride intracellular channel 1	375784	1002	364940	8990	16978, 24966, 32954, 40942, 48930
848	chloride intracellular channel 1	383404	1003	372896	8991	16979, 24967, 32955, 40943, 48931
849	chloride intracellular channel 1	383405	1004	372897	8992	16980, 24968, 32956, 40944, 48932
850	chloride intracellular channel 1	395892	1005	379229	8993	16981, 24969, 32957, 40945, 48933
851	chloride intracellular channel 1	400052	1006	382926	8994	16982, 24970, 32958, 40946, 48934
852	chloride intracellular channel 1	400058	1007	382931	8995	16983, 24971, 32959, 40947, 48935
853	chloride intracellular channel 1	415179	1008	409247	8996	16984, 24972, 32960, 40948, 48936
854	chloride intracellular channel 1	418285	1009	407791	8997	16985, 24973, 32961, 40949, 48937
855	chloride intracellular channel 1	420458	1010	410965	8998	16986, 24974, 32962, 40950, 48938
856	chloride intracellular channel 1	422167	1011	407429	8999	16987, 24975, 32963, 40951, 48939
857	chloride intracellular channel 1	423055	1012	406968	9000	16988, 24976, 32964, 40952, 48940
858	chloride intracellular channel 1	423143	1013	404589	9001	16989, 24977, 32965, 40953, 48941
859	chloride intracellular channel 1	423804	1014	409979	9002	16990, 24978, 32966, 40954, 48942
860	chloride intracellular channel 1	425464	1015	401292	9003	16991, 24979, 32967, 40955, 48943

861	chloride intracellular channel 1	431921	1016	408357	9004	16992, 24980, 32968, 40956, 48944
862	chloride intracellular channel 1	433916	1017	391395	9005	16993, 24981, 32969, 40957, 48945
863	chloride intracellular channel 1	434202	1018	400532	9006	16994, 24982, 32970, 40958, 48946
864	chloride intracellular channel 1	435242	1019	412217	9007	16995, 24983, 32971, 40959, 48947
865	chloride intracellular channel 1	438708	1020	406088	9008	16996, 24984, 32972, 40960, 48948
866	chloride intracellular channel 1	442045	1021	400280	9009	16997, 24985, 32973, 40961, 48949
867	chloride intracellular channel 1	447338	1022	413330	9010	16998, 24986, 32974, 40962, 48950
868	chloride intracellular channel 1	447369	1023	408094	9011	16999, 24987, 32975, 40963, 48951
869	chloride intracellular channel 1	451546	1024	416211	9012	17000, 24988, 32976, 40964, 48952
870	chloride intracellular channel 1	456863	1025	406335	9013	17001, 24989, 32977, 40965, 48953
871	chloride intracellular channel 1	457485	1026	398056	9014	17002, 24990, 32978, 40966, 48954
872	chloride intracellular channel 2	369449	1027	358460	9015	17003, 24991, 32979, 40967, 48955
873	chloride intracellular channel 4	374379	1028	363500	9016	17004, 24992, 32980, 40968, 48956
874	chloride intracellular channel 4	444041	1029	445699	9017	17005, 24993, 32981, 40969, 48957
875	chloride intracellular channel 4	488683	1030	436538	9018	17006, 24994, 32982, 40970, 48958
876	chloride intracellular channel 6	349499	1031	290332	9019	17007, 24995, 32983, 40971, 48959
877	chloride intracellular channel 6	360731	1032	353959	9020	17008, 24996, 32984, 40972, 48960
878	choline dehydrogenase	315251	1033	319851	9021	17009, 24997, 32985, 40973, 48961

879	choline dehydrogenase	467802	1034	419863	9022	17010, 24998, 32986, 40974, 48962
880	choline dehydrogenase	481668	1035	418273	9023	17011, 24999, 32987, 40975, 48963
881	choline phosphotransferase 1	229266	1036	229266	9024	17012, 25000, 32988, 40976, 48964
882	choline phosphotransferase 1	543999	1037	444102	9025	17013, 25001, 32989, 40977, 48965
883	choline/ethanolamine phosphotransferase 1	357172	1038	349696	9026	17014, 25002, 32990, 40978, 48966
884	choline/ethanolamine phosphotransferase 1	545121	1039	441980	9027	17015, 25003, 32991, 40979, 48967
885	chondroitin sulfate N-acetylgalactosaminyl transferase 1	311540	1040	310891	9028	17016, 25004, 32992, 40980, 48968
886	chondroitin sulfate N-acetylgalactosaminyl transferase 1	332246	1041	330805	9029	17017, 25005, 32993, 40981, 48969
887	chondroitin sulfate N-acetylgalactosaminyl transferase 1	454498	1042	411816	9030	17018, 25006, 32994, 40982, 48970
888	chondroitin sulfate N-acetylgalactosaminyl transferase 1	517494	1043	429130	9031	17019, 25007, 32995, 40983, 48971
889	chondroitin sulfate N-acetylgalactosaminyl transferase 1	520003	1044	428774	9032	17020, 25008, 32996, 40984, 48972
890	chondroitin sulfate N-acetylgalactosaminyl transferase 1	522854	1045	429809	9033	17021, 25009, 32997, 40985, 48973
891	chondroitin sulfate N-acetylgalactosaminyl transferase 1	523262	1046	428089	9034	17022, 25010, 32998, 40986, 48974
892	chondroitin sulfate N-acetylgalactosaminyl transferase 1	524213	1047	427740	9035	17023, 25011, 32999, 40987, 48975
893	chondroitin sulfate N-acetylgalactosaminyl transferase 1	544602	1048	442155	9036	17024, 25012, 33000, 40988, 48976

894	chondroitin sulfate N-acetylgalactosaminyl transferase 2	374464	1049	363588	9037	17025, 25013, 33001, 40989, 48977
895	chondroitin sulfate N-acetylgalactosaminyl transferase 2	374466	1050	363590	9038	17026, 25014, 33002, 40990, 48978
896	chondroitin sulfate proteoglycan 5 (neuroglycan C)	264723	1051	264723	9039	17027, 25015, 33003, 40991, 48979
897	chondroitin sulfate proteoglycan 5 (neuroglycan C)	383738	1052	373244	9040	17028, 25016, 33004, 40992, 48980
898	chondroitin sulfate proteoglycan 5 (neuroglycan C)	456150	1053	392096	9041	17029, 25017, 33005, 40993, 48981
899	chondrolectin	299295	1054	299295	9042	17030, 25018, 33006, 40994, 48982
900	chondrolectin	338326	1055	339975	9043	17031, 25019, 33007, 40995, 48983
901	chondrolectin	400127	1056	382992	9044	17032, 25020, 33008, 40996, 48984
902	chondrolectin	400128	1057	382993	9045	17033, 25021, 33009, 40997, 48985
903	chondrolectin	400131	1058	382996	9046	17034, 25022, 33010, 40998, 48986
904	chondrolectin	400135	1059	383001	9047	17035, 25023, 33011, 40999, 48987
905	chondrolectin	427223	1060	390957	9048	17036, 25024, 33012, 41000, 48988
906	chondrolectin	452759	1061	415566	9049	17037, 25025, 33013, 41001, 48989
907	chondrolectin	465099	1062	417423	9050	17038, 25026, 33014, 41002, 48990
908	chondrolectin	543733	1063	443566	9051	17039, 25027, 33015, 41003, 48991
909	CHRNA7 (cholinergic receptor, nicotinic, alpha 7, exons 5-10) and FAM7A (family with sequence similarity 7A, exons A-E) fusion	299847	1064	299847	9052	17040, 25028, 33016, 41004, 48992

910	CHRNA7 (cholinergic receptor, nicotinic, alpha 7, exons 5-10) and FAM7A (family with sequence similarity 7A, exons A-E) fusion	397827	1065	380927	9053	17041, 25029, 33017, 41005, 48993
911	CHRNA7 (cholinergic receptor, nicotinic, alpha 7, exons 5-10) and FAM7A (family with sequence similarity 7A, exons A-E) fusion	401522	1066	385389	9054	17042, 25030, 33018, 41006, 48994
912	chromodomain protein, Y-linked, 2A	250838	1067	250838	9055	17043, 25031, 33019, 41007, 48995
913	chromodomain protein, Y-linked, 2A	426790	1068	402280	9056	17044, 25032, 33020, 41008, 48996
914	chromosome 1 open reading frame 101	366531	1069	355489	9057	17045, 25033, 33021, 41009, 48997
915	chromosome 1 open reading frame 101	366533	1070	355491	9058	17046, 25034, 33022, 41010, 48998
916	chromosome 1 open reading frame 101	366534	1071	355492	9059	17047, 25035, 33023, 41011, 48999
917	chromosome 1 open reading frame 101	391841	1072	375716	9060	17048, 25036, 33024, 41012, 49000
918	chromosome 1 open reading frame 101	428042	1073	395796	9061	17049, 25037, 33025, 41013, 49001
919	chromosome 1 open reading frame 130	374392	1074	363513	9062	17050, 25038, 33026, 41014, 49002
920	chromosome 1 open reading frame 159	294576	1075	294576	9063	17051, 25039, 33027, 41015, 49003
921	chromosome 1 open reading frame 159	379319	1076	368623	9064	17052, 25040, 33028, 41016, 49004
922	chromosome 1 open reading frame 159	379339	1077	368644	9065	17053, 25041, 33029, 41017, 49005
923	chromosome 1 open reading frame 159	421241	1078	400736	9066	17054, 25042, 33030, 41018, 49006
924	chromosome 1 open reading frame 159	437760	1079	399027	9067	17055, 25043, 33031, 41019, 49007

925	chromosome 1 open reading frame 159	442117	1080	416740	9068	17056, 25044, 33032, 41020, 49008
926	chromosome 1 open reading frame 159	448924	1081	392290	9069	17057, 25045, 33033, 41021, 49009
927	chromosome 1 open reading frame 159	457999	1082	414929	9070	17058, 25046, 33034, 41022, 49010
928	chromosome 1 open reading frame 162	343534	1083	344218	9071	17059, 25047, 33035, 41023, 49011
929	chromosome 1 open reading frame 162	369718	1084	358732	9072	17060, 25048, 33036, 41024, 49012
930	chromosome 1 open reading frame 185	371759	1085	360824	9073	17061, 25049, 33037, 41025, 49013
931	chromosome 1 open reading frame 186	331555	1086	356093	9074	17062, 25050, 33038, 41026, 49014
932	chromosome 1 open reading frame 210	423420	1087	429399	9075	17063, 25051, 33039, 41027, 49015
933	chromosome 1 open reading frame 210	523677	1088	430918	9076	17064, 25052, 33040, 41028, 49016
934	chromosome 1 open reading frame 27	287859	1089	287859	9077	17065, 25053, 33041, 41029, 49017
935	chromosome 1 open reading frame 27	367470	1090	356440	9078	17066, 25054, 33042, 41030, 49018
936	chromosome 1 open reading frame 27	419367	1091	395084	9079	17067, 25055, 33043, 41031, 49019
937	chromosome 1 open reading frame 27	432021	1092	402029	9080	17068, 25056, 33044, 41032, 49020
938	chromosome 1 open reading frame 31	366612	1093	355571	9081	17069, 25057, 33045, 41033, 49021
939	chromosome 1 open reading frame 31	366613	1094	355572	9082	17070, 25058, 33046, 41034, 49022
940	chromosome 1 open reading frame 31	366615	1095	355574	9083	17071, 25059, 33047, 41035, 49023
941	chromosome 1 open reading frame 31	424237	1096	392376	9084	17072, 25060, 33048, 41036, 49024
942	chromosome 1 open reading frame 43	350592	1097	271925	9085	17073, 25061, 33049, 41037, 49025

943	chromosome 1 open reading frame 43	362076	1098	354496	9086	17074, 25062, 33050, 41038, 49026
944	chromosome 1 open reading frame 43	368516	1099	357502	9087	17075, 25063, 33051, 41039, 49027
945	chromosome 1 open reading frame 43	368518	1100	357504	9088	17076, 25064, 33052, 41040, 49028
946	chromosome 1 open reading frame 43	368519	1101	357505	9089	17077, 25065, 33053, 41041, 49029
947	chromosome 1 open reading frame 43	368521	1102	357507	9090	17078, 25066, 33054, 41042, 49030
948	chromosome 1 open reading frame 85	362007	1103	354553	9091	17079, 25067, 33055, 41043, 49031
949	chromosome 1 open reading frame 9	263688	1104	263688	9092	17080, 25068, 33056, 41044, 49032
950	chromosome 1 open reading frame 9	367723	1105	356696	9093	17081, 25069, 33057, 41045, 49033
951	chromosome 1 open reading frame 94	373374	1106	362472	9094	17082, 25070, 33058, 41046, 49034
952	chromosome 1 open reading frame 94	488417	1107	435634	9095	17083, 25071, 33059, 41047, 49035
953	chromosome 1 open reading frame 95	366788	1108	355752	9096	17084, 25072, 33060, 41048, 49036
954	chromosome 1 open reading frame 95	366789	1109	355753	9097	17085, 25073, 33061, 41049, 49037
955	chromosome 10 open reading frame 10	298295	1110	298295	9098	17086, 25074, 33062, 41050, 49038
956	chromosome 10 open reading frame 10	432283	1111	392803	9099	17087, 25075, 33063, 41051, 49039
957	chromosome 10 open reading frame 10	448778	1112	414494	9100	17088, 25076, 33064, 41052, 49040
958	chromosome 10 open reading frame 105	398786	1113	381766	9101	17089, 25077, 33065, 41053, 49041
959	chromosome 10 open reading frame 105	441508	1114	403151	9102	17090, 25078, 33066, 41054, 49042
960	chromosome 10 open reading frame 105	545760	1115	440187	9103	17091, 25079, 33067, 41055, 49043

961	chromosome 10 open reading frame 111	378207	1116	367449	9104	17092, 25080, 33068, 41056, 49044
962	chromosome 10 open reading frame 112	377265	1117	366476	9105	17093, 25081, 33069, 41057, 49045
963	chromosome 10 open reading frame 112	377266	1118	366477	9106	17094, 25082, 33070, 41058, 49046
964	chromosome 10 open reading frame 112	441070	1119	404330	9107	17095, 25083, 33071, 41059, 49047
965	chromosome 10 open reading frame 112	454679	1120	412763	9108	17096, 25084, 33072, 41060, 49048
966	chromosome 10 open reading frame 112	455457	1121	391253	9109	17097, 25085, 33073, 41061, 49049
967	chromosome 10 open reading frame 128	474718	1122	417246	9110	17098, 25086, 33074, 41062, 49050
968	chromosome 10 open reading frame 129	341686	1123	340296	9111	17099, 25087, 33075, 41063, 49051
969	chromosome 10 open reading frame 129	394005	1124	377573	9112	17100, 25088, 33076, 41064, 49052
970	chromosome 10 open reading frame 129	430183	1125	400368	9113	17101, 25089, 33077, 41065, 49053
971	chromosome 10 open reading frame 129	539707	1126	438774	9114	17102, 25090, 33078, 41066, 49054
972	chromosome 10 open reading frame 35	373279	1127	362376	9115	17103, 25091, 33079, 41067, 49055
973	chromosome 10 open reading frame 35	421716	1128	398621	9116	17104, 25092, 33080, 41068, 49056
974	chromosome 10 open reading frame 54	263569	1129	263569	9117	17105, 25093, 33081, 41069, 49057
975	chromosome 10 open reading frame 54	394957	1130	378409	9118	17106, 25094, 33082, 41070, 49058
976	chromosome 10 open reading frame 57	372273	1131	361347	9119	17107, 25095, 33083, 41071, 49059
977	chromosome 10 open reading frame 57	372274	1132	361348	9120	17108, 25096, 33084, 41072, 49060
978	chromosome 10 open reading frame 57	372275	1133	361349	9121	17109, 25097, 33085, 41073, 49061

979	chromosome 10 open reading frame 57	372277	1134	361351	9122	17110, 25098, 33086, 41074, 49062
980	chromosome 10 open reading frame 57	372281	1135	361355	9123	17111, 25099, 33087, 41075, 49063
981	chromosome 10 open reading frame 57	450179	1136	393450	9124	17112, 25100, 33088, 41076, 49064
982	chromosome 10 open reading frame 76	263485	1137	263485	9125	17113, 25101, 33089, 41077, 49065
983	chromosome 10 open reading frame 76	311122	1138	312408	9126	17114, 25102, 33090, 41078, 49066
984	chromosome 10 open reading frame 76	370033	1139	359050	9127	17115, 25103, 33091, 41079, 49067
985	chromosome 10 open reading frame 76	456149	1140	413473	9128	17116, 25104, 33092, 41080, 49068
986	chromosome 11 open reading frame 10	257262	1141	257262	9129	17117, 25105, 33093, 41081, 49069
987	chromosome 11 open reading frame 10	537328	1142	443216	9130	17118, 25106, 33094, 41082, 49070
988	chromosome 11 open reading frame 2	279281	1143	279281	9131	17119, 25107, 33095, 41083, 49071
989	chromosome 11 open reading frame 87	327419	1144	331581	9132	17120, 25108, 33096, 41084, 49072
990	chromosome 12 open reading frame 10	267103	1145	267103	9133	17121, 25109, 33097, 41085, 49073
991	chromosome 12 open reading frame 10	545214	1146	437921	9134	17122, 25110, 33098, 41086, 49074
992	chromosome 12 open reading frame 23	280756	1147	280756	9135	17123, 25111, 33099, 41087, 49075
993	chromosome 12 open reading frame 23	547081	1148	449106	9136	17124, 25112, 33100, 41088, 49076
994	chromosome 12 open reading frame 23	547242	1149	446537	9137	17125, 25113, 33101, 41089, 49077
995	chromosome 12 open reading frame 23	548125	1150	449785	9138	17126, 25114, 33102, 41090, 49078
996	chromosome 12 open reading frame 23	550344	1151	446717	9139	17127, 25115, 33103, 41091, 49079

997	chromosome 12 open reading frame 23	551813	1152	450350	9140	17128, 25116, 33104, 41092, 49080
998	chromosome 12 open reading frame 51	377560	1153	366783	9141	17129, 25117, 33105, 41093, 49081
999	chromosome 12 open reading frame 51	430131	1154	404379	9142	17130, 25118, 33106, 41094, 49082
1000	chromosome 12 open reading frame 53	320591	1155	317818	9143	17131, 25119, 33107, 41095, 49083
1001	chromosome 12 open reading frame 53	439553	1156	391992	9144	17132, 25120, 33108, 41096, 49084
1002	chromosome 12 open reading frame 53	534837	1157	443919	9145	17133, 25121, 33109, 41097, 49085
1003	chromosome 12 open reading frame 53	540656	1158	442157	9146	17134, 25122, 33110, 41098, 49086
1004	chromosome 12 open reading frame 59	298530	1159	298530	9147	17135, 25123, 33111, 41099, 49087
1005	chromosome 12 open reading frame 59	381923	1160	371348	9148	17136, 25124, 33112, 41100, 49088
1006	chromosome 12 open reading frame 59	536952	1161	446102	9149	17137, 25125, 33113, 41101, 49089
1007	chromosome 12 open reading frame 59	543484	1162	445582	9150	17138, 25126, 33114, 41102, 49090
1008	chromosome 12 open reading frame 62	317943	1163	326052	9151	17139, 25127, 33115, 41103, 49091
1009	chromosome 12 open reading frame 62	548985	1164	447776	9152	17140, 25128, 33116, 41104, 49092
1010	chromosome 12 open reading frame 62	550487	1165	446524	9153	17141, 25129, 33117, 41105, 49093
1011	chromosome 12 open reading frame 62	550654	1166	450331	9154	17142, 25130, 33118, 41106, 49094
1012	chromosome 12 open reading frame 69	316048	1167	381895	9155	17143, 25131, 33119, 41107, 49095
1013	chromosome 13 open reading frame 16	283547	1168	283547	9156	17144, 25132, 33120, 41108, 49096
1014	chromosome 13 open reading frame 44	400419	1169	383270	9157	17145, 25133, 33121, 41109, 49097

1015	chromosome 14 open reading frame 101	261556	1170	261556	9158	17146, 25134, 33122, 41110, 49098
1016	chromosome 14 open reading frame 101	536419	1171	438742	9159	17147, 25135, 33123, 41111, 49099
1017	chromosome 14 open reading frame 101	538838	1172	441934	9160	17148, 25136, 33124, 41112, 49100
1018	chromosome 14 open reading frame 109	283534	1173	283534	9161	17149, 25137, 33125, 41113, 49101
1019	chromosome 14 open reading frame 109	415050	1174	388431	9162	17150, 25138, 33126, 41114, 49102
1020	chromosome 14 open reading frame 132	421193	1175	440920	9163	17151, 25139, 33127, 41115, 49103
1021	chromosome 14 open reading frame 132	555004	1176	451731	9164	17152, 25140, 33128, 41116, 49104
1022	chromosome 14 open reading frame 135	317623	1177	317396	9165	17153, 25141, 33129, 41117, 49105
1023	chromosome 14 open reading frame 135	404681	1178	385713	9166	17154, 25142, 33130, 41118, 49106
1024	chromosome 14 open reading frame 135	406854	1179	384801	9167	17155, 25143, 33131, 41119, 49107
1025	chromosome 14 open reading frame 135	535349	1180	445644	9168	17156, 25144, 33132, 41120, 49108
1026	chromosome 14 open reading frame 135	555740	1181	450441	9169	17157, 25145, 33133, 41121, 49109
1027	chromosome 14 open reading frame 159	256324	1182	256324	9170	17158, 25146, 33134, 41122, 49110
1028	chromosome 14 open reading frame 159	298858	1183	298858	9171	17159, 25147, 33135, 41123, 49111
1029	chromosome 14 open reading frame 159	412671	1184	404196	9172	17160, 25148, 33136, 41124, 49112
1030	chromosome 14 open reading frame 159	428926	1185	404343	9173	17161, 25149, 33137, 41125, 49113
1031	chromosome 14 open reading frame 159	517362	1186	429806	9174	17162, 25150, 33138, 41126, 49114
1032	chromosome 14 open reading frame 159	517518	1187	428652	9175	17163, 25151, 33139, 41127, 49115

1033	chromosome 14 open reading frame 159	518665	1188	429098	9176	17164, 25152, 33140, 41128, 49116
1034	chromosome 14 open reading frame 159	518868	1189	428263	9177	17165, 25153, 33141, 41129, 49117
1035	chromosome 14 open reading frame 159	518871	1190	429189	9178	17166, 25154, 33142, 41130, 49118
1036	chromosome 14 open reading frame 159	519950	1191	428296	9179	17167, 25155, 33143, 41131, 49119
1037	chromosome 14 open reading frame 159	520328	1192	429453	9180	17168, 25156, 33144, 41132, 49120
1038	chromosome 14 open reading frame 159	521064	1193	429392	9181	17169, 25157, 33145, 41133, 49121
1039	chromosome 14 open reading frame 159	521077	1194	430137	9182	17170, 25158, 33146, 41134, 49122
1040	chromosome 14 open reading frame 159	521081	1195	428997	9183	17171, 25159, 33147, 41135, 49123
1041	chromosome 14 open reading frame 159	521334	1196	430022	9184	17172, 25160, 33148, 41136, 49124
1042	chromosome 14 open reading frame 159	522170	1197	430666	9185	17173, 25161, 33149, 41137, 49125
1043	chromosome 14 open reading frame 159	522322	1198	427953	9186	17174, 25162, 33150, 41138, 49126
1044	chromosome 14 open reading frame 159	522837	1199	427971	9187	17175, 25163, 33151, 41139, 49127
1045	chromosome 14 open reading frame 159	523771	1200	429655	9188	17176, 25164, 33152, 41140, 49128
1046	chromosome 14 open reading frame 159	523816	1201	428974	9189	17177, 25165, 33153, 41141, 49129
1047	chromosome 14 open reading frame 159	523879	1202	428122	9190	17178, 25166, 33154, 41142, 49130
1048	chromosome 14 open reading frame 159	523894	1203	429459	9191	17179, 25167, 33155, 41143, 49131
1049	chromosome 14 open reading frame 159	524232	1204	429097	9192	17180, 25168, 33156, 41144, 49132
1050	chromosome 14 open reading frame 159	525393	1205	435459	9193	17181, 25169, 33157, 41145, 49133

1051	chromosome 14 open reading frame 180	410013	1206	386487	9194	17182, 25170, 33158, 41146, 49134
1052	chromosome 14 open reading frame 180	557649	1207	452502	9195	17183, 25171, 33159, 41147, 49135
1053	chromosome 14 open reading frame 37	267485	1208	267485	9196	17184, 25172, 33160, 41148, 49136
1054	chromosome 15 open reading frame 24	256545	1209	256545	9197	17185, 25173, 33161, 41149, 49137
1055	chromosome 15 open reading frame 27	388942	1210	373594	9198	17186, 25174, 33162, 41150, 49138
1056	chromosome 15 open reading frame 48	344300	1211	341610	9199	17187, 25175, 33163, 41151, 49139
1057	chromosome 15 open reading frame 48	396650	1212	379887	9200	17188, 25176, 33164, 41152, 49140
1058	chromosome 15 open reading frame 62	344320	1213	341178	9201	17189, 25177, 33165, 41153, 49141
1059	chromosome 15 open reading frame 62	559319	1214	453366	9202	17190, 25178, 33166, 41154, 49142
1060	chromosome 16 open reading frame 54	329410	1215	327506	9203	17191, 25179, 33167, 41155, 49143
1061	chromosome 16 open reading frame 58	327237	1216	317579	9204	17192, 25180, 33168, 41156, 49144
1062	chromosome 16 open reading frame 58	430477	1217	398074	9205	17193, 25181, 33169, 41157, 49145
1063	chromosome 16 open reading frame 58	452223	1218	414614	9206	17194, 25182, 33170, 41158, 49146
1064	chromosome 16 open reading frame 58	541442	1219	440050	9207	17195, 25183, 33171, 41159, 49147
1065	chromosome 16 open reading frame 62	251143	1220	251143	9208	17196, 25184, 33172, 41160, 49148
1066	chromosome 16 open reading frame 62	417362	1221	395973	9209	17197, 25185, 33173, 41161, 49149
1067	chromosome 16 open reading frame 62	438132	1222	400815	9210	17198, 25186, 33174, 41162, 49150
1068	chromosome 16 open reading frame 62	448695	1223	398009	9211	17199, 25187, 33175, 41163, 49151

1069	chromosome 16 open reading frame 62	538853	1224	444363	9212	17200, 25188, 33176, 41164, 49152
1070	chromosome 16 open reading frame 62	542263	1225	442468	9213	17201, 25189, 33177, 41165, 49153
1071	chromosome 16 open reading frame 70	219139	1226	219139	9214	17202, 25190, 33178, 41166, 49154
1072	chromosome 16 open reading frame 91	310355	1227	311390	9215	17203, 25191, 33179, 41167, 49155
1073	chromosome 16 open reading frame 91	442039	1228	413100	9216	17204, 25192, 33180, 41168, 49156
1074	chromosome 16 open reading frame 92	300575	1229	300575	9217	17205, 25193, 33181, 41169, 49157
1075	chromosome 17 open reading frame 101	313056	1230	320116	9218	17206, 25194, 33182, 41170, 49158
1076	chromosome 17 open reading frame 101	329197	1231	330075	9219	17207, 25195, 33183, 41171, 49159
1077	chromosome 17 open reading frame 109	375215	1232	364363	9220	17208, 25196, 33184, 41172, 49160
1078	chromosome 17 open reading frame 56	300714	1233	300714	9221	17209, 25197, 33185, 41173, 49161
1079	chromosome 17 open reading frame 56	374769	1234	363901	9222	17210, 25198, 33186, 41174, 49162
1080	chromosome 17 open reading frame 59	389017	1235	373669	9223	17211, 25199, 33187, 41175, 49163
1081	chromosome 17 open reading frame 61	302422	1236	301939	9224	17212, 25200, 33188, 41176, 49164
1082	chromosome 17 open reading frame 62	306645	1237	307765	9225	17213, 25201, 33189, 41177, 49165
1083	chromosome 17 open reading frame 62	336995	1238	337560	9226	17214, 25202, 33190, 41178, 49166
1084	chromosome 17 open reading frame 62	342572	1239	342228	9227	17215, 25203, 33191, 41179, 49167
1085	chromosome 17 open reading frame 62	434650	1240	401626	9228	17216, 25204, 33192, 41180, 49168
1086	chromosome 17 open reading frame 62	437807	1241	388909	9229	17217, 25205, 33193, 41181, 49169

1087	chromosome 17 open reading frame 62	536759	1242	439100	9230	17218, 25206, 33194, 41182, 49170
1088	chromosome 17 open reading frame 78	300618	1243	300618	9231	17219, 25207, 33195, 41183, 49171
1089	chromosome 17 open reading frame 78	321564	1244	318689	9232	17220, 25208, 33196, 41184, 49172
1090	chromosome 17 open reading frame 80	255557	1245	255557	9233	17221, 25209, 33197, 41185, 49173
1091	chromosome 17 open reading frame 80	268942	1246	268942	9234	17222, 25210, 33198, 41186, 49174
1092	chromosome 17 open reading frame 80	359042	1247	351937	9235	17223, 25211, 33199, 41187, 49175
1093	chromosome 17 open reading frame 80	426147	1248	396970	9236	17224, 25212, 33200, 41188, 49176
1094	chromosome 17 open reading frame 80	535032	1249	440551	9237	17225, 25213, 33201, 41189, 49177
1095	chromosome 17 open reading frame 89	431388	1250	400184	9238	17226, 25214, 33202, 41190, 49178
1096	chromosome 17 open reading frame 90	374741	1251	363873	9239	17227, 25215, 33203, 41191, 49179
1097	chromosome 18 open reading frame 26	321600	1252	315265	9240	17228, 25216, 33204, 41192, 49180
1098	chromosome 18 open reading frame 62	382638	1253	372083	9241	17229, 25217, 33205, 41193, 49181
1099	chromosome 18 open reading frame 62	579022	1254	462106	9242	17230, 25218, 33206, 41194, 49182
1100	chromosome 19 open reading frame 18	314391	1255	321519	9243	17231, 25219, 33207, 41195, 49183
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1102	chromosome 19 open reading frame 38	397820	1257	380920	9245	17233, 25221, 33209, 41197, 49185
1103	chromosome 19 open reading frame 46	324444	1258	316130	9246	17234, 25222, 33210, 41198, 49186
1104	chromosome 19 open reading frame 46	340477	1259	343152	9247	17235, 25223, 33211, 41199, 49187

1105	chromosome 19 open reading frame 59	333598	1260	329920	9248	17236, 25224, 33212, 41200, 49188
1106	chromosome 19 open reading frame 70	309324	1261	309561	9249	17237, 25225, 33213, 41201, 49189
1107	chromosome 19 open reading frame 75	316401	1262	321249	9250	17238, 25226, 33214, 41202, 49190
1108	chromosome 19 open reading frame 77	215531	1263	215531	9251	17239, 25227, 33215, 41203, 49191
1109	chromosome 2 open reading frame 18	344420	1264	345528	9252	17240, 25228, 33216, 41204, 49192
1110	chromosome 2 open reading frame 18	416475	1265	413413	9253	17241, 25229, 33217, 41205, 49193
1111	chromosome 2 open reading frame 28	380171	1266	369518	9254	17242, 25230, 33218, 41206, 49194
1112	chromosome 2 open reading frame 28	405489	1267	384033	9255	17243, 25231, 33219, 41207, 49195
1113	chromosome 2 open reading frame 28	419744	1268	397319	9256	17244, 25232, 33220, 41208, 49196
1114	chromosome 2 open reading frame 47	295079	1269	295079	9257	17245, 25233, 33221, 41209, 49197
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1116	chromosome 2 open reading frame 56	2125	1271	2125	9259	17247, 25235, 33223, 41211, 49199, 56079, 56112
1117	chromosome 2 open reading frame 65	290536	1272	290536	9260	17248, 25236, 33224, 41212, 49200
1118	chromosome 2 open reading frame 65	358434	1273	351213	9261	17249, 25237, 33225, 41213, 49201
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1121	chromosome 2 open reading frame 73	398634	1276	381631	9264	17252, 25240, 33228, 41216, 49204
1122	chromosome 2 open reading frame 82	331342	1277	333208	9265	17253, 25241, 33229, 41217, 49205

1123	chromosome 2 open reading frame 82	409230	1278	386804	9266	17254, 25242, 33230, 41218, 49206
1124	chromosome 2 open reading frame 82	409533	1279	387130	9267	17255, 25243, 33231, 41219, 49207
1125	chromosome 2 open reading frame 89	335459	1280	335004	9268	17256, 25244, 33232, 41220, 49208
1126	chromosome 2 open reading frame 89	409520	1281	387075	9269	17257, 25245, 33233, 41221, 49209
1127	chromosome 20 open reading frame 118	217320	1282	217320	9270	17258, 25246, 33234, 41222, 49210
1128	chromosome 20 open reading frame 123	279028	1283	279028	9271	17259, 25247, 33235, 41223, 49211
1129	chromosome 20 open reading frame 24	342422	1284	341213	9272	17260, 25248, 33236, 41224, 49212
1130	chromosome 20 open reading frame 24	344795	1285	340164	9273	17261, 25249, 33237, 41225, 49213
1131	chromosome 20 open reading frame 24	373852	1286	362958	9274	17262, 25250, 33238, 41226, 49214
1132	chromosome 20 open reading frame 3	217456	1287	217456	9275	17263, 25251, 33239, 41227, 49215
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1134	chromosome 20 open reading frame 3	451442	1289	395874	9277	17265, 25253, 33241, 41229, 49217
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1136	chromosome 20 open reading frame 30	342308	1291	341364	9279	17267, 25255, 33243, 41231, 49219
1137	chromosome 20 open reading frame 30	379276	1292	368578	9280	17268, 25256, 33244, 41232, 49220
1138	chromosome 20 open reading frame 30	379277	1293	368579	9281	17269, 25257, 33245, 41233, 49221
1139	chromosome 20 open reading frame 30	379279	1294	368581	9282	17270, 25258, 33246, 41234, 49222
1140	chromosome 20 open reading frame 30	379283	1295	368585	9283	17271, 25259, 33247, 41235, 49223

1141	chromosome 20 open reading frame 30	379286	1296	368588	9284	17272, 25260, 33248, 41236, 49224
1142	chromosome 20 open reading frame 30	379299	1297	368601	9285	17273, 25261, 33249, 41237, 49225
1143	chromosome 20 open reading frame 72	377704	1298	366933	9286	17274, 25262, 33250, 41238, 49226
1144	chromosome 20 open reading frame 72	377709	1299	366938	9287	17275, 25263, 33251, 41239, 49227
1145	chromosome 20 open reading frame 72	377710	1300	366939	9288	17276, 25264, 33252, 41240, 49228
1146	chromosome 21 open reading frame 63	300255	1301	300255	9289	17277, 25265, 33253, 41241, 49229
1147	chromosome 21 open reading frame 67	330551	1302	331610	9290	17278, 25266, 33254, 41242, 49230
1148	chromosome 21 open reading frame 67	380070	1303	369410	9291	17279, 25267, 33255, 41243, 49231
1149	chromosome 22 open reading frame 24	248984	1304	248984	9292	17280, 25268, 33256, 41244, 49232
1150	chromosome 22 open reading frame 24	543051	1305	437643	9293	17281, 25269, 33257, 41245, 49233
1151	chromosome 22 open reading frame 25	327374	1306	332721	9294	17282, 25270, 33258, 41246, 49234
1152	chromosome 22 open reading frame 25	398042	1307	381122	9295	17283, 25271, 33259, 41247, 49235
1153	chromosome 22 open reading frame 25	401886	1308	385662	9296	17284, 25272, 33260, 41248, 49236
1154	chromosome 22 open reading frame 25	420290	1309	396182	9297	17285, 25273, 33261, 41249, 49237
1155	chromosome 22 open reading frame 25	432198	1310	413850	9298	17286, 25274, 33262, 41250, 49238
1156	chromosome 22 open reading frame 25	432883	1311	402926	9299	17287, 25275, 33263, 41251, 49239
1157	chromosome 22 open reading frame 25	434168	1312	411602	9300	17288, 25276, 33264, 41252, 49240
1158	chromosome 22 open reading frame 25	434570	1313	391262	9301	17289, 25277, 33265, 41253, 49241

1159	chromosome 22 open reading frame 25	447208	1314	389797	9302	17290, 25278, 33266, 41254, 49242
1160	chromosome 22 open reading frame 25	450664	1315	415450	9303	17291, 25279, 33267, 41255, 49243
1161	chromosome 22 open reading frame 25	456048	1316	403645	9304	17292, 25280, 33268, 41256, 49244
1162	chromosome 22 open reading frame 32	331479	1317	327467	9305	17293, 25281, 33269, 41257, 49245
1163	chromosome 3 open reading frame 17	314400	1318	320251	9306	17294, 25282, 33270, 41258, 49246
1164	chromosome 3 open reading frame 17	383675	1319	373173	9307	17295, 25283, 33271, 41259, 49247
1165	chromosome 3 open reading frame 17	393857	1320	377438	9308	17296, 25284, 33272, 41260, 49248
1166	chromosome 3 open reading frame 17	412848	1321	411150	9309	17297, 25285, 33273, 41261, 49249
1167	chromosome 3 open reading frame 18	357203	1322	349732	9310	17298, 25286, 33274, 41262, 49250
1168	chromosome 3 open reading frame 18	426034	1323	387606	9311	17299, 25287, 33275, 41263, 49251
1169	chromosome 3 open reading frame 18	441239	1324	414124	9312	17300, 25288, 33276, 41264, 49252
1170	chromosome 3 open reading frame 18	449241	1325	404913	9313	17301, 25289, 33277, 41265, 49253
1171	chromosome 3 open reading frame 20	253697	1326	253697	9314	17302, 25290, 33278, 41266, 49254
1172	chromosome 3 open reading frame 20	412910	1327	396081	9315	17303, 25291, 33279, 41267, 49255
1173	chromosome 3 open reading frame 20	435614	1328	402933	9316	17304, 25292, 33280, 41268, 49256
1174	chromosome 3 open reading frame 23	342649	1329	341539	9317	17305, 25293, 33281, 41269, 49257
1175	chromosome 3 open reading frame 23	383746	1330	373252	9318	17306, 25294, 33282, 41270, 49258
1176	chromosome 3 open reading frame 23	396078	1331	379388	9319	17307, 25295, 33283, 41271, 49259

1177	chromosome 3 open reading frame 23	417237	1332	402581	9320	17308, 25296, 33284, 41272, 49260
1178	chromosome 3 open reading frame 33	340171	1333	342512	9321	17309, 25297, 33285, 41273, 49261
1179	chromosome 3 open reading frame 33	534941	1334	445446	9322	17310, 25298, 33286, 41274, 49262
1180	chromosome 3 open reading frame 33	537385	1335	444116	9323	17311, 25299, 33287, 41275, 49263
1181	chromosome 3 open reading frame 35	328376	1336	331625	9324	17312, 25300, 33288, 41276, 49264
1182	chromosome 3 open reading frame 35	425564	1337	414104	9325	17313, 25301, 33289, 41277, 49265
1183	chromosome 3 open reading frame 35	425932	1338	395513	9326	17314, 25302, 33290, 41278, 49266
1184	chromosome 3 open reading frame 35	426078	1339	392399	9327	17315, 25303, 33291, 41279, 49267
1185	chromosome 3 open reading frame 35	452017	1340	413537	9328	17316, 25304, 33292, 41280, 49268
1186	chromosome 3 open reading frame 43	397537	1341	380671	9329	17317, 25305, 33293, 41281, 49269
1187	chromosome 3 open reading frame 45	316436	1342	315081	9330	17318, 25306, 33294, 41282, 49270
1188	chromosome 3 open reading frame 55	459838	1343	420317	9331	17319, 25307, 33295, 41283, 49271
1189	chromosome 3 open reading frame 71	408959	1344	386193	9332	17320, 25308, 33296, 41284, 49272
1190	chromosome 3 open reading frame 78	477703	1345	417806	9333	17321, 25309, 33297, 41285, 49273
1191	chromosome 4 open reading frame 21	309071	1346	309095	9334	17322, 25310, 33298, 41286, 49274
1192	chromosome 4 open reading frame 21	445203	1347	390505	9335	17323, 25311, 33299, 41287, 49275
1193	chromosome 4 open reading frame 21	503172	1348	424995	9336	17324, 25312, 33300, 41288, 49276
1194	chromosome 4 open reading frame 3	399075	1349	382026	9337	17325, 25313, 33301, 41289, 49277

1195	chromosome 4 open reading frame 3	504110	1350	427214	9338	17326, 25314, 33302, 41290, 49278
1196	chromosome 4 open reading frame 32	309733	1351	310182	9339	17327, 25315, 33303, 41291, 49279
1197	chromosome 4 open reading frame 34	295958	1352	295958	9340	17328, 25316, 33304, 41292, 49280
1198	chromosome 4 open reading frame 34	505729	1353	422904	9341	17329, 25317, 33305, 41293, 49281
1199	chromosome 4 open reading frame 49	398955	1354	381928	9342	17330, 25318, 33306, 41294, 49282
1200	chromosome 5 open reading frame 15	231512	1355	231512	9343	17331, 25319, 33307, 41295, 49283
1201	chromosome 5 open reading frame 15	451255	1356	389086	9344	17332, 25320, 33308, 41296, 49284
1202	chromosome 5 open reading frame 28	397080	1357	380270	9345	17333, 25321, 33309, 41297, 49285
1203	chromosome 5 open reading frame 28	500337	1358	426067	9346	17334, 25322, 33310, 41298, 49286
1204	chromosome 5 open reading frame 28	506860	1359	424720	9347	17335, 25323, 33311, 41299, 49287
1205	chromosome 5 open reading frame 28	512085	1360	422881	9348	17336, 25324, 33312, 41300, 49288
1206	chromosome 5 open reading frame 28	537319	1361	443629	9349	17337, 25325, 33313, 41301, 49289
1207	chromosome 5 open reading frame 4	326080	1362	320604	9350	17338, 25326, 33314, 41302, 49290
1208	chromosome 5 open reading frame 4	517938	1363	430286	9351	17339, 25327, 33315, 41303, 49291
1209	chromosome 5 open reading frame 4	519501	1364	429837	9352	17340, 25328, 33316, 41304, 49292
1210	chromosome 5 open reading frame 4	520461	1365	431015	9353	17341, 25329, 33317, 41305, 49293
1211	chromosome 5 open reading frame 43	339020	1366	339324	9354	17342, 25330, 33318, 41306, 49294
1212	chromosome 5 open reading frame 43	507416	1367	421336	9355	17343, 25331, 33319, 41307, 49295

1213	chromosome 5 open reading frame 62	526627	1368	436897	9356	17344, 25332, 33320, 41308, 49296
1214	chromosome 6 open reading frame 10	305725	1369	303292	9357	17345, 25333, 33321, 41309, 49297
1215	chromosome 6 open reading frame 10	375002	1370	364141	9358	17346, 25334, 33322, 41310, 49298
1216	chromosome 6 open reading frame 10	375007	1371	364146	9359	17347, 25335, 33323, 41311, 49299
1217	chromosome 6 open reading frame 10	383130	1372	372611	9360	17348, 25336, 33324, 41312, 49300
1218	chromosome 6 open reading frame 10	447241	1373	415517	9361	17349, 25337, 33325, 41313, 49301
1219	chromosome 6 open reading frame 10	448986	1374	410514	9362	17350, 25338, 33326, 41314, 49302
1220	chromosome 6 open reading frame 10	547550	1375	449235	9363	17351, 25339, 33327, 41315, 49303
1221	chromosome 6 open reading frame 10	548927	1376	448472	9364	17352, 25340, 33328, 41316, 49304
1222	chromosome 6 open reading frame 10	548975	1377	449655	9365	17353, 25341, 33329, 41317, 49305
1223	chromosome 6 open reading frame 10	551961	1378	447564	9366	17354, 25342, 33330, 41318, 49306
1224	chromosome 6 open reading frame 125	374214	1379	363331	9367	17355, 25343, 33331, 41319, 49307
1225	chromosome 6 open reading frame 125	374231	1380	363348	9368	17356, 25344, 33332, 41320, 49308
1226	chromosome 6 open reading frame 136	293604	1381	293604	9369	17357, 25345, 33333, 41321, 49309
1227	chromosome 6 open reading frame 136	376471	1382	365654	9370	17358, 25346, 33334, 41322, 49310
1228	chromosome 6 open reading frame 136	376473	1383	365656	9371	17359, 25347, 33335, 41323, 49311
1229	chromosome 6 open reading frame 136	528347	1384	431811	9372	17360, 25348, 33336, 41324, 49312
1230	chromosome 6 open reading frame 138	339488	1385	341914	9373	17361, 25349, 33337, 41325, 49313

1231	chromosome 6 open reading frame 138	398738	1386	381722	9374	17362, 25350, 33338, 41326, 49314
1232	chromosome 6 open reading frame 138	543600	1387	439864	9375	17363, 25351, 33339, 41327, 49315
1233	chromosome 6 open reading frame 162	229570	1388	229570	9376	17364, 25352, 33340, 41328, 49316
1234	chromosome 6 open reading frame 162	392863	1389	376603	9377	17365, 25353, 33341, 41329, 49317
1235	chromosome 6 open reading frame 174	368268	1390	357251	9378	17366, 25354, 33342, 41330, 49318
1236	chromosome 6 open reading frame 174	467753	1391	431662	9379	17367, 25355, 33343, 41331, 49319
1237	chromosome 6 open reading frame 174	525778	1392	434570	9380	17368, 25356, 33344, 41332, 49320
1238	chromosome 6 open reading frame 174	556132	1393	451768	9381	17369, 25357, 33345, 41333, 49321
1239	chromosome 6 open reading frame 191	368143	1394	357125	9382	17370, 25358, 33346, 41334, 49322
1240	chromosome 6 open reading frame 191	438392	1395	403755	9383	17371, 25359, 33347, 41335, 49323
1241	chromosome 6 open reading frame 203	311381	1396	310951	9384	17372, 25360, 33348, 41336, 49324
1242	chromosome 6 open reading frame 203	405204	1397	384867	9385	17373, 25361, 33349, 41337, 49325
1243	chromosome 6 open reading frame 203	443043	1398	390153	9386	17374, 25362, 33350, 41338, 49326
1244	chromosome 6 open reading frame 25	375804	1399	364962	9387	17375, 25363, 33351, 41339, 49327
1245	chromosome 6 open reading frame 25	375805	1400	364963	9388	17376, 25364, 33352, 41340, 49328
1246	chromosome 6 open reading frame 25	375806	1401	364964	9389	17377, 25365, 33353, 41341, 49329
1247	chromosome 6 open reading frame 25	375809	1402	364967	9390	17378, 25366, 33354, 41342, 49330
1248	chromosome 6 open reading frame 25	375810	1403	364968	9391	17379, 25367, 33355, 41343, 49331

1249	chromosome 6 open reading frame 25	375814	1404	364972	9392	17380, 25368, 33356, 41344, 49332
1250	chromosome 6 open reading frame 25	383410	1405	372902	9393	17381, 25369, 33357, 41345, 49333
1251	chromosome 6 open reading frame 25	383411	1406	372903	9394	17382, 25370, 33358, 41346, 49334
1252	chromosome 6 open reading frame 25	383412	1407	372904	9395	17383, 25371, 33359, 41347, 49335
1253	chromosome 6 open reading frame 25	400067	1408	382940	9396	17384, 25372, 33360, 41348, 49336
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1257	chromosome 6 open reading frame 25	417610	1412	412747	9400	17388, 25376, 33364, 41352, 49340
1258	chromosome 6 open reading frame 25	422012	1413	398061	9401	17389, 25377, 33365, 41353, 49341
1259	chromosome 6 open reading frame 25	425998	1414	392917	9402	17390, 25378, 33366, 41354, 49342
1260	chromosome 6 open reading frame 25	426729	1415	390272	9403	17391, 25379, 33367, 41355, 49343
1261	chromosome 6 open reading frame 25	428302	1416	404519	9404	17392, 25380, 33368, 41356, 49344
1262	chromosome 6 open reading frame 25	431888	1417	390821	9405	17393, 25381, 33369, 41357, 49345
1263	chromosome 6 open reading frame 25	435007	1418	401892	9406	17394, 25382, 33370, 41358, 49346
1264	chromosome 6 open reading frame 25	436030	1419	406706	9407	17395, 25383, 33371, 41359, 49347
1265	chromosome 6 open reading frame 25	437153	1420	412937	9408	17396, 25384, 33372, 41360, 49348
1266	chromosome 6 open reading frame 25	440063	1421	388982	9409	17397, 25385, 33373, 41361, 49349

1267	chromosome 6 open reading frame 25	444404	1422	415282	9410	17398, 25386, 33374, 41362, 49350
1268	chromosome 6 open reading frame 25	445381	1423	396823	9411	17399, 25387, 33375, 41363, 49351
1269	chromosome 6 open reading frame 25	447587	1424	416447	9412	17400, 25388, 33376, 41364, 49352
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1271	chromosome 6 open reading frame 25	451549	1426	395801	9414	17402, 25390, 33378, 41366, 49354
1272	chromosome 6 open reading frame 25	455185	1427	414824	9415	17403, 25391, 33379, 41367, 49355
1273	chromosome 6 open reading frame 25	457450	1428	395279	9416	17404, 25392, 33380, 41368, 49356
1274	chromosome 6 open reading frame 25	457884	1429	391097	9417	17405, 25393, 33381, 41369, 49357
1275	chromosome 6 open reading frame 70	366771	1430	355733	9418	17406, 25394, 33382, 41370, 49358
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1280	chromosome 6 open reading frame 72	367419	1435	356389	9423	17411, 25399, 33387, 41375, 49363
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1284	chromosome 6 open reading frame 89	359359	1439	352316	9427	17415, 25403, 33391, 41379, 49367

1285	chromosome 6 open reading frame 89	373685	1440	362789	9428	17416, 25404, 33392, 41380, 49368
1286	chromosome 6 open reading frame 89	416621	1441	387562	9429	17417, 25405, 33393, 41381, 49369
1287	chromosome 6 open reading frame 89	510325	1442	445655	9430	17418, 25406, 33394, 41382, 49370
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1290	chromosome 7 open reading frame 23	257637	1445	257637	9433	17421, 25409, 33397, 41385, 49373
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1297	chromosome 7 open reading frame 42	424964	1452	394507	9440	17428, 25416, 33404, 41392, 49380
1298	chromosome 7 open reading frame 44	223336	1453	223336	9441	17429, 25417, 33405, 41393, 49381
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1300	chromosome 7 open reading frame 44	395879	1455	379218	9443	17431, 25419, 33407, 41395, 49383
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1328	chromosome 8 open reading frame 83	519969	1483	429381	9471	17459, 25447, 33435, 41423, 49411
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1341	chromosome 9 open reading frame 125	374848	1496	363981	9484	17472, 25460, 33448, 41436, 49424
1342	chromosome 9 open reading frame 125	374851	1497	363984	9485	17473, 25461, 33449, 41437, 49425
1343	chromosome 9 open reading frame 135	377197	1498	366402	9486	17474, 25462, 33450, 41438, 49426
1344	chromosome 9 open reading frame 167	357503	1499	350102	9487	17475, 25463, 33451, 41439, 49427
1345	chromosome 9 open reading frame 174	357054	1500	349562	9488	17476, 25464, 33452, 41440, 49428
1346	chromosome 9 open reading frame 174	375202	1501	364348	9489	17477, 25465, 33453, 41441, 49429
1347	chromosome 9 open reading frame 174	375205	1502	364351	9490	17478, 25466, 33454, 41442, 49430
1348	chromosome 9 open reading frame 174	395220	1503	378646	9491	17479, 25467, 33455, 41443, 49431
1349	chromosome 9 open reading frame 174	411667	1504	414000	9492	17480, 25468, 33456, 41444, 49432
1350	chromosome 9 open reading frame 174	529487	1505	434727	9493	17481, 25469, 33457, 41445, 49433
1351	chromosome 9 open reading frame 174	541524	1506	437666	9494	17482, 25470, 33458, 41446, 49434
1352	chromosome 9 open reading frame 40	376854	1507	366050	9495	17483, 25471, 33459, 41447, 49435
1353	chromosome 9 open reading frame 46	223864	1508	223864	9496	17484, 25472, 33460, 41448, 49436
1354	chromosome 9 open reading frame 57	377024	1509	366223	9497	17485, 25473, 33461, 41449, 49437
1355	chromosome 9 open reading frame 57	424431	1510	412956	9498	17486, 25474, 33462, 41450, 49438
1356	chromosome 9 open reading frame 71	377311	1511	366528	9499	17487, 25475, 33463, 41451, 49439

1357	chromosome 9 open reading frame 79	325643	1512	322640	9500	17488, 25476, 33464, 41452, 49440
1358	chromosome 9 open reading frame 79	539327	1513	443171	9501	17489, 25477, 33465, 41453, 49441
1359	chromosome 9 open reading frame 91	288502	1514	288502	9502	17490, 25478, 33466, 41454, 49442
1360	chromosome 9 open reading frame 91	374049	1515	363161	9503	17491, 25479, 33467, 41455, 49443
1361	chromosome X open reading frame 23	379682	1516	369004	9504	17492, 25480, 33468, 41456, 49444
1362	chromosome X open reading frame 59	313548	1517	324767	9505	17493, 25481, 33469, 41457, 49445
1363	chromosome X open reading frame 59	378660	1518	367929	9506	17494, 25482, 33470, 41458, 49446
1364	chromosome X open reading frame 59	397458	1519	380599	9507	17495, 25483, 33471, 41459, 49447
1365	chromosome X open reading frame 59	449698	1520	414151	9508	17496, 25484, 33472, 41460, 49448
1366	chromosome X open reading frame 66	370540	1521	359571	9509	17497, 25485, 33473, 41461, 49449
1367	chromosome X open reading frame 68	369529	1522	358542	9510	17498, 25486, 33474, 41462, 49450
1368	ciliary rootlet coiled-coil, rootletin	375541	1523	364691	9511	17499, 25487, 33475, 41463, 49451
1369	ciliary rootlet coiled-coil, rootletin	445545	1524	402626	9512	17500, 25488, 33476, 41464, 49452
1370	cingulin	271636	1525	271636	9513	17501, 25489, 33477, 41465, 49453
1371	cingulin	427934	1526	410836	9514	17502, 25490, 33478, 41466, 49454
1372	cingulin	502442	1527	422299	9515	17503, 25491, 33479, 41467, 49455
1373	cingulin	505188	1528	425532	9516	17504, 25492, 33480, 41468, 49456
1374	clarin 2	511148	1529	424711	9517	17505, 25493, 33481, 41469, 49457

1375	clarin 3	368671	1530	357660	9518	17506, 25494, 33482, 41470, 49458
1376	claudin 10	299339	1531	299339	9519	17507, 25495, 33483, 41471, 49459
1377	claudin 10	376855	1532	366051	9520	17508, 25496, 33484, 41472, 49460
1378	claudin 10	376873	1533	366069	9521	17509, 25497, 33485, 41473, 49461
1379	claudin 12	287916	1534	287916	9522	17510, 25498, 33486, 41474, 49462
1380	claudin 12	394604	1535	378102	9523	17511, 25499, 33487, 41475, 49463
1381	claudin 12	394605	1536	378103	9524	17512, 25500, 33488, 41476, 49464
1382	claudin 12	416322	1537	411399	9525	17513, 25501, 33489, 41477, 49465
1383	claudin 12	422604	1538	394444	9526	17514, 25502, 33490, 41478, 49466
1384	claudin 12	427904	1539	391062	9527	17515, 25503, 33491, 41479, 49467
1385	claudin 12	496677	1540	419053	9528	17516, 25504, 33492, 41480, 49468
1386	claudin 12	535571	1541	443476	9529	17517, 25505, 33493, 41481, 49469
1387	claudin 15	308344	1542	308870	9530	17518, 25506, 33494, 41482, 49470
1388	claudin 15	401528	1543	385300	9531	17519, 25507, 33495, 41483, 49471
1389	claudin 17	286808	1544	286808	9532	17520, 25508, 33496, 41484, 49472
1390	claudin 2	336803	1545	336571	9533	17521, 25509, 33497, 41485, 49473
1391	claudin 2	540876	1546	443230	9534	17522, 25510, 33498, 41486, 49474
1392	claudin 2	541806	1547	441283	9535	17523, 25511, 33499, 41487, 49475

1393	claudin 20	367165	1548	356133	9536	17524, 25512, 33500, 41488, 49476
1394	claudin 22	323319	1549	318113	9537	17525, 25513, 33501, 41489, 49477
1395	claudin 23	519106	1550	428780	9538	17526, 25514, 33502, 41490, 49478
1396	claudin 25	453129	1551	396304	9539	17527, 25515, 33503, 41491, 49479
1397	claudin 6	328796	1552	328674	9540	17528, 25516, 33504, 41492, 49480
1398	claudin 6	396925	1553	380131	9541	17529, 25517, 33505, 41493, 49481
1399	claudin 7	360325	1554	353475	9542	17530, 25518, 33506, 41494, 49482
1400	claudin 7	397317	1555	396638	9543	17531, 25519, 33507, 41495, 49483
1401	claudin 7	538261	1556	445131	9544	17532, 25520, 33508, 41496, 49484
1402	claudin 8	286809	1557	286809	9545	17533, 25521, 33509, 41497, 49485
1403	claudin 8	399899	1558	382783	9546	17534, 25522, 33510, 41498, 49486
1404	claudin 8	536721	1559	439258	9547	17535, 25523, 33511, 41499, 49487
1405	claudin 9	445369	1560	398017	9548	17536, 25524, 33512, 41500, 49488
1406	claudin domain containing 1	341181	1561	340247	9549	17537, 25525, 33513, 41501, 49489
1407	claudin domain containing 1	394180	1562	377734	9550	17538, 25526, 33514, 41502, 49490
1408	claudin domain containing 1	394181	1563	377735	9551	17539, 25527, 33515, 41503, 49491
1409	claudin domain containing 1	394185	1564	377739	9552	17540, 25528, 33516, 41504, 49492
1410	claudin domain containing 1	437922	1565	388457	9553	17541, 25529, 33517, 41505, 49493

1411	claudin domain containing 1	502299	1566	420913	9554	17542, 25530, 33518, 41506, 49494
1412	claudin domain containing 1	503004	1567	421226	9555	17543, 25531, 33519, 41507, 49495
1413	claudin domain containing 1	506575	1568	427042	9556	17544, 25532, 33520, 41508, 49496
1414	claudin domain containing 1	507944	1569	425204	9557	17545, 25533, 33521, 41509, 49497
1415	claudin domain containing 1	508071	1570	425256	9558	17546, 25534, 33522, 41510, 49498
1416	claudin domain containing 1	508659	1571	427658	9559	17547, 25535, 33523, 41511, 49499
1417	claudin domain containing 1	508902	1572	421413	9560	17548, 25536, 33524, 41512, 49500
1418	claudin domain containing 1	510545	1573	423590	9561	17549, 25537, 33525, 41513, 49501
1419	claudin domain containing 1	511081	1574	424669	9562	17550, 25538, 33526, 41514, 49502
1420	claudin domain containing 1	513130	1575	426079	9563	17551, 25539, 33527, 41515, 49503
1421	claudin domain containing 1	513287	1576	426869	9564	17552, 25540, 33528, 41516, 49504
1422	claudin domain containing 1	513452	1577	425539	9565	17553, 25541, 33529, 41517, 49505
1423	claudin domain containing 1	514537	1578	423151	9566	17554, 25542, 33530, 41518, 49506
1424	claudin domain containing 1	515620	1579	423093	9567	17555, 25543, 33531, 41519, 49507
1425	claudin domain containing 2	291715	1580	291715	9568	17556, 25544, 33532, 41520, 49508
1426	clavesin 1	325897	1581	325506	9569	17557, 25545, 33533, 41521, 49509
1427	clavesin 1	519846	1582	428402	9570	17558, 25546, 33534, 41522, 49510
1428	clavesin 1	522621	1583	428986	9571	17559, 25547, 33535, 41523, 49511

1429	clavesin 2	275162	1584	275162	9572	17560, 25548, 33536, 41524, 49512
1430	clavesin 2	368438	1585	357423	9573	17561, 25549, 33537, 41525, 49513
1431	cleft lip and palate associated transmembrane protein 1	337392	1586	336994	9574	17562, 25550, 33538, 41526, 49514
1432	cleft lip and palate associated transmembrane protein 1	347493	1587	270281	9575	17563, 25551, 33539, 41527, 49515
1433	cleft lip and palate associated transmembrane protein 1	541297	1588	442011	9576	17564, 25552, 33540, 41528, 49516
1434	cleft lip and palate associated transmembrane protein 1	546079	1589	443192	9577	17565, 25553, 33541, 41529, 49517
1435	ClpB caseinolytic peptidase B homolog (E. coli)	294053	1590	294053	9578	17566, 25554, 33542, 41530, 49518
1436	ClpB caseinolytic peptidase B homolog (E. coli)	437826	1591	407296	9579	17567, 25555, 33543, 41531, 49519
1437	ClpB caseinolytic peptidase B homolog (E. coli)	538039	1592	441518	9580	17568, 25556, 33544, 41532, 49520
1438	ClpB caseinolytic peptidase B homolog (E. coli)	543042	1593	439746	9581	17569, 25557, 33545, 41533, 49521
1439	ClpX caseinolytic peptidase X homolog (E. coli)	300107	1594	300107	9582	17570, 25558, 33546, 41534, 49522
1440	ClpX caseinolytic peptidase X homolog (E. coli)	546194	1595	440853	9583	17571, 25559, 33547, 41535, 49523
1441	coatomer protein complex, subunit gamma	314797	1596	325002	9584	17572, 25560, 33548, 41536, 49524
1442	coatomer protein complex, subunit zeta 1	262061	1597	262061	9585	17573, 25561, 33549, 41537, 49525
1443	coatomer protein complex, subunit zeta 1	416254	1598	388141	9586	17574, 25562, 33550, 41538, 49526
1444	coatomer protein complex, subunit zeta 1	455864	1599	410620	9587	17575, 25563, 33551, 41539, 49527
1445	coatomer protein complex, subunit zeta 1	552848	1600	449414	9588	17576, 25564, 33552, 41540, 49528

1446	coenzyme Q10 homolog A (S. cerevisiae)	308197	1601	312587	9589	17577, 25565, 33553, 41541, 49529
1447	coenzyme Q10 homolog A (S. cerevisiae)	433805	1602	407843	9590	17578, 25566, 33554, 41542, 49530
1448	coenzyme Q10 homolog A (S. cerevisiae)	546544	1603	446723	9591	17579, 25567, 33555, 41543, 49531
1449	coenzyme Q10 homolog A (S. cerevisiae)	551814	1604	447964	9592	17580, 25568, 33556, 41544, 49532
1450	coenzyme Q10 homolog B (S. cerevisiae)	263960	1605	263960	9593	17581, 25569, 33557, 41545, 49533
1451	coenzyme Q10 homolog B (S. cerevisiae)	409010	1606	387223	9594	17582, 25570, 33558, 41546, 49534
1452	coenzyme Q10 homolog B (S. cerevisiae)	545340	1607	442520	9595	17583, 25571, 33559, 41547, 49535
1453	coenzyme Q5 homolog, methyltransferase (S. cerevisiae)	288532	1608	288532	9596	17584, 25572, 33560, 41548, 49536
1454	coenzyme Q5 homolog, methyltransferase (S. cerevisiae)	302223	1609	302233	9597	17585, 25573, 33561, 41549, 49537
1455	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	238709	1610	238709	9598	17586, 25574, 33562, 41550, 49538
1456	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	334571	1611	333946	9599	17587, 25575, 33563, 41551, 49539
1457	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	394026	1612	377594	9600	17588, 25576, 33564, 41552, 49540
1458	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	545052	1613	439592	9601	17589, 25577, 33565, 41553, 49541
1459	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	554153	1614	451685	9602	17590, 25578, 33566, 41554, 49542
1460	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	554320	1615	451123	9603	17591, 25579, 33567, 41555, 49543

1461	coenzyme Q6 homolog, monooxygenase (S. cerevisiae)	555376	1616	450526	9604	17592, 25580, 33568, 41556, 49544
1462	coiled-coil domain containing 107	327351	1617	330327	9605	17593, 25581, 33569, 41557, 49545
1463	coiled-coil domain containing 107	378406	1618	367661	9606	17594, 25582, 33570, 41558, 49546
1464	coiled-coil domain containing 107	378407	1619	367662	9607	17595, 25583, 33571, 41559, 49547
1465	coiled-coil domain containing 107	378409	1620	367665	9608	17596, 25584, 33572, 41560, 49548
1466	coiled-coil domain containing 107	421582	1621	413003	9609	17597, 25585, 33573, 41561, 49549
1467	coiled-coil domain containing 107	426546	1622	414964	9610	17598, 25586, 33574, 41562, 49550
1468	coiled-coil domain containing 109B	394650	1623	378145	9611	17599, 25587, 33575, 41563, 49551
1469	coiled-coil domain containing 155	447857	1624	404220	9612	17600, 25588, 33576, 41564, 49552
1470	coiled-coil domain containing 167	373405	1625	362504	9613	17601, 25589, 33577, 41565, 49553
1471	coiled-coil domain containing 167	373408	1626	362507	9614	17602, 25590, 33578, 41566, 49554
1472	coiled-coil domain containing 167	411755	1627	407966	9615	17603, 25591, 33579, 41567, 49555
1473	coiled-coil domain containing 47	225726	1628	225726	9616	17604, 25592, 33580, 41568, 49556
1474	coiled-coil domain containing 47	403162	1629	384888	9617	17605, 25593, 33581, 41569, 49557
1475	coiled-coil domain containing 51	395694	1630	379047	9618	17606, 25594, 33582, 41570, 49558
1476	coiled-coil domain containing 51	395696	1631	379049	9619	17607, 25595, 33583, 41571, 49559
1477	coiled-coil domain containing 51	412398	1632	401194	9620	17608, 25596, 33584, 41572, 49560
1478	coiled-coil domain containing 51	438370	1633	408197	9621	17609, 25597, 33585, 41573, 49561

1479	coiled-coil domain containing 51	442740	1634	392898	9622	17610, 25598, 33586, 41574, 49562
1480	coiled-coil domain containing 51	446140	1635	409494	9623	17611, 25599, 33587, 41575, 49563
1481	coiled-coil domain containing 51	447018	1636	412300	9624	17612, 25600, 33588, 41576, 49564
1482	coiled-coil domain containing 56	328434	1637	354762	9625	17613, 25601, 33589, 41577, 49565
1483	coiled-coil domain containing 58	291458	1638	291458	9626	17614, 25602, 33590, 41578, 49566
1484	coiled-coil domain containing 90A	359495	1639	352475	9627	17615, 25603, 33591, 41579, 49567
1485	coiled-coil domain containing 90A	379170	1640	368468	9628	17616, 25604, 33592, 41580, 49568
1486	coiled-coil domain containing 90B	455220	1641	390990	9629	17617, 25605, 33593, 41581, 49569
1487	coiled-coil domain containing 90B	525503	1642	431424	9630	17618, 25606, 33594, 41582, 49570
1488	coiled-coil domain containing 90B	529611	1643	431345	9631	17619, 25607, 33595, 41583, 49571
1489	coiled-coil domain containing 90B	529689	1644	434724	9632	17620, 25608, 33596, 41584, 49572
1490	coiled-coil domain containing 91	306172	1645	305075	9633	17621, 25609, 33597, 41585, 49573
1491	coiled-coil domain containing 91	381256	1646	370655	9634	17622, 25610, 33598, 41586, 49574
1492	coiled-coil domain containing 91	381259	1647	370658	9635	17623, 25611, 33599, 41587, 49575
1493	coiled-coil domain containing 91	536442	1648	445660	9636	17624, 25612, 33600, 41588, 49576
1494	coiled-coil domain containing 91	538586	1649	440194	9637	17625, 25613, 33601, 41589, 49577
1495	coiled-coil domain containing 91	539107	1650	440513	9638	17626, 25614, 33602, 41590, 49578
1496	coiled-coil domain containing 91	543534	1651	446045	9639	17627, 25615, 33603, 41591, 49579

1497	coiled-coil domain containing 91	545336	1652	438040	9640	17628, 25616, 33604, 41592, 49580
1498	coiled-coil-helix-coiled-coil-helix domain containing 1	372833	1653	361923	9641	17629, 25617, 33605, 41593, 49581
1499	coiled-coil-helix-coiled-coil-helix domain containing 1	372837	1654	361928	9642	17630, 25618, 33606, 41594, 49582
1500	coiled-coil-helix-coiled-coil-helix domain containing 10	484558	1655	418428	9643	17631, 25619, 33607, 41595, 49583
1501	coiled-coil-helix-coiled-coil-helix domain containing 2	395422	1656	378812	9644	17632, 25620, 33608, 41596, 49584
1502	coiled-coil-helix-coiled-coil-helix domain containing 4	295767	1657	295767	9645	17633, 25621, 33609, 41597, 49585
1503	coiled-coil-helix-coiled-coil-helix domain containing 4	396914	1658	380122	9646	17634, 25622, 33610, 41598, 49586
1504	complement component 3a receptor 1	307637	1659	302079	9647	17635, 25623, 33611, 41599, 49587
1505	complement component 3a receptor 1	546241	1660	444500	9648	17636, 25624, 33612, 41600, 49588
1506	complement component 5a receptor 1	355085	1661	347197	9649	17637, 25625, 33613, 41601, 49589
1507	complexin 3	395018	1662	378464	9650	17638, 25626, 33614, 41602, 49590
1508	connector enhancer of kinase suppressor of Ras 1	361530	1663	354609	9651	17639, 25627, 33615, 41603, 49591
1509	connector enhancer of kinase suppressor of Ras 1	374253	1664	363371	9652	17640, 25628, 33616, 41604, 49592
1510	connector enhancer of kinase suppressor of Ras 1	422547	1665	390945	9653	17641, 25629, 33617, 41605, 49593
1511	contactin associated protein 1	264638	1666	264638	9654	17642, 25630, 33618, 41606, 49594
1512	contactin associated protein-like 3B	276974	1667	276974	9655	17643, 25631, 33619, 41607, 49595
1513	contactin associated protein-like 3B	341990	1668	340890	9656	17644, 25632, 33620, 41608, 49596
1514	contactin associated protein-like 3B	377555	1669	366778	9657	17645, 25633, 33621, 41609, 49597

1515	contactin associated protein-like 3B	377561	1670	366784	9658	17646, 25634, 33622, 41610, 49598
1516	contactin associated protein-like 3B	377564	1671	366787	9659	17647, 25635, 33623, 41611, 49599
1517	contactin associated protein-like 3B	403166	1672	385153	9660	17648, 25636, 33624, 41612, 49600
1518	contactin associated protein-like 5	431078	1673	399013	9661	17649, 25637, 33625, 41613, 49601
1519	corin, serine peptidase	273857	1674	273857	9662	17650, 25638, 33626, 41614, 49602
1520	corin, serine peptidase	502252	1675	424212	9663	17651, 25639, 33627, 41615, 49603
1521	corin, serine peptidase	505909	1676	425401	9664	17652, 25640, 33628, 41616, 49604
1522	cornichon homolog (Drosophila)	216416	1677	216416	9665	17653, 25641, 33629, 41617, 49605
1523	cornichon homolog (Drosophila)	395573	1678	378940	9666	17654, 25642, 33630, 41618, 49606
1524	cornichon homolog 2 (Drosophila)	311445	1679	310003	9667	17655, 25643, 33631, 41619, 49607
1525	cornichon homolog 3 (Drosophila)	272133	1680	272133	9668	17656, 25644, 33632, 41620, 49608
1526	cornichon homolog 4 (Drosophila)	366856	1681	355821	9669	17657, 25645, 33633, 41621, 49609
1527	cornichon homolog 4 (Drosophila)	366857	1682	355822	9670	17658, 25646, 33634, 41622, 49610
1528	cornichon homolog 4 (Drosophila)	366858	1683	355823	9671	17659, 25647, 33635, 41623, 49611
1529	cornichon homolog 4 (Drosophila)	465271	1684	420443	9672	17660, 25648, 33636, 41624, 49612
1530	cortexin 3	379445	1685	368758	9673	17661, 25649, 33637, 41625, 49613
1531	cortexin 3	395322	1686	378732	9674	17662, 25650, 33638, 41626, 49614
1532	corticotropin-releasing factor receptor 1 isoform 1 precursor	547258	1687	448155	9675	17663, 25651, 33639, 41627, 49615

1533	corticotropin-releasing factor receptor 1 isoform 1 precursor	548394	1688	449671	9676	17664, 25652, 33640, 41628, 49616
1534	corticotropin-releasing factor receptor 1 isoform 1 precursor	548791	1689	448783	9677	17665, 25653, 33641, 41629, 49617
1535	corticotropin-releasing factor receptor 1 isoform 1 precursor	550606	1690	448894	9678	17666, 25654, 33642, 41630, 49618
1536	corticotropin-releasing factor receptor 1 isoform 1 precursor	551221	1691	446568	9679	17667, 25655, 33643, 41631, 49619
1537	corticotropin-releasing factor receptor 1 isoform 1 precursor	551817	1692	447617	9680	17668, 25656, 33644, 41632, 49620
1538	corticotropin-releasing factor receptor 1 isoform 1 precursor	552616	1693	448216	9681	17669, 25657, 33645, 41633, 49621
1539	corticotropin-releasing factor receptor 1 isoform 1 precursor	552724	1694	448734	9682	17670, 25658, 33646, 41634, 49622
1540	COX assembly mitochondrial protein homolog (S. cerevisiae)	466830	1695	418348	9683	17671, 25659, 33647, 41635, 49623
1541	COX16 cytochrome c oxidase assembly homolog (S. cerevisiae)	389912	1696	374562	9684	17672, 25660, 33648, 41636, 49624
1542	COX18 cytochrome c oxidase assembly homolog (S. cerevisiae)	295890	1697	295890	9685	17673, 25661, 33649, 41637, 49625
1543	COX18 cytochrome c oxidase assembly homolog (S. cerevisiae)	507544	1698	425261	9686	17674, 25662, 33650, 41638, 49626
1544	CTAGE family, member 4	486333	1699	419539	9687	17675, 25663, 33651, 41639, 49627
1545	CTAGE family, member 8	487179	1700	417289	9688	17676, 25664, 33652, 41640, 49628
1546	CTAGE family, member 9	314099	1701	395587	9689	17677, 25665, 33653, 41641, 49629

1547	CTD nuclear envelope phosphatase 1	318988	1702	321732	9690	17678, 25666, 33654, 41642, 49630
1548	CTD nuclear envelope phosphatase 1	574322	1703	460683	9691	17679, 25667, 33655, 41643, 49631
1549	C-type lectin domain family 1, member B	298527	1704	298527	9692	17680, 25668, 33656, 41644, 49632
1550	C-type lectin domain family 1, member B	348658	1705	327169	9693	17681, 25669, 33657, 41645, 49633
1551	C-type lectin domain family 1, member B	398939	1706	381912	9694	17682, 25670, 33658, 41646, 49634
1552	C-type lectin domain family 1, member B	428126	1707	406338	9695	17683, 25671, 33659, 41647, 49635
1553	C-type lectin domain family 12, member B	338896	1708	344563	9696	17684, 25672, 33660, 41648, 49636
1554	C-type lectin domain family 12, member B	396502	1709	379759	9697	17685, 25673, 33661, 41649, 49637
1555	C-type lectin domain family 14, member A	342213	1710	353013	9698	17686, 25674, 33662, 41650, 49638
1556	C-type lectin domain family 14, member A	546356	1711	443662	9699	17687, 25675, 33663, 41651, 49639
1557	C-type lectin domain family 17, member A	397439	1712	380581	9700	17688, 25676, 33664, 41652, 49640
1558	C-type lectin domain family 17, member A	417570	1713	393719	9701	17689, 25677, 33665, 41653, 49641
1559	C-type lectin domain family 17, member A	547437	1714	450065	9702	17690, 25678, 33666, 41654, 49642
1560	C-type lectin domain family 4, member F	272367	1715	272367	9703	17691, 25679, 33667, 41655, 49643
1561	C-type lectin domain family 4, member G	328853	1716	327599	9704	17692, 25680, 33668, 41656, 49644
1562	C-type lectin domain family 4, member G	381308	1717	370709	9705	17693, 25681, 33669, 41657, 49645
1563	C-type lectin domain family 9, member A	355819	1718	348074	9706	17694, 25682, 33670, 41658, 49646
1564	C-type lectin-like 1	327839	1719	331766	9707	17695, 25683, 33671, 41659, 49647

1565	C-type lectin-like 1	540988	1720	444947	9708	17696, 25684, 33672, 41660, 49648
1566	CUB and zona pellucida-like domains 1	338948	1721	340905	9709	17697, 25685, 33673, 41661, 49649
1567	CUB and zona pellucida-like domains 1	368899	1722	357895	9710	17698, 25686, 33674, 41662, 49650
1568	CUB and zona pellucida-like domains 1	368900	1723	357896	9711	17699, 25687, 33675, 41663, 49651
1569	CUB and zona pellucida-like domains 1	368901	1724	357897	9712	17700, 25688, 33676, 41664, 49652
1570	CUB and zona pellucida-like domains 1	368904	1725	357900	9713	17701, 25689, 33677, 41665, 49653
1571	cutaneous T-cell lymphoma-associated antigen 1	391403	1726	375220	9714	17702, 25690, 33678, 41666, 49654
1572	Cutaneous T-cell lymphoma-associated antigen 1	525417	1727	436900	9715	17703, 25691, 33679, 41667, 49655
1573	cut-like homeobox 1	292535	1728	292535	9716	17704, 25692, 33680, 41668, 49656
1574	cut-like homeobox 1	292538	1729	292538	9717	17705, 25693, 33681, 41669, 49657
1575	cut-like homeobox 1	360264	1730	353401	9718	17706, 25694, 33682, 41670, 49658
1576	cut-like homeobox 1	393824	1731	377410	9719	17707, 25695, 33683, 41671, 49659
1577	cut-like homeobox 1	425244	1732	409745	9720	17708, 25696, 33684, 41672, 49660
1578	cut-like homeobox 1	437600	1733	414091	9721	17709, 25697, 33685, 41673, 49661
1579	cut-like homeobox 1	546411	1734	450125	9722	17710, 25698, 33686, 41674, 49662
1580	cut-like homeobox 1	547394	1735	449371	9723	17711, 25699, 33687, 41675, 49663
1581	cut-like homeobox 1	549414	1736	446630	9724	17712, 25700, 33688, 41676, 49664
1582	cut-like homeobox 1	550008	1737	447373	9725	17713, 25701, 33689, 41677, 49665

1583	cut-like homeobox 1	556210	1738	451558	9726	17714, 25702, 33690, 41678, 49666
1584	cut-like homeobox 1	558836	1739	453088	9727	17715, 25703, 33691, 41679, 49667
1585	cut-like homeobox 1	560541	1740	453533	9728	17716, 25704, 33692, 41680, 49668
1586	CXXC finger protein 11	343216	1741	345374	9729	17717, 25705, 33693, 41681, 49669
1587	cyclic nucleotide gated channel alpha 4	379936	1742	369268	9730	17718, 25706, 33694, 41682, 49670
1588	cyclin J-like	257536	1743	257536	9731	17719, 25707, 33695, 41683, 49671
1589	cyclin J-like	393977	1744	377547	9732	17720, 25708, 33696, 41684, 49672
1590	cyclin J-like	505287	1745	444778	9733	17721, 25709, 33697, 41685, 49673
1591	cyclin J-like	519673	1746	427960	9734	17722, 25710, 33698, 41686, 49674
1592	cyclin J-like	541762	1747	446367	9735	17723, 25711, 33699, 41687, 49675
1593	cyclin Pas1/PHO80 domain containing 1	360507	1748	353698	9736	17724, 25712, 33700, 41688, 49676
1594	cyclin Pas1/PHO80 domain containing 1	409789	1749	386277	9737	17725, 25713, 33701, 41689, 49677
1595	cyclin Pas1/PHO80 domain containing 1	453038	1750	410109	9738	17726, 25714, 33702, 41690, 49678
1596	cyclin-dependent kinase 14	265741	1751	265741	9739	17727, 25715, 33703, 41691, 49679
1597	cyclin-dependent kinase 14	380050	1752	369390	9740	17728, 25716, 33704, 41692, 49680
1598	cyclin-dependent kinase 14	436577	1753	398936	9741	17729, 25717, 33705, 41693, 49681
1599	cyclin-dependent kinase 20	286878	1754	286878	9742	17730, 25718, 33706, 41694, 49682
1600	cyclin-dependent kinase 20	325303	1755	322343	9743	17731, 25719, 33707, 41695, 49683

1601	cyclin-dependent kinase 20	336654	1756	338975	9744	17732, 25720, 33708, 41696, 49684
1602	cyclin-dependent kinase 20	375871	1757	365031	9745	17733, 25721, 33709, 41697, 49685
1603	cyclin-dependent kinase 20	375883	1758	365043	9746	17734, 25722, 33710, 41698, 49686
1604	cysteine/tyrosine-rich 1	299340	1759	299340	9747	17735, 25723, 33711, 41699, 49687
1605	cysteine/tyrosine-rich 1	435845	1760	401313	9748	17736, 25724, 33712, 41700, 49688
1606	cysteine-rich hydrophobic domain 1	373502	1761	362601	9749	17737, 25725, 33713, 41701, 49689
1607	cysteine-rich hydrophobic domain 1	373504	1762	362603	9750	17738, 25726, 33714, 41702, 49690
1608	cysteine-rich PAK1 inhibitor	324803	1763	323978	9751	17739, 25727, 33715, 41703, 49691
1609	cysteine-rich PAK1 inhibitor	382944	1764	372402	9752	17740, 25728, 33716, 41704, 49692
1610	cytochrome b reductase 1	321348	1765	319141	9753	17741, 25729, 33717, 41705, 49693
1611	cytochrome b reductase 1	375252	1766	364401	9754	17742, 25730, 33718, 41706, 49694
1612	cytochrome b reductase 1	409484	1767	386739	9755	17743, 25731, 33719, 41707, 49695
1613	cytochrome b, ascorbate dependent 3	294072	1768	294072	9756	17744, 25732, 33720, 41708, 49696
1614	cytochrome b, ascorbate dependent 3	426130	1769	398979	9757	17745, 25733, 33721, 41709, 49697
1615	cytochrome b, ascorbate dependent 3	536915	1770	437390	9758	17746, 25734, 33722, 41710, 49698
1616	cytochrome b, ascorbate dependent 3	537364	1771	438725	9759	17747, 25735, 33723, 41711, 49699
1617	cytochrome b, ascorbate dependent 3	537680	1772	439702	9760	17748, 25736, 33724, 41712, 49700
1618	cytochrome b, ascorbate dependent 3	539128	1773	443005	9761	17749, 25737, 33725, 41713, 49701

1619	cytochrome b, ascorbate dependent 3	542361	1774	443321	9762	17750, 25738, 33726, 41714, 49702
1620	cytochrome b, ascorbate dependent 3	545361	1775	437819	9763	17751, 25739, 33727, 41715, 49703
1621	cytochrome b5 reductase 1	367249	1776	356218	9764	17752, 25740, 33728, 41716, 49704
1622	cytochrome b5 reductase 1	446185	1777	396382	9765	17753, 25741, 33729, 41717, 49705
1623	cytochrome b-561 domain containing 1	310611	1778	309324	9766	17754, 25742, 33730, 41718, 49706
1624	cytochrome b-561 domain containing 1	369868	1779	358884	9767	17755, 25743, 33731, 41719, 49707
1625	cytochrome b-561 domain containing 1	393709	1780	377312	9768	17756, 25744, 33732, 41720, 49708
1626	cytochrome b-561 domain containing 1	420578	1781	413530	9769	17757, 25745, 33733, 41721, 49709
1627	cytochrome b-561 domain containing 1	430195	1782	416898	9770	17758, 25746, 33734, 41722, 49710
1628	cytochrome C oxidase assembly factor 5	328709	1783	330730	9771	17759, 25747, 33735, 41723, 49711
1629	cytochrome c oxidase subunit VIa polypeptide 1 pseudogene 2	423336	1784	404078	9772	17760, 25748, 33736, 41724, 49712
1630	cytochrome c oxidase subunit VIa polypeptide 2	287490	1785	287490	9773	17761, 25749, 33737, 41725, 49713
1631	cytochrome c oxidase subunit VIb polypeptide 2 (testis)	326529	1786	320672	9774	17762, 25750, 33738, 41726, 49714
1632	cytochrome c oxidase subunit VIIb	481445	1787	417656	9775	17763, 25751, 33739, 41727, 49715
1633	cytochrome c oxidase subunit VIIIA (ubiquitous)	314133	1788	321260	9776	17764, 25752, 33740, 41728, 49716
1634	cytochrome c oxidase subunit VIIIC	342144	1789	340568	9777	17765, 25753, 33741, 41729, 49717
1635	cytochrome P450 family 11 subfamily A polypeptide 1	358632	1790	351455	9778	17766, 25754, 33742, 41730, 49718
1636	cytochrome P450, family 11, subfamily A, polypeptide 1	268053	1791	268053	9779	17767, 25755, 33743, 41731, 49719

1637	cytochrome P450, family 11, subfamily A, polypeptide 1	419019	1792	405488	9780	17768, 25756, 33744, 41732, 49720
1638	cytochrome P450, family 11, subfamily A, polypeptide 1	435365	1793	391081	9781	17769, 25757, 33745, 41733, 49721
1639	cytochrome P450, family 11, subfamily A, polypeptide 1	452422	1794	391041	9782	17770, 25758, 33746, 41734, 49722
1640	cytochrome P450, family 11, subfamily A, polypeptide 1	541301	1795	439750	9783	17771, 25759, 33747, 41735, 49723
1641	cytochrome P450, family 2, subfamily C, polypeptide 18	285979	1796	285979	9784	17772, 25760, 33748, 41736, 49724
1642	cytochrome P450, family 2, subfamily C, polypeptide 18	339022	1797	341293	9785	17773, 25761, 33749, 41737, 49725
1643	cytochrome P450, family 2, subfamily W, polypeptide 1	308919	1798	310149	9786	17774, 25762, 33750, 41738, 49726
1644	cytochrome P450, family 20, subfamily A, polypeptide 1	356079	1799	348380	9787	17775, 25763, 33751, 41739, 49727
1645	cytochrome P450, family 20, subfamily A, polypeptide 1	421618	1800	397114	9788	17776, 25764, 33752, 41740, 49728
1646	cytochrome P450, family 26, subfamily B, polypeptide 1	1146	1801	1146	9789	17777, 25765, 33753, 41741, 49729, 56080, 56113
1647	cytochrome P450, family 26, subfamily B, polypeptide 1	546307	1802	443304	9790	17778, 25766, 33754, 41742, 49730
1648	cytochrome P450, family 4, subfamily A, polypeptide 22	294337	1803	294337	9791	17779, 25767, 33755, 41743, 49731
1649	cytochrome P450, family 4, subfamily A, polypeptide 22	371890	1804	360957	9792	17780, 25768, 33756, 41744, 49732
1650	cytochrome P450, family 4, subfamily A, polypeptide 22	371891	1805	360958	9793	17781, 25769, 33757, 41745, 49733
1651	cytochrome P450, family 4, subfamily B, polypeptide 1	271153	1806	271153	9794	17782, 25770, 33758, 41746, 49734
1652	cytochrome P450, family 4, subfamily B, polypeptide 1	371919	1807	360987	9795	17783, 25771, 33759, 41747, 49735
1653	cytochrome P450, family 4, subfamily B, polypeptide 1	371923	1808	360991	9796	17784, 25772, 33760, 41748, 49736

1654	cytochrome P450, family 4, subfamily F, polypeptide 2	11989	1809	11989	9797	17785, 25773, 33761, 41749, 49737, 56081, 56114
1655	cytochrome P450, family 4, subfamily F, polypeptide 2	221700	1810	221700	9798	17786, 25774, 33762, 41750, 49738
1656	cytochrome P450, family 4, subfamily F, polypeptide 2	392846	1811	376588	9799	17787, 25775, 33763, 41751, 49739
1657	cytochrome P450, family 4, subfamily X, polypeptide 1	371901	1812	360968	9800	17788, 25776, 33764, 41752, 49740
1658	cytochrome P450, family 4, subfamily X, polypeptide 1	538609	1813	445965	9801	17789, 25777, 33765, 41753, 49741
1659	cytochrome P450, family 4, subfamily Z, polypeptide 1	334194	1814	334246	9802	17790, 25778, 33766, 41754, 49742
1660	cytoskeleton-associated protein 4	378026	1815	367265	9803	17791, 25779, 33767, 41755, 49743
1661	dachsous 1 (Drosophila)	299441	1816	299441	9804	17792, 25780, 33768, 41756, 49744
1662	dachsous 1 (Drosophila)	442153	1817	390601	9805	17793, 25781, 33769, 41757, 49745
1663	DC-STAMP domain containing 1	295542	1818	295542	9806	17794, 25782, 33770, 41758, 49746
1664	DC-STAMP domain containing 1	368419	1819	357404	9807	17795, 25783, 33771, 41759, 49747
1665	DC-STAMP domain containing 1	392480	1820	376271	9808	17796, 25784, 33772, 41760, 49748
1666	DC-STAMP domain containing 1	423025	1821	387369	9809	17797, 25785, 33773, 41761, 49749
1667	DC-STAMP domain containing 2	295536	1822	295536	9810	17798, 25786, 33774, 41762, 49750
1668	DC-STAMP domain containing 2	368424	1823	357409	9811	17799, 25787, 33775, 41763, 49751
1669	DDB1 and CUL4 associated factor 17	375255	1824	364404	9812	17800, 25788, 33776, 41764, 49752
1670	DDB1 and CUL4 associated factor 17	429466	1825	389290	9813	17801, 25789, 33777, 41765, 49753
1671	DDB1 and CUL4 associated factor 17	539783	1826	442238	9814	17802, 25790, 33778, 41766, 49754

1672	DDRGK domain containing 1	354488	1827	346483	9815	17803, 25791, 33779, 41767, 49755
1673	DDRGK domain containing 1	380201	1828	369548	9816	17804, 25792, 33780, 41768, 49756
1674	DDRGK domain containing 1	380213	1829	369561	9817	17805, 25793, 33781, 41769, 49757
1675	death associated protein-like 1	309950	1830	309538	9818	17806, 25794, 33782, 41770, 49758
1676	dehydrogenase E1 and transketolase domain containing 1	263035	1831	263035	9819	17807, 25795, 33783, 41771, 49759
1677	dehydrogenase E1 and transketolase domain containing 1	415935	1832	400625	9820	17808, 25796, 33784, 41772, 49760
1678	dehydrogenase E1 and transketolase domain containing 1	437298	1833	388163	9821	17809, 25797, 33785, 41773, 49761
1679	dehydrogenase E1 and transketolase domain containing 1	448829	1834	398482	9822	17810, 25798, 33786, 41774, 49762
1680	dehydrogenase/reductase (SDR family) member 1	288111	1835	288111	9823	17811, 25799, 33787, 41775, 49763
1681	dehydrogenase/reductase (SDR family) member 1	396813	1836	380027	9824	17812, 25800, 33788, 41776, 49764
1682	dehydrogenase/reductase (SDR family) member 7B	346603	1837	320352	9825	17813, 25801, 33789, 41777, 49765
1683	dehydrogenase/reductase (SDR family) member 7B	395511	1838	378887	9826	17814, 25802, 33790, 41778, 49766
1684	deleted in liver cancer 1	276297	1839	276297	9827	17815, 25803, 33791, 41779, 49767
1685	deleted in liver cancer 1	316609	1840	321034	9828	17816, 25804, 33792, 41780, 49768
1686	deleted in liver cancer 1	358919	1841	351797	9829	17817, 25805, 33793, 41781, 49769
1687	delta(4)-desaturase, sphingolipid 1	323699	1842	316476	9830	17818, 25806, 33794, 41782, 49770
1688	delta(4)-desaturase, sphingolipid 1	391877	1843	375749	9831	17819, 25807, 33795, 41783, 49771
1689	delta(4)-desaturase, sphingolipid 1	415210	1844	400545	9832	17820, 25808, 33796, 41784, 49772

1690	delta-like 2 homolog (Drosophila)	357338	1845	349893	9833	17821, 25809, 33797, 41785, 49773
1691	delta-like 2 homolog (Drosophila)	372485	1846	361563	9834	17822, 25810, 33798, 41786, 49774
1692	delta-like 2 homolog (Drosophila)	372488	1847	361566	9835	17823, 25811, 33799, 41787, 49775
1693	delta-like 2 homolog (Drosophila)	372496	1848	361574	9836	17824, 25812, 33800, 41788, 49776
1694	delta-like 2 homolog (Drosophila)	414245	1849	398906	9837	17825, 25813, 33801, 41789, 49777
1695	delta-like 2 homolog (Drosophila)	430324	1850	399829	9838	17826, 25814, 33802, 41790, 49778
1696	DENN/MADD domain containing 4C	307015	1851	305795	9839	17827, 25815, 33803, 41791, 49779
1697	DENN/MADD domain containing 4C	361024	1852	354301	9840	17828, 25816, 33804, 41792, 49780
1698	DENN/MADD domain containing 4C	380424	1853	369789	9841	17829, 25817, 33805, 41793, 49781
1699	DENN/MADD domain containing 4C	380427	1854	369792	9842	17830, 25818, 33806, 41794, 49782
1700	DENN/MADD domain containing 4C	380432	1855	369797	9843	17831, 25819, 33807, 41795, 49783
1701	DENN/MADD domain containing 4C	380437	1856	369802	9844	17832, 25820, 33808, 41796, 49784
1702	DENN/MADD domain containing 4C	453857	1857	394407	9845	17833, 25821, 33809, 41797, 49785
1703	DENN/MADD domain containing 4C	540671	1858	443804	9846	17834, 25822, 33810, 41798, 49786
1704	DENN/MADD domain containing 5A	328194	1859	328524	9847	17835, 25823, 33811, 41799, 49787
1705	DENN/MADD domain containing 5A	527700	1860	432549	9848	17836, 25824, 33812, 41800, 49788
1706	DENN/MADD domain containing 5A	530044	1861	435866	9849	17837, 25825, 33813, 41801, 49789
1707	DENN/MADD domain containing 5B	306833	1862	306482	9850	17838, 25826, 33814, 41802, 49790

1708	DENN/MADD domain containing 5B	354285	1863	346238	9851	17839, 25827, 33815, 41803, 49791
1709	DENN/MADD domain containing 5B	389082	1864	373734	9852	17840, 25828, 33816, 41804, 49792
1710	DENN/MADD domain containing 5B	536562	1865	444889	9853	17841, 25829, 33817, 41805, 49793
1711	dephospho-CoA kinase domain containing	310604	1866	308515	9854	17842, 25830, 33818, 41806, 49794
1712	dephospho-CoA kinase domain containing	342350	1867	341504	9855	17843, 25831, 33819, 41807, 49795
1713	dephospho-CoA kinase domain containing	452796	1868	413483	9856	17844, 25832, 33820, 41808, 49796
1714	Der1-like domain family, member 1	259512	1869	259512	9857	17845, 25833, 33821, 41809, 49797
1715	Der1-like domain family, member 1	405944	1870	384289	9858	17846, 25834, 33822, 41810, 49798
1716	Der1-like domain family, member 1	419562	1871	389965	9859	17847, 25835, 33823, 41811, 49799
1717	Der1-like domain family, member 2	158771	1872	158771	9860	17848, 25836, 33824, 41812, 49800, 56082, 56115
1718	Der1-like domain family, member 3	318109	1873	315303	9861	17849, 25837, 33825, 41813, 49801
1719	Der1-like domain family, member 3	476077	1874	419399	9862	17850, 25838, 33826, 41814, 49802
1720	derlin 3	406855	1875	384744	9863	17851, 25839, 33827, 41815, 49803
1721	diacylglycerol kinase zeta	343674	1876	343065	9864	17852, 25840, 33828, 41816, 49804
1722	diacylglycerol kinase zeta	527911	1877	436291	9865	17853, 25841, 33829, 41817, 49805
1723	diacylglycerol kinase, eta	261491	1878	261491	9866	17854, 25842, 33830, 41818, 49806
1724	diacylglycerol kinase, eta	337343	1879	337572	9867	17855, 25843, 33831, 41819, 49807
1725	diacylglycerol kinase, eta	379274	1880	368576	9868	17856, 25844, 33832, 41820, 49808

1726	diacylglycerol kinase, eta	536612	1881	445114	9869	17857, 25845, 33833, 41821, 49809
1727	diacylglycerol kinase, eta	538674	1882	441308	9870	17858, 25846, 33834, 41822, 49810
1728	diacylglycerol kinase, eta	540693	1883	440823	9871	17859, 25847, 33835, 41823, 49811
1729	diacylglycerol kinase, zeta	318201	1884	320340	9872	17860, 25848, 33836, 41824, 49812
1730	diacylglycerol kinase, zeta	395574	1885	378941	9873	17861, 25849, 33837, 41825, 49813
1731	diacylglycerol kinase, zeta	421244	1886	391021	9874	17862, 25850, 33838, 41826, 49814
1732	diacylglycerol kinase, zeta	454345	1887	412178	9875	17863, 25851, 33839, 41827, 49815
1733	diacylglycerol kinase, zeta	456247	1888	395684	9876	17864, 25852, 33840, 41828, 49816
1734	diacylglycerol kinase, zeta	543978	1889	438417	9877	17865, 25853, 33841, 41829, 49817
1735	diacylglycerol O-acyltransferase 2-like 6	333026	1890	328036	9878	17866, 25854, 33842, 41830, 49818
1736	diazepam binding inhibitor (GABA receptor modulator acyl-CoA binding protein)	393103	1891	376815	9879	17867, 25855, 33843, 41831, 49819
1737	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	311521	1892	311117	9880	17868, 25856, 33844, 41832, 49820
1738	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	355857	1893	348116	9881	17869, 25857, 33845, 41833, 49821
1739	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	409094	1894	386486	9882	17870, 25858, 33846, 41834, 49822
1740	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	535617	1895	442917	9883	17871, 25859, 33847, 41835, 49823

1741	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	535757	1896	439012	9884	17872, 25860, 33848, 41836, 49824
1742	diazepam binding inhibitor (GABA receptor modulator, acyl-CoA binding protein)	542275	1897	440698	9885	17873, 25861, 33849, 41837, 49825
1743	dihydrofolate reductase-like 1	314636	1898	319170	9886	17874, 25862, 33850, 41838, 49826
1744	dihydrofolate reductase-like 1	394221	1899	377768	9887	17875, 25863, 33851, 41839, 49827
1745	dihydrofolate reductase-like 1	461173	1900	418415	9888	17876, 25864, 33852, 41840, 49828
1746	dihydrofolate reductase-like 1	496983	1901	420810	9889	17877, 25865, 33853, 41841, 49829
1747	DIRAS family, GTP-binding RAS-like 1	323469	1902	325836	9890	17878, 25866, 33854, 41842, 49830
1748	DIRAS family, GTP-binding RAS-like 2	375765	1903	364919	9891	17879, 25867, 33855, 41843, 49831
1749	DIRAS family, GTP-binding RAS-like 3	370981	1904	360020	9892	17880, 25868, 33856, 41844, 49832
1750	DIRAS family, GTP-binding RAS-like 3	395201	1905	378627	9893	17881, 25869, 33857, 41845, 49833
1751	discoidin domain receptor tyrosine kinase 1	413044	1906	396609	9894	17882, 25870, 33858, 41846, 49834
1752	discoidin domain receptor tyrosine kinase 1	413115	1907	414878	9895	17883, 25871, 33859, 41847, 49835
1753	discoidin domain receptor tyrosine kinase 1	414077	1908	395405	9896	17884, 25872, 33860, 41848, 49836
1754	discoidin domain receptor tyrosine kinase 1	421499	1909	402013	9897	17885, 25873, 33861, 41849, 49837
1755	discoidin domain receptor tyrosine kinase 1	421672	1910	403454	9898	17886, 25874, 33862, 41850, 49838
1756	discoidin domain receptor tyrosine kinase 1	422275	1911	393056	9899	17887, 25875, 33863, 41851, 49839
1757	discoidin domain receptor tyrosine kinase 1	422628	1912	396187	9900	17888, 25876, 33864, 41852, 49840

1758	discoidin domain receptor tyrosine kinase 1	426303	1913	401304	9901	17889, 25877, 33865, 41853, 49841
1759	discoidin domain receptor tyrosine kinase 1	429955	1914	402647	9902	17890, 25878, 33866, 41854, 49842
1760	discoidin domain receptor tyrosine kinase 1	430486	1915	404054	9903	17891, 25879, 33867, 41855, 49843
1761	discoidin domain receptor tyrosine kinase 1	433322	1916	398904	9904	17892, 25880, 33868, 41856, 49844
1762	discoidin domain receptor tyrosine kinase 1	433393	1917	389085	9905	17893, 25881, 33869, 41857, 49845
1763	discoidin domain receptor tyrosine kinase 1	434428	1918	388866	9906	17894, 25882, 33870, 41858, 49846
1764	discoidin domain receptor tyrosine kinase 1	439604	1919	398343	9907	17895, 25883, 33871, 41859, 49847
1765	discoidin domain receptor tyrosine kinase 1	439772	1920	402992	9908	17896, 25884, 33872, 41860, 49848
1766	discoidin domain receptor tyrosine kinase 1	440427	1921	414928	9909	17897, 25885, 33873, 41861, 49849
1767	discoidin domain receptor tyrosine kinase 1	444160	1922	391895	9910	17898, 25886, 33874, 41862, 49850
1768	discoidin domain receptor tyrosine kinase 1	445749	1923	395136	9911	17899, 25887, 33875, 41863, 49851
1769	discoidin domain receptor tyrosine kinase 1	448537	1924	412396	9912	17900, 25888, 33876, 41864, 49852
1770	discoidin domain receptor tyrosine kinase 1	454377	1925	406865	9913	17901, 25889, 33877, 41865, 49853
1771	discoidin domain receptor tyrosine kinase 1	458576	1926	406688	9914	17902, 25890, 33878, 41866, 49854
1772	discoidin domain receptor tyrosine kinase 1	549169	1927	447523	9915	17903, 25891, 33879, 41867, 49855
1773	discoidin, CUB and LCCL domain containing 1	296955	1928	296955	9916	17904, 25892, 33880, 41868, 49856
1774	discoidin, CUB and LCCL domain containing 1	338728	1929	342422	9917	17905, 25893, 33881, 41869, 49857
1775	discoidin, CUB and LCCL domain containing 1	368503	1930	357489	9918	17906, 25894, 33882, 41870, 49858

1776	discoidin, CUB and LCCL domain containing 1	392504	1931	376292	9919	17907, 25895, 33883, 41871, 49859
1777	discoidin, CUB and LCCL domain containing 2	326840	1932	321573	9920	17908, 25896, 33884, 41872, 49860
1778	discoidin, CUB and LCCL domain containing 2	326857	1933	321646	9921	17909, 25897, 33885, 41873, 49861
1779	discoidin, CUB and LCCL domain containing 2	404023	1934	385656	9922	17910, 25898, 33886, 41874, 49862
1780	discs large (Drosophila) homolog-associated protein 1	400145	1935	383010	9923	17911, 25899, 33887, 41875, 49863
1781	discs large (Drosophila) homolog-associated protein 1	400150	1936	383014	9924	17912, 25900, 33888, 41876, 49864
1782	discs large (Drosophila) homolog-associated protein 1	400155	1937	383019	9925	17913, 25901, 33889, 41877, 49865
1783	discs large (Drosophila) homolog-associated protein 1	581527	1938	463864	9926	17914, 25902, 33890, 41878, 49866
1784	discs, large (Drosophila) homolog-associated protein 1	315677	1939	316377	9927	17915, 25903, 33891, 41879, 49867
1785	discs, large (Drosophila) homolog-associated protein 1	400147	1940	383011	9928	17916, 25904, 33892, 41880, 49868
1786	discs, large (Drosophila) homolog-associated protein 1	515196	1941	445973	9929	17917, 25905, 33893, 41881, 49869
1787	discs, large (Drosophila) homolog-associated protein 1	534970	1942	437817	9930	17918, 25906, 33894, 41882, 49870
1788	discs, large (Drosophila) homolog-associated protein 1	539435	1943	446312	9931	17919, 25907, 33895, 41883, 49871
1789	discs, large (Drosophila) homolog-associated protein 3	235180	1944	235180	9932	17920, 25908, 33896, 41884, 49872
1790	discs, large (Drosophila) homolog-associated	373347	1945	362444	9933	17921, 25909, 33897, 41885, 49873

	protein 3					
1791	discs, large (Drosophila) homolog-associated protein 3	542913	1946	445209	9934	17922, 25910, 33898, 41886, 49874
1792	dishevelled, dsh homolog 2 (Drosophila)	5340	1947	5340	9935	17923, 25911, 33899, 41887, 49875, 56083, 56116
1793	dispatched homolog 1 (Drosophila)	284476	1948	284476	9936	17924, 25912, 33900, 41888, 49876
1794	dispatched homolog 1 (Drosophila)	360254	1949	355848	9937	17925, 25913, 33901, 41889, 49877
1795	dispatched homolog 2 (Drosophila)	267889	1950	267889	9938	17926, 25914, 33902, 41890, 49878
1796	DIX domain containing 1	315253	1951	314068	9939	17927, 25915, 33903, 41891, 49879
1797	DIX domain containing 1	440460	1952	394352	9940	17928, 25916, 33904, 41892, 49880
1798	DIX domain containing 1	531396	1953	432959	9941	17929, 25917, 33905, 41893, 49881
1799	DnaJ (Hsp40) homolog, subfamily B, member 14	442697	1954	404381	9942	17930, 25918, 33906, 41894, 49882
1800	DnaJ (Hsp40) homolog, subfamily B, member 4	370763	1955	359799	9943	17931, 25919, 33907, 41895, 49883
1801	DnaJ (Hsp40) homolog, subfamily B, member 4	426517	1956	399494	9944	17932, 25920, 33908, 41896, 49884
1802	DnaJ (Hsp40) homolog, subfamily C , member 25	313525	1957	320650	9945	17933, 25921, 33909, 41897, 49885
1803	DnaJ (Hsp40) homolog, subfamily C , member 25	556107	1958	451984	9946	17934, 25922, 33910, 41898, 49886
1804	DnaJ (Hsp40) homolog, subfamily C, member 1	376946	1959	366145	9947	17935, 25923, 33911, 41899, 49887
1805	DnaJ (Hsp40) homolog, subfamily C, member 1	376980	1960	366179	9948	17936, 25924, 33912, 41900, 49888
1806	DnaJ (Hsp40) homolog, subfamily C, member 1	447548	1961	398185	9949	17937, 25925, 33913, 41901, 49889
1807	DnaJ (Hsp40) homolog, subfamily	294401	1962	294401	9950	17938, 25926, 33914, 41902,

	C, member 11					49890
1808	DnaJ (Hsp40) homolog, subfamily C, member 11	349363	1963	326304	9951	17939, 25927, 33915, 41903, 49891
1809	DnaJ (Hsp40) homolog, subfamily C, member 11	377573	1964	366796	9952	17940, 25928, 33916, 41904, 49892
1810	DnaJ (Hsp40) homolog, subfamily C, member 11	377577	1965	366800	9953	17941, 25929, 33917, 41905, 49893
1811	DnaJ (Hsp40) homolog, subfamily C, member 11	426784	1966	410194	9954	17942, 25930, 33918, 41906, 49894
1812	DnaJ (Hsp40) homolog, subfamily C, member 11	451196	1967	415871	9955	17943, 25931, 33919, 41907, 49895
1813	DnaJ (Hsp40) homolog, subfamily C, member 11	542246	1968	444020	9956	17944, 25932, 33920, 41908, 49896
1814	DnaJ (Hsp40) homolog, subfamily C, member 14	317269	1969	316240	9957	17945, 25933, 33921, 41909, 49897
1815	DnaJ (Hsp40) homolog, subfamily C, member 14	317287	1970	317500	9958	17946, 25934, 33922, 41910, 49898
1816	DnaJ (Hsp40) homolog, subfamily C, member 14	357606	1971	350223	9959	17947, 25935, 33923, 41911, 49899
1817	DnaJ (Hsp40) homolog, subfamily C, member 14	537962	1972	443945	9960	17948, 25936, 33924, 41912, 49900
1818	DnaJ (Hsp40) homolog, subfamily C, member 14	540330	1973	441495	9961	17949, 25937, 33925, 41913, 49901
1819	DnaJ (Hsp40) homolog, subfamily C, member 14	546957	1974	448876	9962	17950, 25938, 33926, 41914, 49902
1820	DnaJ (Hsp40) homolog, subfamily C, member 14	547445	1975	450196	9963	17951, 25939, 33927, 41915, 49903
1821	DnaJ (Hsp40) homolog, subfamily C, member 15	379221	1976	368523	9964	17952, 25940, 33928, 41916, 49904
1822	DnaJ (Hsp40) homolog, subfamily C, member 16	375838	1977	364998	9965	17953, 25941, 33929, 41917, 49905
1823	DnaJ (Hsp40) homolog, subfamily C, member 16	375847	1978	365007	9966	17954, 25942, 33930, 41918, 49906
1824	DnaJ (Hsp40) homolog, subfamily C, member 16	375849	1979	365009	9967	17955, 25943, 33931, 41919, 49907

1825	DnaJ (Hsp40) homolog, subfamily C, member 16	546230	1980	440636	9968	17956, 25944, 33932, 41920, 49908
1826	DnaJ (Hsp40) homolog, subfamily C, member 18	302060	1981	302843	9969	17957, 25945, 33933, 41921, 49909
1827	DnaJ (Hsp40) homolog, subfamily C, member 18	512473	1982	426819	9970	17958, 25946, 33934, 41922, 49910
1828	DnaJ (Hsp40) homolog, subfamily C, member 18	515277	1983	425523	9971	17959, 25947, 33935, 41923, 49911
1829	DnaJ (Hsp40) homolog, subfamily C, member 18	515581	1984	424572	9972	17960, 25948, 33936, 41924, 49912
1830	DnaJ (Hsp40) homolog, subfamily C, member 22	395069	1985	378508	9973	17961, 25949, 33937, 41925, 49913
1831	DnaJ (Hsp40) homolog, subfamily C, member 22	549441	1986	446830	9974	17962, 25950, 33938, 41926, 49914
1832	DnaJ (Hsp40) homolog, subfamily C, member 30	395176	1987	378605	9975	17963, 25951, 33939, 41927, 49915
1833	DnaJ (Hsp40) homolog, subfamily C, member 30	539255	1988	443739	9976	17964, 25952, 33940, 41928, 49916
1834	DnaJ (Hsp40) homolog, subfamily C, member 4	321685	1989	396896	9977	17965, 25953, 33941, 41929, 49917
1835	DNL-type zinc finger	371738	1990	360803	9978	17966, 25954, 33942, 41930, 49918
1836	dolichol kinase	372586	1991	361667	9979	17967, 25955, 33943, 41931, 49919
1837	dolichol kinase	515348	1992	445830	9980	17968, 25956, 33944, 41932, 49920
1838	dolichyl pyrophosphate phosphatase 1	372546	1993	361625	9981	17969, 25957, 33945, 41933, 49921
1839	dolichyl pyrophosphate phosphatase 1	406974	1994	384043	9982	17970, 25958, 33946, 41934, 49922
1840	dolichyl pyrophosphate phosphatase 1	540102	1995	440218	9983	17971, 25959, 33947, 41935, 49923
1841	dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosamineph osphotransferase 1 (GlcNAc-1-P	354202	1996	346142	9984	17972, 25960, 33948, 41936, 49924

	transferase)					
1842	dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (GlcNAc-1-P transferase)	409993	1997	386597	9985	17973, 25961, 33949, 41937, 49925
1843	dolichyl-phosphate (UDP-N-acetylglucosamine) N-acetylglucosaminephosphotransferase 1 (GlcNAc-1-P transferase)	432443	1998	404036	9986	17974, 25962, 33950, 41938, 49926
1844	dolichyl-phosphate mannosyltransferase polypeptide 2, regulatory subunit	314392	1999	322181	9987	17975, 25963, 33951, 41939, 49927
1845	dolichyl-phosphate mannosyltransferase polypeptide 2, regulatory subunit	373110	2000	362202	9988	17976, 25964, 33952, 41940, 49928
1846	dopey family member 1	237163	2001	237163	9989	17977, 25965, 33953, 41941, 49929
1847	dopey family member 1	349129	2002	195654	9990	17978, 25966, 33954, 41942, 49930
1848	dopey family member 1	369739	2003	358754	9991	17979, 25967, 33955, 41943, 49931
1849	dopey family member 1	536812	2004	439675	9992	17980, 25968, 33956, 41944, 49932
1850	dual specificity phosphatase 10	323825	2005	322015	9993	17981, 25969, 33957, 41945, 49933
1851	dual specificity phosphatase 10	366899	2006	355866	9994	17982, 25970, 33958, 41946, 49934
1852	dual specificity phosphatase 10	418487	2007	390238	9995	17983, 25971, 33959, 41947, 49935
1853	dual specificity phosphatase 10	544095	2008	441302	9996	17984, 25972, 33960, 41948, 49936

1854	dual specificity phosphatase 15	278979	2009	278979	9997	17985, 25973, 33961, 41949, 49937
1855	dual specificity phosphatase 15	339738	2010	341658	9998	17986, 25974, 33962, 41950, 49938
1856	dual specificity phosphatase 15	375953	2011	365120	9999	17987, 25975, 33963, 41951, 49939
1857	dual specificity phosphatase 15	375966	2012	365133	10000	17988, 25976, 33964, 41952, 49940
1858	dual specificity phosphatase 15	398083	2013	381157	10001	17989, 25977, 33965, 41953, 49941
1859	dual specificity phosphatase 15	398084	2014	381158	10002	17990, 25978, 33966, 41954, 49942
1860	dual specificity phosphatase 15	447647	2015	397486	10003	17991, 25979, 33967, 41955, 49943
1861	dual specificity phosphatase 15	486996	2016	419818	10004	17992, 25980, 33968, 41956, 49944
1862	dynein, axonemal, assembly factor 2	298292	2017	298292	10005	17993, 25981, 33969, 41957, 49945
1863	dynein, axonemal, assembly factor 2	406043	2018	384862	10006	17994, 25982, 33970, 41958, 49946
1864	dynein, axonemal, light chain 4	216068	2019	216068	10007	17995, 25983, 33971, 41959, 49947
1865	dynein, cytoplasmic 1, light intermediate chain 1	273130	2020	273130	10008	17996, 25984, 33972, 41960, 49948
1866	dynein, light chain, Tctex-type 3	378578	2021	367841	10009	17997, 25985, 33973, 41961, 49949
1867	dynein, light chain, Tctex-type 3	378581	2022	367844	10010	17998, 25986, 33974, 41962, 49950
1868	dynein, light chain, Tctex-type 3	432389	2023	402695	10011	17999, 25987, 33975, 41963, 49951
1869	dystrotelin	452335	2024	396593	10012	18000, 25988, 33976, 41964, 49952
1870	E2F-associated phosphoprotein	250454	2025	250454	10013	18001, 25989, 33977, 41965, 49953
1871	early endosome antigen 1	322349	2026	317955	10014	18002, 25990, 33978, 41966, 49954

1872	early endosome antigen 1	540777	2027	441243	10015	18003, 25991, 33979, 41967, 49955
1873	ectonucleoside triphosphate diphosphohydrolase 4	356206	2028	348536	10016	18004, 25992, 33980, 41968, 49956
1874	ectonucleoside triphosphate diphosphohydrolase 4	358689	2029	351520	10017	18005, 25993, 33981, 41969, 49957
1875	ectonucleoside triphosphate diphosphohydrolase 4	417069	2030	408573	10018	18006, 25994, 33982, 41970, 49958
1876	ectonucleoside triphosphate diphosphohydrolase 7	370489	2031	359520	10019	18007, 25995, 33983, 41971, 49959
1877	ectonucleoside triphosphate diphosphohydrolase 8	344119	2032	344089	10020	18008, 25996, 33984, 41972, 49960
1878	ectonucleoside triphosphate diphosphohydrolase 8	371506	2033	360561	10021	18009, 25997, 33985, 41973, 49961
1879	ectonucleoside triphosphate diphosphohydrolase 8	472938	2034	420531	10022	18010, 25998, 33986, 41974, 49962
1880	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)	321037	2035	318066	10023	18011, 25999, 33987, 41975, 49963
1881	ectonucleotide pyrophosphatase/phosphodiesterase 4 (putative)	371401	2036	360454	10024	18012, 26000, 33988, 41976, 49964
1882	ectonucleotide pyrophosphatase/phosphodiesterase 7	328313	2037	332656	10025	18013, 26001, 33989, 41977, 49965
1883	EF-hand domain family, member A1	382374	2038	371811	10026	18014, 26002, 33990, 41978, 49966
1884	EF-hand domain family, member A2	318063	2039	321455	10027	18015, 26003, 33991, 41979, 49967
1885	EF-hand domain family, member D2	375975	2040	365142	10028	18016, 26004, 33992, 41980, 49968
1886	EF-hand domain family, member D2	375980	2041	365147	10029	18017, 26005, 33993, 41981, 49969

1887	EF-hand domain family, member D2	445566	2042	395153	10030	18018, 26006, 33994, 41982, 49970
1888	EGF, latrophilin and seven transmembrane domain containing 1	370742	2043	359778	10031	18019, 26007, 33995, 41983, 49971
1889	EGF, latrophilin and seven transmembrane domain containing 1	401034	2044	383813	10032	18020, 26008, 33996, 41984, 49972
1890	egf-like module containing mucin-like hormone receptor-like 2	596991	2045	472280	10033	18021, 26009, 33997, 41985, 49973
1891	egf-like module containing, mucin-like, hormone receptor-like 2	315576	2046	319883	10034	18022, 26010, 33998, 41986, 49974
1892	egf-like module containing, mucin-like, hormone receptor-like 2	346057	2047	263380	10035	18023, 26011, 33999, 41987, 49975
1893	egf-like module containing, mucin-like, hormone receptor-like 2	353005	2048	319838	10036	18024, 26012, 34000, 41988, 49976
1894	egf-like module containing, mucin-like, hormone receptor-like 2	353876	2049	319454	10037	18025, 26013, 34001, 41989, 49977
1895	egf-like module containing, mucin-like, hormone receptor-like 2	360222	2050	353356	10038	18026, 26014, 34002, 41990, 49978
1896	egf-like module containing, mucin-like, hormone receptor-like 2	392962	2051	376689	10039	18027, 26015, 34003, 41991, 49979
1897	egf-like module containing, mucin-like, hormone receptor-like 2	392964	2052	376691	10040	18028, 26016, 34004, 41992, 49980
1898	egf-like module containing, mucin-like, hormone receptor-like 2	392965	2053	376692	10041	18029, 26017, 34005, 41993, 49981
1899	egf-like module containing, mucin-like, hormone receptor-like 2	392967	2054	376694	10042	18030, 26018, 34006, 41994, 49982
1900	ELKS/RAB6-interacting/CAST family member 2	288221	2055	288221	10043	18031, 26019, 34007, 41995, 49983

1901	ELKS/RAB6-interacting/CAST family member 2	460849	2056	417445	10044	18032, 26020, 34008, 41996, 49984
1902	ELKS/RAB6-interacting/CAST family member 2	492584	2057	417280	10045	18033, 26021, 34009, 41997, 49985
1903	embigin	303221	2058	302289	10046	18034, 26022, 34010, 41998, 49986
1904	emopamil binding protein-like	242827	2059	242827	10047	18035, 26023, 34011, 41999, 49987
1905	emopamil binding protein-like	378274	2060	367523	10048	18036, 26024, 34012, 42000, 49988
1906	Enah/Vasp-like	392920	2061	376652	10049	18037, 26025, 34013, 42001, 49989
1907	Enah/Vasp-like	402714	2062	384720	10050	18038, 26026, 34014, 42002, 49990
1908	Enah/Vasp-like	539470	2063	440743	10051	18039, 26027, 34015, 42003, 49991
1909	Enah/Vasp-like	544450	2064	437904	10052	18040, 26028, 34016, 42004, 49992
1910	Enah/Vasp-like	554695	2065	451821	10053	18041, 26029, 34017, 42005, 49993
1911	endogenous retrovirus group FRD, member 1	472091	2066	420174	10054	18042, 26030, 34018, 42006, 49994
1912	endogenous retrovirus group FRD, member 1	542862	2067	444461	10055	18043, 26031, 34019, 42007, 49995
1913	endogenous retrovirus group W, member 1	493463	2068	419945	10056	18044, 26032, 34020, 42008, 49996
1914	endonuclease/exonuclease/phosphatase family domain containing 1	242108	2069	242108	10057	18045, 26033, 34021, 42009, 49997
1915	endonuclease/exonuclease/phosphatase family domain containing 1	534978	2070	442692	10058	18046, 26034, 34022, 42010, 49998
1916	endoplasmic reticulum protein 27	266397	2071	266397	10059	18047, 26035, 34023, 42011, 49999
1917	endoplasmic reticulum to nucleus signaling 1	433197	2072	401445	10060	18048, 26036, 34024, 42012, 50000

1918	endoplasmic reticulum-golgi intermediate compartment (ERGIC) 1	393784	2073	377374	10061	18049, 26037, 34025, 42013, 50001
1919	endothelial cell-specific chemotaxis regulator	510908	2074	421010	10062	18050, 26038, 34026, 42014, 50002
1920	endothelial cell-specific chemotaxis regulator	515823	2075	421364	10063	18051, 26039, 34027, 42015, 50003
1921	endothelin converting enzyme 2	324557	2076	314295	10064	18052, 26040, 34028, 42016, 50004
1922	endothelin converting enzyme 2	359140	2077	352052	10065	18053, 26041, 34029, 42017, 50005
1923	endothelin converting enzyme 2	402825	2078	384223	10066	18054, 26042, 34030, 42018, 50006
1924	endothelin converting enzyme 2	404464	2079	385846	10067	18055, 26043, 34031, 42019, 50007
1925	endothelin converting enzyme 2	357474	2080	350066	10068	18056, 26044, 34032, 42020, 50008
1926	enoyl CoA hydratase domain containing 2	358358	2081	351125	10069	18057, 26045, 34033, 42021, 50009
1927	enoyl CoA hydratase domain containing 2	371522	2082	360577	10070	18058, 26046, 34034, 42022, 50010
1928	enoyl CoA hydratase domain containing 2	536120	2083	439264	10071	18059, 26047, 34035, 42023, 50011
1929	enoyl CoA hydratase domain containing 2	541281	2084	445358	10072	18060, 26048, 34036, 42024, 50012
1930	enoyl CoA hydratase domain containing 2	467988	2085	441962	10073	18061, 26049, 34037, 42025, 50013
1931	enoyl CoA hydratase domain containing 3	379215	2086	368517	10074	18062, 26050, 34038, 42026, 50014
1932	enoyl CoA hydratase domain containing 3	420401	2087	405584	10075	18063, 26051, 34039, 42027, 50015
1933	enoyl CoA hydratase domain containing 3	422887	2088	398429	10076	18064, 26052, 34040, 42028, 50016
1934	enoyl-CoA delta isomerase 1	301729	2089	301729	10077	18065, 26053, 34041, 42029, 50017

1935	enoyl-CoA delta isomerase 1	562238	2090	456319	10078	18066, 26054, 34042, 42030, 50018
1936	enoyl-CoA delta isomerase 2	361538	2091	354737	10079	18067, 26055, 34043, 42031, 50019
1937	enoyl-CoA delta isomerase 2	380118	2092	369461	10080	18068, 26056, 34044, 42032, 50020
1938	enoyl-CoA delta isomerase 2	380125	2093	369468	10081	18069, 26057, 34045, 42033, 50021
1939	enoyl-CoA delta isomerase 2	413766	2094	406969	10082	18070, 26058, 34046, 42034, 50022
1940	enoyl-CoA delta isomerase 2	465828	2095	420309	10083	18071, 26059, 34047, 42035, 50023
1941	EPH receptor A4	281821	2096	281821	10084	18072, 26060, 34048, 42036, 50024
1942	EPH receptor A4	392071	2097	375923	10085	18073, 26061, 34049, 42037, 50025
1943	EPH receptor A4	409854	2098	386276	10086	18074, 26062, 34050, 42038, 50026
1944	EPH receptor A4	409938	2099	386829	10087	18075, 26063, 34051, 42039, 50027
1945	EPH receptor A4	434266	2100	404089	10088	18076, 26064, 34052, 42040, 50028
1946	EPH receptor A4	541600	2101	444085	10089	18077, 26065, 34053, 42041, 50029
1947	EPH receptor A7	369297	2102	358303	10090	18078, 26066, 34054, 42042, 50030
1948	EPH receptor A7	369303	2103	358309	10091	18079, 26067, 34055, 42043, 50031
1949	ephrin-A5	333274	2104	328777	10092	18080, 26068, 34056, 42044, 50032
1950	epidermal growth factor receptor pathway substrate 15-like 1	248070	2105	248070	10093	18081, 26069, 34057, 42045, 50033
1951	epidermal growth factor receptor pathway substrate 15-like 1	455140	2106	393313	10094	18082, 26070, 34058, 42046, 50034

1952	epidermal growth factor receptor pathway substrate 15-like 1	535753	2107	440103	10095	18083, 26071, 34059, 42047, 50035
1953	epidermal growth factor receptor pathway substrate 15-like 1	597937	2108	472267	10096	18084, 26072, 34060, 42048, 50036
1954	EPM2A (laforin) interacting protein 1	322716	2109	406027	10097	18085, 26073, 34061, 42049, 50037
1955	epoxide hydrolase 4	370383	2110	359410	10098	18086, 26074, 34062, 42050, 50038
1956	ER degradation enhancer, mannosidase alpha-like 1	256497	2111	256497	10099	18087, 26075, 34063, 42051, 50039
1957	ER degradation enhancer, mannosidase alpha-like 1	419550	2112	402075	10100	18088, 26076, 34064, 42052, 50040
1958	ER degradation enhancer, mannosidase alpha-like 1	445686	2113	394099	10101	18089, 26077, 34065, 42053, 50041
1959	ER degradation enhancer, mannosidase alpha-like 3	318130	2114	318147	10102	18090, 26078, 34066, 42054, 50042
1960	ER degradation enhancer, mannosidase alpha-like 3	367512	2115	356482	10103	18091, 26079, 34067, 42055, 50043
1961	Era G-protein-like 1 (E. coli)	254928	2116	254928	10104	18092, 26080, 34068, 42056, 50044
1962	Era G-protein-like 1 (E. coli)	412138	2117	396125	10105	18093, 26081, 34069, 42057, 50045
1963	ERGIC and golgi 3	279052	2118	279052	10106	18094, 26082, 34070, 42058, 50046
1964	ERGIC and golgi 3	348547	2119	341358	10107	18095, 26083, 34071, 42059, 50047
1965	ERGIC and golgi 3	355563	2120	347762	10108	18096, 26084, 34072, 42060, 50048
1966	ERGIC and golgi 3	357394	2121	349970	10109	18097, 26085, 34073, 42061, 50049
1967	ERGIC and golgi 3	447986	2122	392341	10110	18098, 26086, 34074, 42062, 50050

1968	ERO1-like (S. cerevisiae)	395686	2123	379042	10111	18099, 26087, 34075, 42063, 50051
1969	ERO1-like beta (S. cerevisiae)	264181	2124	264181	10112	18100, 26088, 34076, 42064, 50052
1970	ERO1-like beta (S. cerevisiae)	327333	2125	377574	10113	18101, 26089, 34077, 42065, 50053
1971	ERO1-like beta (S. cerevisiae)	354619	2126	346635	10114	18102, 26090, 34078, 42066, 50054
1972	ERO1-like beta (S. cerevisiae)	366589	2127	355548	10115	18103, 26091, 34079, 42067, 50055
1973	ES cell expressed Ras	338270	2128	339136	10116	18104, 26092, 34080, 42068, 50056
1974	exocyst complex component 8	360394	2129	353564	10117	18105, 26093, 34081, 42069, 50057
1975	exocyst complex component 8	366645	2130	355605	10118	18106, 26094, 34082, 42070, 50058
1976	extended synaptotagmin-like protein 1	267113	2131	267113	10119	18107, 26095, 34083, 42071, 50059
1977	extended synaptotagmin-like protein 1	394048	2132	377612	10120	18108, 26096, 34084, 42072, 50060
1978	extended synaptotagmin-like protein 1	402331	2133	386045	10121	18109, 26097, 34085, 42073, 50061
1979	extended synaptotagmin-like protein 1	541590	2134	445952	10122	18110, 26098, 34086, 42074, 50062
1980	extended synaptotagmin-like protein 3	389567	2135	374218	10123	18111, 26099, 34087, 42075, 50063
1981	extracellular leucine-rich repeat and fibronectin type III domain containing 2	349653	2136	300147	10124	18112, 26100, 34088, 42076, 50064
1982	extracellular leucine-rich repeat and fibronectin type III domain containing 2	402918	2137	385277	10125	18113, 26101, 34089, 42077, 50065
1983	FAM18B2-CDRT4 readthrough	557349	2138	450826	10126	18114, 26102, 34090, 42078, 50066
1984	family with sequence similarity 118, member A	216214	2139	216214	10127	18115, 26103, 34091, 42079, 50067

1985	family with sequence similarity 118, member A	405548	2140	384836	10128	18116, 26104, 34092, 42080, 50068
1986	family with sequence similarity 118, member A	427777	2141	395194	10129	18117, 26105, 34093, 42081, 50069
1987	family with sequence similarity 118, member A	441876	2142	395892	10130	18118, 26106, 34094, 42082, 50070
1988	family with sequence similarity 125, member A	317040	2143	324810	10131	18119, 26107, 34095, 42083, 50071
1989	family with sequence similarity 125, member A	392702	2144	376466	10132	18120, 26108, 34096, 42084, 50072
1990	family with sequence similarity 125, member A	543795	2145	444653	10133	18121, 26109, 34097, 42085, 50073
1991	family with sequence similarity 125, member B	361171	2146	354772	10134	18122, 26110, 34098, 42086, 50074
1992	family with sequence similarity 125, member B	402437	2147	384751	10135	18123, 26111, 34099, 42087, 50075
1993	family with sequence similarity 125, member B	436593	2148	401379	10136	18124, 26112, 34100, 42088, 50076
1994	family with sequence similarity 125, member B	535766	2149	442846	10137	18125, 26113, 34101, 42089, 50077
1995	family with sequence similarity 125, member B	545391	2150	441988	10138	18126, 26114, 34102, 42090, 50078
1996	family with sequence similarity 129, member A	367511	2151	356481	10139	18127, 26115, 34103, 42091, 50079
1997	family with sequence similarity 129, member A	417056	2152	414039	10140	18128, 26116, 34104, 42092, 50080
1998	family with sequence similarity 134, member A	430297	2153	395249	10141	18129, 26117, 34105, 42093, 50081
1999	family with sequence similarity 134, member A	443518	2154	398910	10142	18130, 26118, 34106, 42094, 50082
2000	family with sequence similarity 134, member C	309428	2155	309432	10143	18131, 26119, 34107, 42095, 50083
2001	family with sequence similarity 134, member C	543197	2156	446235	10144	18132, 26120, 34108, 42096, 50084
2002	family with sequence similarity 135, member A	361499	2157	354913	10145	18133, 26121, 34109, 42097, 50085

2003	family with sequence similarity 135, member A	370479	2158	359510	10146	18134, 26122, 34110, 42098, 50086
2004	family with sequence similarity 135, member A	418814	2159	410768	10147	18135, 26123, 34111, 42099, 50087
2005	family with sequence similarity 135, member A	457062	2160	409201	10148	18136, 26124, 34112, 42100, 50088
2006	family with sequence similarity 135, member A	507085	2161	425101	10149	18137, 26125, 34113, 42101, 50089
2007	family with sequence similarity 135, member A	515280	2162	421505	10150	18138, 26126, 34114, 42102, 50090
2008	family with sequence similarity 135, member A	515323	2163	422406	10151	18139, 26127, 34115, 42103, 50091
2009	family with sequence similarity 135, member B	160713	2164	160713	10152	18140, 26128, 34116, 42104, 50092, 56084, 56117
2010	family with sequence similarity 135, member B	395297	2165	378710	10153	18141, 26129, 34117, 42105, 50093
2011	family with sequence similarity 135, member B	520380	2166	428017	10154	18142, 26130, 34118, 42106, 50094
2012	family with sequence similarity 151, member A	294370	2167	294370	10155	18143, 26131, 34119, 42107, 50095
2013	family with sequence similarity 151, member A	302250	2168	306888	10156	18144, 26132, 34120, 42108, 50096
2014	family with sequence similarity 151, member A	371304	2169	360353	10157	18145, 26133, 34121, 42109, 50097
2015	family with sequence similarity 155, member A	375915	2170	365080	10158	18146, 26134, 34122, 42110, 50098
2016	family with sequence similarity 155, member B	252338	2171	252338	10159	18147, 26135, 34123, 42111, 50099
2017	family with sequence similarity 156, member A	316310	2172	318182	10160	18148, 26136, 34124, 42112, 50100
2018	family with sequence similarity 156, member A	330025	2173	328443	10161	18149, 26137, 34125, 42113, 50101
2019	family with sequence similarity 156, member A	356333	2174	348687	10162	18150, 26138, 34126, 42114, 50102
2020	family with sequence similarity 156, member A	375473	2175	364622	10163	18151, 26139, 34127, 42115, 50103

2021	family with sequence similarity 156, member A	411516	2176	427693	10164	18152, 26140, 34128, 42116, 50104
2022	family with sequence similarity 156, member A	414076	2177	405771	10165	18153, 26141, 34129, 42117, 50105
2023	family with sequence similarity 156, member A	416923	2178	412234	10166	18154, 26142, 34130, 42118, 50106
2024	family with sequence similarity 156, member A	438003	2179	398565	10167	18155, 26143, 34131, 42119, 50107
2025	family with sequence similarity 156, member A	447562	2180	414701	10168	18156, 26144, 34132, 42120, 50108
2026	family with sequence similarity 156, member A	451084	2181	412585	10169	18157, 26145, 34133, 42121, 50109
2027	family with sequence similarity 156, member A	503775	2182	421939	10170	18158, 26146, 34134, 42122, 50110
2028	family with sequence similarity 156, member A	505988	2183	424378	10171	18159, 26147, 34135, 42123, 50111
2029	family with sequence similarity 156, member A	510517	2184	425216	10172	18160, 26148, 34136, 42124, 50112
2030	family with sequence similarity 156, member A	512364	2185	426868	10173	18161, 26149, 34137, 42125, 50113
2031	family with sequence similarity 156, member B	412319	2186	422884	10174	18162, 26150, 34138, 42126, 50114
2032	family with sequence similarity 156, member B	416841	2187	424864	10175	18163, 26151, 34139, 42127, 50115
2033	family with sequence similarity 156, member B	430150	2188	425174	10176	18164, 26152, 34140, 42128, 50116
2034	family with sequence similarity 156, member B	452021	2189	426113	10177	18165, 26153, 34141, 42129, 50117
2035	family with sequence similarity 156, member B	452154	2190	420954	10178	18166, 26154, 34142, 42130, 50118
2036	family with sequence similarity 156, member B	509613	2191	422411	10179	18167, 26155, 34143, 42131, 50119
2037	family with sequence similarity 159, member A	517870	2192	429726	10180	18168, 26156, 34144, 42132, 50120
2038	family with sequence similarity 162, member A	440333	2193	405770	10181	18169, 26157, 34145, 42133, 50121

2039	family with sequence similarity 162, member A	477892	2194	419088	10182	18170, 26158, 34146, 42134, 50122
2040	family with sequence similarity 162, member B	368557	2195	357545	10183	18171, 26159, 34147, 42135, 50123
2041	family with sequence similarity 163, member A	341785	2196	354891	10184	18172, 26160, 34148, 42136, 50124
2042	family with sequence similarity 163, member B	356873	2197	349336	10185	18173, 26161, 34149, 42137, 50125
2043	family with sequence similarity 163, member B	496132	2198	419867	10186	18174, 26162, 34150, 42138, 50126
2044	family with sequence similarity 165, member A	369586	2199	358599	10187	18175, 26163, 34151, 42139, 50127
2045	family with sequence similarity 165, member B	399292	2200	382231	10188	18176, 26164, 34152, 42140, 50128
2046	family with sequence similarity 165, member B	399295	2201	382234	10189	18177, 26165, 34153, 42141, 50129
2047	family with sequence similarity 171, member A1	378114	2202	367354	10190	18178, 26166, 34154, 42142, 50130
2048	family with sequence similarity 171, member A1	378116	2203	367356	10191	18179, 26167, 34155, 42143, 50131
2049	family with sequence similarity 171, member A1	396781	2204	380001	10192	18180, 26168, 34156, 42144, 50132
2050	family with sequence similarity 171, member A1	455654	2205	407796	10193	18181, 26169, 34157, 42145, 50133
2051	family with sequence similarity 171, member A2	293443	2206	293443	10194	18182, 26170, 34158, 42146, 50134
2052	family with sequence similarity 171, member B	272804	2207	272804	10195	18183, 26171, 34159, 42147, 50135
2053	family with sequence similarity 171, member B	304698	2208	304108	10196	18184, 26172, 34160, 42148, 50136
2054	family with sequence similarity 173 member A	569529	2209	454380	10197	18185, 26173, 34161, 42149, 50137
2055	family with sequence similarity 173, member A	219535	2210	219535	10198	18186, 26174, 34162, 42150, 50138
2056	family with sequence similarity 173, member B	511437	2211	422338	10199	18187, 26175, 34163, 42151, 50139

2057	family with sequence similarity 174, member A	312637	2212	307954	10200	18188, 26176, 34164, 42152, 50140
2058	family with sequence similarity 174, member B	327355	2213	329040	10201	18189, 26177, 34165, 42153, 50141
2059	family with sequence similarity 176, member A	233712	2214	233712	10202	18190, 26178, 34166, 42154, 50142
2060	family with sequence similarity 176, member A	393913	2215	377490	10203	18191, 26179, 34167, 42155, 50143
2061	family with sequence similarity 176, member A	410071	2216	386930	10204	18192, 26180, 34168, 42156, 50144
2062	family with sequence similarity 176, member A	410113	2217	386435	10205	18193, 26181, 34169, 42157, 50145
2063	family with sequence similarity 176, member A	432649	2218	398249	10206	18194, 26182, 34170, 42158, 50146
2064	family with sequence similarity 176, member A	452003	2219	388105	10207	18195, 26183, 34171, 42159, 50147
2065	family with sequence similarity 18 member B2	518321	2220	464052	10208	18196, 26184, 34172, 42160, 50148
2066	family with sequence similarity 18, member A	299866	2221	299866	10209	18197, 26185, 34173, 42161, 50149
2067	family with sequence similarity 18, member A	456096	2222	411972	10210	18198, 26186, 34174, 42162, 50150
2068	family with sequence similarity 18, member B1	307767	2223	305654	10211	18199, 26187, 34175, 42163, 50151
2069	family with sequence similarity 18, member B2	225576	2224	225576	10212	18200, 26188, 34176, 42164, 50152
2070	family with sequence similarity 18, member B2	428082	2225	406387	10213	18201, 26189, 34177, 42165, 50153
2071	family with sequence similarity 18, member B2	519970	2226	428961	10214	18202, 26190, 34178, 42166, 50154
2072	family with sequence similarity 187, member B	324675	2227	323355	10215	18203, 26191, 34179, 42167, 50155
2073	family with sequence similarity 189, member A1	261275	2228	261275	10216	18204, 26192, 34180, 42168, 50156
2074	family with sequence similarity 189, member A2	257515	2229	257515	10217	18205, 26193, 34181, 42169, 50157

2075	family with sequence similarity 189, member A2	303068	2230	304435	10218	18206, 26194, 34182, 42170, 50158
2076	family with sequence similarity 189, member A2	377216	2231	366422	10219	18207, 26195, 34183, 42171, 50159
2077	family with sequence similarity 189, member A2	377225	2232	366432	10220	18208, 26196, 34184, 42172, 50160
2078	family with sequence similarity 189, member A2	455972	2233	395675	10221	18209, 26197, 34185, 42173, 50161
2079	family with sequence similarity 189, member B	323361	2234	323164	10222	18210, 26198, 34186, 42174, 50162
2080	family with sequence similarity 189, member B	333966	2235	333944	10223	18211, 26199, 34187, 42175, 50163
2081	family with sequence similarity 189, member B	350210	2236	307128	10224	18212, 26200, 34188, 42176, 50164
2082	family with sequence similarity 189, member B	361361	2237	354958	10225	18213, 26201, 34189, 42177, 50165
2083	family with sequence similarity 189, member B	368368	2238	357352	10226	18214, 26202, 34190, 42178, 50166
2084	family with sequence similarity 189, member B	487649	2239	427520	10227	18215, 26203, 34191, 42179, 50167
2085	family with sequence similarity 198 member B	585682	2240	465976	10228	18216, 26204, 34192, 42180, 50168
2086	family with sequence similarity 198, member B	296530	2241	296530	10229	18217, 26205, 34193, 42181, 50169
2087	family with sequence similarity 198, member B	337222	2242	338886	10230	18218, 26206, 34194, 42182, 50170
2088	family with sequence similarity 198, member B	393807	2243	377396	10231	18219, 26207, 34195, 42183, 50171
2089	family with sequence similarity 198, member B	417442	2244	409135	10232	18220, 26208, 34196, 42184, 50172
2090	family with sequence similarity 200, member A	408938	2245	386191	10233	18221, 26209, 34197, 42185, 50173
2091	family with sequence similarity 200, member A	449309	2246	411372	10234	18222, 26210, 34198, 42186, 50174
2092	family with sequence similarity 205, member A	378788	2247	417711	10235	18223, 26211, 34199, 42187, 50175

2093	family with sequence similarity 209, member A	371328	2248	360379	10236	18224, 26212, 34200, 42188, 50176
2094	family with sequence similarity 209, member B	371325	2249	360376	10237	18225, 26213, 34201, 42189, 50177
2095	family with sequence similarity 21, member A	282633	2250	282633	10238	18226, 26214, 34202, 42190, 50178
2096	family with sequence similarity 21, member A	314664	2251	314417	10239	18227, 26215, 34203, 42191, 50179
2097	family with sequence similarity 21, member A	351071	2252	344037	10240	18228, 26216, 34204, 42192, 50180
2098	family with sequence similarity 21, member A	399339	2253	382277	10241	18229, 26217, 34205, 42193, 50181
2099	family with sequence similarity 21, member A	434114	2254	403781	10242	18230, 26218, 34206, 42194, 50182
2100	family with sequence similarity 21, member A	454806	2255	398095	10243	18231, 26219, 34207, 42195, 50183
2101	family with sequence similarity 21, member B	355876	2256	348138	10244	18232, 26220, 34208, 42196, 50184
2102	family with sequence similarity 21, member B	358474	2257	351259	10245	18233, 26221, 34209, 42197, 50185
2103	family with sequence similarity 21, member B	430074	2258	416073	10246	18234, 26222, 34210, 42198, 50186
2104	family with sequence similarity 21, member B	535219	2259	438386	10247	18235, 26223, 34211, 42199, 50187
2105	family with sequence similarity 21, member B	543972	2260	440306	10248	18236, 26224, 34212, 42200, 50188
2106	family with sequence similarity 210, member A	322247	2261	323635	10249	18237, 26225, 34213, 42201, 50189
2107	family with sequence similarity 210, member A	402563	2262	386115	10250	18238, 26226, 34214, 42202, 50190
2108	family with sequence similarity 210, member B	371384	2263	360437	10251	18239, 26227, 34215, 42203, 50191
2109	family with sequence similarity 26, member D	368596	2264	357585	10252	18240, 26228, 34216, 42204, 50192
2110	family with sequence similarity 26, member D	368597	2265	357586	10253	18241, 26229, 34217, 42205, 50193

2111	family with sequence similarity 26, member D	405399	2266	385836	10254	18242, 26230, 34218, 42206, 50194
2112	family with sequence similarity 26, member D	416171	2267	416976	10255	18243, 26231, 34219, 42207, 50195
2113	family with sequence similarity 26, member D	452373	2268	409556	10256	18244, 26232, 34220, 42208, 50196
2114	family with sequence similarity 26, member E	368599	2269	357588	10257	18245, 26233, 34221, 42209, 50197
2115	family with sequence similarity 26, member F	368605	2270	357594	10258	18246, 26234, 34222, 42210, 50198
2116	family with sequence similarity 27, member C	377542	2271	366765	10259	18247, 26235, 34223, 42211, 50199
2117	family with sequence similarity 36, member A	366528	2272	355486	10260	18248, 26236, 34224, 42212, 50200
2118	family with sequence similarity 36, member A	411948	2273	406327	10261	18249, 26237, 34225, 42213, 50201
2119	family with sequence similarity 55, member B	389586	2274	374237	10262	18250, 26238, 34226, 42214, 50202
2120	family with sequence similarity 55, member B	505358	2275	439889	10263	18251, 26239, 34227, 42215, 50203
2121	family with sequence similarity 57, member B	279389	2276	279389	10264	18252, 26240, 34228, 42216, 50204
2122	family with sequence similarity 57, member B	380495	2277	369863	10265	18253, 26241, 34229, 42217, 50205
2123	family with sequence similarity 69, member A	370310	2278	359333	10266	18254, 26242, 34230, 42218, 50206
2124	family with sequence similarity 69, member A	401027	2279	383809	10267	18255, 26243, 34231, 42219, 50207
2125	family with sequence similarity 69, member B	371691	2280	360756	10268	18256, 26244, 34232, 42220, 50208
2126	family with sequence similarity 69, member B	371692	2281	360757	10269	18257, 26245, 34233, 42221, 50209
2127	family with sequence similarity 69, member C	343998	2282	344331	10270	18258, 26246, 34234, 42222, 50210
2128	family with sequence similarity 70, member A	309720	2283	310110	10271	18259, 26247, 34235, 42223, 50211

2129	family with sequence similarity 70, member A	371352	2284	360403	10272	18260, 26248, 34236, 42224, 50212
2130	family with sequence similarity 70, member A	371369	2285	360420	10273	18261, 26249, 34237, 42225, 50213
2131	family with sequence similarity 70, member A	440464	2286	405781	10274	18262, 26250, 34238, 42226, 50214
2132	family with sequence similarity 70, member B	375353	2287	364502	10275	18263, 26251, 34239, 42227, 50215
2133	family with sequence similarity 73, member A	370791	2288	359827	10276	18264, 26252, 34240, 42228, 50216
2134	family with sequence similarity 73, member A	443751	2289	393675	10277	18265, 26253, 34241, 42229, 50217
2135	family with sequence similarity 73, member B	277475	2290	277475	10278	18266, 26254, 34242, 42230, 50218
2136	family with sequence similarity 73, member B	358369	2291	351138	10279	18267, 26255, 34243, 42231, 50219
2137	family with sequence similarity 73, member B	406926	2292	384662	10280	18268, 26256, 34244, 42232, 50220
2138	family with sequence similarity 73, member B	450073	2293	409348	10281	18269, 26257, 34245, 42233, 50221
2139	family with sequence similarity 74, member A1	434519	2294	388519	10282	18270, 26258, 34246, 42234, 50222
2140	family with sequence similarity 74, member A2	427006	2295	415978	10283	18271, 26259, 34247, 42235, 50223
2141	family with sequence similarity 75, member A1	377647	2296	366875	10284	18272, 26260, 34248, 42236, 50224
2142	family with sequence similarity 75, member A2	456183	2297	406957	10285	18273, 26261, 34249, 42237, 50225
2143	family with sequence similarity 75, member A3	356699	2298	349132	10286	18274, 26262, 34250, 42238, 50226
2144	family with sequence similarity 75, member A4	377509	2299	366731	10287	18275, 26263, 34251, 42239, 50227
2145	family with sequence similarity 75, member A4	429767	2300	411237	10288	18276, 26264, 34252, 42240, 50228
2146	family with sequence similarity 75, member A5	377621	2301	366847	10289	18277, 26265, 34253, 42241, 50229

2147	family with sequence similarity 75, member A6	332857	2302	329825	10290	18278, 26266, 34254, 42242, 50230
2148	family with sequence similarity 75, member A7	355045	2303	347153	10291	18279, 26267, 34255, 42243, 50231
2149	family with sequence similarity 75, member D1	344803	2304	341988	10292	18280, 26268, 34256, 42244, 50232
2150	family with sequence similarity 8, member A1	259963	2305	259963	10293	18281, 26269, 34257, 42245, 50233
2151	family with sequence similarity 8, member A1	542476	2306	446393	10294	18282, 26270, 34258, 42246, 50234
2152	family with sequence similarity 92, member B	393246	2307	376937	10295	18283, 26271, 34259, 42247, 50235
2153	family with sequence similarity 92, member B	539556	2308	443411	10296	18284, 26272, 34260, 42248, 50236
2154	Fas (TNFRSF6) binding factor 1	319129	2309	324292	10297	18285, 26273, 34261, 42249, 50237
2155	Fas (TNFRSF6) binding factor 1	337792	2310	337039	10298	18286, 26274, 34262, 42250, 50238
2156	Fas (TNFRSF6) binding factor 1	389570	2311	374221	10299	18287, 26275, 34263, 42251, 50239
2157	Fas (TNFRSF6) binding factor 1	427433	2312	401215	10300	18288, 26276, 34264, 42252, 50240
2158	FAST kinase domains 1	445210	2313	399551	10301	18289, 26277, 34265, 42253, 50241
2159	FAST kinase domains 1	453153	2314	400513	10302	18290, 26278, 34266, 42254, 50242
2160	FAST kinase domains 1	453929	2315	403229	10303	18291, 26279, 34267, 42255, 50243
2161	FAST kinase domains 3	264669	2316	264669	10304	18292, 26280, 34268, 42256, 50244
2162	FAST kinase domains 3	504695	2317	426008	10305	18293, 26281, 34269, 42257, 50245
2163	fat storage-inducing transmembrane protein 1	267426	2318	267426	10306	18294, 26282, 34270, 42258, 50246
2164	fat storage-inducing transmembrane protein 2	396825	2319	380037	10307	18295, 26283, 34271, 42259, 50247

2165	fatty acid desaturase domain family, member 6	310226	2320	307821	10308	18296, 26284, 34272, 42260, 50248
2166	fatty acid desaturase domain family, member 6	413142	2321	396743	10309	18297, 26285, 34273, 42261, 50249
2167	fatty acyl CoA reductase 1	354817	2322	346874	10310	18298, 26286, 34274, 42262, 50250
2168	fatty acyl CoA reductase 1	355107	2323	347226	10311	18299, 26287, 34275, 42263, 50251
2169	fatty acyl CoA reductase 2	182377	2324	182377	10312	18300, 26288, 34276, 42264, 50252
2170	fatty acyl CoA reductase 2	536681	2325	443291	10313	18301, 26289, 34277, 42265, 50253
2171	Fc receptor-like 2	292389	2326	292389	10314	18302, 26290, 34278, 42266, 50254
2172	Fc receptor-like 2	361516	2327	355157	10315	18303, 26291, 34279, 42267, 50255
2173	Fc receptor-like 2	368181	2328	357163	10316	18304, 26292, 34280, 42268, 50256
2174	Fc receptor-like 2	392274	2329	376100	10317	18305, 26293, 34281, 42269, 50257
2175	Fc receptor-like 2	469986	2330	417393	10318	18306, 26294, 34282, 42270, 50258
2176	Fc receptor-like 3	292392	2331	292392	10319	18307, 26295, 34283, 42271, 50259
2177	Fc receptor-like 3	368184	2332	357167	10320	18308, 26296, 34284, 42272, 50260
2178	Fc receptor-like 3	368186	2333	357169	10321	18309, 26297, 34285, 42273, 50261
2179	Fc receptor-like 3	485028	2334	434331	10322	18310, 26298, 34286, 42274, 50262
2180	Fc receptor-like 4	271532	2335	271532	10323	18311, 26299, 34287, 42275, 50263
2181	Fc receptor-like 5	356953	2336	349434	10324	18312, 26300, 34288, 42276, 50264
2182	Fc receptor-like 5	361835	2337	354691	10325	18313, 26301, 34289, 42277, 50265

2183	Fc receptor-like 5	368188	2338	357171	10326	18314, 26302, 34290, 42278, 50266
2184	Fc receptor-like 5	368189	2339	357172	10327	18315, 26303, 34291, 42279, 50267
2185	Fc receptor-like 5	368190	2340	357173	10328	18316, 26304, 34292, 42280, 50268
2186	Fc receptor-like 5	368191	2341	357174	10329	18317, 26305, 34293, 42281, 50269
2187	Fc receptor-like 6	339348	2342	340949	10330	18318, 26306, 34294, 42282, 50270
2188	Fc receptor-like 6	368106	2343	357086	10331	18319, 26307, 34295, 42283, 50271
2189	Fc receptor-like 6	392235	2344	376068	10332	18320, 26308, 34296, 42284, 50272
2190	Feline leukemia virus subgroup C receptor-related protein 2	238667	2345	238667	10333	18321, 26309, 34297, 42285, 50273
2191	Feline leukemia virus subgroup C receptor-related protein 2	539311	2346	443439	10334	18322, 26310, 34298, 42286, 50274
2192	fer-1-like 6 (C. elegans)	399018	2347	381982	10335	18323, 26311, 34299, 42287, 50275
2193	fer-1-like 6 (C. elegans)	522917	2348	428280	10336	18324, 26312, 34300, 42288, 50276
2194	FERM and PDZ domain containing 1	359927	2349	439868	10337	18325, 26313, 34301, 42289, 50277
2195	FERM and PDZ domain containing 1	377765	2350	366995	10338	18326, 26314, 34302, 42290, 50278
2196	FERM and PDZ domain containing 1	536622	2351	437762	10339	18327, 26315, 34303, 42291, 50279
2197	FERM and PDZ domain containing 1	539465	2352	444411	10340	18328, 26316, 34304, 42292, 50280
2198	FERM and PDZ domain containing 1	541302	2353	444804	10341	18329, 26317, 34305, 42293, 50281
2199	FERM domain containing 5	417257	2354	403067	10342	18330, 26318, 34306, 42294, 50282

2200	FERM domain containing 5	484674	2355	452968	10343	18331, 26319, 34307, 42295, 50283
2201	FERM domain containing 6	344768	2356	343899	10344	18332, 26320, 34308, 42296, 50284
2202	FERM domain containing 6	356218	2357	348550	10345	18333, 26321, 34309, 42297, 50285
2203	FERM domain containing 6	395718	2358	379068	10346	18334, 26322, 34310, 42298, 50286
2204	FERM domain containing 6	553556	2359	452529	10347	18335, 26323, 34311, 42299, 50287
2205	FERM domain containing 6	554778	2360	452122	10348	18336, 26324, 34312, 42300, 50288
2206	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	319562	2361	322926	10349	18337, 26325, 34313, 42301, 50289
2207	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	376581	2362	365765	10350	18338, 26326, 34314, 42302, 50290
2208	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	376584	2363	365768	10351	18339, 26327, 34315, 42303, 50291
2209	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	376586	2364	365771	10352	18340, 26328, 34316, 42304, 50292
2210	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	423063	2365	410930	10353	18341, 26329, 34317, 42305, 50293
2211	FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived)	457029	2366	406623	10354	18342, 26330, 34318, 42306, 50294

2212	FERM, RhoGEF and pleckstrin domain protein 2	264042	2367	264042	10355	18343, 26331, 34319, 42307, 50295
2213	FERM, RhoGEF and pleckstrin domain protein 2	373287	2368	362384	10356	18344, 26332, 34320, 42308, 50296
2214	FERM, RhoGEF and pleckstrin domain protein 2	412332	2369	403437	10357	18345, 26333, 34321, 42309, 50297
2215	FERM, RhoGEF and pleckstrin domain protein 2	418082	2370	393376	10358	18346, 26334, 34322, 42310, 50298
2216	FERM, RhoGEF and pleckstrin domain protein 2	445489	2371	388167	10359	18347, 26335, 34323, 42311, 50299
2217	FERM, RhoGEF and pleckstrin domain protein 2	545004	2372	443876	10360	18348, 26336, 34324, 42312, 50300
2218	fermitin family member 1	217289	2373	217289	10361	18349, 26337, 34325, 42313, 50301
2219	fermitin family member 1	339538	2374	342074	10362	18350, 26338, 34326, 42314, 50302
2220	fermitin family member 1	378844	2375	368121	10363	18351, 26339, 34327, 42315, 50303
2221	fermitin family member 1	536936	2376	441063	10364	18352, 26340, 34328, 42316, 50304
2222	ferredoxin 1-like	393708	2377	377311	10365	18353, 26341, 34329, 42317, 50305
2223	ferredoxin 1-like	541276	2378	441093	10366	18354, 26342, 34330, 42318, 50306
2224	fetal and adult testis expressed 1	370350	2379	359375	10367	18355, 26343, 34331, 42319, 50307
2225	fibroblast growth factor receptor substrate 2	299293	2380	299293	10368	18356, 26344, 34332, 42320, 50308
2226	fibroblast growth factor receptor substrate 2	397997	2381	381083	10369	18357, 26345, 34333, 42321, 50309
2227	fibroblast growth factor receptor substrate 2	547219	2382	447724	10370	18358, 26346, 34334, 42322, 50310
2228	fibroblast growth factor receptor substrate 2	548154	2383	449105	10371	18359, 26347, 34335, 42323, 50311
2229	fibroblast growth factor receptor substrate 2	549092	2384	449111	10372	18360, 26348, 34336, 42324, 50312

2230	fibroblast growth factor receptor substrate 2	549921	2385	450048	10373	18361, 26349, 34337, 42325, 50313
2231	fibroblast growth factor receptor substrate 2	550169	2386	447978	10374	18362, 26350, 34338, 42326, 50314
2232	fibroblast growth factor receptor substrate 2	550316	2387	450000	10375	18363, 26351, 34339, 42327, 50315
2233	fibroblast growth factor receptor substrate 2	550389	2388	447241	10376	18364, 26352, 34340, 42328, 50316
2234	fibroblast growth factor receptor substrate 2	550937	2389	447804	10377	18365, 26353, 34341, 42329, 50317
2235	fibroblast growth factor receptor substrate 2	551325	2390	449432	10378	18366, 26354, 34342, 42330, 50318
2236	fibroblast growth factor receptor substrate 3	259748	2391	259748	10379	18367, 26355, 34343, 42331, 50319
2237	fibroblast growth factor receptor substrate 3	373018	2392	362109	10380	18368, 26356, 34344, 42332, 50320
2238	fibroblast growth factor receptor substrate 3	422888	2393	413214	10381	18369, 26357, 34345, 42333, 50321
2239	fibroblast growth factor receptor substrate 3	426290	2394	396715	10382	18370, 26358, 34346, 42334, 50322
2240	fibronectin type III domain containing 3A	337156	2395	338579	10383	18371, 26359, 34347, 42335, 50323
2241	fibronectin type III domain containing 3A	398316	2396	381362	10384	18372, 26360, 34348, 42336, 50324
2242	fibronectin type III domain containing 3A	492622	2397	417257	10385	18373, 26361, 34349, 42337, 50325
2243	fibronectin type III domain containing 3A	541916	2398	441831	10386	18374, 26362, 34350, 42338, 50326
2244	fibronectin type III domain containing 3A	484074	2399	420275	10387	18375, 26363, 34351, 42339, 50327
2245	fibronectin type III domain containing 9	312349	2400	310594	10388	18376, 26364, 34352, 42340, 50328
2246	fibronectin type III domain containing 9	520782	2401	429434	10389	18377, 26365, 34353, 42341, 50329
2247	fibrous sheath interacting protein 2	326147	2402	321903	10390	18378, 26366, 34354, 42342, 50330

2248	fibrous sheath interacting protein 2	343098	2403	344403	10391	18379, 26367, 34355, 42343, 50331
2249	fibrous sheath interacting protein 2	424728	2404	401306	10392	18380, 26368, 34356, 42344, 50332
2250	fibrous sheath interacting protein 2	429412	2405	395888	10393	18381, 26369, 34357, 42345, 50333
2251	fibrous sheath interacting protein 2	546113	2406	439530	10394	18382, 26370, 34358, 42346, 50334
2252	FIC domain containing	552695	2407	446479	10395	18383, 26371, 34359, 42347, 50335
2253	filamin binding LIM protein 1	332305	2408	364920	10396	18384, 26372, 34360, 42348, 50336
2254	filamin binding LIM protein 1	375766	2409	364921	10397	18385, 26373, 34361, 42349, 50337
2255	filamin binding LIM protein 1	375771	2410	364926	10398	18386, 26374, 34362, 42350, 50338
2256	filamin binding LIM protein 1	400773	2411	383584	10399	18387, 26375, 34363, 42351, 50339
2257	filamin binding LIM protein 1	430076	2412	387595	10400	18388, 26376, 34364, 42352, 50340
2258	filamin binding LIM protein 1	431771	2413	402401	10401	18389, 26377, 34365, 42353, 50341
2259	filamin binding LIM protein 1	441801	2414	416387	10402	18390, 26378, 34366, 42354, 50342
2260	filamin binding LIM protein 1	483633	2415	427052	10403	18391, 26379, 34367, 42355, 50343
2261	filamin binding LIM protein 1	496928	2416	422862	10404	18392, 26380, 34368, 42356, 50344
2262	filamin binding LIM protein 1	502638	2417	422075	10405	18393, 26381, 34369, 42357, 50345
2263	filamin binding LIM protein 1	502739	2418	424920	10406	18394, 26382, 34370, 42358, 50346
2264	filamin binding LIM protein 1	508310	2419	423471	10407	18395, 26383, 34371, 42359, 50347
2265	filamin binding LIM protein 1	510393	2420	421885	10408	18396, 26384, 34372, 42360, 50348

2266	filamin binding LIM protein 1	510929	2421	421764	10409	18397, 26385, 34373, 42361, 50349
2267	FK506 binding protein 11, 19 kDa	444214	2422	412403	10410	18398, 26386, 34374, 42362, 50350
2268	FK506 binding protein 11, 19 kDa	453172	2423	396874	10411	18399, 26387, 34375, 42363, 50351
2269	FK506 binding protein 11, 19 kDa	550765	2424	449751	10412	18400, 26388, 34376, 42364, 50352
2270	FK506 binding protein 14, 22 kDa	222803	2425	222803	10413	18401, 26389, 34377, 42365, 50353
2271	FK506 binding protein 9, 63 kDa	242209	2426	242209	10414	18402, 26390, 34378, 42366, 50354
2272	FK506 binding protein 9, 63 kDa	490776	2427	441317	10415	18403, 26391, 34379, 42367, 50355
2273	FK506 binding protein 9, 63 kDa	538336	2428	439250	10416	18404, 26392, 34380, 42368, 50356
2274	FK506 binding protein 9, 63 kDa	538443	2429	437504	10417	18405, 26393, 34381, 42369, 50357
2275	formin 1	320930	2430	325166	10418	18406, 26394, 34382, 42370, 50358
2276	formin 1	334528	2431	333950	10419	18407, 26395, 34383, 42371, 50359
2277	formin 1	558197	2432	452984	10420	18408, 26396, 34384, 42372, 50360
2278	formin 1	559047	2433	454047	10421	18409, 26397, 34385, 42373, 50361
2279	fragile X mental retardation 1 neighbor	370467	2434	359498	10422	18410, 26398, 34386, 42374, 50362
2280	free fatty acid receptor 1	246553	2435	246553	10423	18411, 26399, 34387, 42375, 50363
2281	free fatty acid receptor 2	246549	2436	246549	10424	18412, 26400, 34388, 42376, 50364
2282	free fatty acid receptor 3	327809	2437	328230	10425	18413, 26401, 34389, 42377, 50365
2283	frizzled family receptor 5	295417	2438	354607	10426	18414, 26402, 34390, 42378, 50366

2284	FtsJ methyltransferase domain containing 1	338099	2439	337512	10427	18415, 26403, 34391, 42379, 50367
2285	FtsJ methyltransferase domain containing 1	434935	2440	411148	10428	18416, 26404, 34392, 42380, 50368
2286	fucosyltransferase 10 (alpha (1,3) fucosyltransferase)	327671	2441	332757	10429	18417, 26405, 34393, 42381, 50369
2287	fucosyltransferase 10 (alpha (1,3) fucosyltransferase)	335589	2442	334997	10430	18418, 26406, 34394, 42382, 50370
2288	fucosyltransferase 10 (alpha (1,3) fucosyltransferase)	380081	2443	369421	10431	18419, 26407, 34395, 42383, 50371
2289	fucosyltransferase 11 (alpha (1,3) fucosyltransferase)	372841	2444	361932	10432	18420, 26408, 34396, 42384, 50372
2290	fucosyltransferase 11 (alpha (1,3) fucosyltransferase)	394790	2445	378270	10433	18421, 26409, 34397, 42385, 50373
2291	FUN14 domain containing 2	369498	2446	358510	10434	18422, 26410, 34398, 42386, 50374
2292	furry homolog (Drosophila)	267067	2447	267067	10435	18423, 26411, 34399, 42387, 50375
2293	furry homolog (Drosophila)	380217	2448	369565	10436	18424, 26412, 34400, 42388, 50376
2294	furry homolog (Drosophila)	380235	2449	369584	10437	18425, 26413, 34401, 42389, 50377
2295	furry homolog (Drosophila)	380250	2450	369600	10438	18426, 26414, 34402, 42390, 50378
2296	furry homolog (Drosophila)	380257	2451	369607	10439	18427, 26415, 34403, 42391, 50379
2297	furry homolog (Drosophila)	436046	2452	398010	10440	18428, 26416, 34404, 42392, 50380
2298	furry homolog (Drosophila)	542859	2453	445043	10441	18429, 26417, 34405, 42393, 50381
2299	FXYD domain containing ion transport regulator 4	374451	2454	363575	10442	18430, 26418, 34406, 42394, 50382
2300	FXYD domain containing ion transport regulator 4	458363	2455	388004	10443	18431, 26419, 34407, 42395, 50383
2301	G elongation factor, mitochondrial 2	296805	2456	296805	10444	18432, 26420, 34408, 42396, 50384

2302	G elongation factor, mitochondrial 2	345239	2457	296804	10445	18433, 26421, 34409, 42397, 50385
2303	G elongation factor, mitochondrial 2	427854	2458	405808	10446	18434, 26422, 34410, 42398, 50386
2304	G elongation factor, mitochondrial 2	509430	2459	427004	10447	18435, 26423, 34411, 42399, 50387
2305	G elongation factor, mitochondrial 2	546082	2460	437810	10448	18436, 26424, 34412, 42400, 50388
2306	G kinase anchoring protein 1	376365	2461	365544	10449	18437, 26425, 34413, 42401, 50389
2307	G kinase anchoring protein 1	376371	2462	365550	10450	18438, 26426, 34414, 42402, 50390
2308	G kinase anchoring protein 1	388782	2463	373434	10451	18439, 26427, 34415, 42403, 50391
2309	G kinase anchoring protein 1	485742	2464	417621	10452	18440, 26428, 34416, 42404, 50392
2310	G protein regulated inducer of neurite outgrowth 1	303991	2465	305839	10453	18441, 26429, 34417, 42405, 50393
2311	G protein regulated inducer of neurite outgrowth 1	335532	2466	335279	10454	18442, 26430, 34418, 42406, 50394
2312	G protein-coupled receptor 107	347136	2467	336988	10455	18443, 26431, 34419, 42407, 50395
2313	G protein-coupled receptor 107	372406	2468	361483	10456	18444, 26432, 34420, 42408, 50396
2314	G protein-coupled receptor 107	372410	2469	361487	10457	18445, 26433, 34421, 42409, 50397
2315	G protein-coupled receptor 107	455412	2470	402109	10458	18446, 26434, 34422, 42410, 50398
2316	G protein-coupled receptor 108	264080	2471	264080	10459	18447, 26435, 34423, 42411, 50399
2317	G protein-coupled receptor 108	430424	2472	401284	10460	18448, 26436, 34424, 42412, 50400
2318	G protein-coupled receptor 110	283297	2473	283297	10461	18449, 26437, 34425, 42413, 50401
2319	G protein-coupled receptor 110	371243	2474	360289	10462	18450, 26438, 34426, 42414, 50402

2320	G protein-coupled receptor 110	371252	2475	360298	10463	18451, 26439, 34427, 42415, 50403
2321	G protein-coupled receptor 110	371253	2476	360299	10464	18452, 26440, 34428, 42416, 50404
2322	G protein-coupled receptor 111	296862	2477	296862	10465	18453, 26441, 34429, 42417, 50405
2323	G protein-coupled receptor 111	398742	2478	381727	10466	18454, 26442, 34430, 42418, 50406
2324	G protein-coupled receptor 111	467205	2479	425269	10467	18455, 26443, 34431, 42419, 50407
2325	G protein-coupled receptor 112	287534	2480	287534	10468	18456, 26444, 34432, 42420, 50408
2326	G protein-coupled receptor 112	370652	2481	359686	10469	18457, 26445, 34433, 42421, 50409
2327	G protein-coupled receptor 112	394143	2482	377699	10470	18458, 26446, 34434, 42422, 50410
2328	G protein-coupled receptor 112	412101	2483	416526	10471	18459, 26447, 34435, 42423, 50411
2329	G protein-coupled receptor 113	311519	2484	307831	10472	18460, 26448, 34436, 42424, 50412
2330	G protein-coupled receptor 113	333478	2485	327396	10473	18461, 26449, 34437, 42425, 50413
2331	G protein-coupled receptor 113	541401	2486	445729	10474	18462, 26450, 34438, 42426, 50414
2332	G protein-coupled receptor 113	421160	2487	388537	10475	18463, 26451, 34439, 42427, 50415
2333	G protein-coupled receptor 114	340339	2488	342981	10476	18464, 26452, 34440, 42428, 50416
2334	G protein-coupled receptor 114	349457	2489	290823	10477	18465, 26453, 34441, 42429, 50417
2335	G protein-coupled receptor 114	394361	2490	377888	10478	18466, 26454, 34442, 42430, 50418
2336	G protein-coupled receptor 116	265417	2491	265417	10479	18467, 26455, 34443, 42431, 50419
2337	G protein-coupled receptor 116	283296	2492	283296	10480	18468, 26456, 34444, 42432, 50420

2338	G protein-coupled receptor 116	362015	2493	354563	10481	18469, 26457, 34445, 42433, 50421
2339	G protein-coupled receptor 116	452370	2494	394590	10482	18470, 26458, 34446, 42434, 50422
2340	G protein-coupled receptor 116	456426	2495	412866	10483	18471, 26459, 34447, 42435, 50423
2341	G protein-coupled receptor 116	545557	2496	440867	10484	18472, 26460, 34448, 42436, 50424
2342	G protein-coupled receptor 116	545669	2497	441581	10485	18473, 26461, 34449, 42437, 50425
2343	G protein-coupled receptor 119	276218	2498	276218	10486	18474, 26462, 34450, 42438, 50426
2344	G protein-coupled receptor 135	395116	2499	378548	10487	18475, 26463, 34451, 42439, 50427
2345	G protein-coupled receptor 135	481661	2500	432696	10488	18476, 26464, 34452, 42440, 50428
2346	G protein-coupled receptor 135	539022	2501	444314	10489	18477, 26465, 34453, 42441, 50429
2347	G protein-coupled receptor 137	313074	2502	321698	10490	18478, 26466, 34454, 42442, 50430
2348	G protein-coupled receptor 137	377702	2503	366931	10491	18479, 26467, 34455, 42443, 50431
2349	G protein-coupled receptor 137	411458	2504	411827	10492	18480, 26468, 34456, 42444, 50432
2350	G protein-coupled receptor 137	438980	2505	415698	10493	18481, 26469, 34457, 42445, 50433
2351	G protein-coupled receptor 137	535675	2506	446342	10494	18482, 26470, 34458, 42446, 50434
2352	G protein-coupled receptor 137	538032	2507	445000	10495	18483, 26471, 34459, 42447, 50435
2353	G protein-coupled receptor 137	538244	2508	442322	10496	18484, 26472, 34460, 42448, 50436
2354	G protein-coupled receptor 137	539833	2509	438716	10497	18485, 26473, 34461, 42449, 50437
2355	G protein-coupled receptor 137	539851	2510	442792	10498	18486, 26474, 34462, 42450, 50438

2356	G protein-coupled receptor 137	540370	2511	446387	10499	18487, 26475, 34463, 42451, 50439
2357	G protein-coupled receptor 137	540969	2512	437739	10500	18488, 26476, 34464, 42452, 50440
2358	G protein-coupled receptor 137	543383	2513	441003	10501	18489, 26477, 34465, 42453, 50441
2359	G protein-coupled receptor 137B	366591	2514	355550	10502	18490, 26478, 34466, 42454, 50442
2360	G protein-coupled receptor 137B	366592	2515	355551	10503	18491, 26479, 34467, 42455, 50443
2361	G protein-coupled receptor 137B	391852	2516	375725	10504	18492, 26480, 34468, 42456, 50444
2362	G protein-coupled receptor 137B	419162	2517	401841	10505	18493, 26481, 34469, 42457, 50445
2363	G protein-coupled receptor 137B	454895	2518	395814	10506	18494, 26482, 34470, 42458, 50446
2364	G protein-coupled receptor 137C	321662	2519	315106	10507	18495, 26483, 34471, 42459, 50447
2365	G protein-coupled receptor 139	326571	2520	370779	10508	18496, 26484, 34472, 42460, 50448
2366	G protein-coupled receptor 139	570682	2521	458791	10509	18497, 26485, 34473, 42461, 50449
2367	G protein-coupled receptor 141	334425	2522	334540	10510	18498, 26486, 34474, 42462, 50450
2368	G protein-coupled receptor 141	447769	2523	390410	10511	18499, 26487, 34475, 42463, 50451
2369	G protein-coupled receptor 141	450180	2524	396300	10512	18500, 26488, 34476, 42464, 50452
2370	G protein-coupled receptor 142	335666	2525	335158	10513	18501, 26489, 34477, 42465, 50453
2371	G protein-coupled receptor 144	334810	2526	335156	10514	18502, 26490, 34478, 42466, 50454
2372	G protein-coupled receptor 144	439837	2527	405734	10515	18503, 26491, 34479, 42467, 50455
2373	G protein-coupled receptor 144	446588	2528	414478	10516	18504, 26492, 34480, 42468, 50456

2374	G protein-coupled receptor 144	536897	2529	443708	10517	18505, 26493, 34481, 42469, 50457
2375	G protein-coupled receptor 146	297468	2530	297468	10518	18506, 26494, 34482, 42470, 50458
2376	G protein-coupled receptor 146	397095	2531	380283	10519	18507, 26495, 34483, 42471, 50459
2377	G protein-coupled receptor 146	444847	2532	410743	10520	18508, 26496, 34484, 42472, 50460
2378	G protein-coupled receptor 146	500070	2533	444126	10521	18509, 26497, 34485, 42473, 50461
2379	G protein-coupled receptor 148	309926	2534	308908	10522	18510, 26498, 34486, 42474, 50462
2380	G protein-coupled receptor 149	389740	2535	374390	10523	18511, 26499, 34487, 42475, 50463
2381	G protein-coupled receptor 150	380007	2536	369344	10524	18512, 26500, 34488, 42476, 50464
2382	G protein-coupled receptor 151	311104	2537	308733	10525	18513, 26501, 34489, 42477, 50465
2383	G protein-coupled receptor 152	312457	2538	310255	10526	18514, 26502, 34490, 42478, 50466
2384	G protein-coupled receptor 155	295500	2539	295500	10527	18515, 26503, 34491, 42479, 50467
2385	G protein-coupled receptor 155	392551	2540	376334	10528	18516, 26504, 34492, 42480, 50468
2386	G protein-coupled receptor 155	392552	2541	376335	10529	18517, 26505, 34493, 42481, 50469
2387	G protein-coupled receptor 155	510236	2542	446160	10530	18518, 26506, 34494, 42482, 50470
2388	G protein-coupled receptor 157	377408	2543	366625	10531	18519, 26507, 34495, 42483, 50471
2389	G protein-coupled receptor 157	377411	2544	366628	10532	18520, 26508, 34496, 42484, 50472
2390	G protein-coupled receptor 157	414642	2545	411172	10533	18521, 26509, 34497, 42485, 50473
2391	G protein-coupled receptor 158	376351	2546	365529	10534	18522, 26510, 34498, 42486, 50474

2392	G protein-coupled receptor 160	355897	2547	348161	10535	18523, 26511, 34499, 42487, 50475
2393	G protein-coupled receptor 160	473675	2548	420751	10536	18524, 26512, 34500, 42488, 50476
2394	G protein-coupled receptor 160	482710	2549	419400	10537	18525, 26513, 34501, 42489, 50477
2395	G protein-coupled receptor 160	492492	2550	418531	10538	18526, 26514, 34502, 42490, 50478
2396	G protein-coupled receptor 162	311268	2551	311528	10539	18527, 26515, 34503, 42491, 50479
2397	G protein-coupled receptor 162	428545	2552	399670	10540	18528, 26516, 34504, 42492, 50480
2398	G protein-coupled receptor 171	309180	2553	308479	10541	18529, 26517, 34505, 42493, 50481
2399	G protein-coupled receptor 171	480322	2554	420109	10542	18530, 26518, 34506, 42494, 50482
2400	G protein-coupled receptor 173	332582	2555	331600	10543	18531, 26519, 34507, 42495, 50483
2401	G protein-coupled receptor 173	375466	2556	364615	10544	18532, 26520, 34508, 42496, 50484
2402	G protein-coupled receptor 174	276077	2557	276077	10545	18533, 26521, 34509, 42497, 50485
2403	G protein-coupled receptor 179	342292	2558	345060	10546	18534, 26522, 34510, 42498, 50486
2404	G protein-coupled receptor 180	376958	2559	366157	10547	18535, 26523, 34511, 42499, 50487
2405	G protein-coupled receptor 182	300098	2560	300098	10548	18536, 26524, 34512, 42500, 50488
2406	G protein-coupled receptor 37 like 1	367282	2561	356251	10549	18537, 26525, 34513, 42501, 50489
2407	G protein-coupled receptor 37 like 1	541334	2562	439451	10550	18538, 26526, 34514, 42502, 50490
2408	G protein-coupled receptor 77	257267	2563	257267	10551	18539, 26527, 34515, 42503, 50491
2409	G protein-coupled receptor 77	600626	2564	471184	10552	18540, 26528, 34516, 42504, 50492

2410	G protein-coupled receptor 88	315033	2565	314223	10553	18541, 26529, 34517, 42505, 50493
2411	G protein-coupled receptor 89C	447947	2566	399563	10554	18542, 26530, 34518, 42506, 50494
2412	G protein-coupled receptor 97	327655	2567	331199	10555	18543, 26531, 34519, 42507, 50495
2413	G protein-coupled receptor 97	333493	2568	332900	10556	18544, 26532, 34520, 42508, 50496
2414	G protein-coupled receptor 97	450388	2569	404803	10557	18545, 26533, 34521, 42509, 50497
2415	G protein-coupled receptor, family C, group 5, member A	14914	2570	14914	10558	18546, 26534, 34522, 42510, 50498, 56085, 56118
2416	G protein-coupled receptor, family C, group 5, member A	534831	2571	441627	10559	18547, 26535, 34523, 42511, 50499
2417	G protein-coupled receptor, family C, group 6, member A	310357	2572	309493	10560	18548, 26536, 34524, 42512, 50500
2418	G protein-coupled receptor, family C, group 6, member A	368549	2573	357537	10561	18549, 26537, 34525, 42513, 50501
2419	G protein-coupled receptor, family C, group 6, member A	530250	2574	433465	10562	18550, 26538, 34526, 42514, 50502
2420	gametogenetin binding protein 1	374458	2575	363582	10563	18551, 26539, 34527, 42515, 50503
2421	gamma-aminobutyric acid (GABA) B receptor, 1	418225	2576	416731	10564	18552, 26540, 34528, 42516, 50504
2422	gamma-aminobutyric acid (GABA) B receptor, 1	440316	2577	412044	10565	18553, 26541, 34529, 42517, 50505
2423	gamma-aminobutyric acid (GABA) B receptor, 1	448754	2578	405709	10566	18554, 26542, 34530, 42518, 50506
2424	gamma-aminobutyric acid (GABA) B receptor, 1	458612	2579	416903	10567	18555, 26543, 34531, 42519, 50507
2425	gamma-aminobutyric acid (GABA) B receptor, 1	550820	2580	448763	10568	18556, 26544, 34532, 42520, 50508

2426	gamma-glutamyltransferase 7	336431	2581	338964	10569	18557, 26545, 34533, 42521, 50509
2427	GDNF family receptor alpha like	340465	2582	343636	10570	18558, 26546, 34534, 42522, 50510
2428	GH3 domain containing	301671	2583	301671	10571	18559, 26547, 34535, 42523, 50511
2429	GH3 domain containing	393854	2584	377436	10572	18560, 26548, 34536, 42524, 50512
2430	GH3 domain containing	414034	2585	399952	10573	18561, 26549, 34537, 42525, 50513
2431	GH3 domain containing	428494	2586	410945	10574	18562, 26550, 34538, 42526, 50514
2432	GH3 domain containing	436923	2587	402654	10575	18563, 26551, 34539, 42527, 50515
2433	GH3 domain containing	587427	2588	467585	10576	18564, 26552, 34540, 42528, 50516
2434	GIPC PDZ domain containing family, member 1	345425	2589	340698	10577	18565, 26553, 34541, 42529, 50517
2435	GIPC PDZ domain containing family, member 1	351277	2590	341425	10578	18566, 26554, 34542, 42530, 50518
2436	GIPC PDZ domain containing family, member 1	393028	2591	376748	10579	18567, 26555, 34543, 42531, 50519
2437	GIPC PDZ domain containing family, member 1	393029	2592	376749	10580	18568, 26556, 34544, 42532, 50520
2438	GIPC PDZ domain containing family, member 1	393033	2593	376753	10581	18569, 26557, 34545, 42533, 50521
2439	GLI pathogenesis-related 1 like 2	320460	2594	317385	10582	18570, 26558, 34546, 42534, 50522
2440	GLI pathogenesis-related 1 like 2	378689	2595	367960	10583	18571, 26559, 34547, 42535, 50523
2441	GLI pathogenesis-related 1 like 2	378692	2596	367963	10584	18572, 26560, 34548, 42536, 50524
2442	GLI pathogenesis-related 1 like 2	435775	2597	398328	10585	18573, 26561, 34549, 42537, 50525
2443	GLI pathogenesis-related 1 like 2	441218	2598	405273	10586	18574, 26562, 34550, 42538, 50526

2444	GLI pathogenesis-related 1 like 2	550916	2599	448248	10587	18575, 26563, 34551, 42539, 50527
2445	glucosamine-phosphate N-acetyltransferase 1	216410	2600	216410	10588	18576, 26564, 34552, 42540, 50528
2446	glucosamine-phosphate N-acetyltransferase 1	557604	2601	452032	10589	18577, 26565, 34553, 42541, 50529
2447	glucosaminyl (N-acetyl) transferase 4, core 2	322348	2602	317027	10590	18578, 26566, 34554, 42542, 50530
2448	glucosaminyl (N-acetyl) transferase family member 7	243913	2603	243913	10591	18579, 26567, 34555, 42543, 50531
2449	glucosidase, beta (bile acid) 2	378088	2604	367328	10592	18580, 26568, 34556, 42544, 50532
2450	glucosidase, beta (bile acid) 2	378094	2605	367334	10593	18581, 26569, 34557, 42545, 50533
2451	glucosidase, beta (bile acid) 2	378103	2606	367343	10594	18582, 26570, 34558, 42546, 50534
2452	glucosidase, beta (bile acid) 2	545786	2607	442372	10595	18583, 26571, 34559, 42547, 50535
2453	glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein	457091	2608	397351	10596	18584, 26572, 34560, 42548, 50536
2454	glutamate receptor, ionotropic, N-methyl-D-aspartate 3B	234389	2609	234389	10597	18585, 26573, 34561, 42549, 50537
2455	glutamate receptor, metabotropic 5	305432	2610	305905	10598	18586, 26574, 34562, 42550, 50538
2456	glutamate receptor, metabotropic 5	305447	2611	306138	10599	18587, 26575, 34563, 42551, 50539
2457	glutamate receptor, metabotropic 5	393297	2612	376975	10600	18588, 26576, 34564, 42552, 50540
2458	glutamate receptor, metabotropic 5	418177	2613	402912	10601	18589, 26577, 34565, 42553, 50541
2459	glutamate receptor, metabotropic 5	455756	2614	405690	10602	18590, 26578, 34566, 42554, 50542
2460	glutaminyl-peptide cyclotransferase-like	12049	2615	12049	10603	18591, 26579, 34567, 42555, 50543, 56086, 56119

2461	glutaminyl-peptide cyclotransferase-like	366382	2616	387944	10604	18592, 26580, 34568, 42556, 50544
2462	glutaminyl-tRNA synthase (glutamine-hydrolyzing)-like 1	369044	2617	358040	10605	18593, 26581, 34569, 42557, 50545
2463	glutaminyl-tRNA synthase (glutamine-hydrolyzing)-like 1	369046	2618	358042	10606	18594, 26582, 34570, 42558, 50546
2464	Glutamyl-tRNA(Gln) amidotransferase subunit C, mitochondrial	551765	2619	446872	10607	18595, 26583, 34571, 42559, 50547
2465	glutathione peroxidase 8 (putative)	503787	2620	423822	10608	18596, 26584, 34572, 42560, 50548
2466	glycerol-3-phosphate acyltransferase 2, mitochondrial	359548	2621	352547	10609	18597, 26585, 34573, 42561, 50549
2467	glycerol-3-phosphate acyltransferase 2, mitochondrial	377137	2622	366341	10610	18598, 26586, 34574, 42562, 50550
2468	glycerol-3-phosphate acyltransferase 2, mitochondrial	434632	2623	389395	10611	18599, 26587, 34575, 42563, 50551
2469	glycerol-3-phosphate acyltransferase 2, mitochondrial	439254	2624	401334	10612	18600, 26588, 34576, 42564, 50552
2470	glycerol-3-phosphate acyltransferase, mitochondrial	348367	2625	265276	10613	18601, 26589, 34577, 42565, 50553
2471	glycerol-3-phosphate acyltransferase, mitochondrial	369425	2626	358433	10614	18602, 26590, 34578, 42566, 50554
2472	glycerol-3-phosphate acyltransferase, mitochondrial	423155	2627	409242	10615	18603, 26591, 34579, 42567, 50555
2473	glycerophosphodiester phosphodiesterase domain containing 1	284116	2628	284116	10616	18604, 26592, 34580, 42568, 50556
2474	glycerophosphodiester phosphodiesterase domain containing 1	581140	2629	463273	10617	18605, 26593, 34581, 42569, 50557

2475	glycerophosphodiester phosphodiesterase domain containing 1	581276	2630	464690	10618	18606, 26594, 34582, 42570, 50558
2476	glycerophosphodiester phosphodiesterase domain containing 2	374382	2631	363503	10619	18607, 26595, 34583, 42571, 50559
2477	glycerophosphodiester phosphodiesterase domain containing 2	453994	2632	414019	10620	18608, 26596, 34584, 42572, 50560
2478	glycerophosphodiester phosphodiesterase domain containing 2	536730	2633	445982	10621	18609, 26597, 34585, 42573, 50561
2479	glycerophosphodiester phosphodiesterase domain containing 2	538649	2634	444601	10622	18610, 26598, 34586, 42574, 50562
2480	glycerophosphodiester phosphodiesterase domain containing 3	360688	2635	353909	10623	18611, 26599, 34587, 42575, 50563
2481	glycerophosphodiester phosphodiesterase domain containing 3	406256	2636	384363	10624	18612, 26600, 34588, 42576, 50564
2482	glycerophosphodiester phosphodiesterase domain containing 4	315938	2637	320815	10625	18613, 26601, 34589, 42577, 50565
2483	glycerophosphodiester phosphodiesterase domain containing 4	376217	2638	365390	10626	18614, 26602, 34590, 42578, 50566
2484	glycine receptor, alpha 4	372617	2639	361700	10627	18615, 26603, 34591, 42579, 50567
2485	glycine-N-acyltransferase-like 1	300079	2640	300079	10628	18616, 26604, 34592, 42580, 50568
2486	glycine-N-acyltransferase-like 1	317391	2641	322223	10629	18617, 26605, 34593, 42581, 50569
2487	glycine-N-acyltransferase-like 1	444580	2642	401353	10630	18618, 26606, 34594, 42582, 50570
2488	glycine-N-acyltransferase-like 1	525608	2643	433716	10631	18619, 26607, 34595, 42583, 50571
2489	glycine-N-acyltransferase-like 1	532726	2644	436116	10632	18620, 26608, 34596, 42584, 50572

2490	glycine-N-acyltransferase-like 2	287275	2645	287275	10633	18621, 26609, 34597, 42585, 50573
2491	glycine-N-acyltransferase-like 2	532258	2646	434277	10634	18622, 26610, 34598, 42586, 50574
2492	glycine-N-acyltransferase-like 3	371197	2647	360240	10635	18623, 26611, 34599, 42587, 50575
2493	glycine-N-acyltransferase-like 3	545705	2648	440029	10636	18624, 26612, 34600, 42588, 50576
2494	glycoprotein (transmembrane) nmb	258733	2649	258733	10637	18625, 26613, 34601, 42589, 50577
2495	glycoprotein (transmembrane) nmb	381990	2650	371420	10638	18626, 26614, 34602, 42590, 50578
2496	glycoprotein (transmembrane) nmb	409458	2651	386476	10639	18627, 26615, 34603, 42591, 50579
2497	glycoprotein (transmembrane) nmb	425903	2652	396994	10640	18628, 26616, 34604, 42592, 50580
2498	glycoprotein (transmembrane) nmb	435486	2653	409199	10641	18629, 26617, 34605, 42593, 50581
2499	glycoprotein (transmembrane) nmb	453162	2654	405586	10642	18630, 26618, 34606, 42594, 50582
2500	glycoprotein (transmembrane) nmb	539136	2655	445266	10643	18631, 26619, 34607, 42595, 50583
2501	glycoprotein A33 (transmembrane)	367868	2656	356842	10644	18632, 26620, 34608, 42596, 50584
2502	glycoprotein V (platelet)	323007	2657	319286	10645	18633, 26621, 34609, 42597, 50585
2503	glycoprotein V (platelet)	401815	2658	383931	10646	18634, 26622, 34610, 42598, 50586
2504	glycosyltransferase 25 domain containing 1	252599	2659	252599	10647	18635, 26623, 34611, 42599, 50587
2505	glycosyltransferase 25 domain containing 1	379714	2660	369036	10648	18636, 26624, 34612, 42600, 50588
2506	glycosyltransferase 25 domain containing 2	361927	2661	354960	10649	18637, 26625, 34613, 42601, 50589
2507	glycosyltransferase 25 domain containing 2	367520	2662	356490	10650	18638, 26626, 34614, 42602, 50590

2508	glycosyltransferase 25 domain containing 2	367521	2663	356491	10651	18639, 26627, 34615, 42603, 50591
2509	glycosyltransferase 25 domain containing 2	546159	2664	439112	10652	18640, 26628, 34616, 42604, 50592
2510	glycosyltransferase 8 domain containing 2	360814	2665	354053	10653	18641, 26629, 34617, 42605, 50593
2511	glycosyltransferase 8 domain containing 2	546436	2666	449750	10654	18642, 26630, 34618, 42606, 50594
2512	glycosyltransferase 8 domain containing 2	548660	2667	447450	10655	18643, 26631, 34619, 42607, 50595
2513	glyoxalase domain containing 4	301328	2668	301328	10656	18644, 26632, 34620, 42608, 50596
2514	glyoxalase domain containing 4	301329	2669	301329	10657	18645, 26633, 34621, 42609, 50597
2515	glyoxalase domain containing 4	397393	2670	380548	10658	18646, 26634, 34622, 42610, 50598
2516	glyoxalase domain containing 4	536578	2671	444315	10659	18647, 26635, 34623, 42611, 50599
2517	golgi reassembly stacking protein 2, 55kDa	234160	2672	234160	10660	18648, 26636, 34624, 42612, 50600
2518	golgi reassembly stacking protein 2, 55kDa	452526	2673	410208	10661	18649, 26637, 34625, 42613, 50601
2519	golgi transport 1A	308302	2674	308535	10662	18650, 26638, 34626, 42614, 50602
2520	golgi transport 1B	229314	2675	229314	10663	18651, 26639, 34627, 42615, 50603
2521	golgi-associated, gamma adaptin ear containing, ARF binding protein 2	309859	2676	311962	10664	18652, 26640, 34628, 42616, 50604
2522	golgi-associated, gamma adaptin ear containing, ARF binding protein 2	498959	2677	442062	10665	18653, 26641, 34629, 42617, 50605
2523	golgin A2	342583	2678	342692	10666	18654, 26642, 34630, 42618, 50606
2524	golgin A2	421699	2679	416097	10667	18655, 26643, 34631, 42619, 50607

2525	golgin A2	450617	2680	409271	10668	18656, 26644, 34632, 42620, 50608
2526	golgin A7	357743	2681	350378	10669	18657, 26645, 34633, 42621, 50609
2527	golgin A7	405786	2682	386030	10670	18658, 26646, 34634, 42622, 50610
2528	golgin A7	518270	2683	429329	10671	18659, 26647, 34635, 42623, 50611
2529	golgin A7	520817	2684	429480	10672	18660, 26648, 34636, 42624, 50612
2530	G-protein signaling modulator 1	291775	2685	291775	10673	18661, 26649, 34637, 42625, 50613
2531	G-protein signaling modulator 1	354753	2686	346797	10674	18662, 26650, 34638, 42626, 50614
2532	G-protein signaling modulator 1	392944	2687	376673	10675	18663, 26651, 34639, 42627, 50615
2533	G-protein signaling modulator 1	392945	2688	376674	10676	18664, 26652, 34640, 42628, 50616
2534	G-protein signaling modulator 1	429455	2689	390705	10677	18665, 26653, 34641, 42629, 50617
2535	G-protein signaling modulator 1	440944	2690	392828	10678	18666, 26654, 34642, 42630, 50618
2536	GRAM domain containing 1A	317991	2691	441032	10679	18667, 26655, 34643, 42631, 50619
2537	GRAM domain containing 1A	411896	2692	439267	10680	18668, 26656, 34644, 42632, 50620
2538	GRAM domain containing 1A	453966	2693	441346	10681	18669, 26657, 34645, 42633, 50621
2539	GRAM domain containing 1A	504615	2694	423728	10682	18670, 26658, 34646, 42634, 50622
2540	GRAM domain containing 1B	322282	2695	325628	10683	18671, 26659, 34647, 42635, 50623
2541	GRAM domain containing 1B	529750	2696	436500	10684	18672, 26660, 34648, 42636, 50624
2542	GRAM domain containing 1B	539133	2697	444667	10685	18673, 26661, 34649, 42637, 50625

2543	GRAM domain containing 1C	358160	2698	350881	10686	18674, 26662, 34650, 42638, 50626
2544	GRAM domain containing 1C	440446	2699	408135	10687	18675, 26663, 34651, 42639, 50627
2545	GRAM domain containing 1C	452134	2700	399844	10688	18676, 26664, 34652, 42640, 50628
2546	GRAM domain containing 1C	462838	2701	418302	10689	18677, 26665, 34653, 42641, 50629
2547	GRAM domain containing 2	309731	2702	311657	10690	18678, 26666, 34654, 42642, 50630
2548	GRB2-binding adaptor protein, transmembrane	318469	2703	323075	10691	18679, 26667, 34655, 42643, 50631
2549	GRB2-binding adaptor protein, transmembrane	396776	2704	379997	10692	18680, 26668, 34656, 42644, 50632
2550	GRB2-binding adaptor protein, transmembrane	502276	2705	423113	10693	18681, 26669, 34657, 42645, 50633
2551	GRB2-binding adaptor protein, transmembrane	511930	2706	422645	10694	18682, 26670, 34658, 42646, 50634
2552	growth differentiation factor 5 opposite strand	374375	2707	363495	10695	18683, 26671, 34659, 42647, 50635
2553	growth hormone inducible transmembrane protein	339736	2708	342214	10696	18684, 26672, 34660, 42648, 50636
2554	growth hormone inducible transmembrane protein	372134	2709	361207	10697	18685, 26673, 34661, 42649, 50637
2555	growth hormone inducible transmembrane protein	436406	2710	397663	10698	18686, 26674, 34662, 42650, 50638
2556	growth hormone inducible transmembrane protein	538477	2711	444366	10699	18687, 26675, 34663, 42651, 50639
2557	growth regulation by estrogen in breast cancer-like	269218	2712	269218	10700	18688, 26676, 34664, 42652, 50640
2558	growth regulation by estrogen in breast cancer-like	400483	2713	383331	10701	18689, 26677, 34665, 42653, 50641
2559	growth regulation by estrogen in breast cancer-like	424526	2714	412060	10702	18690, 26678, 34666, 42654, 50642

2560	growth regulation by estrogen in breast cancer-like	431264	2715	393125	10703	18691, 26679, 34667, 42655, 50643
2561	GSG1-like	380897	2716	370282	10704	18692, 26680, 34668, 42656, 50644
2562	GSG1-like	380898	2717	370283	10705	18693, 26681, 34669, 42657, 50645
2563	GSG1-like	395724	2718	379074	10706	18694, 26682, 34670, 42658, 50646
2564	GSG1-like	447459	2719	394954	10707	18695, 26683, 34671, 42659, 50647
2565	GTP binding protein 3 (mitochondrial)	324894	2720	313818	10708	18696, 26684, 34672, 42660, 50648
2566	GTP binding protein 3 (mitochondrial)	358792	2721	351644	10709	18697, 26685, 34673, 42661, 50649
2567	GTP binding protein 3 (mitochondrial)	361619	2722	354598	10710	18698, 26686, 34674, 42662, 50650
2568	GTP binding protein 3 (mitochondrial)	546035	2723	438301	10711	18699, 26687, 34675, 42663, 50651
2569	GTP binding protein 3 (mitochondrial)	600625	2724	473150	10712	18700, 26688, 34676, 42664, 50652
2570	GTP binding protein 4	360059	2725	353168	10713	18701, 26689, 34677, 42665, 50653
2571	GTP binding protein 4	360803	2726	354040	10714	18702, 26690, 34678, 42666, 50654
2572	GTP binding protein 4	538293	2727	444277	10715	18703, 26691, 34679, 42667, 50655
2573	GTP binding protein 4	545048	2728	445473	10716	18704, 26692, 34680, 42668, 50656
2574	GTPase, IMAP family member 8	307271	2729	305107	10717	18705, 26693, 34681, 42669, 50657
2575	GTP-binding protein 8 (putative)	305485	2730	303802	10718	18706, 26694, 34682, 42670, 50658
2576	GTP-binding protein 8 (putative)	383677	2731	373175	10719	18707, 26695, 34683, 42671, 50659
2577	GTP-binding protein 8 (putative)	383678	2732	373176	10720	18708, 26696, 34684, 42672, 50660

2578	GTP-binding protein 8 (putative)	467752	2733	417632	10721	18709, 26697, 34685, 42673, 50661
2579	GTP-binding protein 8 (putative)	473129	2734	418514	10722	18710, 26698, 34686, 42674, 50662
2580	GTP-binding protein 8 (putative)	485330	2735	418877	10723	18711, 26699, 34687, 42675, 50663
2581	guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1	456394	2736	394470	10724	18712, 26700, 34688, 42676, 50664
2582	guanine nucleotide binding protein (G protein), beta polypeptide 2-like 1	512805	2737	426909	10725	18713, 26701, 34689, 42677, 50665
2583	guanine nucleotide binding protein (G protein), gamma 10	374293	2738	363411	10726	18714, 26702, 34690, 42678, 50666
2584	guanine nucleotide binding protein (G protein), gamma 12	370982	2739	360021	10727	18715, 26703, 34691, 42679, 50667
2585	guanine nucleotide binding protein (G protein), gamma 3	294117	2740	294117	10728	18716, 26704, 34692, 42680, 50668
2586	guanine nucleotide binding protein (G protein), gamma 4	366597	2741	355556	10729	18717, 26705, 34693, 42681, 50669
2587	guanine nucleotide binding protein (G protein), gamma 4	366598	2742	355557	10730	18718, 26706, 34694, 42682, 50670
2588	guanine nucleotide binding protein (G protein), gamma 4	391854	2743	375727	10731	18719, 26707, 34695, 42683, 50671
2589	guanine nucleotide binding protein (G protein), gamma 4	450593	2744	398629	10732	18720, 26708, 34696, 42684, 50672
2590	guanine nucleotide binding protein (G protein), gamma 7	382159	2745	371594	10733	18721, 26709, 34697, 42685, 50673
2591	guanine nucleotide binding protein (G protein), gamma transducing activity polypeptide 1	428834	2746	401781	10734	18722, 26710, 34698, 42686, 50674
2592	guanine nucleotide binding protein (G protein), gamma transducing activity polypeptide 1	430875	2747	395756	10735	18723, 26711, 34699, 42687, 50675
2593	guanine nucleotide binding protein (G protein), gamma transducing activity	455502	2748	395857	10736	18724, 26712, 34700, 42688, 50676

	polypeptide 1					
2594	guanine nucleotide binding protein, alpha transducing 3	398291	2749	381339	10737	18725, 26713, 34701, 42689, 50677
2595	guanine nucleotide binding protein-like 3 (nucleolar)-like	336470	2750	338573	10738	18726, 26714, 34702, 42690, 50678
2596	guanine nucleotide binding protein-like 3 (nucleolar)-like	360845	2751	354091	10739	18727, 26715, 34703, 42691, 50679
2597	GUF1 GTPase homolog (S. cerevisiae)	281543	2752	281543	10740	18728, 26716, 34704, 42692, 50680
2598	haloacid dehalogenase-like hydrolase domain containing 3	238379	2753	238379	10741	18729, 26717, 34705, 42693, 50681
2599	haloacid dehalogenase-like hydrolase domain containing 3	374180	2754	363295	10742	18730, 26718, 34706, 42694, 50682
2600	HCG2044188Seven transmembrane helix receptorUncharacterized protein	316517	2755	321173	10743	18731, 26719, 34707, 42695, 50683
2601	HD domain containing 2	318787	2756	316242	10744	18732, 26720, 34708, 42696, 50684
2602	HD domain containing 2	398153	2757	381220	10745	18733, 26721, 34709, 42697, 50685
2603	HEAT repeat containing 8	339553	2758	343211	10746	18734, 26722, 34710, 42698, 50686
2604	HEAT repeat containing 8	371287	2759	360336	10747	18735, 26723, 34711, 42699, 50687
2605	HEAT repeat containing 8	395690	2760	379044	10748	18736, 26724, 34712, 42700, 50688
2606	HEAT repeat containing 8	414867	2761	403054	10749	18737, 26725, 34713, 42701, 50689
2607	HEAT repeat containing 8	421030	2762	396622	10750	18738, 26726, 34714, 42702, 50690
2608	HEAT repeat containing 8	454855	2763	401130	10751	18739, 26727, 34715, 42703, 50691
2609	HEAT repeat containing 8	545244	2764	442333	10752	18740, 26728, 34716, 42704, 50692

2610	heat shock protein 70kDa family, member 13	285667	2765	285667	10753	18741, 26729, 34717, 42705, 50693
2611	heat shock protein 70kDa family, member 13	544452	2766	441986	10754	18742, 26730, 34718, 42706, 50694
2612	hedgehog acyltransferase-like	310417	2767	310621	10755	18743, 26731, 34719, 42707, 50695
2613	hedgehog acyltransferase-like	341477	2768	341177	10756	18744, 26732, 34720, 42708, 50696
2614	hedgehog acyltransferase-like	416756	2769	395779	10757	18745, 26733, 34721, 42709, 50697
2615	hedgehog acyltransferase-like	441594	2770	405423	10758	18746, 26734, 34722, 42710, 50698
2616	hematopoietic cell signal transducer	246551	2771	246551	10759	18747, 26735, 34723, 42711, 50699
2617	hematopoietic cell signal transducer	437550	2772	400516	10760	18748, 26736, 34724, 42712, 50700
2618	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	2596	2773	2596	10761	18749, 26737, 34725, 42713, 50701, 56087, 56120
2619	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	510712	2774	422629	10762	18750, 26738, 34726, 42714, 50702
2620	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	514690	2775	425673	10763	18751, 26739, 34727, 42715, 50703
2621	heparan sulfate (glucosamine) 3-O-sulfotransferase 6	293937	2776	293937	10764	18752, 26740, 34728, 42716, 50704
2622	heparan sulfate (glucosamine) 3-O-sulfotransferase 6	443547	2777	390354	10765	18753, 26741, 34729, 42717, 50705
2623	heparan sulfate (glucosamine) 3-O-sulfotransferase 6	454677	2778	416741	10766	18754, 26742, 34730, 42718, 50706
2624	hepatitis A virus cellular receptor 2	307851	2779	312002	10767	18755, 26743, 34731, 42719, 50707
2625	hephaestin-like 1	315765	2780	313699	10768	18756, 26744, 34732, 42720, 50708
2626	HERPUD family member 2	311350	2781	310729	10769	18757, 26745, 34733, 42721, 50709
2627	HERPUD family member 2	396081	2782	379390	10770	18758, 26746, 34734, 42722, 50710

2628	HERV-H LTR-associating 2	357759	2783	350402	10771	18759, 26747, 34735, 42723, 50711
2629	HERV-H LTR-associating 2	462629	2784	419911	10772	18760, 26748, 34736, 42724, 50712
2630	HERV-H LTR-associating 2	463019	2785	419940	10773	18761, 26749, 34737, 42725, 50713
2631	HERV-H LTR-associating 2	467761	2786	419207	10774	18762, 26750, 34738, 42726, 50714
2632	HERV-H LTR-associating 2	482430	2787	418174	10775	18763, 26751, 34739, 42727, 50715
2633	HERV-H LTR-associating 2	489514	2788	417856	10776	18764, 26752, 34740, 42728, 50716
2634	heterogeneous nuclear ribonucleoprotein M	325495	2789	325376	10777	18765, 26753, 34741, 42729, 50717
2635	heterogeneous nuclear ribonucleoprotein M	348943	2790	325732	10778	18766, 26754, 34742, 42730, 50718
2636	heterogeneous nuclear ribonucleoprotein M	539473	2791	443840	10779	18767, 26755, 34743, 42731, 50719
2637	heterogeneous nuclear ribonucleoprotein M	544159	2792	442876	10780	18768, 26756, 34744, 42732, 50720
2638	hexokinase domain containing 1	354624	2793	346643	10781	18769, 26757, 34745, 42733, 50721
2639	hexokinase domain containing 1	395086	2794	378521	10782	18770, 26758, 34746, 42734, 50722
2640	hexokinase domain containing 1	395087	2795	378522	10783	18771, 26759, 34747, 42735, 50723
2641	HIG1 hypoxia inducible domain family, member 1A	321331	2796	319393	10784	18772, 26760, 34748, 42736, 50724
2642	HIG1 hypoxia inducible domain family, member 1A	418900	2797	402160	10785	18773, 26761, 34749, 42737, 50725
2643	HIG1 hypoxia inducible domain family, member 1A	452906	2798	398064	10786	18774, 26762, 34750, 42738, 50726
2644	HIG1 hypoxia inducible domain family, member 1B	253410	2799	253410	10787	18775, 26763, 34751, 42739, 50727
2645	HIG1 hypoxia inducible domain family, member 2A	274787	2800	274787	10788	18776, 26764, 34752, 42740, 50728

2646	HIG1 hypoxia inducible domain family, member 2B	311755	2801	307951	10789	18777, 26765, 34753, 42741, 50729
2647	hippocampus abundant transcript 1	370152	2802	359171	10790	18778, 26766, 34754, 42742, 50730
2648	hippocampus abundant transcript 1	421661	2803	411185	10791	18779, 26767, 34755, 42743, 50731
2649	hippocampus abundant transcript-like 1	277183	2804	277183	10792	18780, 26768, 34756, 42744, 50732
2650	hippocampus abundant transcript-like 1	375344	2805	364493	10793	18781, 26769, 34757, 42745, 50733
2651	hippocampus abundant transcript-like 1	428393	2806	405909	10794	18782, 26770, 34758, 42746, 50734
2652	hippocampus abundant transcript-like 2	375223	2807	364371	10795	18783, 26771, 34759, 42747, 50735
2653	histidine rich carboxyl terminus 1	354323	2808	346283	10796	18784, 26772, 34760, 42748, 50736
2654	hydroxycarboxylic acid receptor 1	356987	2809	349478	10797	18785, 26773, 34761, 42749, 50737
2655	hydroxycarboxylic acid receptor 1	432564	2810	389255	10798	18786, 26774, 34762, 42750, 50738
2656	hydroxycarboxylic acid receptor 1	436083	2811	409980	10799	18787, 26775, 34763, 42751, 50739
2657	hydroxycarboxylic acid receptor 2	328880	2812	375066	10800	18788, 26776, 34764, 42752, 50740
2658	hydroxycarboxylic acid receptor 2	536970	2813	443556	10801	18789, 26777, 34765, 42753, 50741
2659	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	322165	2814	318631	10802	18790, 26778, 34766, 42754, 50742
2660	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	554150	2815	452273	10803	18791, 26779, 34767, 42755, 50743
2661	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	554155	2816	451497	10804	18792, 26780, 34768, 42756, 50744
2662	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	554643	2817	451406	10805	18793, 26781, 34769, 42757, 50745
2663	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	555159	2818	450698	10806	18794, 26782, 34770, 42758, 50746

2664	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	555805	2819	451753	10807	18795, 26783, 34771, 42759, 50747
2665	hydroxysteroid (17-beta) dehydrogenase 6 homolog (mouse)	556650	2820	452103	10808	18796, 26784, 34772, 42760, 50748
2666	hydroxysteroid dehydrogenase like 1	219439	2821	219439	10809	18797, 26785, 34773, 42761, 50749
2667	hydroxysteroid dehydrogenase like 1	434463	2822	407437	10810	18798, 26786, 34774, 42762, 50750
2668	hyperpolarization activated cyclic nucleotide-gated potassium channel 1	303230	2823	307342	10811	18799, 26787, 34775, 42763, 50751
2669	hypocretin (orexin) receptor 1	373705	2824	362809	10812	18800, 26788, 34776, 42764, 50752
2670	hypocretin (orexin) receptor 1	373706	2825	362810	10813	18801, 26789, 34777, 42765, 50753
2671	hypocretin (orexin) receptor 1	403528	2826	384387	10814	18802, 26790, 34778, 42766, 50754
2672	hypocretin (orexin) receptor 2	370862	2827	359899	10815	18803, 26791, 34779, 42767, 50755
2673	IKBKB interacting protein	299157	2828	299157	10816	18804, 26792, 34780, 42768, 50756
2674	IKBKB interacting protein	342502	2829	343471	10817	18805, 26793, 34781, 42769, 50757
2675	IKBKB interacting protein	393042	2830	376762	10818	18806, 26794, 34782, 42770, 50758
2676	IKBKB interacting protein	420861	2831	398023	10819	18807, 26795, 34783, 42771, 50759
2677	immunoglobulin superfamily, DCC subclass, member 3	327987	2832	332773	10820	18808, 26796, 34784, 42772, 50760
2678	immunoglobulin superfamily, DCC subclass, member 3	443278	2833	388643	10821	18809, 26797, 34785, 42773, 50761
2679	immunoglobulin superfamily, DCC subclass, member 4	352385	2834	319623	10822	18810, 26798, 34786, 42774, 50762
2680	immunoglobulin superfamily, DCC subclass, member 4	356152	2835	348473	10823	18811, 26799, 34787, 42775, 50763
2681	immunoglobulin superfamily, member 11	354673	2836	346700	10824	18812, 26800, 34788, 42776, 50764

2682	immunoglobulin superfamily, member 11	393775	2837	377370	10825	18813, 26801, 34789, 42777, 50765
2683	immunoglobulin superfamily, member 11	425327	2838	406092	10826	18814, 26802, 34790, 42778, 50766
2684	immunoglobulin superfamily, member 23	402988	2839	385592	10827	18815, 26803, 34791, 42779, 50767
2685	immunoglobulin superfamily, member 5	380588	2840	369962	10828	18816, 26804, 34792, 42780, 50768
2686	immunoglobulin-like domain containing receptor 2	271417	2841	271417	10829	18817, 26805, 34793, 42781, 50769
2687	inositol 1,4,5-trisphosphate receptor interacting protein	278071	2842	278071	10830	18818, 26806, 34794, 42782, 50770
2688	inositol 1,4,5-trisphosphate receptor interacting protein	337478	2843	337178	10831	18819, 26807, 34795, 42783, 50771
2689	inositol 1,4,5-trisphosphate receptor interacting protein	358187	2844	350915	10832	18820, 26808, 34796, 42784, 50772
2690	inositol 1,4,5-trisphosphate receptor interacting protein	458723	2845	414141	10833	18821, 26809, 34797, 42785, 50773
2691	inositol 1,4,5-trisphosphate receptor interacting protein-like 1	361124	2846	355121	10834	18822, 26810, 34798, 42786, 50774
2692	inositol 1,4,5-trisphosphate receptor interacting protein-like 1	439118	2847	389308	10835	18823, 26811, 34799, 42787, 50775
2693	inositol 1,4,5-trisphosphate receptor interacting protein-like 1	536814	2848	439566	10836	18824, 26812, 34800, 42788, 50776
2694	inositol 1,4,5-trisphosphate receptor interacting protein-like 1	542887	2849	438212	10837	18825, 26813, 34801, 42789, 50777
2695	inositol 1,4,5-trisphosphate receptor interacting protein-like 2	381440	2850	370849	10838	18826, 26814, 34802, 42790, 50778
2696	insulin receptor substrate 4	372129	2851	361202	10839	18827, 26815, 34803, 42791, 50779

2697	integrator complex subunit 1	389470	2852	374121	10840	18828, 26816, 34804, 42792, 50780
2698	integrator complex subunit 1	404767	2853	385722	10841	18829, 26817, 34805, 42793, 50781
2699	integrator complex subunit 2	251334	2854	251334	10842	18830, 26818, 34806, 42794, 50782
2700	integrator complex subunit 2	444766	2855	414237	10843	18831, 26819, 34807, 42795, 50783
2701	integrator complex subunit 5	330574	2856	327889	10844	18832, 26820, 34808, 42796, 50784
2702	integrin alpha FG-GAP repeat containing 3	301678	2857	301678	10845	18833, 26821, 34809, 42797, 50785
2703	integrin alpha FG-GAP repeat containing 3	399932	2858	382814	10846	18834, 26822, 34810, 42798, 50786
2704	integrin alpha FG-GAP repeat containing 3	417499	2859	405659	10847	18835, 26823, 34811, 42799, 50787
2705	integrin alpha FG-GAP repeat containing 3	419173	2860	388726	10848	18836, 26824, 34812, 42800, 50788
2706	integrin alpha FG-GAP repeat containing 3	420046	2861	398433	10849	18837, 26825, 34813, 42801, 50789
2707	integrin alpha FG-GAP repeat containing 3	426695	2862	392612	10850	18838, 26826, 34814, 42802, 50790
2708	integrin alpha FG-GAP repeat containing 3	442458	2863	397477	10851	18839, 26827, 34815, 42803, 50791
2709	integrin alpha FG-GAP repeat containing 3	447499	2864	395334	10852	18840, 26828, 34816, 42804, 50792
2710	integrin alpha FG-GAP repeat containing 3	450082	2865	411394	10853	18841, 26829, 34817, 42805, 50793
2711	integrin alpha FG-GAP repeat containing 3	453430	2866	399150	10854	18842, 26830, 34818, 42806, 50794
2712	integrin, alpha 10	369304	2867	358310	10855	18843, 26831, 34819, 42807, 50795
2713	integrin, alpha 10	538811	2868	440011	10856	18844, 26832, 34820, 42808, 50796
2714	integrin, alpha 10	539363	2869	439894	10857	18845, 26833, 34821, 42809, 50797

2715	integrin, alpha 10	543043	2870	439105	10858	18846, 26834, 34822, 42810, 50798
2716	integrin, alpha 8	378076	2871	367316	10859	18847, 26835, 34823, 42811, 50799
2717	integrin, alpha 8	538044	2872	443785	10860	18848, 26836, 34824, 42812, 50800
2718	integrin, alpha E (antigen CD103, human mucosal lymphocyte antigen 1; alpha polypeptide)	263087	2873	263087	10861	18849, 26837, 34825, 42813, 50801
2719	integrin, beta 5	296181	2874	296181	10862	18850, 26838, 34826, 42814, 50802
2720	integrin, beta 8	222573	2875	222573	10863	18851, 26839, 34827, 42815, 50803
2721	integrin, beta 8	537992	2876	441561	10864	18852, 26840, 34828, 42816, 50804
2722	interaction protein for cytohesin exchange factors 1	265198	2877	265198	10865	18853, 26841, 34829, 42817, 50805
2723	interaction protein for cytohesin exchange factors 1	367220	2878	356189	10866	18854, 26842, 34830, 42818, 50806
2724	interaction protein for cytohesin exchange factors 1	422970	2879	394751	10867	18855, 26843, 34831, 42819, 50807
2725	interaction protein for cytohesin exchange factors 1	520261	2880	431004	10868	18856, 26844, 34832, 42820, 50808
2726	interferon alpha responsive protein isoform a	553856	2881	452581	10869	18857, 26845, 34833, 42821, 50809
2727	interferon induced transmembrane protein 10	340134	2882	344430	10870	18858, 26846, 34834, 42822, 50810
2728	interferon induced transmembrane protein 5	382614	2883	372059	10871	18859, 26847, 34835, 42823, 50811
2729	interferon regulatory factor 7	330243	2884	329411	10872	18860, 26848, 34836, 42824, 50812
2730	interferon regulatory factor 7	348655	2885	331803	10873	18861, 26849, 34837, 42825, 50813
2731	interferon regulatory factor 7	397562	2886	380693	10874	18862, 26850, 34838, 42826, 50814

2732	interferon regulatory factor 7	397566	2887	380697	10875	18863, 26851, 34839, 42827, 50815
2733	interferon regulatory factor 7	397570	2888	380700	10876	18864, 26852, 34840, 42828, 50816
2734	interferon regulatory factor 7	397574	2889	380704	10877	18865, 26853, 34841, 42829, 50817
2735	interferon, alpha-inducible protein 27-like 1	393115	2890	376824	10878	18866, 26854, 34842, 42830, 50818
2736	interferon, alpha-inducible protein 27-like 1	555523	2891	451851	10879	18867, 26855, 34843, 42831, 50819
2737	interferon, alpha-inducible protein 27-like 2	238609	2892	238609	10880	18868, 26856, 34844, 42832, 50820
2738	interferon, alpha-inducible protein 6	339145	2893	342513	10881	18869, 26857, 34845, 42833, 50821
2739	interferon, alpha-inducible protein 6	361157	2894	354736	10882	18870, 26858, 34846, 42834, 50822
2740	interferon, alpha-inducible protein 6	362020	2895	355152	10883	18871, 26859, 34847, 42835, 50823
2741	interleukin 10 receptor, beta	290200	2896	290200	10884	18872, 26860, 34848, 42836, 50824
2742	interleukin 10 receptor, beta	539894	2897	442753	10885	18873, 26861, 34849, 42837, 50825
2743	interleukin 20 receptor beta	309741	2898	311979	10886	18874, 26862, 34850, 42838, 50826
2744	interleukin 20 receptor beta	329582	2899	328133	10887	18875, 26863, 34851, 42839, 50827
2745	interleukin 22 receptor, alpha 1	270800	2900	270800	10888	18876, 26864, 34852, 42840, 50828
2746	interleukin 27 receptor, alpha	263379	2901	263379	10889	18877, 26865, 34853, 42841, 50829
2747	interleukin 7 receptor	511982	2902	425309	10890	18878, 26866, 34854, 42842, 50830
2748	interleukin 7 receptor	514217	2903	427688	10891	18879, 26867, 34855, 42843, 50831
2749	IQ motif containing E	325979	2904	313772	10892	18880, 26868, 34856, 42844, 50832

2750	IQ motif containing E	402050	2905	385597	10893	18881, 26869, 34857, 42845, 50833
2751	IQ motif containing E	404984	2906	385945	10894	18882, 26870, 34858, 42846, 50834
2752	IQ motif containing E	422276	2907	402108	10895	18883, 26871, 34859, 42847, 50835
2753	IQ motif containing E	423395	2908	413570	10896	18884, 26872, 34860, 42848, 50836
2754	IQ motif containing E	438376	2909	396178	10897	18885, 26873, 34861, 42849, 50837
2755	IQ motif containing GTPase activating protein 3	361170	2910	354451	10898	18886, 26874, 34862, 42850, 50838
2756	iron-sulfur cluster assembly 2 homolog (S. cerevisiae)	556816	2911	452007	10899	18887, 26875, 34863, 42851, 50839
2757	IZUMO family member 2	293405	2912	293405	10900	18888, 26876, 34864, 42852, 50840
2758	IZUMO family member 2	377000	2913	366199	10901	18889, 26877, 34865, 42853, 50841
2759	IZUMO family member 3	543880	2914	438895	10902	18890, 26878, 34866, 42854, 50842
2760	izumo sperm-egg fusion 1	332955	2915	327786	10903	18891, 26879, 34867, 42855, 50843
2761	jagunal homolog 1 (Drosophila)	307768	2916	306106	10904	18892, 26880, 34868, 42856, 50844
2762	jagunal homolog 1 (Drosophila)	543379	2917	442889	10905	18893, 26881, 34869, 42857, 50845
2763	janus kinase and microtubule interacting protein 1	282924	2918	282924	10906	18894, 26882, 34870, 42858, 50846
2764	janus kinase and microtubule interacting protein 1	409021	2919	386711	10907	18895, 26883, 34871, 42859, 50847
2765	janus kinase and microtubule interacting protein 1	409371	2920	387042	10908	18896, 26884, 34872, 42860, 50848
2766	janus kinase and microtubule interacting protein 1	409831	2921	386925	10909	18897, 26885, 34873, 42861, 50849
2767	janus kinase and microtubule interacting protein 1	418227	2922	406526	10910	18898, 26886, 34874, 42862, 50850

2768	janus kinase and microtubule interacting protein 1	425341	2923	401449	10911	18899, 26887, 34875, 42863, 50851
2769	janus kinase and microtubule interacting protein 1	429819	2924	398750	10912	18900, 26888, 34876, 42864, 50852
2770	janus kinase and microtubule interacting protein 2	265272	2925	265272	10913	18901, 26889, 34877, 42865, 50853
2771	janus kinase and microtubule interacting protein 2	333010	2926	328989	10914	18902, 26890, 34878, 42866, 50854
2772	janus kinase and microtubule interacting protein 2	507386	2927	421398	10915	18903, 26891, 34879, 42867, 50855
2773	janus kinase and microtubule interacting protein 2	539401	2928	439220	10916	18904, 26892, 34880, 42868, 50856
2774	Janus kinase and microtubule interacting protein 3	298622	2929	298622	10917	18905, 26893, 34881, 42869, 50857
2775	junctional sarcoplasmic reticulum protein 1	300961	2930	300961	10918	18906, 26894, 34882, 42870, 50858
2776	junctophilin 4	356300	2931	348648	10919	18907, 26895, 34883, 42871, 50859
2777	junctophilin 4	397118	2932	380307	10920	18908, 26896, 34884, 42872, 50860
2778	junctophilin 4	543864	2933	445800	10921	18909, 26897, 34885, 42873, 50861
2779	KDEL (Lys-Asp-Glu-Leu) containing 2	323468	2934	315386	10922	18910, 26898, 34886, 42874, 50862
2780	KDEL (Lys-Asp-Glu-Leu) containing 2	375648	2935	364799	10923	18911, 26899, 34887, 42875, 50863
2781	KDEL (Lys-Asp-Glu-Leu) containing 2	434945	2936	413429	10924	18912, 26900, 34888, 42876, 50864
2782	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 1	330720	2937	329471	10925	18913, 26901, 34889, 42877, 50865
2783	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2	258739	2938	258739	10926	18914, 26902, 34890, 42878, 50866

2784	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 2	490996	2939	420501	10927	18915, 26903, 34891, 42879, 50867
2785	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	216014	2940	216014	10928	18916, 26904, 34892, 42880, 50868
2786	KDEL (Lys-Asp-Glu-Leu) endoplasmic reticulum protein retention receptor 3	409006	2941	386918	10929	18917, 26905, 34893, 42881, 50869
2787	kelch domain containing 7A	400664	2942	383505	10930	18918, 26906, 34894, 42882, 50870
2788	kelch domain containing 7A	540290	2943	439465	10931	18919, 26907, 34895, 42883, 50871
2789	kelch-like 17 (Drosophila)	338591	2944	343930	10932	18920, 26908, 34896, 42884, 50872
2790	kelch-like 17 (Drosophila)	455747	2945	389373	10933	18921, 26909, 34897, 42885, 50873
2791	kelch-like 17 (Drosophila)	540863	2946	439107	10934	18922, 26910, 34898, 42886, 50874
2792	keratinocyte associated protein 2	295682	2947	295682	10935	18923, 26911, 34899, 42887, 50875
2793	keratinocyte associated protein 3	288873	2948	288873	10936	18924, 26912, 34900, 42888, 50876
2794	keratinocyte associated protein 3	407293	2949	384689	10937	18925, 26913, 34901, 42889, 50877
2795	keratinocyte associated protein 3	452499	2950	388115	10938	18926, 26914, 34902, 42890, 50878
2796	keratinocyte associated protein 3	543753	2951	442400	10939	18927, 26915, 34903, 42891, 50879
2797	KIAA0090	477853	2952	420608	10940	18928, 26916, 34904, 42892, 50880
2798	KIAA0195	314256	2953	313885	10941	18929, 26917, 34905, 42893, 50881
2799	KIAA0247	342745	2954	344424	10942	18930, 26918, 34906, 42894, 50882

2800	KIAA0317	356357	2955	348714	10943	18931, 26919, 34907, 42895, 50883
2801	KIAA0319-like	325722	2956	318406	10944	18932, 26920, 34908, 42896, 50884
2802	KIAA0922	409663	2957	386574	10945	18933, 26921, 34909, 42897, 50885
2803	KIAA1009	403245	2958	385215	10946	18934, 26922, 34910, 42898, 50886
2804	KIAA1024	305428	2959	307461	10947	18935, 26923, 34911, 42899, 50887
2805	KIAA1244	251691	2960	251691	10948	18936, 26924, 34912, 42900, 50888
2806	KIAA1324	369939	2961	358955	10949	18937, 26925, 34913, 42901, 50889
2807	KIAA1467	197268	2962	197268	10950	18938, 26926, 34914, 42902, 50890
2808	KIAA1467	416494	2963	394063	10951	18939, 26927, 34915, 42903, 50891
2809	KIAA1644	381176	2964	370568	10952	18940, 26928, 34916, 42904, 50892
2810	KIAA1683	359737	2965	352774	10953	18941, 26929, 34917, 42905, 50893
2811	KIAA1797	338382	2966	344307	10954	18942, 26930, 34918, 42906, 50894
2812	KIAA1797	380249	2967	369599	10955	18943, 26931, 34919, 42907, 50895
2813	KIAA1919	368847	2968	357840	10956	18944, 26932, 34920, 42908, 50896
2814	KIAA2013	376572	2969	365756	10957	18945, 26933, 34921, 42909, 50897
2815	killer cell immunoglobulin-like receptor, three domains, long cytoplasmic tail, 3	291860	2970	291860	10958	18946, 26934, 34922, 42910, 50898
2816	killer cell lectin-like receptor subfamily F, member 2	535540	2971	438244	10959	18947, 26935, 34923, 42911, 50899

2817	killer cell lectin-like receptor subfamily G, member 2	340940	2972	339356	10960	18948, 26936, 34924, 42912, 50900
2818	killer cell lectin-like receptor subfamily G, member 2	393039	2973	376759	10961	18949, 26937, 34925, 42913, 50901
2819	kin of IRRE like (Drosophila)	359209	2974	352138	10962	18950, 26938, 34926, 42914, 50902
2820	kin of IRRE like (Drosophila)	360089	2975	353202	10963	18951, 26939, 34927, 42915, 50903
2821	kin of IRRE like (Drosophila)	368173	2976	357155	10964	18952, 26940, 34928, 42916, 50904
2822	kin of IRRE like (Drosophila)	392272	2977	376098	10965	18953, 26941, 34929, 42917, 50905
2823	kin of IRRE like (Drosophila)	416935	2978	389674	10966	18954, 26942, 34930, 42918, 50906
2824	kinase D-interacting substrate, 220kDa	256707	2979	256707	10967	18955, 26943, 34931, 42919, 50907
2825	kinase D-interacting substrate, 220kDa	319688	2980	319947	10968	18956, 26944, 34932, 42920, 50908
2826	kinase D-interacting substrate, 220kDa	418530	2981	414923	10969	18957, 26945, 34933, 42921, 50909
2827	kinase D-interacting substrate, 220kDa	427284	2982	411849	10970	18958, 26946, 34934, 42922, 50910
2828	kinase D-interacting substrate, 220kDa	473731	2983	418974	10971	18959, 26947, 34935, 42923, 50911
2829	kinase D-interacting substrate, 220kDa	541927	2984	446229	10972	18960, 26948, 34936, 42924, 50912
2830	kinesin family member 16B	354981	2985	347076	10973	18961, 26949, 34937, 42925, 50913
2831	kinesin family member 16B	355755	2986	347995	10974	18962, 26950, 34938, 42926, 50914
2832	kinesin family member 16B	377997	2987	367236	10975	18963, 26951, 34939, 42927, 50915
2833	kinesin family member 16B	378003	2988	367242	10976	18964, 26952, 34940, 42928, 50916
2834	kinesin family member 16B	408042	2989	384164	10977	18965, 26953, 34941, 42929, 50917

2835	kinesin family member 18A	263181	2990	263181	10978	18966, 26954, 34942, 42930, 50918
2836	kringle containing transmembrane protein 1	327813	2991	331242	10979	18967, 26955, 34943, 42931, 50919
2837	kringle containing transmembrane protein 1	400335	2992	383189	10980	18968, 26956, 34944, 42932, 50920
2838	kringle containing transmembrane protein 1	400338	2993	383192	10981	18969, 26957, 34945, 42933, 50921
2839	kringle containing transmembrane protein 1	407188	2994	385431	10982	18970, 26958, 34946, 42934, 50922
2840	lactamase, beta 2	276590	2995	276590	10983	18971, 26959, 34947, 42935, 50923
2841	lactamase, beta 2	522447	2996	428801	10984	18972, 26960, 34948, 42936, 50924
2842	lactase-like	341509	2997	343490	10985	18973, 26961, 34949, 42937, 50925
2843	lactase-like	537670	2998	445419	10986	18974, 26962, 34950, 42938, 50926
2844	lactation elevated 1	368977	2999	357973	10987	18975, 26963, 34951, 42939, 50927
2845	late endosomal/lysosomal adaptor, MAPK and MTOR activator 1	278671	3000	278671	10988	18976, 26964, 34952, 42940, 50928
2846	late endosomal/lysosomal adaptor, MAPK and MTOR activator 2	368302	3001	357285	10989	18977, 26965, 34953, 42941, 50929
2847	late endosomal/lysosomal adaptor, MAPK and MTOR activator 2	368304	3002	357287	10990	18978, 26966, 34954, 42942, 50930
2848	late endosomal/lysosomal adaptor, MAPK and MTOR activator 2	368305	3003	357288	10991	18979, 26967, 34955, 42943, 50931
2849	late endosomal/lysosomal adaptor, MAPK and MTOR activator 3	499666	3004	424183	10992	18980, 26968, 34956, 42944, 50932

2850	latrophilin 1	340736	3005	340688	10993	18981, 26969, 34957, 42945, 50933
2851	latrophilin 1	361434	3006	355328	10994	18982, 26970, 34958, 42946, 50934
2852	latrophilin 2	271029	3007	271029	10995	18983, 26971, 34959, 42947, 50935
2853	latrophilin 2	319517	3008	322270	10996	18984, 26972, 34960, 42948, 50936
2854	latrophilin 2	335786	3009	337306	10997	18985, 26973, 34961, 42949, 50937
2855	latrophilin 2	359929	3010	353006	10998	18986, 26974, 34962, 42950, 50938
2856	latrophilin 2	370713	3011	359748	10999	18987, 26975, 34963, 42951, 50939
2857	latrophilin 2	370715	3012	359750	11000	18988, 26976, 34964, 42952, 50940
2858	latrophilin 2	370717	3013	359752	11001	18989, 26977, 34965, 42953, 50941
2859	latrophilin 2	370721	3014	359756	11002	18990, 26978, 34966, 42954, 50942
2860	latrophilin 2	370723	3015	359758	11003	18991, 26979, 34967, 42955, 50943
2861	latrophilin 2	370725	3016	359760	11004	18992, 26980, 34968, 42956, 50944
2862	latrophilin 2	370727	3017	359762	11005	18993, 26981, 34969, 42957, 50945
2863	latrophilin 2	370728	3018	359763	11006	18994, 26982, 34970, 42958, 50946
2864	latrophilin 2	370730	3019	359765	11007	18995, 26983, 34971, 42959, 50947
2865	latrophilin 2	394879	3020	378344	11008	18996, 26984, 34972, 42960, 50948
2866	latrophilin 2	402328	3021	385853	11009	18997, 26985, 34973, 42961, 50949
2867	latrophilin 2	449420	3022	397740	11010	18998, 26986, 34974, 42962, 50950

2868	latrophilin 3	280009	3023	280009	11011	18999, 26987, 34975, 42963, 50951
2869	latrophilin 3	295349	3024	295349	11012	19000, 26988, 34976, 42964, 50952
2870	latrophilin 3	502815	3025	424402	11013	19001, 26989, 34977, 42965, 50953
2871	latrophilin 3	504896	3026	423434	11014	19002, 26990, 34978, 42966, 50954
2872	latrophilin 3	506700	3027	424120	11015	19003, 26991, 34979, 42967, 50955
2873	latrophilin 3	506720	3028	420931	11016	19004, 26992, 34980, 42968, 50956
2874	latrophilin 3	506746	3029	425884	11017	19005, 26993, 34981, 42969, 50957
2875	latrophilin 3	507164	3030	421476	11018	19006, 26994, 34982, 42970, 50958
2876	latrophilin 3	507625	3031	421372	11019	19007, 26995, 34983, 42971, 50959
2877	latrophilin 3	508693	3032	424030	11020	19008, 26996, 34984, 42972, 50960
2878	latrophilin 3	508946	3033	421627	11021	19009, 26997, 34985, 42973, 50961
2879	latrophilin 3	509896	3034	423787	11022	19010, 26998, 34986, 42974, 50962
2880	latrophilin 3	511324	3035	425033	11023	19011, 26999, 34987, 42975, 50963
2881	latrophilin 3	512091	3036	423388	11024	19012, 27000, 34988, 42976, 50964
2882	latrophilin 3	514157	3037	425201	11025	19013, 27001, 34989, 42977, 50965
2883	latrophilin 3	514591	3038	422533	11026	19014, 27002, 34990, 42978, 50966
2884	latrophilin 3	514996	3039	424258	11027	19015, 27003, 34991, 42979, 50967
2885	latrophilin 3	534975	3040	437800	11028	19016, 27004, 34992, 42980, 50968

2886	latrophilin 3	545650	3041	439831	11029	19017, 27005, 34993, 42981, 50969
2887	layilin	375614	3042	364764	11030	19018, 27006, 34994, 42982, 50970
2888	layilin	375615	3043	364765	11031	19019, 27007, 34995, 42983, 50971
2889	layilin	436913	3044	392942	11032	19020, 27008, 34996, 42984, 50972
2890	layilin	541011	3045	439524	11033	19021, 27009, 34997, 42985, 50973
2891	layilin	525866	3046	434300	11034	19022, 27010, 34998, 42986, 50974
2892	lectin, mannose-binding 2	303127	3047	303366	11035	19023, 27011, 34999, 42987, 50975
2893	lectin, mannose-binding 2	539488	3048	445179	11036	19024, 27012, 35000, 42988, 50976
2894	lectin, mannose-binding 2-like	264963	3049	264963	11037	19025, 27013, 35001, 42989, 50977
2895	lectin, mannose-binding 2-like	377079	3050	366280	11038	19026, 27014, 35002, 42990, 50978
2896	lectin, mannose-binding 2-like	426463	3051	396391	11039	19027, 27015, 35003, 42991, 50979
2897	lectin, mannose-binding 2-like	534882	3052	438501	11040	19028, 27016, 35004, 42992, 50980
2898	lectin, mannose-binding 2-like	537039	3053	441701	11041	19029, 27017, 35005, 42993, 50981
2899	lectin, mannose-binding, 1 like	309664	3054	310431	11042	19030, 27018, 35006, 42994, 50982
2900	lectin, mannose-binding, 1 like	379709	3055	369031	11043	19031, 27019, 35007, 42995, 50983
2901	lectin, mannose-binding, 1 like	456603	3056	407216	11044	19032, 27020, 35008, 42996, 50984
2902	LEM domain containing 1	367149	3057	356117	11045	19033, 27021, 35009, 42997, 50985
2903	LEM domain containing 1	367151	3058	356119	11046	19034, 27022, 35010, 42998, 50986

2904	LEM domain containing 1	367152	3059	356120	11047	19035, 27023, 35011, 42999, 50987
2905	LEM domain containing 1	367153	3060	356121	11048	19036, 27024, 35012, 43000, 50988
2906	LEM domain containing 1	367154	3061	356122	11049	19037, 27025, 35013, 43001, 50989
2907	LEM domain containing 1	391936	3062	375801	11050	19038, 27026, 35014, 43002, 50990
2908	LEM domain containing 2	293760	3063	293760	11051	19039, 27027, 35015, 43003, 50991
2909	LEM domain containing 2	508327	3064	421704	11052	19040, 27028, 35016, 43004, 50992
2910	LEM domain containing 2	513701	3065	423619	11053	19041, 27029, 35017, 43005, 50993
2911	lemur tyrosine kinase 3	270238	3066	270238	11054	19042, 27030, 35018, 43006, 50994
2912	leprecan-like 2	290510	3067	290510	11055	19043, 27031, 35019, 43007, 50995
2913	leprecan-like 2	396725	3068	379951	11056	19044, 27032, 35020, 43008, 50996
2914	leprecan-like 2	451242	3069	410202	11057	19045, 27033, 35021, 43009, 50997
2915	LETM1 domain containing 1	262055	3070	262055	11058	19046, 27034, 35022, 43010, 50998
2916	LETM1 domain containing 1	380123	3071	369466	11059	19047, 27035, 35023, 43011, 50999
2917	LETM1 domain containing 1	448283	3072	397107	11060	19048, 27036, 35024, 43012, 51000
2918	LETM1 domain containing 1	550929	3073	450163	11061	19049, 27037, 35025, 43013, 51001
2919	LETM1 domain containing 1	418425	3074	389903	11062	19050, 27038, 35026, 43014, 51002
2920	leucine rich repeat and Ig domain containing 4	368820	3075	357810	11063	19051, 27039, 35027, 43015, 51003
2921	leucine rich repeat containing 15	347624	3076	306276	11064	19052, 27040, 35028, 43016, 51004

2922	leucine rich repeat containing 15	428839	3077	413707	11065	19053, 27041, 35029, 43017, 51005
2923	leucine rich repeat containing 15	439944	3078	389128	11066	19054, 27042, 35030, 43018, 51006
2924	leucine rich repeat containing 19	380055	3079	369395	11067	19055, 27043, 35031, 43019, 51007
2925	leucine rich repeat containing 24	529415	3080	434849	11068	19056, 27044, 35032, 43020, 51008
2926	leucine rich repeat containing 3	291592	3081	291592	11069	19057, 27045, 35033, 43021, 51009
2927	leucine rich repeat containing 3	471776	3082	441142	11070	19058, 27046, 35034, 43022, 51010
2928	leucine rich repeat containing 32	260061	3083	260061	11071	19059, 27047, 35035, 43023, 51011
2929	leucine rich repeat containing 32	404995	3084	385766	11072	19060, 27048, 35036, 43024, 51012
2930	leucine rich repeat containing 32	407242	3085	384126	11073	19061, 27049, 35037, 43025, 51013
2931	leucine rich repeat containing 32	421973	3086	413331	11074	19062, 27050, 35038, 43026, 51014
2932	leucine rich repeat containing 33	328557	3087	328625	11075	19063, 27051, 35039, 43027, 51015
2933	leucine rich repeat containing 37 member A3	584306	3088	464535	11076	19064, 27052, 35040, 43028, 51016
2934	leucine rich repeat containing 37, member A3	319651	3089	325713	11077	19065, 27053, 35041, 43029, 51017
2935	leucine rich repeat containing 37, member A3	334962	3090	335617	11078	19066, 27054, 35042, 43030, 51018
2936	leucine rich repeat containing 37, member A3	339474	3091	344298	11079	19067, 27055, 35043, 43031, 51019
2937	leucine rich repeat containing 37, member A3	400877	3092	383674	11080	19068, 27056, 35044, 43032, 51020
2938	leucine rich repeat containing 37A	320254	3093	326324	11081	19069, 27057, 35045, 43033, 51021
2939	leucine rich repeat containing 37A	393466	3094	377109	11082	19070, 27058, 35046, 43034, 51022

2940	leucine rich repeat containing 37B	327564	3095	332536	11083	19071, 27059, 35047, 43035, 51023
2941	leucine rich repeat containing 37B	341671	3096	340519	11084	19072, 27060, 35048, 43036, 51024
2942	leucine rich repeat containing 37B	394713	3097	378202	11085	19073, 27061, 35049, 43037, 51025
2943	leucine rich repeat containing 37B	543378	3098	443345	11086	19074, 27062, 35050, 43038, 51026
2944	leucine rich repeat containing 38	376085	3099	365253	11087	19075, 27063, 35051, 43039, 51027
2945	leucine rich repeat containing 3B	396641	3100	379880	11088	19076, 27064, 35052, 43040, 51028
2946	leucine rich repeat containing 3B	414619	3101	389764	11089	19077, 27065, 35053, 43041, 51029
2947	leucine rich repeat containing 3B	417744	3102	406370	11090	19078, 27066, 35054, 43042, 51030
2948	leucine rich repeat containing 3B	432040	3103	398184	11091	19079, 27067, 35055, 43043, 51031
2949	leucine rich repeat containing 3B	456208	3104	394940	11092	19080, 27068, 35056, 43044, 51032
2950	leucine rich repeat containing 3C	377924	3105	367157	11093	19081, 27069, 35057, 43045, 51033
2951	leucine rich repeat containing 4	249363	3106	249363	11094	19082, 27070, 35058, 43046, 51034
2952	leucine rich repeat containing 4	476782	3107	418093	11095	19083, 27071, 35059, 43047, 51035
2953	leucine rich repeat containing 4	478726	3108	417795	11096	19084, 27072, 35060, 43048, 51036
2954	leucine rich repeat containing 4B	389201	3109	373853	11097	19085, 27073, 35061, 43049, 51037
2955	leucine rich repeat containing 4B	535879	3110	440583	11098	19086, 27074, 35062, 43050, 51038
2956	leucine rich repeat containing 52	294818	3111	294818	11099	19087, 27075, 35063, 43051, 51039
2957	leucine rich repeat containing 55	497933	3112	419542	11100	19088, 27076, 35064, 43052, 51040

2958	leucine rich repeat containing 59	225972	3113	225972	11101	19089, 27077, 35065, 43053, 51041
2959	leucine rich repeat containing 66	343457	3114	341944	11102	19090, 27078, 35066, 43054, 51042
2960	leucine rich repeat containing 70	334994	3115	399441	11103	19091, 27079, 35067, 43055, 51043
2961	leucine rich repeat neuronal 1	319331	3116	314901	11104	19092, 27080, 35068, 43056, 51044
2962	leucine rich repeat neuronal 2	367175	3117	356143	11105	19093, 27081, 35069, 43057, 51045
2963	leucine rich repeat neuronal 2	367176	3118	356144	11106	19094, 27082, 35070, 43058, 51046
2964	leucine rich repeat neuronal 2	367177	3119	356145	11107	19095, 27083, 35071, 43059, 51047
2965	leucine rich repeat neuronal 3	308478	3120	312001	11108	19096, 27084, 35072, 43060, 51048
2966	leucine rich repeat neuronal 3	422987	3121	412417	11109	19097, 27085, 35073, 43061, 51049
2967	leucine rich repeat neuronal 3	451085	3122	397312	11110	19098, 27086, 35074, 43062, 51050
2968	leucine rich repeat neuronal 4	378858	3123	368135	11111	19099, 27087, 35075, 43063, 51051
2969	leucine zipper-EF-hand containing transmembrane protein 2	297720	3124	297720	11112	19100, 27088, 35076, 43064, 51052
2970	leucine zipper-EF-hand containing transmembrane protein 2	379957	3125	369291	11113	19101, 27089, 35077, 43065, 51053
2971	leucine zipper-EF-hand containing transmembrane protein 2	524874	3126	431211	11114	19102, 27090, 35078, 43066, 51054
2972	leucine zipper-EF-hand containing transmembrane protein 2	526356	3127	432955	11115	19103, 27091, 35079, 43067, 51055
2973	leucine zipper-EF-hand containing transmembrane protein 2	527334	3128	432080	11116	19104, 27092, 35080, 43068, 51056

2974	leucine zipper-EF-hand containing transmembrane protein 2	527710	3129	434867	11117	19105, 27093, 35081, 43069, 51057
2975	leucine zipper-EF-hand containing transmembrane protein 2	518883	3130	429019	11118	19106, 27094, 35082, 43070, 51058
2976	leucine zipper-EF-hand containing transmembrane protein 2	523983	3131	428765	11119	19107, 27095, 35083, 43071, 51059
2977	leucine-rich repeat, immunoglobulin-like and transmembrane domains 1	372105	3132	361177	11120	19108, 27096, 35084, 43072, 51060
2978	leucine-rich repeat, immunoglobulin-like and transmembrane domains 3	327908	3133	328222	11121	19109, 27097, 35085, 43073, 51061
2979	leucine-rich repeat, immunoglobulin-like and transmembrane domains 3	379920	3134	369252	11122	19110, 27098, 35086, 43074, 51062
2980	leucine-rich repeat, immunoglobulin-like and transmembrane domains 3	409621	3135	386734	11123	19111, 27099, 35087, 43075, 51063
2981	leucine-rich repeats and immunoglobulin-like domains 3	320743	3136	326759	11124	19112, 27100, 35088, 43076, 51064
2982	leucine-rich repeats and immunoglobulin-like domains 3	379141	3137	368436	11125	19113, 27101, 35089, 43077, 51065
2983	leucine-rich repeats and transmembrane domains 1	273286	3138	273286	11126	19114, 27102, 35090, 43078, 51066
2984	leucine-rich repeats and transmembrane domains 1	493075	3139	419772	11127	19115, 27103, 35091, 43079, 51067
2985	leucine-rich repeats and transmembrane domains 2	299194	3140	299194	11128	19116, 27104, 35092, 43080, 51068
2986	leucine-rich repeats and transmembrane domains 2	424079	3141	394967	11129	19117, 27105, 35093, 43081, 51069
2987	leucine-rich repeats and transmembrane domains 2	535041	3142	444737	11130	19118, 27106, 35094, 43082, 51070

2988	leucine-rich repeats and transmembrane domains 2	543818	3143	446278	11131	19119, 27107, 35095, 43083, 51071
2989	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4	291759	3144	291759	11132	19120, 27108, 35096, 43084, 51072
2990	LIM and senescent cell antigen-like domains 1	332345	3145	331775	11133	19121, 27109, 35097, 43085, 51073
2991	LIM and senescent cell antigen-like domains 1	338045	3146	337598	11134	19122, 27110, 35098, 43086, 51074
2992	LIM and senescent cell antigen-like domains 1	393310	3147	376987	11135	19123, 27111, 35099, 43087, 51075
2993	LIM and senescent cell antigen-like domains 1	393314	3148	376990	11136	19124, 27112, 35100, 43088, 51076
2994	LIM and senescent cell antigen-like domains 1	409441	3149	387264	11137	19125, 27113, 35101, 43089, 51077
2995	LIM and senescent cell antigen-like domains 1	410093	3150	386926	11138	19126, 27114, 35102, 43090, 51078
2996	LIM and senescent cell antigen-like domains 1	542845	3151	446121	11139	19127, 27115, 35103, 43091, 51079
2997	LIM and senescent cell antigen-like domains 1	544547	3152	437912	11140	19128, 27116, 35104, 43092, 51080
2998	LIM and senescent cell antigen-like domains 2	324938	3153	326888	11141	19129, 27117, 35105, 43093, 51081
2999	LIM and senescent cell antigen-like domains 2	342067	3154	339689	11142	19130, 27118, 35106, 43094, 51082
3000	LIM and senescent cell antigen-like domains 2	355119	3155	347240	11143	19131, 27119, 35107, 43095, 51083
3001	LIM and senescent cell antigen-like domains 2	409254	3156	386907	11144	19132, 27120, 35108, 43096, 51084
3002	LIM and senescent cell antigen-like domains 2	409286	3157	386252	11145	19133, 27121, 35109, 43097, 51085
3003	LIM and senescent cell antigen-like domains 2	409455	3158	386383	11146	19134, 27122, 35110, 43098, 51086
3004	LIM and senescent cell antigen-like domains 2	409754	3159	386345	11147	19135, 27123, 35111, 43099, 51087

3005	LIM and senescent cell antigen-like domains 2	409808	3160	386637	11148	19136, 27124, 35112, 43100, 51088
3006	LIM and senescent cell antigen-like domains 2	410011	3161	387002	11149	19137, 27125, 35113, 43101, 51089
3007	LIM and senescent cell antigen-like domains 2	410038	3162	386570	11150	19138, 27126, 35114, 43102, 51090
3008	LIM and senescent cell antigen-like domains 2	410109	3163	386240	11151	19139, 27127, 35115, 43103, 51091
3009	LIM and senescent cell antigen-like domains 2	422034	3164	416224	11152	19140, 27128, 35116, 43104, 51092
3010	LIM and senescent cell antigen-like domains 2	537572	3165	446212	11153	19141, 27129, 35117, 43105, 51093
3011	LIM and senescent cell antigen-like domains 2	544917	3166	437681	11154	19142, 27130, 35118, 43106, 51094
3012	LIM and senescent cell antigen-like domains 2	545738	3167	443794	11155	19143, 27131, 35119, 43107, 51095
3013	lin-7 homolog A (C. elegans)	552864	3168	447488	11156	19144, 27132, 35120, 43108, 51096
3014	lipase maturation factor 2	216080	3169	216080	11157	19145, 27133, 35121, 43109, 51097
3015	lipase maturation factor 2	380796	3170	370173	11158	19146, 27134, 35122, 43110, 51098
3016	lipase maturation factor 2	474879	3171	424381	11159	19147, 27135, 35123, 43111, 51099
3017	Lipid phosphate phosphatase-related protein type 1	374871	3172	364005	11160	19148, 27136, 35124, 43112, 51100
3018	Lipid phosphate phosphatase-related protein type 1	374874	3173	364008	11161	19149, 27137, 35125, 43113, 51101
3019	Lipid phosphate phosphatase-related protein type 1	395056	3174	378496	11162	19150, 27138, 35126, 43114, 51102
3020	Lipid phosphate phosphatase-related protein type 1	456287	3175	410223	11163	19151, 27139, 35127, 43115, 51103
3021	Lipid phosphate phosphatase-related protein type 2	251473	3176	251473	11164	19152, 27140, 35128, 43116, 51104
3022	Lipid phosphate phosphatase-related protein type 2	591608	3177	466898	11165	19153, 27141, 35129, 43117, 51105

3023	Lipid phosphate phosphatase-related protein type 3	300947	3178	300947	11166	19154, 27142, 35130, 43118, 51106
3024	Lipid phosphate phosphatase-related protein type 3	359894	3179	352962	11167	19155, 27143, 35131, 43119, 51107
3025	Lipid phosphate phosphatase-related protein type 3	520876	3180	430297	11168	19156, 27144, 35132, 43120, 51108
3026	Lipid phosphate phosphatase-related protein type 4	263178	3181	263178	11169	19157, 27145, 35133, 43121, 51109
3027	Lipid phosphate phosphatase-related protein type 4	370184	3182	359203	11170	19158, 27146, 35134, 43122, 51110
3028	Lipid phosphate phosphatase-related protein type 4	370185	3183	359204	11171	19159, 27147, 35135, 43123, 51111
3029	Lipid phosphate phosphatase-related protein type 4	457765	3184	394913	11172	19160, 27148, 35136, 43124, 51112
3030	Lipid phosphate phosphatase-related protein type 5	263177	3185	263177	11173	19161, 27149, 35137, 43125, 51113
3031	Lipid phosphate phosphatase-related protein type 5	370188	3186	359207	11174	19162, 27150, 35138, 43126, 51114
3032	lipoma HMGIC fusion partner-like 4	287585	3187	287585	11175	19163, 27151, 35139, 43127, 51115
3033	LMBR1 domain containing 2	296603	3188	296603	11176	19164, 27152, 35140, 43128, 51116
3034	LMBR1 domain containing 2	546130	3189	444863	11177	19165, 27153, 35141, 43129, 51117
3035	low density lipoprotein receptor class A domain containing 1	371360	3190	360411	11178	19166, 27154, 35142, 43130, 51118
3036	low density lipoprotein receptor class A domain containing 1	371362	3191	360413	11179	19167, 27155, 35143, 43131, 51119
3037	low density lipoprotein receptor class A domain containing 2	344642	3192	340988	11180	19168, 27156, 35144, 43132, 51120
3038	low density lipoprotein receptor class A domain containing 2	543870	3193	444097	11181	19169, 27157, 35145, 43133, 51121
3039	low density lipoprotein receptor class A domain	315571	3194	318607	11182	19170, 27158, 35146, 43134, 51122

	containing 3					
3040	low density lipoprotein receptor class A domain containing 3	545142	3195	438737	11183	19171, 27159, 35147, 43135, 51123
3041	low density lipoprotein receptor-related protein 11	239367	3196	239367	11184	19172, 27160, 35148, 43136, 51124
3042	low density lipoprotein receptor-related protein 11	367368	3197	356338	11185	19173, 27161, 35149, 43137, 51125
3043	low density lipoprotein receptor-related protein 11	546019	3198	440196	11186	19174, 27162, 35150, 43138, 51126
3044	low density lipoprotein receptor-related protein 12	276654	3199	276654	11187	19175, 27163, 35151, 43139, 51127
3045	low density lipoprotein receptor-related protein 12	424843	3200	399148	11188	19176, 27164, 35152, 43140, 51128
3046	LPS-responsive vesicle trafficking, beach and anchor containing	357115	3201	349629	11189	19177, 27165, 35153, 43141, 51129
3047	LPS-responsive vesicle trafficking, beach and anchor containing	535741	3202	446299	11190	19178, 27166, 35154, 43142, 51130
3048	LRRN4 C-terminal like	317449	3203	325808	11191	19179, 27167, 35155, 43143, 51131
3049	LY6/PLAUR domain containing 1	345008	3204	340563	11192	19180, 27168, 35156, 43144, 51132
3050	LY6/PLAUR domain containing 1	397463	3205	380605	11193	19181, 27169, 35157, 43145, 51133
3051	LY6/PLAUR domain containing 1	409034	3206	386311	11194	19182, 27170, 35158, 43146, 51134
3052	LY6/PLAUR domain containing 2	359228	3207	352163	11195	19183, 27171, 35159, 43147, 51135
3053	LY6/PLAUR domain containing 4	330743	3208	328737	11196	19184, 27172, 35160, 43148, 51136
3054	LY6/PLAUR domain containing 4	343055	3209	339568	11197	19185, 27173, 35161, 43149, 51137
3055	LY6/PLAUR domain containing 5	377950	3210	367185	11198	19186, 27174, 35162, 43150, 51138

3056	LY6/PLAUR domain containing 5	414615	3211	408433	11199	19187, 27175, 35163, 43151, 51139
3057	LY6/PLAUR domain containing 6B	280115	3212	280115	11200	19188, 27176, 35164, 43152, 51140
3058	LY6/PLAUR domain containing 6B	409029	3213	386650	11201	19189, 27177, 35165, 43153, 51141
3059	LY6/PLAUR domain containing 6B	409642	3214	387077	11202	19190, 27178, 35166, 43154, 51142
3060	LY6/PLAUR domain containing 6B	409876	3215	386479	11203	19191, 27179, 35167, 43155, 51143
3061	lymphocyte antigen 6 complex, locus G6C	375819	3216	364978	11204	19192, 27180, 35168, 43156, 51144
3062	lymphocyte antigen 6 complex, locus G6C	383413	3217	372905	11205	19193, 27181, 35169, 43157, 51145
3063	lymphocyte antigen 6 complex, locus G6C	419939	3218	388591	11206	19194, 27182, 35170, 43158, 51146
3064	lymphocyte antigen 6 complex, locus G6C	428121	3219	411365	11207	19195, 27183, 35171, 43159, 51147
3065	lymphocyte antigen 6 complex, locus G6C	428498	3220	410398	11208	19196, 27184, 35172, 43160, 51148
3066	lymphocyte antigen 6 complex, locus G6C	434915	3221	415732	11209	19197, 27185, 35173, 43161, 51149
3067	lymphocyte antigen 6 complex, locus G6C	448386	3222	409428	11210	19198, 27186, 35174, 43162, 51150
3068	lymphocyte antigen 6 complex, locus G6C	495859	3223	433207	11211	19199, 27187, 35175, 43163, 51151
3069	lymphocyte antigen 6 complex, locus G6C	497123	3224	431133	11212	19200, 27188, 35176, 43164, 51152
3070	lymphocyte antigen 6 complex, locus G6F	375832	3225	364992	11213	19201, 27189, 35177, 43165, 51153
3071	lymphocyte antigen 6 complex, locus G6F	446062	3226	404884	11214	19202, 27190, 35178, 43166, 51154
3072	lymphocyte antigen 6 complex, locus G6F	447811	3227	409959	11215	19203, 27191, 35179, 43167, 51155
3073	lymphocyte antigen 6 complex, locus G6F	453044	3228	389102	11216	19204, 27192, 35180, 43168, 51156

3074	lymphocyte antigen 6 complex, locus G6F	455632	3229	407535	11217	19205, 27193, 35181, 43169, 51157
3075	lymphocyte antigen 6 complex, locus G6F	554860	3230	451668	11218	19206, 27194, 35182, 43170, 51158
3076	lymphocyte antigen 6 complex, locus G6F	556581	3231	452432	11219	19207, 27195, 35183, 43171, 51159
3077	lymphocyte antigen 6 complex, locus G6F	557698	3232	452228	11220	19208, 27196, 35184, 43172, 51160
3078	lymphocyte antigen 75	263636	3233	263636	11221	19209, 27197, 35185, 43173, 51161
3079	lymphocyte antigen 75	553424	3234	451446	11222	19210, 27198, 35186, 43174, 51162
3080	lymphocyte antigen 75	554112	3235	451511	11223	19211, 27199, 35187, 43175, 51163
3081	lymphocyte transmembrane adaptor 1	367217	3236	356186	11224	19212, 27200, 35188, 43176, 51164
3082	lymphocyte transmembrane adaptor 1	442561	3237	406970	11225	19213, 27201, 35189, 43177, 51165
3083	LYR motif containing 1	219168	3238	219168	11226	19214, 27202, 35190, 43178, 51166
3084	LYR motif containing 1	396052	3239	379367	11227	19215, 27203, 35191, 43179, 51167
3085	LYR motif containing 1	412082	3240	396868	11228	19216, 27204, 35192, 43180, 51168
3086	LYR motif containing 1	439021	3241	407883	11229	19217, 27205, 35193, 43181, 51169
3087	LYR motif containing 2	523377	3242	430025	11230	19218, 27206, 35194, 43182, 51170
3088	LYR motif containing 5	381356	3243	370761	11231	19219, 27207, 35195, 43183, 51171
3089	LYR motif containing 5	556198	3244	452130	11232	19220, 27208, 35196, 43184, 51172
3090	LYR motif containing 5	556351	3245	452146	11233	19221, 27209, 35197, 43185, 51173
3091	LYR motif containing 5	556885	3246	451494	11234	19222, 27210, 35198, 43186, 51174

3092	LYR motif containing 5	556927	3247	450443	11235	19223, 27211, 35199, 43187, 51175
3093	LYR motif containing 5	557540	3248	450584	11236	19224, 27212, 35200, 43188, 51176
3094	Lyrm7 homolog (mouse)	379380	3249	368688	11237	19225, 27213, 35201, 43189, 51177
3095	lysM and putative peptidoglycan-binding domain-containing protein 3	554351	3250	451382	11238	19226, 27214, 35202, 43190, 51178
3096	LysM, putative peptidoglycan-binding, domain containing 3	315948	3251	314518	11239	19227, 27215, 35203, 43191, 51179
3097	LysM, putative peptidoglycan-binding, domain containing 3	509384	3252	427683	11240	19228, 27216, 35204, 43192, 51180
3098	LysM, putative peptidoglycan-binding, domain containing 4	332728	3253	333008	11241	19229, 27217, 35205, 43193, 51181
3099	LysM, putative peptidoglycan-binding, domain containing 4	344791	3254	342840	11242	19230, 27218, 35206, 43194, 51182
3100	LysM, putative peptidoglycan-binding, domain containing 4	409796	3255	386283	11243	19231, 27219, 35207, 43195, 51183
3101	LysM, putative peptidoglycan-binding, domain containing 4	545021	3256	445357	11244	19232, 27220, 35208, 43196, 51184
3102	lysophosphatidylcholine acyltransferase 2	262134	3257	262134	11245	19233, 27221, 35209, 43197, 51185
3103	lysophosphatidylglycerol acyltransferase 1	366996	3258	355963	11246	19234, 27222, 35210, 43198, 51186
3104	lysophosphatidylglycerol acyltransferase 1	366997	3259	355964	11247	19235, 27223, 35211, 43199, 51187
3105	lysosomal protein transmembrane 4 alpha	175091	3260	175091	11248	19236, 27224, 35212, 43200, 51188
3106	lysosomal-associated membrane protein 3	265598	3261	265598	11249	19237, 27225, 35213, 43201, 51189
3107	lysosomal-associated membrane protein 3	476015	3262	419059	11250	19238, 27226, 35214, 43202, 51190

3108	lysosomal-associated membrane protein family, member 5	246070	3263	246070	11251	19239, 27227, 35215, 43203, 51191
3109	lysosomal-associated membrane protein family, member 5	427562	3264	406360	11252	19240, 27228, 35216, 43204, 51192
3110	MACRO domain containing 1	255681	3265	255681	11253	19241, 27229, 35217, 43205, 51193
3111	macrophage expressed 1	361050	3266	354335	11254	19242, 27230, 35218, 43206, 51194
3112	macrophage expressed 1	545098	3267	444560	11255	19243, 27231, 35219, 43207, 51195
3113	major facilitator superfamily domain containing 1	264266	3268	264266	11256	19244, 27232, 35220, 43208, 51196
3114	major facilitator superfamily domain containing 1	361159	3269	355227	11257	19245, 27233, 35221, 43209, 51197
3115	major facilitator superfamily domain containing 1	392813	3270	376560	11258	19246, 27234, 35222, 43210, 51198
3116	major facilitator superfamily domain containing 1	415822	3271	403117	11259	19247, 27235, 35223, 43211, 51199
3117	major facilitator superfamily domain containing 10	329687	3272	332646	11260	19248, 27236, 35224, 43212, 51200
3118	major facilitator superfamily domain containing 10	355443	3273	347619	11261	19249, 27237, 35225, 43213, 51201
3119	major facilitator superfamily domain containing 11	336509	3274	337240	11262	19250, 27238, 35226, 43214, 51202
3120	major facilitator superfamily domain containing 11	355954	3275	348225	11263	19251, 27239, 35227, 43215, 51203
3121	major facilitator superfamily domain containing 12	355415	3276	347583	11264	19252, 27240, 35228, 43216, 51204
3122	major facilitator superfamily domain containing 12	389395	3277	374046	11265	19253, 27241, 35229, 43217, 51205
3123	major facilitator superfamily domain containing 12	398558	3278	381566	11266	19254, 27242, 35230, 43218, 51206
3124	major facilitator superfamily domain containing 3	301327	3279	301327	11267	19255, 27243, 35231, 43219, 51207

3125	major facilitator superfamily domain containing 4	367147	3280	356115	11268	19256, 27244, 35232, 43220, 51208
3126	major facilitator superfamily domain containing 4	536357	3281	440183	11269	19257, 27245, 35233, 43221, 51209
3127	major facilitator superfamily domain containing 4	539267	3282	445329	11270	19258, 27246, 35234, 43222, 51210
3128	major facilitator superfamily domain containing 5	328704	3283	331231	11271	19259, 27247, 35235, 43223, 51211
3129	major facilitator superfamily domain containing 5	329548	3284	332624	11272	19260, 27248, 35236, 43224, 51212
3130	major facilitator superfamily domain containing 5	534842	3285	442688	11273	19261, 27249, 35237, 43225, 51213
3131	major facilitator superfamily domain containing 5	551660	3286	449354	11274	19262, 27250, 35238, 43226, 51214
3132	major facilitator superfamily domain containing 6-like	329805	3287	330051	11275	19263, 27251, 35239, 43227, 51215
3133	major facilitator superfamily domain containing 7	322224	3288	320234	11276	19264, 27252, 35240, 43228, 51216
3134	major facilitator superfamily domain containing 7	347950	3289	307545	11277	19265, 27253, 35241, 43229, 51217
3135	major facilitator superfamily domain containing 7	404286	3290	384616	11278	19266, 27254, 35242, 43230, 51218
3136	major facilitator superfamily domain containing 9	258436	3291	258436	11279	19267, 27255, 35243, 43231, 51219
3137	major histocompatibility complex, class I, A	355767	3292	348012	11280	19268, 27256, 35244, 43232, 51220
3138	major histocompatibility complex, class I, A	376802	3293	365998	11281	19269, 27257, 35245, 43233, 51221
3139	major histocompatibility complex, class I, A	376806	3294	366002	11282	19270, 27258, 35246, 43234, 51222
3140	major histocompatibility complex, class I, A	376809	3295	366005	11283	19271, 27259, 35247, 43235, 51223
3141	major histocompatibility complex, class I, A	376822	3296	366018	11284	19272, 27260, 35248, 43236, 51224
3142	major histocompatibility complex, class I, A	383605	3297	373100	11285	19273, 27261, 35249, 43237, 51225

3143	major histocompatibility complex, class I, A	383619	3298	373114	11286	19274, 27262, 35250, 43238, 51226
3144	major histocompatibility complex, class I, A	396634	3299	379873	11287	19275, 27263, 35251, 43239, 51227
3145	major histocompatibility complex, class I, A	413609	3300	390225	11288	19276, 27264, 35252, 43240, 51228
3146	major histocompatibility complex, class I, A	414592	3301	394582	11289	19277, 27265, 35253, 43241, 51229
3147	major histocompatibility complex, class I, A	416096	3302	394889	11290	19278, 27266, 35254, 43242, 51230
3148	major histocompatibility complex, class I, A	417978	3303	388724	11291	19279, 27267, 35255, 43243, 51231
3149	major histocompatibility complex, class I, A	431930	3304	406366	11292	19280, 27268, 35256, 43244, 51232
3150	major histocompatibility complex, class I, A	438861	3305	388526	11293	19281, 27269, 35257, 43245, 51233
3151	major histocompatibility complex, class I, A	442939	3306	397962	11294	19282, 27270, 35258, 43246, 51234
3152	major histocompatibility complex, class I, A	443552	3307	404678	11295	19283, 27271, 35259, 43247, 51235
3153	major histocompatibility complex, class I, A	444289	3308	398188	11296	19284, 27272, 35260, 43248, 51236
3154	major histocompatibility complex, class I, A	450342	3309	391738	11297	19285, 27273, 35261, 43249, 51237
3155	major histocompatibility complex, class I, A	453057	3310	403922	11298	19286, 27274, 35262, 43250, 51238
3156	major histocompatibility complex, class I, A	453975	3311	392547	11299	19287, 27275, 35263, 43251, 51239
3157	major histocompatibility complex, class I, A	454091	3312	410645	11300	19288, 27276, 35264, 43252, 51240
3158	major histocompatibility complex, class I, A	455882	3313	416233	11301	19289, 27277, 35265, 43253, 51241
3159	major histocompatibility complex, class I, A	456012	3314	408986	11302	19290, 27278, 35266, 43254, 51242
3160	major histocompatibility complex, class I, A	457879	3315	403575	11303	19291, 27279, 35267, 43255, 51243

3161	major histocompatibility complex, class I, A	470780	3316	432736	11304	19292, 27280, 35268, 43256, 51244
3162	major histocompatibility complex, class I, A	536480	3317	440033	11305	19293, 27281, 35269, 43257, 51245
3163	major histocompatibility complex, class I, A	547112	3318	448887	11306	19294, 27282, 35270, 43258, 51246
3164	major histocompatibility complex, class I, A	547271	3319	447962	11307	19295, 27283, 35271, 43259, 51247
3165	major histocompatibility complex, class I, A	547522	3320	448077	11308	19296, 27284, 35272, 43260, 51248
3166	major histocompatibility complex, class I, A	549224	3321	447990	11309	19297, 27285, 35273, 43261, 51249
3167	major histocompatibility complex, class I, A	549835	3322	446814	11310	19298, 27286, 35274, 43262, 51250
3168	major histocompatibility complex, class I, A	549869	3323	447635	11311	19299, 27287, 35275, 43263, 51251
3169	major histocompatibility complex, class I, A	550707	3324	450284	11312	19300, 27288, 35276, 43264, 51252
3170	major histocompatibility complex, class I, A	550728	3325	450169	11313	19301, 27289, 35277, 43265, 51253
3171	major histocompatibility complex, class I, A	551120	3326	449453	11314	19302, 27290, 35278, 43266, 51254
3172	major histocompatibility complex, class I, A	551190	3327	450314	11315	19303, 27291, 35279, 43267, 51255
3173	major histocompatibility complex, class I, A	551578	3328	448239	11316	19304, 27292, 35280, 43268, 51256
3174	major histocompatibility complex, class I, A	552193	3329	447614	11317	19305, 27293, 35281, 43269, 51257
3175	major histocompatibility complex, class I, A	552493	3330	448992	11318	19306, 27294, 35282, 43270, 51258
3176	major histocompatibility complex, class I, A	552498	3331	448516	11319	19307, 27295, 35283, 43271, 51259
3177	major histocompatibility complex, class I, B	359635	3332	352656	11320	19308, 27296, 35284, 43272, 51260
3178	major histocompatibility complex, class I, B	412585	3333	399168	11321	19309, 27297, 35285, 43273, 51261

3179	major histocompatibility complex, class I, B	416726	3334	392099	11322	19310, 27298, 35286, 43274, 51262
3180	major histocompatibility complex, class I, B	418147	3335	411954	11323	19311, 27299, 35287, 43275, 51263
3181	major histocompatibility complex, class I, B	421349	3336	405365	11324	19312, 27300, 35288, 43276, 51264
3182	major histocompatibility complex, class I, B	425798	3337	401443	11325	19313, 27301, 35289, 43277, 51265
3183	major histocompatibility complex, class I, B	425848	3338	400842	11326	19314, 27302, 35290, 43278, 51266
3184	major histocompatibility complex, class I, B	426590	3339	392626	11327	19315, 27303, 35291, 43279, 51267
3185	major histocompatibility complex, class I, B	428231	3340	401183	11328	19316, 27304, 35292, 43280, 51268
3186	major histocompatibility complex, class I, B	430299	3341	416672	11329	19317, 27305, 35293, 43281, 51269
3187	major histocompatibility complex, class I, B	434333	3342	405931	11330	19318, 27306, 35294, 43282, 51270
3188	major histocompatibility complex, class I, B	435618	3343	405178	11331	19319, 27307, 35295, 43283, 51271
3189	major histocompatibility complex, class I, B	436729	3344	403471	11332	19320, 27308, 35296, 43284, 51272
3190	major histocompatibility complex, class I, B	437265	3345	398100	11333	19321, 27309, 35297, 43285, 51273
3191	major histocompatibility complex, class I, B	437866	3346	392235	11334	19322, 27310, 35298, 43286, 51274
3192	major histocompatibility complex, class I, B	445222	3347	399675	11335	19323, 27311, 35299, 43287, 51275
3193	major histocompatibility complex, class I, B	445610	3348	396397	11336	19324, 27312, 35300, 43288, 51276
3194	major histocompatibility complex, class I, B	450871	3349	388208	11337	19325, 27313, 35301, 43289, 51277
3195	major histocompatibility complex, class I, B	452596	3350	396980	11338	19326, 27314, 35302, 43290, 51278
3196	major histocompatibility complex, class I, B	461583	3351	436637	11339	19327, 27315, 35303, 43291, 51279

3197	major histocompatibility complex, class I, B	471639	3352	435221	11340	19328, 27316, 35304, 43292, 51280
3198	major histocompatibility complex, class I, B	479203	3353	433363	11341	19329, 27317, 35305, 43293, 51281
3199	major histocompatibility complex, class I, B	481283	3354	435817	11342	19330, 27318, 35306, 43294, 51282
3200	major histocompatibility complex, class I, B	498484	3355	435083	11343	19331, 27319, 35307, 43295, 51283
3201	major histocompatibility complex, class I, B	546599	3356	446558	11344	19332, 27320, 35308, 43296, 51284
3202	major histocompatibility complex, class I, B	550965	3357	449246	11345	19333, 27321, 35309, 43297, 51285
3203	major histocompatibility complex, class I, B	553172	3358	447662	11346	19334, 27322, 35310, 43298, 51286
3204	major histocompatibility complex, class I, E	376630	3359	365817	11347	19335, 27323, 35311, 43299, 51287
3205	major histocompatibility complex, class I, E	383597	3360	373091	11348	19336, 27324, 35312, 43300, 51288
3206	major histocompatibility complex, class I, E	415289	3361	409910	11349	19337, 27325, 35313, 43301, 51289
3207	major histocompatibility complex, class I, E	415649	3362	390707	11350	19338, 27326, 35314, 43302, 51290
3208	major histocompatibility complex, class I, E	425603	3363	402694	11351	19339, 27327, 35315, 43303, 51291
3209	major histocompatibility complex, class I, E	427936	3364	397420	11352	19340, 27328, 35316, 43304, 51292
3210	major histocompatibility complex, class I, E	444683	3365	400458	11353	19341, 27329, 35317, 43305, 51293
3211	major histocompatibility complex, class I, E	547304	3366	450038	11354	19342, 27330, 35318, 43306, 51294
3212	major histocompatibility complex, class I, F	259951	3367	259951	11355	19343, 27331, 35319, 43307, 51295
3213	major histocompatibility complex, class I, F	334668	3368	334263	11356	19344, 27332, 35320, 43308, 51296
3214	major histocompatibility complex, class I, F	342322	3369	345828	11357	19345, 27333, 35321, 43309, 51297

3215	major histocompatibility complex, class I, F	359076	3370	351977	11358	19346, 27334, 35322, 43310, 51298
3216	major histocompatibility complex, class I, F	376844	3371	366040	11359	19347, 27335, 35323, 43311, 51299
3217	major histocompatibility complex, class I, F	376848	3372	366044	11360	19348, 27336, 35324, 43312, 51300
3218	major histocompatibility complex, class I, F	376861	3373	366057	11361	19349, 27337, 35325, 43313, 51301
3219	major histocompatibility complex, class I, F	383515	3374	373007	11362	19350, 27338, 35326, 43314, 51302
3220	major histocompatibility complex, class I, F	383516	3375	373008	11363	19351, 27339, 35327, 43315, 51303
3221	major histocompatibility complex, class I, F	383626	3376	373121	11364	19352, 27340, 35328, 43316, 51304
3222	major histocompatibility complex, class I, F	383627	3377	373123	11365	19353, 27341, 35329, 43317, 51305
3223	major histocompatibility complex, class I, F	399258	3378	382201	11366	19354, 27342, 35330, 43318, 51306
3224	major histocompatibility complex, class I, F	414333	3379	389590	11367	19355, 27343, 35331, 43319, 51307
3225	major histocompatibility complex, class I, F	414958	3380	409934	11368	19356, 27344, 35332, 43320, 51308
3226	major histocompatibility complex, class I, F	418017	3381	405190	11369	19357, 27345, 35333, 43321, 51309
3227	major histocompatibility complex, class I, F	420024	3382	416426	11370	19358, 27346, 35334, 43322, 51310
3228	major histocompatibility complex, class I, F	420067	3383	393535	11371	19359, 27347, 35335, 43323, 51311
3229	major histocompatibility complex, class I, F	420414	3384	407836	11372	19360, 27348, 35336, 43324, 51312
3230	major histocompatibility complex, class I, F	420923	3385	400112	11373	19361, 27349, 35337, 43325, 51313
3231	major histocompatibility complex, class I, F	422439	3386	414318	11374	19362, 27350, 35338, 43326, 51314
3232	major histocompatibility complex, class I, F	422711	3387	395853	11375	19363, 27351, 35339, 43327, 51315

3233	major histocompatibility complex, class I, F	425139	3388	412140	11376	19364, 27352, 35340, 43328, 51316
3234	major histocompatibility complex, class I, F	426470	3389	404395	11377	19365, 27353, 35341, 43329, 51317
3235	major histocompatibility complex, class I, F	426675	3390	415401	11378	19366, 27354, 35342, 43330, 51318
3236	major histocompatibility complex, class I, F	428296	3391	387786	11379	19367, 27355, 35343, 43331, 51319
3237	major histocompatibility complex, class I, F	429294	3392	416998	11380	19368, 27356, 35344, 43332, 51320
3238	major histocompatibility complex, class I, F	430472	3393	397705	11381	19369, 27357, 35345, 43333, 51321
3239	major histocompatibility complex, class I, F	433515	3394	398913	11382	19370, 27358, 35346, 43334, 51322
3240	major histocompatibility complex, class I, F	434407	3395	397376	11383	19371, 27359, 35347, 43335, 51323
3241	major histocompatibility complex, class I, F	435058	3396	408540	11384	19372, 27360, 35348, 43336, 51324
3242	major histocompatibility complex, class I, F	437020	3397	396776	11385	19373, 27361, 35349, 43337, 51325
3243	major histocompatibility complex, class I, F	437226	3398	400299	11386	19374, 27362, 35350, 43338, 51326
3244	major histocompatibility complex, class I, F	440587	3399	404130	11387	19375, 27363, 35351, 43339, 51327
3245	major histocompatibility complex, class I, F	440590	3400	399835	11388	19376, 27364, 35352, 43340, 51328
3246	major histocompatibility complex, class I, F	441200	3401	405198	11389	19377, 27365, 35353, 43341, 51329
3247	major histocompatibility complex, class I, F	444057	3402	389555	11390	19378, 27366, 35354, 43342, 51330
3248	major histocompatibility complex, class I, F	444621	3403	392251	11391	19379, 27367, 35355, 43343, 51331
3249	major histocompatibility complex, class I, F	444891	3404	402853	11392	19380, 27368, 35356, 43344, 51332
3250	major histocompatibility complex, class I, F	445657	3405	414905	11393	19381, 27369, 35357, 43345, 51333

3251	major histocompatibility complex, class I, F	447400	3406	388133	11394	19382, 27370, 35358, 43346, 51334
3252	major histocompatibility complex, class I, F	448064	3407	399120	11395	19383, 27371, 35359, 43347, 51335
3253	major histocompatibility complex, class I, F	449921	3408	415312	11396	19384, 27372, 35360, 43348, 51336
3254	major histocompatibility complex, class I, F	452916	3409	415017	11397	19385, 27373, 35361, 43349, 51337
3255	major histocompatibility complex, class I, F	454646	3410	414500	11398	19386, 27374, 35362, 43350, 51338
3256	major histocompatibility complex, class I, F	454779	3411	390887	11399	19387, 27375, 35363, 43351, 51339
3257	major histocompatibility complex, class I, F	458026	3412	399043	11400	19388, 27376, 35364, 43352, 51340
3258	major histocompatibility complex, class I, F	547126	3413	450176	11401	19389, 27377, 35365, 43353, 51341
3259	major histocompatibility complex, class I, F	547128	3414	450179	11402	19390, 27378, 35366, 43354, 51342
3260	major histocompatibility complex, class I, F	547132	3415	446947	11403	19391, 27379, 35367, 43355, 51343
3261	major histocompatibility complex, class I, F	547503	3416	450111	11404	19392, 27380, 35368, 43356, 51344
3262	major histocompatibility complex, class I, F	547953	3417	449390	11405	19393, 27381, 35369, 43357, 51345
3263	major histocompatibility complex, class I, F	548879	3418	446526	11406	19394, 27382, 35370, 43358, 51346
3264	major histocompatibility complex, class I, F	549067	3419	450053	11407	19395, 27383, 35371, 43359, 51347
3265	major histocompatibility complex, class I, F	549166	3420	450301	11408	19396, 27384, 35372, 43360, 51348
3266	major histocompatibility complex, class I, F	549254	3421	446505	11409	19397, 27385, 35373, 43361, 51349
3267	major histocompatibility complex, class I, F	549422	3422	450119	11410	19398, 27386, 35374, 43362, 51350
3268	major histocompatibility complex, class I, F	550237	3423	448113	11411	19399, 27387, 35375, 43363, 51351

3269	major histocompatibility complex, class I, F	550932	3424	450300	11412	19400, 27388, 35376, 43364, 51352
3270	major histocompatibility complex, class I, F	550980	3425	447195	11413	19401, 27389, 35377, 43365, 51353
3271	major histocompatibility complex, class I, F	551026	3426	450148	11414	19402, 27390, 35378, 43366, 51354
3272	major histocompatibility complex, class I, F	551205	3427	449164	11415	19403, 27391, 35379, 43367, 51355
3273	major histocompatibility complex, class I, F	551347	3428	447078	11416	19404, 27392, 35380, 43368, 51356
3274	major histocompatibility complex, class I, F	551780	3429	447401	11417	19405, 27393, 35381, 43369, 51357
3275	major histocompatibility complex, class I, F	552082	3430	447228	11418	19406, 27394, 35382, 43370, 51358
3276	major histocompatibility complex, class I, F	552732	3431	448096	11419	19407, 27395, 35383, 43371, 51359
3277	major histocompatibility complex, class I, F	552880	3432	448638	11420	19408, 27396, 35384, 43372, 51360
3278	major histocompatibility complex, class I, G	360323	3433	353472	11421	19409, 27397, 35385, 43373, 51361
3279	major histocompatibility complex, class I, G	376815	3434	366011	11422	19410, 27398, 35386, 43374, 51362
3280	major histocompatibility complex, class I, G	376818	3435	366014	11423	19411, 27399, 35387, 43375, 51363
3281	major histocompatibility complex, class I, G	376828	3436	366024	11424	19412, 27400, 35388, 43376, 51364
3282	major histocompatibility complex, class I, G	383621	3437	373116	11425	19413, 27401, 35389, 43377, 51365
3283	major histocompatibility complex, class I, G	383622	3438	373117	11426	19414, 27402, 35390, 43378, 51366
3284	major histocompatibility complex, class I, G	383623	3439	373118	11427	19415, 27403, 35391, 43379, 51367
3285	major histocompatibility complex, class I, G	400665	3440	383506	11428	19416, 27404, 35392, 43380, 51368
3286	major histocompatibility complex, class I, G	400682	3441	383521	11429	19417, 27405, 35393, 43381, 51369

3287	major histocompatibility complex, class I, G	412263	3442	397733	11430	19418, 27406, 35394, 43382, 51370
3288	major histocompatibility complex, class I, G	415687	3443	389969	11431	19419, 27407, 35395, 43383, 51371
3289	major histocompatibility complex, class I, G	420559	3444	397331	11432	19420, 27408, 35396, 43384, 51372
3290	major histocompatibility complex, class I, G	422371	3445	387624	11433	19421, 27409, 35397, 43385, 51373
3291	major histocompatibility complex, class I, G	423011	3446	389522	11434	19422, 27410, 35398, 43386, 51374
3292	major histocompatibility complex, class I, G	423373	3447	405238	11435	19423, 27411, 35399, 43387, 51375
3293	major histocompatibility complex, class I, G	426863	3448	392075	11436	19424, 27412, 35400, 43388, 51376
3294	major histocompatibility complex, class I, G	428701	3449	412927	11437	19425, 27413, 35401, 43389, 51377
3295	major histocompatibility complex, class I, G	428952	3450	388176	11438	19426, 27414, 35402, 43390, 51378
3296	major histocompatibility complex, class I, G	429890	3451	401326	11439	19427, 27415, 35403, 43391, 51379
3297	major histocompatibility complex, class I, G	430253	3452	396594	11440	19428, 27416, 35404, 43392, 51380
3298	major histocompatibility complex, class I, G	434881	3453	392347	11441	19429, 27417, 35405, 43393, 51381
3299	major histocompatibility complex, class I, G	434907	3454	408461	11442	19430, 27418, 35406, 43394, 51382
3300	major histocompatibility complex, class I, G	444098	3455	398200	11443	19431, 27419, 35407, 43395, 51383
3301	major histocompatibility complex, class I, G	445373	3456	416408	11444	19432, 27420, 35408, 43396, 51384
3302	major histocompatibility complex, class I, G	448306	3457	413926	11445	19433, 27421, 35409, 43397, 51385
3303	major histocompatibility complex, class I, G	449127	3458	408773	11446	19434, 27422, 35410, 43398, 51386
3304	major histocompatibility complex, class I, G	450984	3459	409132	11447	19435, 27423, 35411, 43399, 51387

3305	major histocompatibility complex, class I, G	452577	3460	415905	11448	19436, 27424, 35412, 43400, 51388
3306	major histocompatibility complex, class I, G	452715	3461	390678	11449	19437, 27425, 35413, 43401, 51389
3307	major histocompatibility complex, class I, G	457132	3462	410247	11450	19438, 27426, 35414, 43402, 51390
3308	major histocompatibility complex, class I, G	466488	3463	433426	11451	19439, 27427, 35415, 43403, 51391
3309	major histocompatibility complex, class I, G	467814	3464	434622	11452	19440, 27428, 35416, 43404, 51392
3310	major histocompatibility complex, class I, G	469347	3465	437036	11453	19441, 27429, 35417, 43405, 51393
3311	major histocompatibility complex, class I, G	469472	3466	432220	11454	19442, 27430, 35418, 43406, 51394
3312	major histocompatibility complex, class I, G	478519	3467	436375	11455	19443, 27431, 35419, 43407, 51395
3313	major histocompatibility complex, class I, G	486553	3468	432239	11456	19444, 27432, 35420, 43408, 51396
3314	major histocompatibility complex, class I, G	546545	3469	447762	11457	19445, 27433, 35421, 43409, 51397
3315	major histocompatibility complex, class I, G	546634	3470	447780	11458	19446, 27434, 35422, 43410, 51398
3316	major histocompatibility complex, class I, G	547241	3471	448085	11459	19447, 27435, 35423, 43411, 51399
3317	major histocompatibility complex, class I, G	547931	3472	448363	11460	19448, 27436, 35424, 43412, 51400
3318	major histocompatibility complex, class I, G	550897	3473	449903	11461	19449, 27437, 35425, 43413, 51401
3319	major histocompatibility complex, class I, G	553052	3474	449291	11462	19450, 27438, 35426, 43414, 51402
3320	major histocompatibility complex, class II, DM alpha	341486	3475	345804	11463	19451, 27439, 35427, 43415, 51403
3321	major histocompatibility complex, class II, DM alpha	374843	3476	363976	11464	19452, 27440, 35428, 43416, 51404

3322	major histocompatibility complex, class II, DM alpha	383227	3477	372714	11465	19453, 27441, 35429, 43417, 51405
3323	major histocompatibility complex, class II, DM alpha	383228	3478	372715	11466	19454, 27442, 35430, 43418, 51406
3324	major histocompatibility complex, class II, DM alpha	383230	3479	372717	11467	19455, 27443, 35431, 43419, 51407
3325	major histocompatibility complex, class II, DM alpha	395303	3480	378714	11468	19456, 27444, 35432, 43420, 51408
3326	major histocompatibility complex, class II, DM alpha	395305	3481	378716	11469	19457, 27445, 35433, 43421, 51409
3327	major histocompatibility complex, class II, DM alpha	412394	3482	412550	11470	19458, 27446, 35434, 43422, 51410
3328	major histocompatibility complex, class II, DM alpha	416297	3483	398728	11471	19459, 27447, 35435, 43423, 51411
3329	major histocompatibility complex, class II, DM alpha	416806	3484	405637	11472	19460, 27448, 35436, 43424, 51412
3330	major histocompatibility complex, class II, DM alpha	418042	3485	395579	11473	19461, 27449, 35437, 43425, 51413
3331	major histocompatibility complex, class II, DM alpha	419041	3486	394366	11474	19462, 27450, 35438, 43426, 51414
3332	major histocompatibility complex, class II, DM alpha	419231	3487	407671	11475	19463, 27451, 35439, 43427, 51415
3333	major histocompatibility complex, class II, DM alpha	420299	3488	414945	11476	19464, 27452, 35440, 43428, 51416
3334	major histocompatibility complex, class II, DM alpha	420931	3489	402739	11477	19465, 27453, 35441, 43429, 51417
3335	major histocompatibility complex, class II,	422196	3490	409144	11478	19466, 27454, 35442, 43430, 51418

	DM alpha					
3336	major histocompatibility complex, class II, DM alpha	422832	3491	403122	11479	19467, 27455, 35443, 43431, 51419
3337	major histocompatibility complex, class II, DM alpha	426176	3492	395056	11480	19468, 27456, 35444, 43432, 51420
3338	major histocompatibility complex, class II, DM alpha	432991	3493	389962	11481	19469, 27457, 35445, 43433, 51421
3339	major histocompatibility complex, class II, DM alpha	433630	3494	411774	11482	19470, 27458, 35446, 43434, 51422
3340	major histocompatibility complex, class II, DM alpha	434337	3495	407198	11483	19471, 27459, 35447, 43435, 51423
3341	major histocompatibility complex, class II, DM alpha	435503	3496	390001	11484	19472, 27460, 35448, 43436, 51424
3342	major histocompatibility complex, class II, DM alpha	437285	3497	399386	11485	19473, 27461, 35449, 43437, 51425
3343	major histocompatibility complex, class II, DM alpha	439054	3498	403906	11486	19474, 27462, 35450, 43438, 51426
3344	major histocompatibility complex, class II, DM alpha	440717	3499	415844	11487	19475, 27463, 35451, 43439, 51427
3345	major histocompatibility complex, class II, DM alpha	441171	3500	400783	11488	19476, 27464, 35452, 43440, 51428
3346	major histocompatibility complex, class II, DM alpha	441375	3501	410591	11489	19477, 27465, 35453, 43441, 51429
3347	major histocompatibility complex, class II, DM alpha	443447	3502	398951	11490	19478, 27466, 35454, 43442, 51430
3348	major histocompatibility complex, class II, DM alpha	450601	3503	392842	11491	19479, 27467, 35455, 43443, 51431

3349	major histocompatibility complex, class II, DM alpha	451148	3504	414016	11492	19480, 27468, 35456, 43444, 51432
3350	major histocompatibility complex, class II, DM alpha	451753	3505	409734	11493	19481, 27469, 35457, 43445, 51433
3351	major histocompatibility complex, class II, DM alpha	452330	3506	398742	11494	19482, 27470, 35458, 43446, 51434
3352	major histocompatibility complex, class II, DM alpha	452434	3507	412100	11495	19483, 27471, 35459, 43447, 51435
3353	major histocompatibility complex, class II, DM alpha	452615	3508	395349	11496	19484, 27472, 35460, 43448, 51436
3354	major histocompatibility complex, class II, DM alpha	452703	3509	405208	11497	19485, 27473, 35461, 43449, 51437
3355	major histocompatibility complex, class II, DM alpha	453490	3510	404018	11498	19486, 27474, 35462, 43450, 51438
3356	major histocompatibility complex, class II, DM alpha	454298	3511	414631	11499	19487, 27475, 35463, 43451, 51439
3357	major histocompatibility complex, class II, DM alpha	456486	3512	408520	11500	19488, 27476, 35464, 43452, 51440
3358	major histocompatibility complex, class II, DM alpha	456800	3513	409668	11501	19489, 27477, 35465, 43453, 51441
3359	major histocompatibility complex, class II, DM alpha	457285	3514	399032	11502	19490, 27478, 35466, 43454, 51442
3360	major histocompatibility complex, class II, DM alpha	458066	3515	408141	11503	19491, 27479, 35467, 43455, 51443
3361	major histocompatibility complex, class II, DM beta	383231	3516	372718	11504	19492, 27480, 35468, 43456, 51444
3362	major histocompatibility complex, class II,	395312	3517	378723	11505	19493, 27481, 35469, 43457, 51445

	DM beta					
3363	major histocompatibility complex, class II, DM beta	412948	3518	413471	11506	19494, 27482, 35470, 43458, 51446
3364	major histocompatibility complex, class II, DM beta	413038	3519	410077	11507	19495, 27483, 35471, 43459, 51447
3365	major histocompatibility complex, class II, DM beta	413617	3520	394789	11508	19496, 27484, 35472, 43460, 51448
3366	major histocompatibility complex, class II, DM beta	413696	3521	405790	11509	19497, 27485, 35473, 43461, 51449
3367	major histocompatibility complex, class II, DM beta	414017	3522	411276	11510	19498, 27486, 35474, 43462, 51450
3368	major histocompatibility complex, class II, DM beta	415090	3523	398843	11511	19499, 27487, 35475, 43463, 51451
3369	major histocompatibility complex, class II, DM beta	415927	3524	414153	11512	19500, 27488, 35476, 43464, 51452
3370	major histocompatibility complex, class II, DM beta	416244	3525	391010	11513	19501, 27489, 35477, 43465, 51453
3371	major histocompatibility complex, class II, DM beta	418107	3526	398890	11514	19502, 27490, 35478, 43466, 51454
3372	major histocompatibility complex, class II, DM beta	418759	3527	394997	11515	19503, 27491, 35479, 43467, 51455
3373	major histocompatibility complex, class II, DM beta	421456	3528	410609	11516	19504, 27492, 35480, 43468, 51456
3374	major histocompatibility complex, class II, DM beta	424822	3529	414817	11517	19505, 27493, 35481, 43469, 51457
3375	major histocompatibility complex, class II, DM beta	424874	3530	394737	11518	19506, 27494, 35482, 43470, 51458

3376	major histocompatibility complex, class II, DM beta	428420	3531	393646	11519	19507, 27495, 35483, 43471, 51459
3377	major histocompatibility complex, class II, DM beta	428864	3532	402800	11520	19508, 27496, 35484, 43472, 51460
3378	Major histocompatibility complex, class II, DM beta	429234	3533	412457	11521	19509, 27497, 35485, 43473, 51461
3379	major histocompatibility complex, class II, DM beta	430099	3534	412415	11522	19510, 27498, 35486, 43474, 51462
3380	major histocompatibility complex, class II, DM beta	430115	3535	401587	11523	19511, 27499, 35487, 43475, 51463
3381	major histocompatibility complex, class II, DM beta	433242	3536	401238	11524	19512, 27500, 35488, 43476, 51464
3382	major histocompatibility complex, class II, DM beta	435056	3537	410908	11525	19513, 27501, 35489, 43477, 51465
3383	major histocompatibility complex, class II, DM beta	435204	3538	391679	11526	19514, 27502, 35490, 43478, 51466
3384	major histocompatibility complex, class II, DM beta	437382	3539	391352	11527	19515, 27503, 35491, 43479, 51467
3385	major histocompatibility complex, class II, DM beta	437583	3540	405746	11528	19516, 27504, 35492, 43480, 51468
3386	major histocompatibility complex, class II, DM beta	438310	3541	399634	11529	19517, 27505, 35493, 43481, 51469
3387	major histocompatibility complex, class II, DM beta	438510	3542	390848	11530	19518, 27506, 35494, 43482, 51470
3388	major histocompatibility complex, class II, DM beta	439344	3543	413062	11531	19519, 27507, 35495, 43483, 51471
3389	major histocompatibility complex, class II,	440078	3544	411321	11532	19520, 27508, 35496, 43484, 51472

	DM beta					
3390	major histocompatibility complex, class II, DM beta	440269	3545	406776	11533	19521, 27509, 35497, 43485, 51473
3391	major histocompatibility complex, class II, DM beta	441177	3546	393285	11534	19522, 27510, 35498, 43486, 51474
3392	major histocompatibility complex, class II, DM beta	446948	3547	393569	11535	19523, 27511, 35499, 43487, 51475
3393	major histocompatibility complex, class II, DM beta	447454	3548	396075	11536	19524, 27512, 35500, 43488, 51476
3394	major histocompatibility complex, class II, DM beta	448590	3549	389736	11537	19525, 27513, 35501, 43489, 51477
3395	major histocompatibility complex, class II, DM beta	448798	3550	398332	11538	19526, 27514, 35502, 43490, 51478
3396	major histocompatibility complex, class II, DM beta	449417	3551	410329	11539	19527, 27515, 35503, 43491, 51479
3397	major histocompatibility complex, class II, DM beta	449679	3552	404072	11540	19528, 27516, 35504, 43492, 51480
3398	major histocompatibility complex, class II, DM beta	450897	3553	408453	11541	19529, 27517, 35505, 43493, 51481
3399	major histocompatibility complex, class II, DM beta	451921	3554	399759	11542	19530, 27518, 35506, 43494, 51482
3400	major histocompatibility complex, class II, DM beta	452407	3555	399130	11543	19531, 27519, 35507, 43495, 51483
3401	major histocompatibility complex, class II, DM beta	456428	3556	416157	11544	19532, 27520, 35508, 43496, 51484
3402	major histocompatibility complex, class II, DM beta	546470	3557	447781	11545	19533, 27521, 35509, 43497, 51485

3403	major histocompatibility complex, class II, DM beta	546855	3558	450237	11546	19534, 27522, 35510, 43498, 51486
3404	major histocompatibility complex, class II, DM beta	547313	3559	449487	11547	19535, 27523, 35511, 43499, 51487
3405	major histocompatibility complex, class II, DM beta	547391	3560	449127	11548	19536, 27524, 35512, 43500, 51488
3406	major histocompatibility complex, class II, DM beta	547478	3561	448541	11549	19537, 27525, 35513, 43501, 51489
3407	major histocompatibility complex, class II, DM beta	548183	3562	450057	11550	19538, 27526, 35514, 43502, 51490
3408	major histocompatibility complex, class II, DM beta	548290	3563	446674	11551	19539, 27527, 35515, 43503, 51491
3409	major histocompatibility complex, class II, DM beta	548611	3564	448875	11552	19540, 27528, 35516, 43504, 51492
3410	major histocompatibility complex, class II, DM beta	549152	3565	449375	11553	19541, 27529, 35517, 43505, 51493
3411	major histocompatibility complex, class II, DM beta	549556	3566	446912	11554	19542, 27530, 35518, 43506, 51494
3412	major histocompatibility complex, class II, DM beta	549676	3567	448564	11555	19543, 27531, 35519, 43507, 51495
3413	major histocompatibility complex, class II, DM beta	550052	3568	450287	11556	19544, 27532, 35520, 43508, 51496
3414	major histocompatibility complex, class II, DM beta	550933	3569	447570	11557	19545, 27533, 35521, 43509, 51497
3415	major histocompatibility complex, class II, DM beta	551036	3570	446547	11558	19546, 27534, 35522, 43510, 51498
3416	major histocompatibility complex, class II,	551481	3571	447325	11559	19547, 27535, 35523, 43511, 51499

	DM beta					
3417	major histocompatibility complex, class II, DM beta	551515	3572	446560	11560	19548, 27536, 35524, 43512, 51500
3418	major histocompatibility complex, class II, DM beta	552299	3573	449810	11561	19549, 27537, 35525, 43513, 51501
3419	major histocompatibility complex, class II, DM beta	552389	3574	447573	11562	19550, 27538, 35526, 43514, 51502
3420	major histocompatibility complex, class II, DM beta	553199	3575	449606	11563	19551, 27539, 35527, 43515, 51503
3421	major histocompatibility complex, class II, DO alpha	229829	3576	229829	11564	19552, 27540, 35528, 43516, 51504
3422	major histocompatibility complex, class II, DO alpha	374813	3577	363946	11565	19553, 27541, 35529, 43517, 51505
3423	major histocompatibility complex, class II, DO alpha	383225	3578	372712	11566	19554, 27542, 35530, 43518, 51506
3424	major histocompatibility complex, class II, DO alpha	383226	3579	372713	11567	19555, 27543, 35531, 43519, 51507
3425	major histocompatibility complex, class II, DO alpha	416763	3580	402076	11568	19556, 27544, 35532, 43520, 51508
3426	major histocompatibility complex, class II, DO alpha	418857	3581	405153	11569	19557, 27545, 35533, 43521, 51509
3427	major histocompatibility complex, class II, DO alpha	426070	3582	401504	11570	19558, 27546, 35534, 43522, 51510
3428	major histocompatibility complex, class II, DO alpha	426685	3583	397945	11571	19559, 27547, 35535, 43523, 51511
3429	major histocompatibility complex, class II, DO alpha	432150	3584	412819	11572	19560, 27548, 35536, 43524, 51512

3430	major histocompatibility complex, class II, DO alpha	434335	3585	416448	11573	19561, 27549, 35537, 43525, 51513
3431	major histocompatibility complex, class II, DO alpha	438987	3586	395737	11574	19562, 27550, 35538, 43526, 51514
3432	major histocompatibility complex, class II, DO alpha	444109	3587	402347	11575	19563, 27551, 35539, 43527, 51515
3433	major histocompatibility complex, class II, DO alpha	450833	3588	403896	11576	19564, 27552, 35540, 43528, 51516
3434	major histocompatibility complex, class II, DO alpha	452598	3589	398819	11577	19565, 27553, 35541, 43529, 51517
3435	major histocompatibility complex, class II, DO alpha	455325	3590	402487	11578	19566, 27554, 35542, 43530, 51518
3436	major histocompatibility complex, class II, DO alpha	457663	3591	409491	11579	19567, 27555, 35543, 43531, 51519
3437	major histocompatibility complex, class II, DO alpha	546375	3592	447202	11580	19568, 27556, 35544, 43532, 51520
3438	major histocompatibility complex, class II, DO alpha	547284	3593	446715	11581	19569, 27557, 35545, 43533, 51521
3439	major histocompatibility complex, class II, DO alpha	547661	3594	449987	11582	19570, 27558, 35546, 43534, 51522
3440	major histocompatibility complex, class II, DO alpha	548708	3595	448280	11583	19571, 27559, 35547, 43535, 51523
3441	major histocompatibility complex, class II, DO alpha	549720	3596	446832	11584	19572, 27560, 35548, 43536, 51524
3442	major histocompatibility complex, class II, DO alpha	549845	3597	449183	11585	19573, 27561, 35549, 43537, 51525
3443	major histocompatibility complex, class II,	549849	3598	449760	11586	19574, 27562, 35550, 43538, 51526

	DO alpha					
3444	major histocompatibility complex, class II, DO alpha	549880	3599	448865	11587	19575, 27563, 35551, 43539, 51527
3445	major histocompatibility complex, class II, DO alpha	549881	3600	446500	11588	19576, 27564, 35552, 43540, 51528
3446	major histocompatibility complex, class II, DO alpha	550072	3601	449395	11589	19577, 27565, 35553, 43541, 51529
3447	major histocompatibility complex, class II, DO alpha	552368	3602	449656	11590	19578, 27566, 35554, 43542, 51530
3448	major histocompatibility complex, class II, DO alpha	553212	3603	449347	11591	19579, 27567, 35555, 43543, 51531
3449	major histocompatibility complex, class II, DO beta	413252	3604	390574	11592	19580, 27568, 35556, 43544, 51532
3450	major histocompatibility complex, class II, DO beta	426644	3605	395780	11593	19581, 27569, 35557, 43545, 51533
3451	major histocompatibility complex, class II, DO beta	438763	3606	390020	11594	19582, 27570, 35558, 43546, 51534
3452	major histocompatibility complex, class II, DO beta	439310	3607	401290	11595	19583, 27571, 35559, 43547, 51535
3453	major histocompatibility complex, class II, DO beta	447178	3608	405108	11596	19584, 27572, 35560, 43548, 51536
3454	major histocompatibility complex, class II, DO beta	447394	3609	394860	11597	19585, 27573, 35561, 43549, 51537
3455	major histocompatibility complex, class II, DO beta	448690	3610	413915	11598	19586, 27574, 35562, 43550, 51538
3456	major histocompatibility complex, class II, DO beta	453971	3611	391708	11599	19587, 27575, 35563, 43551, 51539

3457	major histocompatibility complex, class II, DO beta	454286	3612	397268	11600	19588, 27576, 35564, 43552, 51540
3458	major histocompatibility complex, class II, DO beta	454969	3613	410390	11601	19589, 27577, 35565, 43553, 51541
3459	major histocompatibility complex, class II, DO beta	455155	3614	406128	11602	19590, 27578, 35566, 43554, 51542
3460	major histocompatibility complex, class II, DO beta	456406	3615	394783	11603	19591, 27579, 35567, 43555, 51543
3461	major histocompatibility complex, class II, DQ beta 1	490862	3616	433300	11604	19592, 27580, 35568, 43556, 51544
3462	major histocompatibility complex, class II, DQ beta 2	323109	3617	322293	11605	19593, 27581, 35569, 43557, 51545
3463	major histocompatibility complex, class II, DQ beta 2	399658	3618	382566	11606	19594, 27582, 35570, 43558, 51546
3464	major histocompatibility complex, class II, DQ beta 2	399661	3619	382569	11607	19595, 27583, 35571, 43559, 51547
3465	major histocompatibility complex, class II, DQ beta 2	411527	3620	390431	11608	19596, 27584, 35572, 43560, 51548
3466	major histocompatibility complex, class II, DQ beta 2	415137	3621	387578	11609	19597, 27585, 35573, 43561, 51549
3467	major histocompatibility complex, class II, DQ beta 2	416131	3622	396323	11610	19598, 27586, 35574, 43562, 51550
3468	major histocompatibility complex, class II, DQ beta 2	417780	3623	394016	11611	19599, 27587, 35575, 43563, 51551
3469	major histocompatibility complex, class II, DQ beta 2	418419	3624	411739	11612	19600, 27588, 35576, 43564, 51552
3470	major histocompatibility complex, class II,	419109	3625	414496	11613	19601, 27589, 35577, 43565, 51553

	DQ beta 2					
3471	major histocompatibility complex, class II, DQ beta 2	419519	3626	406872	11614	19602, 27590, 35578, 43566, 51554
3472	major histocompatibility complex, class II, DQ beta 2	419685	3627	416466	11615	19603, 27591, 35579, 43567, 51555
3473	major histocompatibility complex, class II, DQ beta 2	421468	3628	403201	11616	19604, 27592, 35580, 43568, 51556
3474	major histocompatibility complex, class II, DQ beta 2	424579	3629	401270	11617	19605, 27593, 35581, 43569, 51557
3475	major histocompatibility complex, class II, DQ beta 2	426733	3630	393969	11618	19606, 27594, 35582, 43570, 51558
3476	major histocompatibility complex, class II, DQ beta 2	427449	3631	415997	11619	19607, 27595, 35583, 43571, 51559
3477	major histocompatibility complex, class II, DQ beta 2	428972	3632	407691	11620	19608, 27596, 35584, 43572, 51560
3478	major histocompatibility complex, class II, DQ beta 2	429783	3633	388849	11621	19609, 27597, 35585, 43573, 51561
3479	major histocompatibility complex, class II, DQ beta 2	430668	3634	392299	11622	19610, 27598, 35586, 43574, 51562
3480	major histocompatibility complex, class II, DQ beta 2	430849	3635	389067	11623	19611, 27599, 35587, 43575, 51563
3481	major histocompatibility complex, class II, DQ beta 2	432486	3636	410132	11624	19612, 27600, 35588, 43576, 51564
3482	major histocompatibility complex, class II, DQ beta 2	433114	3637	400295	11625	19613, 27601, 35589, 43577, 51565
3483	major histocompatibility complex, class II, DQ beta 2	433801	3638	391938	11626	19614, 27602, 35590, 43578, 51566

3484	major histocompatibility complex, class II, DQ beta 2	435081	3639	403893	11627	19615, 27603, 35591, 43579, 51567
3485	major histocompatibility complex, class II, DQ beta 2	435145	3640	410512	11628	19616, 27604, 35592, 43580, 51568
3486	major histocompatibility complex, class II, DQ beta 2	437316	3641	396330	11629	19617, 27605, 35593, 43581, 51569
3487	major histocompatibility complex, class II, DQ beta 2	438757	3642	408884	11630	19618, 27606, 35594, 43582, 51570
3488	major histocompatibility complex, class II, DQ beta 2	442043	3643	394272	11631	19619, 27607, 35595, 43583, 51571
3489	major histocompatibility complex, class II, DQ beta 2	442806	3644	394759	11632	19620, 27608, 35596, 43584, 51572
3490	major histocompatibility complex, class II, DQ beta 2	447979	3645	397883	11633	19621, 27609, 35597, 43585, 51573
3491	major histocompatibility complex, class II, DQ beta 2	455520	3646	409159	11634	19622, 27610, 35598, 43586, 51574
3492	major histocompatibility complex, class II, DQ beta 2	456529	3647	399594	11635	19623, 27611, 35599, 43587, 51575
3493	major histocompatibility complex, class II, DQ beta 2	457432	3648	396502	11636	19624, 27612, 35600, 43588, 51576
3494	major histocompatibility complex, class II, DQ beta 2	547371	3649	449924	11637	19625, 27613, 35601, 43589, 51577
3495	major histocompatibility complex, class II, DQ beta 2	547495	3650	447469	11638	19626, 27614, 35602, 43590, 51578
3496	major histocompatibility complex, class II, DQ beta 2	547938	3651	447018	11639	19627, 27615, 35603, 43591, 51579
3497	major histocompatibility complex, class II,	548910	3652	449156	11640	19628, 27616, 35604, 43592, 51580

	DQ beta 2					
3498	major histocompatibility complex, class II, DQ beta 2	549204	3653	449357	11641	19629, 27617, 35605, 43593, 51581
3499	major histocompatibility complex, class II, DQ beta 2	549642	3654	447790	11642	19630, 27618, 35606, 43594, 51582
3500	major histocompatibility complex, class II, DQ beta 2	549667	3655	450007	11643	19631, 27619, 35607, 43595, 51583
3501	major histocompatibility complex, class II, DQ beta 2	550427	3656	449451	11644	19632, 27620, 35608, 43596, 51584
3502	major histocompatibility complex, class II, DQ beta 2	551426	3657	450184	11645	19633, 27621, 35609, 43597, 51585
3503	major histocompatibility complex, class II, DQ beta 2	551510	3658	450207	11646	19634, 27622, 35610, 43598, 51586
3504	major histocompatibility complex, class II, DQ beta 2	552751	3659	446755	11647	19635, 27623, 35611, 43599, 51587
3505	major histocompatibility complex, class II, DR alpha	374982	3660	364121	11648	19636, 27624, 35612, 43600, 51588
3506	major histocompatibility complex, class II, DR alpha	383127	3661	372608	11649	19637, 27625, 35613, 43601, 51589
3507	major histocompatibility complex, class II, DR alpha	383258	3662	372745	11650	19638, 27626, 35614, 43602, 51590
3508	major histocompatibility complex, class II, DR alpha	383259	3663	372746	11651	19639, 27627, 35615, 43603, 51591
3509	major histocompatibility complex, class II, DR alpha	395388	3664	378786	11652	19640, 27628, 35616, 43604, 51592
3510	major histocompatibility complex, class II, DR alpha	411505	3665	411610	11653	19641, 27629, 35617, 43605, 51593

3511	major histocompatibility complex, class II, DR alpha	411524	3666	405295	11654	19642, 27630, 35618, 43606, 51594
3512	major histocompatibility complex, class II, DR alpha	414698	3667	402951	11655	19643, 27631, 35619, 43607, 51595
3513	major histocompatibility complex, class II, DR alpha	415767	3668	392789	11656	19644, 27632, 35620, 43608, 51596
3514	major histocompatibility complex, class II, DR alpha	416883	3669	410443	11657	19645, 27633, 35621, 43609, 51597
3515	major histocompatibility complex, class II, DR alpha	418111	3670	412562	11658	19646, 27634, 35622, 43610, 51598
3516	major histocompatibility complex, class II, DR alpha	427753	3671	398838	11659	19647, 27635, 35623, 43611, 51599
3517	major histocompatibility complex, class II, DR alpha	434866	3672	403385	11660	19648, 27636, 35624, 43612, 51600
3518	major histocompatibility complex, class II, DR alpha	442960	3673	404533	11661	19649, 27637, 35625, 43613, 51601
3519	major histocompatibility complex, class II, DR alpha	542549	3674	443327	11662	19650, 27638, 35626, 43614, 51602
3520	major histocompatibility complex, class II, DR alpha	546379	3675	447577	11663	19651, 27639, 35627, 43615, 51603
3521	major histocompatibility complex, class II, DR alpha	546550	3676	447027	11664	19652, 27640, 35628, 43616, 51604
3522	major histocompatibility complex, class II, DR alpha	546589	3677	448422	11665	19653, 27641, 35629, 43617, 51605
3523	major histocompatibility complex, class II, DR alpha	547499	3678	446911	11666	19654, 27642, 35630, 43618, 51606
3524	major histocompatibility complex, class II,	547909	3679	449599	11667	19655, 27643, 35631, 43619, 51607

	DR alpha					
3525	major histocompatibility complex, class II, DR alpha	548099	3680	448765	11668	19656, 27644, 35632, 43620, 51608
3526	major histocompatibility complex, class II, DR alpha	548168	3681	447052	11669	19657, 27645, 35633, 43621, 51609
3527	major histocompatibility complex, class II, DR alpha	549449	3682	447849	11670	19658, 27646, 35634, 43622, 51610
3528	major histocompatibility complex, class II, DR alpha	549531	3683	449251	11671	19659, 27647, 35635, 43623, 51611
3529	major histocompatibility complex, class II, DR alpha	550055	3684	450200	11672	19660, 27648, 35636, 43624, 51612
3530	major histocompatibility complex, class II, DR alpha	550966	3685	450172	11673	19661, 27649, 35637, 43625, 51613
3531	major histocompatibility complex, class II, DR alpha	551689	3686	446751	11674	19662, 27650, 35638, 43626, 51614
3532	major histocompatibility complex, class II, DR alpha	551750	3687	447755	11675	19663, 27651, 35639, 43627, 51615
3533	major histocompatibility complex, class II, DR alpha	552078	3688	446742	11676	19664, 27652, 35640, 43628, 51616
3534	major histocompatibility complex, class II, DR alpha	552804	3689	447375	11677	19665, 27653, 35641, 43629, 51617
3535	major histocompatibility complex, class II, DR alpha	553193	3690	446750	11678	19666, 27654, 35642, 43630, 51618
3536	major histocompatibility complex, class II, DR beta 4	411565	3691	410857	11679	19667, 27655, 35643, 43631, 51619
3537	major histocompatibility complex, class II, DR beta 4	411959	3692	410046	11680	19668, 27656, 35644, 43632, 51620

3538	major histocompatibility complex, class II, DR beta 4	457451	3693	412031	11681	19669, 27657, 35645, 43633, 51621
3539	malonyl CoA:ACP acyltransferase (mitochondrial)	290429	3694	290429	11682	19670, 27658, 35646, 43634, 51622
3540	malonyl CoA:ACP acyltransferase (mitochondrial)	327555	3695	331306	11683	19671, 27659, 35647, 43635, 51623
3541	MAM domain containing 4	317446	3696	319388	11684	19672, 27660, 35648, 43636, 51624
3542	MAM domain containing 4	413647	3697	400009	11685	19673, 27661, 35649, 43637, 51625
3543	MAM domain containing 4	445819	3698	411339	11686	19674, 27662, 35650, 43638, 51626
3544	mannosidase, alpha, class 1C, member 1	263979	3699	263979	11687	19675, 27663, 35651, 43639, 51627
3545	mannosidase, alpha, class 1C, member 1	374329	3700	363449	11688	19676, 27664, 35652, 43640, 51628
3546	mannosidase, alpha, class 1C, member 1	374331	3701	363451	11689	19677, 27665, 35653, 43641, 51629
3547	mannosidase, alpha, class 1C, member 1	374332	3702	363452	11690	19678, 27666, 35654, 43642, 51630
3548	mannosidase, beta A, lysosomal-like	373605	3703	362707	11691	19679, 27667, 35655, 43643, 51631
3549	mannosidase, beta A, lysosomal-like	373606	3704	362708	11692	19680, 27668, 35656, 43644, 51632
3550	mannosidase, beta A, lysosomal-like	397150	3705	380337	11693	19681, 27669, 35657, 43645, 51633
3551	mannosidase, beta A, lysosomal-like	397151	3706	380338	11694	19682, 27670, 35658, 43646, 51634
3552	mannosidase, beta A, lysosomal-like	397152	3707	380339	11695	19683, 27671, 35659, 43647, 51635
3553	mannosidase, beta A, lysosomal-like	397156	3708	380342	11696	19684, 27672, 35660, 43648, 51636
3554	mannosidase, endo-alpha-like	329006	3709	328770	11697	19685, 27673, 35661, 43649, 51637
3555	mannosidase, endo-alpha-like	373045	3710	362136	11698	19686, 27674, 35662, 43650, 51638

3556	mannosidase, endo-alpha-like	397631	3711	380755	11699	19687, 27675, 35663, 43651, 51639
3557	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	332156	3712	331664	11700	19688, 27676, 35664, 43652, 51640
3558	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	393205	3713	376900	11701	19689, 27677, 35665, 43653, 51641
3559	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	547225	3714	449172	11702	19690, 27678, 35666, 43654, 51642
3560	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	548651	3715	447253	11703	19691, 27679, 35667, 43655, 51643
3561	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	549405	3716	449022	11704	19692, 27680, 35668, 43656, 51644
3562	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	550460	3717	448690	11705	19693, 27681, 35669, 43657, 51645
3563	mannosyl (alpha-1,3-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase, isozyme C (putative)	552808	3718	446647	11706	19694, 27682, 35670, 43658, 51646
3564	mannosyl-oligosaccharide glucosidase	233616	3719	233616	11707	19695, 27683, 35671, 43659, 51647
3565	mannosyl-oligosaccharide glucosidase	452063	3720	388201	11708	19696, 27684, 35672, 43660, 51648
3566	mannosyl-oligosaccharide glucosidase	535045	3721	439971	11709	19697, 27685, 35673, 43661, 51649

3567	MANSC domain containing 1	535902	3722	438205	11710	19698, 27686, 35674, 43662, 51650
3568	MANSC domain containing 1	543314	3723	437624	11711	19699, 27687, 35675, 43663, 51651
3569	matrix-remodelling associated 7	355797	3724	348050	11712	19700, 27688, 35676, 43664, 51652
3570	matrix-remodelling associated 7	375036	3725	364176	11713	19701, 27689, 35677, 43665, 51653
3571	matrix-remodelling associated 7	392488	3726	376279	11714	19702, 27690, 35678, 43666, 51654
3572	matrix-remodelling associated 7	449428	3727	391466	11715	19703, 27691, 35679, 43667, 51655
3573	matrix-remodelling associated 8	309212	3728	307887	11716	19704, 27692, 35680, 43668, 51656
3574	matrix-remodelling associated 8	342753	3729	344998	11717	19705, 27693, 35681, 43669, 51657
3575	matrix-remodelling associated 8	378864	3730	368141	11718	19706, 27694, 35682, 43670, 51658
3576	matrix-remodelling associated 8	445648	3731	399229	11719	19707, 27695, 35683, 43671, 51659
3577	mature T-cell proliferation 1 neighbor	369479	3732	358491	11720	19708, 27696, 35684, 43672, 51660
3578	mature T-cell proliferation 1 neighbor	369484	3733	358496	11721	19709, 27697, 35685, 43673, 51661
3579	melanocortin 2 receptor accessory protein 2	257776	3734	257776	11722	19710, 27698, 35686, 43674, 51662
3580	melanoma antigen family A, 1 (directs expression of antigen MZ2-E)	356661	3735	349085	11723	19711, 27699, 35687, 43675, 51663
3581	membrane associated guanylate kinase, WW and PDZ domain containing 2	354212	3736	346151	11724	19712, 27700, 35688, 43676, 51664
3582	membrane associated guanylate kinase, WW and PDZ domain containing 2	419488	3737	405766	11725	19713, 27701, 35689, 43677, 51665

3583	membrane associated guanylate kinase, WW and PDZ domain containing 2	535697	3738	441603	11726	19714, 27702, 35690, 43678, 51666
3584	membrane associated guanylate kinase, WW and PDZ domain containing 2	536298	3739	445041	11727	19715, 27703, 35691, 43679, 51667
3585	membrane associated guanylate kinase, WW and PDZ domain containing 2	536571	3740	441584	11728	19716, 27704, 35692, 43680, 51668
3586	membrane bound O-acyltransferase domain containing 7	245615	3741	245615	11729	19717, 27705, 35693, 43681, 51669
3587	membrane bound O-acyltransferase domain containing 7	338624	3742	344377	11730	19718, 27706, 35694, 43682, 51670
3588	membrane bound O-acyltransferase domain containing 7	391754	3743	375634	11731	19719, 27707, 35695, 43683, 51671
3589	membrane bound O-acyltransferase domain containing 7	414665	3744	388250	11732	19720, 27708, 35696, 43684, 51672
3590	membrane bound O-acyltransferase domain containing 7	431666	3745	410503	11733	19721, 27709, 35697, 43685, 51673
3591	membrane bound O-acyltransferase domain containing 7	453320	3746	410320	11734	19722, 27710, 35698, 43686, 51674
3592	Membrane frizzled-related protein	449574	3747	391664	11735	19723, 27711, 35699, 43687, 51675
3593	Membrane frizzled-related protein	555262	3748	450509	11736	19724, 27712, 35700, 43688, 51676
3594	membrane magnesium transporter 1	305963	3749	306220	11737	19725, 27713, 35701, 43689, 51677
3595	membrane magnesium transporter 1	433339	3750	411359	11738	19726, 27714, 35702, 43690, 51678
3596	membrane-spanning 4-domains subfamily A member 14	531783	3751	433761	11739	19727, 27715, 35703, 43691, 51679

3597	membrane-spanning 4-domains, subfamily A, member 13	378185	3752	367427	11740	19728, 27716, 35704, 43692, 51680
3598	membrane-spanning 4-domains, subfamily A, member 13	378186	3753	367428	11741	19729, 27717, 35705, 43693, 51681
3599	membrane-spanning 4-domains, subfamily A, member 13	437058	3754	415535	11742	19730, 27718, 35706, 43694, 51682
3600	membrane-spanning 4-domains, subfamily A, member 14	300187	3755	300187	11743	19731, 27719, 35707, 43695, 51683
3601	membrane-spanning 4-domains, subfamily A, member 14	395001	3756	378449	11744	19732, 27720, 35708, 43696, 51684
3602	membrane-spanning 4-domains, subfamily A, member 14	395005	3757	378453	11745	19733, 27721, 35709, 43697, 51685
3603	membrane-spanning 4-domains, subfamily A, member 14	531787	3758	437222	11746	19734, 27722, 35710, 43698, 51686
3604	membrane-spanning 4-domains, subfamily A, member 15	337911	3759	338692	11747	19735, 27723, 35711, 43699, 51687
3605	membrane-spanning 4-domains, subfamily A, member 15	405633	3760	386022	11748	19736, 27724, 35712, 43700, 51688
3606	mesothelin-like	293892	3761	293892	11749	19737, 27725, 35713, 43701, 51689
3607	mesothelin-like	442466	3762	415767	11750	19738, 27726, 35714, 43702, 51690
3608	metaxin 2	249442	3763	249442	11751	19739, 27727, 35715, 43703, 51691
3609	metaxin 2	392529	3764	376314	11752	19740, 27728, 35716, 43704, 51692
3610	metaxin 3	328496	3765	331672	11753	19741, 27729, 35717, 43705, 51693
3611	metaxin 3	418095	3766	392181	11754	19742, 27730, 35718, 43706, 51694

3612	metaxin 3	509852	3767	423302	11755	19743, 27731, 35719, 43707, 51695
3613	metaxin 3	512528	3768	424798	11756	19744, 27732, 35720, 43708, 51696
3614	metaxin 3	512560	3769	423600	11757	19745, 27733, 35721, 43709, 51697
3615	methionyl aminopeptidase type 1D (mitochondrial)	315796	3770	315152	11758	19746, 27734, 35722, 43710, 51698
3616	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	264090	3771	264090	11759	19747, 27735, 35723, 43711, 51699
3617	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	394050	3772	377614	11760	19748, 27736, 35724, 43712, 51700
3618	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	394053	3773	377617	11761	19749, 27737, 35725, 43713, 51701
3619	methylsterol monooxygenase 1	261507	3774	261507	11762	19750, 27738, 35726, 43714, 51702
3620	methylsterol monooxygenase 1	393766	3775	377361	11763	19751, 27739, 35727, 43715, 51703
3621	methylsterol monooxygenase 1	505270	3776	425112	11764	19752, 27740, 35728, 43716, 51704
3622	methylsterol monooxygenase 1	507013	3777	425241	11765	19753, 27741, 35729, 43717, 51705
3623	methyltransferase like 12	532971	3778	431287	11766	19754, 27742, 35730, 43718, 51706
3624	methyltransferase like 21A	406927	3779	385481	11767	19755, 27743, 35731, 43719, 51707
3625	methyltransferase like 21A	411432	3780	415115	11768	19756, 27744, 35732, 43720, 51708

3626	methyltransferase like 21A	425132	3781	400730	11769	19757, 27745, 35733, 43721, 51709
3627	methyltransferase like 21A	426075	3782	403317	11770	19758, 27746, 35734, 43722, 51710
3628	methyltransferase like 21A	442521	3783	392062	11771	19759, 27747, 35735, 43723, 51711
3629	methyltransferase like 21A	448007	3784	407622	11772	19760, 27748, 35736, 43724, 51712
3630	methyltransferase like 21A	458426	3785	389684	11773	19761, 27749, 35737, 43725, 51713
3631	methyltransferase like 21B	300209	3786	300209	11774	19762, 27750, 35738, 43726, 51714
3632	methyltransferase like 21B	333012	3787	327425	11775	19763, 27751, 35739, 43727, 51715
3633	methyltransferase like 23	317409	3788	316862	11776	19764, 27752, 35740, 43728, 51716
3634	methyltransferase like 23	341249	3789	341543	11777	19765, 27753, 35741, 43729, 51717
3635	methyltransferase like 23	586752	3790	466203	11778	19766, 27754, 35742, 43730, 51718
3636	methyltransferase like 23	588822	3791	465430	11779	19767, 27755, 35743, 43731, 51719
3637	methyltransferase like 23	590964	3792	465890	11780	19768, 27756, 35744, 43732, 51720
3638	MICAL-like 2	297508	3793	297508	11781	19769, 27757, 35745, 43733, 51721
3639	MICAL-like 2	405088	3794	385928	11782	19770, 27758, 35746, 43734, 51722
3640	microfibrillar-associated protein 3-like	361618	3795	354583	11783	19771, 27759, 35747, 43735, 51723
3641	microfibrillar-associated protein 3-like	393704	3796	377307	11784	19772, 27760, 35748, 43736, 51724
3642	microfibrillar-associated protein 3-like	502832	3797	423722	11785	19773, 27761, 35749, 43737, 51725
3643	microfibrillar-associated protein 3-like	504999	3798	425303	11786	19774, 27762, 35750, 43738, 51726

3644	microfibrillar-associated protein 3-like	506764	3799	426247	11787	19775, 27763, 35751, 43739, 51727
3645	microfibrillar-associated protein 3-like	510306	3800	423549	11788	19776, 27764, 35752, 43740, 51728
3646	microfibrillar-associated protein 3-like	512698	3801	422791	11789	19777, 27765, 35753, 43741, 51729
3647	microtubule-associated protein 1 light chain 3 alpha	360668	3802	353886	11790	19778, 27766, 35754, 43742, 51730
3648	microtubule-associated protein 1 light chain 3 alpha	397709	3803	380821	11791	19779, 27767, 35755, 43743, 51731
3649	microtubule-associated protein 1 light chain 3 alpha	374837	3804	363970	11792	19780, 27768, 35756, 43744, 51732
3650	microtubule-associated protein 1 light chain 3 beta	268607	3805	268607	11793	19781, 27769, 35757, 43745, 51733
3651	microtubule-associated protein 1 light chain 3 beta	534986	3806	441125	11794	19782, 27770, 35758, 43746, 51734
3652	microtubule-associated protein 1 light chain 3 gamma	357246	3807	349785	11795	19783, 27771, 35759, 43747, 51735
3653	microtubule-associated protein 7	345567	3808	344217	11796	19784, 27772, 35760, 43748, 51736
3654	microtubule-associated protein 7	354570	3809	346581	11797	19785, 27773, 35761, 43749, 51737
3655	microtubule-associated protein 7	432797	3810	414879	11798	19786, 27774, 35762, 43750, 51738
3656	microtubule-associated protein 7	438100	3811	400790	11799	19787, 27775, 35763, 43751, 51739
3657	microtubule-associated protein 7	454590	3812	414712	11800	19788, 27776, 35764, 43752, 51740
3658	microtubule-associated protein 7	544465	3813	445737	11801	19789, 27777, 35765, 43753, 51741
3659	mindbomb homolog 1 (Drosophila)	261537	3814	261537	11802	19790, 27778, 35766, 43754, 51742
3660	MIT, microtubule interacting and transport, domain containing 1	289359	3815	289359	11803	19791, 27779, 35767, 43755, 51743
3661	MIT, microtubule interacting and transport, domain	422537	3816	413371	11804	19792, 27780, 35768, 43756, 51744

	containing 1					
3662	mitochondrial calcium uptake 1	361114	3817	354415	11805	19793, 27781, 35769, 43757, 51745
3663	mitochondrial calcium uptake 1	398761	3818	381745	11806	19794, 27782, 35770, 43758, 51746
3664	mitochondrial calcium uptake 1	398763	3819	381747	11807	19795, 27783, 35771, 43759, 51747
3665	mitochondrial calcium uptake 1	401998	3820	384068	11808	19796, 27784, 35772, 43760, 51748
3666	mitochondrial calcium uptake 1	418483	3821	402470	11809	19797, 27785, 35773, 43761, 51749
3667	mitochondrial carrier 1	337855	3822	338712	11810	19798, 27786, 35774, 43762, 51750
3668	mitochondrial carrier 1	373550	3823	362651	11811	19799, 27787, 35775, 43763, 51751
3669	mitochondrial carrier 1	373565	3824	362666	11812	19800, 27788, 35776, 43764, 51752
3670	mitochondrial carrier 1	373616	3825	362718	11813	19801, 27789, 35777, 43765, 51753
3671	mitochondrial carrier 1	373627	3826	362730	11814	19802, 27790, 35778, 43766, 51754
3672	mitochondrial carrier 1	418541	3827	399187	11815	19803, 27791, 35779, 43767, 51755
3673	mitochondrial carrier 1	460219	3828	419739	11816	19804, 27792, 35780, 43768, 51756
3674	mitochondrial carrier 1	538808	3829	437660	11817	19805, 27793, 35781, 43769, 51757
3675	mitochondrial carrier triple repeat 1	242275	3830	242275	11818	19806, 27794, 35782, 43770, 51758
3676	mitochondrial carrier triple repeat 1	377716	3831	366945	11819	19807, 27795, 35783, 43771, 51759
3677	mitochondrial carrier triple repeat 1	380590	3832	369964	11820	19808, 27796, 35784, 43772, 51760
3678	mitochondrial carrier triple repeat 2	269205	3833	372612	11821	19809, 27797, 35785, 43773, 51761

3679	mitochondrial carrier triple repeat 2	535708	3834	443889	11822	19810, 27798, 35786, 43774, 51762
3680	mitochondrial carrier triple repeat 6	357421	3835	361681	11823	19811, 27799, 35787, 43775, 51763
3681	mitochondrial fission factor	304593	3836	304898	11824	19812, 27800, 35788, 43776, 51764
3682	mitochondrial fission factor	337110	3837	338412	11825	19813, 27801, 35789, 43777, 51765
3683	mitochondrial fission factor	349901	3838	304134	11826	19814, 27802, 35790, 43778, 51766
3684	mitochondrial fission factor	353339	3839	302037	11827	19815, 27803, 35791, 43779, 51767
3685	mitochondrial fission factor	354503	3840	346498	11828	19816, 27804, 35792, 43780, 51768
3686	mitochondrial fission factor	392059	3841	375912	11829	19817, 27805, 35793, 43781, 51769
3687	mitochondrial fission factor	409565	3842	386964	11830	19818, 27806, 35794, 43782, 51770
3688	mitochondrial fission factor	409616	3843	386641	11831	19819, 27807, 35795, 43783, 51771
3689	mitochondrial fission factor	418961	3844	407547	11832	19820, 27808, 35796, 43784, 51772
3690	mitochondrial fission factor	423098	3845	390165	11833	19821, 27809, 35797, 43785, 51773
3691	mitochondrial fission factor	436237	3846	411386	11834	19822, 27810, 35798, 43786, 51774
3692	mitochondrial fission factor	443428	3847	391829	11835	19823, 27811, 35799, 43787, 51775
3693	mitochondrial fission factor	452930	3848	415996	11836	19824, 27812, 35800, 43788, 51776
3694	mitochondrial fission factor	525195	3849	436920	11837	19825, 27813, 35801, 43789, 51777
3695	mitochondrial fission process 1	266263	3850	266263	11838	19826, 27814, 35802, 43790, 51778
3696	mitochondrial fission process 1	355143	3851	347267	11839	19827, 27815, 35803, 43791, 51779

3697	mitochondrial fission regulator 1	262146	3852	262146	11840	19828, 27816, 35804, 43792, 51780
3698	mitochondrial fission regulator 1	458689	3853	391502	11841	19829, 27817, 35805, 43793, 51781
3699	Mitochondrial GTPase 1	317502	3854	323047	11842	19830, 27818, 35806, 43794, 51782
3700	Mitochondrial GTPase 1	432508	3855	393480	11843	19831, 27819, 35807, 43795, 51783
3701	Mitochondrial GTPase 1	537620	3856	438503	11844	19832, 27820, 35808, 43796, 51784
3702	mitochondrial inner membrane organizing system 1	322753	3857	325562	11845	19833, 27821, 35809, 43797, 51785
3703	Mitochondrial ribonuclease P protein 3	250377	3858	250377	11846	19834, 27822, 35810, 43798, 51786
3704	Mitochondrial ribonuclease P protein 3	321130	3859	324697	11847	19835, 27823, 35811, 43799, 51787
3705	Mitochondrial ribonuclease P protein 3	534898	3860	440915	11848	19836, 27824, 35812, 43800, 51788
3706	Mitochondrial ribonuclease P protein 3	553978	3861	451940	11849	19837, 27825, 35813, 43801, 51789
3707	Mitochondrial ribonuclease P protein 3	554727	3862	452604	11850	19838, 27826, 35814, 43802, 51790
3708	Mitochondrial ribonuclease P protein 3	554896	3863	450779	11851	19839, 27827, 35815, 43803, 51791
3709	Mitochondrial ribonuclease P protein 3	556115	3864	452471	11852	19840, 27828, 35816, 43804, 51792
3710	Mitochondrial ribonuclease P protein 3	556121	3865	452094	11853	19841, 27829, 35817, 43805, 51793
3711	mitochondrial ribonuclease P protein 3 isoform 2	556912	3866	451707	11854	19842, 27830, 35818, 43806, 51794
3712	mitochondrial ribosome recycling factor	297908	3867	297908	11855	19843, 27831, 35819, 43807, 51795
3713	mitochondrial ribosome recycling factor	344641	3868	343867	11856	19844, 27832, 35820, 43808, 51796
3714	mitochondrial ribosome recycling factor	373723	3869	362828	11857	19845, 27833, 35821, 43809, 51797

3715	mitochondrial ribosome recycling factor	373724	3870	362829	11858	19846, 27834, 35822, 43810, 51798
3716	mitochondrial ribosome recycling factor	373727	3871	362832	11859	19847, 27835, 35823, 43811, 51799
3717	mitochondrial ribosome recycling factor	373728	3872	362833	11860	19848, 27836, 35824, 43812, 51800
3718	mitochondrial ribosome recycling factor	373729	3873	362834	11861	19849, 27837, 35825, 43813, 51801
3719	mitochondrial ribosome recycling factor	373730	3874	362835	11862	19850, 27838, 35826, 43814, 51802
3720	mitochondrial ribosome recycling factor	394315	3875	377850	11863	19851, 27839, 35827, 43815, 51803
3721	mitochondrial ribosome recycling factor	441707	3876	395072	11864	19852, 27840, 35828, 43816, 51804
3722	mitochondrial ribosome recycling factor	546115	3877	445588	11865	19853, 27841, 35829, 43817, 51805
3723	mitochondrial rRNA methyltransferase 1 homolog (S. cerevisiae)	250156	3878	250156	11866	19854, 27842, 35830, 43818, 51806
3724	mitochondrial translational initiation factor 3	381116	3879	370508	11867	19855, 27843, 35831, 43819, 51807
3725	mitochondrial translational initiation factor 3	381120	3880	370512	11868	19856, 27844, 35832, 43820, 51808
3726	mitochondrial translational initiation factor 3	405591	3881	384659	11869	19857, 27845, 35833, 43821, 51809
3727	mitochondrial translational initiation factor 3	431572	3882	400084	11870	19858, 27846, 35834, 43822, 51810
3728	mitochondrially encoded ATP synthase 6	361899	3883	354632	11871	19859, 27847, 35835, 43823, 51811
3729	mitochondrially encoded cytochrome b	361789	3884	354554	11872	19860, 27848, 35836, 43824, 51812
3730	mitochondrially encoded cytochrome c oxidase I	361624	3885	354499	11873	19861, 27849, 35837, 43825, 51813
3731	mitochondrially encoded cytochrome c oxidase II	361739	3886	354876	11874	19862, 27850, 35838, 43826, 51814
3732	mitochondrially encoded cytochrome c oxidase III	362079	3887	354982	11875	19863, 27851, 35839, 43827, 51815

3733	mitochondrially encoded NADH dehydrogenase 1	361390	3888	354687	11876	19864, 27852, 35840, 43828, 51816
3734	mitochondrially encoded NADH dehydrogenase 2	361453	3889	355046	11877	19865, 27853, 35841, 43829, 51817
3735	mitochondrially encoded NADH dehydrogenase 3	361227	3890	355206	11878	19866, 27854, 35842, 43830, 51818
3736	mitochondrially encoded NADH dehydrogenase 4	361381	3891	354961	11879	19867, 27855, 35843, 43831, 51819
3737	mitochondrially encoded NADH dehydrogenase 4L	361335	3892	354728	11880	19868, 27856, 35844, 43832, 51820
3738	mitochondrially encoded NADH dehydrogenase 5	361567	3893	354813	11881	19869, 27857, 35845, 43833, 51821
3739	mitochondrially encoded NADH dehydrogenase 6	361681	3894	354665	11882	19870, 27858, 35846, 43834, 51822
3740	mitofusin 1	263969	3895	263969	11883	19871, 27859, 35847, 43835, 51823
3741	mitofusin 1	280653	3896	280653	11884	19872, 27860, 35848, 43836, 51824
3742	mitofusin 1	467174	3897	419134	11885	19873, 27861, 35849, 43837, 51825
3743	mitofusin 1	471841	3898	420617	11886	19874, 27862, 35850, 43838, 51826
3744	mitofusin 1	539169	3899	445566	11887	19875, 27863, 35851, 43839, 51827
3745	mitogen-activated protein kinase 8 interacting protein 3	250894	3900	250894	11888	19876, 27864, 35852, 43840, 51828
3746	mitogen-activated protein kinase 8 interacting protein 3	356010	3901	348290	11889	19877, 27865, 35853, 43841, 51829
3747	mitogen-activated protein kinase associated protein 1	265960	3902	265960	11890	19878, 27866, 35854, 43842, 51830
3748	mitogen-activated protein kinase associated protein 1	350766	3903	265961	11891	19879, 27867, 35855, 43843, 51831
3749	mitogen-activated protein kinase associated protein 1	373496	3904	362595	11892	19880, 27868, 35856, 43844, 51832
3750	mitogen-activated protein kinase associated protein 1	373497	3905	362596	11893	19881, 27869, 35857, 43845, 51833

3751	mitogen-activated protein kinase associated protein 1	373498	3906	362597	11894	19882, 27870, 35858, 43846, 51834
3752	mitogen-activated protein kinase associated protein 1	373503	3907	362602	11895	19883, 27871, 35859, 43847, 51835
3753	mitogen-activated protein kinase associated protein 1	373505	3908	362604	11896	19884, 27872, 35860, 43848, 51836
3754	mitogen-activated protein kinase associated protein 1	373511	3909	362610	11897	19885, 27873, 35861, 43849, 51837
3755	mitogen-activated protein kinase associated protein 1	394063	3910	377627	11898	19886, 27874, 35862, 43850, 51838
3756	mitogen-activated protein kinase associated protein 1	433483	3911	390024	11899	19887, 27875, 35863, 43851, 51839
3757	mitogen-activated protein kinase associated protein 1	444226	3912	412485	11900	19888, 27876, 35864, 43852, 51840
3758	mitogen-activated protein kinase associated protein 1	394060	3913	377624	11901	19889, 27877, 35865, 43853, 51841
3759	monoacylglycerol O-acyltransferase 1	446656	3914	406674	11902	19890, 27878, 35866, 43854, 51842
3760	monoacylglycerol O-acyltransferase 2	198801	3915	198801	11903	19891, 27879, 35867, 43855, 51843
3761	monoacylglycerol O-acyltransferase 2	526712	3916	436283	11904	19892, 27880, 35868, 43856, 51844
3762	monoacylglycerol O-acyltransferase 3	223114	3917	223114	11905	19893, 27881, 35869, 43857, 51845
3763	monoacylglycerol O-acyltransferase 3	379423	3918	368734	11906	19894, 27882, 35870, 43858, 51846
3764	monoacylglycerol O-acyltransferase 3	440203	3919	403756	11907	19895, 27883, 35871, 43859, 51847
3765	motile sperm domain containing 1	370777	3920	359813	11908	19896, 27884, 35872, 43860, 51848
3766	motile sperm domain containing 1	370779	3921	359815	11909	19897, 27885, 35873, 43861, 51849
3767	motile sperm domain containing 1	370783	3922	359819	11910	19898, 27886, 35874, 43862, 51850
3768	motile sperm domain containing 2	380492	3923	369860	11911	19899, 27887, 35875, 43863, 51851

3769	motile sperm domain containing 3	223054	3924	223054	11912	19900, 27888, 35876, 43864, 51852
3770	motile sperm domain containing 3	379527	3925	368842	11913	19901, 27889, 35877, 43865, 51853
3771	motile sperm domain containing 3	393950	3926	377522	11914	19902, 27890, 35878, 43866, 51854
3772	motile sperm domain containing 3	393953	3927	377525	11915	19903, 27891, 35879, 43867, 51855
3773	motile sperm domain containing 3	424091	3928	404626	11916	19904, 27892, 35880, 43868, 51856
3774	MPV17 mitochondrial membrane protein-like	287594	3929	287594	11917	19905, 27893, 35881, 43869, 51857
3775	MPV17 mitochondrial membrane protein-like	396385	3930	379669	11918	19906, 27894, 35882, 43870, 51858
3776	MPV17 mitochondrial membrane protein-like 2	247712	3931	247712	11919	19907, 27895, 35883, 43871, 51859
3777	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	274747	3932	274747	11920	19908, 27896, 35884, 43872, 51860
3778	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	378353	3933	367604	11921	19909, 27897, 35885, 43873, 51861
3779	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	378386	3934	367637	11922	19910, 27898, 35886, 43874, 51862
3780	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	443868	3935	399585	11923	19911, 27899, 35887, 43875, 51863
3781	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	446191	3936	387441	11924	19912, 27900, 35888, 43876, 51864
3782	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	535061	3937	441839	11925	19913, 27901, 35889, 43877, 51865
3783	MRS2 magnesium homeostasis factor homolog (S. cerevisiae)	543597	3938	438118	11926	19914, 27902, 35890, 43878, 51866

3784	MTERF domain containing 1	287025	3939	287025	11927	19915, 27903, 35891, 43879, 51867
3785	MTERF domain containing 3	240050	3940	240050	11928	19916, 27904, 35892, 43880, 51868
3786	MTERF domain containing 3	392830	3941	376575	11929	19917, 27905, 35893, 43881, 51869
3787	MTERF domain containing 3	548101	3942	448343	11930	19918, 27906, 35894, 43882, 51870
3788	MTERF domain containing 3	550496	3943	448246	11931	19919, 27907, 35895, 43883, 51871
3789	MTERF domain containing 3	550736	3944	448854	11932	19920, 27908, 35896, 43884, 51872
3790	MTERF domain containing 3	552029	3945	447651	11933	19921, 27909, 35897, 43885, 51873
3791	mucin 21, cell surface associated	376296	3946	365473	11934	19922, 27910, 35898, 43886, 51874
3792	mucin 21, cell surface associated	450707	3947	402251	11935	19923, 27911, 35899, 43887, 51875
3793	mucosal vascular addressin cell adhesion molecule 1	215637	3948	215637	11936	19924, 27912, 35900, 43888, 51876
3794	mucosal vascular addressin cell adhesion molecule 1	346144	3949	304247	11937	19925, 27913, 35901, 43889, 51877
3795	mucosal vascular addressin cell adhesion molecule 1	382683	3950	372130	11938	19926, 27914, 35902, 43890, 51878
3796	mucosal vascular addressin cell adhesion molecule 1	537731	3951	444768	11939	19927, 27915, 35903, 43891, 51879
3797	mucosal vascular addressin cell adhesion molecule 1	542525	3952	438655	11940	19928, 27916, 35904, 43892, 51880
3798	mucosal vascular addressin cell adhesion molecule 1	543297	3953	443089	11941	19929, 27917, 35905, 43893, 51881
3799	multiple C2 domains transmembrane 2	557742	3954	454847	11942	19930, 27918, 35906, 43894, 51882
3800	multiple C2 domains, transmembrane 1	312216	3955	308957	11943	19931, 27919, 35907, 43895, 51883
3801	multiple C2 domains, transmembrane 1	415885	3956	405735	11944	19932, 27920, 35908, 43896, 51884

3802	multiple C2 domains, transmembrane 1	429576	3957	391639	11945	19933, 27921, 35909, 43897, 51885
3803	multiple C2 domains, transmembrane 1	505078	3958	426417	11946	19934, 27922, 35910, 43898, 51886
3804	multiple C2 domains, transmembrane 1	505208	3959	426438	11947	19935, 27923, 35911, 43899, 51887
3805	multiple C2 domains, transmembrane 1	505465	3960	422317	11948	19936, 27924, 35912, 43900, 51888
3806	multiple C2 domains, transmembrane 1	515393	3961	424126	11949	19937, 27925, 35913, 43901, 51889
3807	multiple C2 domains, transmembrane 2	331706	3962	329646	11950	19938, 27926, 35914, 43902, 51890
3808	multiple C2 domains, transmembrane 2	357742	3963	350377	11951	19939, 27927, 35915, 43903, 51891
3809	multiple C2 domains, transmembrane 2	451018	3964	395109	11952	19940, 27928, 35916, 43904, 51892
3810	multiple C2 domains, transmembrane 2	543482	3965	438521	11953	19941, 27929, 35917, 43905, 51893
3811	murine retrovirus integration site 1 homolog	308763	3966	307885	11954	19942, 27930, 35918, 43906, 51894
3812	murine retrovirus integration site 1 homolog	421747	3967	414598	11955	19943, 27931, 35919, 43907, 51895
3813	murine retrovirus integration site 1 homolog	424001	3968	401205	11956	19944, 27932, 35920, 43908, 51896
3814	murine retrovirus integration site 1 homolog	436272	3969	412229	11957	19945, 27933, 35921, 43909, 51897
3815	murine retrovirus integration site 1 homolog	527509	3970	432067	11958	19946, 27934, 35922, 43910, 51898
3816	murine retrovirus integration site 1 homolog	545852	3971	441971	11959	19947, 27935, 35923, 43911, 51899
3817	murine retrovirus integration site 1 homolog	547195	3972	448278	11960	19948, 27936, 35924, 43912, 51900
3818	murine retrovirus integration site 1 homolog	552103	3973	446764	11961	19949, 27937, 35925, 43913, 51901
3819	murine retrovirus integration site 1 homolog	558540	3974	453013	11962	19950, 27938, 35926, 43914, 51902

3820	murine retrovirus integration site 1 homolog	423302	3975	412130	11963	19951, 27939, 35927, 43915, 51903
3821	murine retrovirus integration site 1 homolog	531107	3976	432436	11964	19952, 27940, 35928, 43916, 51904
3822	murine retrovirus integration site 1 homolog	541483	3977	437784	11965	19953, 27941, 35929, 43917, 51905
3823	myelin expression factor 2	267836	3978	267836	11966	19954, 27942, 35930, 43918, 51906
3824	myelin expression factor 2	324324	3979	316950	11967	19955, 27943, 35931, 43919, 51907
3825	myelin expression factor 2	454655	3980	406195	11968	19956, 27944, 35932, 43920, 51908
3826	myelin expression factor 2	560172	3981	452918	11969	19957, 27945, 35933, 43921, 51909
3827	myelin protein zero-like 1	359523	3982	352513	11970	19958, 27946, 35934, 43922, 51910
3828	myelin protein zero-like 1	474859	3983	420455	11971	19959, 27947, 35935, 43923, 51911
3829	myelin protein zero-like 1	392121	3984	375968	11972	19960, 27948, 35936, 43924, 51912
3830	myoferlin	358334	3985	351094	11973	19961, 27949, 35937, 43925, 51913
3831	myoferlin	359263	3986	352208	11974	19962, 27950, 35938, 43926, 51914
3832	myoferlin	371488	3987	360543	11975	19963, 27951, 35939, 43927, 51915
3833	myoferlin	371489	3988	360544	11976	19964, 27952, 35940, 43928, 51916
3834	myoferlin	371501	3989	360556	11977	19965, 27953, 35941, 43929, 51917
3835	myoferlin	371502	3990	360557	11978	19966, 27954, 35942, 43930, 51918
3836	myo-inositol oxygenase	216075	3991	216075	11979	19967, 27955, 35943, 43931, 51919
3837	myo-inositol oxygenase	395732	3992	379081	11980	19968, 27956, 35944, 43932, 51920

3838	myo-inositol oxygenase	395733	3993	379082	11981	19969, 27957, 35945, 43933, 51921
3839	myo-inositol oxygenase	451761	3994	409894	11982	19970, 27958, 35946, 43934, 51922
3840	myosin XVI	251041	3995	251041	11983	19971, 27959, 35947, 43935, 51923
3841	myosin XVI	356711	3996	349145	11984	19972, 27960, 35948, 43936, 51924
3842	myosin XVI	357550	3997	350160	11985	19973, 27961, 35949, 43937, 51925
3843	myosin XVI	375857	3998	365017	11986	19974, 27962, 35950, 43938, 51926
3844	myosin XVI	397258	3999	380429	11987	19975, 27963, 35951, 43939, 51927
3845	myosin XVI	457511	4000	401633	11988	19976, 27964, 35952, 43940, 51928
3846	myosin, light chain 10, regulatory	223167	4001	223167	11989	19977, 27965, 35953, 43941, 51929
3847	myristoylated alanine-rich protein kinase C substrate	368635	4002	357624	11990	19978, 27966, 35954, 43942, 51930
3848	N(alpha)-acetyltransferase 30, NatC catalytic subunit	395257	4003	378676	11991	19979, 27967, 35955, 43943, 51931
3849	N(alpha)-acetyltransferase 30, NatC catalytic subunit	556492	4004	452521	11992	19980, 27968, 35956, 43944, 51932
3850	N(alpha)-acetyltransferase 35, NatC auxiliary subunit	361671	4005	354972	11993	19981, 27969, 35957, 43945, 51933
3851	N(alpha)-acetyltransferase 35, NatC auxiliary subunit	376040	4006	365208	11994	19982, 27970, 35958, 43946, 51934
3852	N(alpha)-acetyltransferase 35, NatC auxiliary subunit	416045	4007	399595	11995	19983, 27971, 35959, 43947, 51935
3853	N-acetyltransferase 14 (GCN5-related, putative)	205194	4008	205194	11996	19984, 27972, 35960, 43948, 51936

3854	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	329428	4009	329886	11997	19985, 27973, 35961, 43949, 51937
3855	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	374028	4010	363140	11998	19986, 27974, 35962, 43950, 51938
3856	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	395526	4011	378897	11999	19987, 27975, 35963, 43951, 51939
3857	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	443575	4012	392766	12000	19988, 27976, 35964, 43952, 51940
3858	N-acylsphingosine amidohydrolase (non-lysosomal ceramidase) 2	447815	4013	388206	12001	19989, 27977, 35965, 43953, 51941
3859	NAD kinase domain containing 1	282512	4014	282512	12002	19990, 27978, 35966, 43954, 51942
3860	NAD kinase domain containing 1	381937	4015	371362	12003	19991, 27979, 35967, 43955, 51943
3861	NAD kinase domain containing 1	397338	4016	380499	12004	19992, 27980, 35968, 43956, 51944
3862	NAD kinase domain containing 1	506945	4017	422250	12005	19993, 27981, 35969, 43957, 51945
3863	NAD kinase domain containing 1	514504	4018	421029	12006	19994, 27982, 35970, 43958, 51946
3864	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 12	547986	4019	450130	12007	19995, 27983, 35971, 43959, 51947
3865	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 12	327772	4020	330737	12008	19996, 27984, 35972, 43960, 51948
3866	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	417328	4021	410363	12009	19997, 27985, 35973, 43961, 51949
3867	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	419113	4022	398290	12010	19998, 27986, 35974, 43962, 51950

3868	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 3, 9kDa	485876	4023	418438	12011	19999, 27987, 35975, 43963, 51951
3869	NADH dehydrogenase (ubiquinone) 1 alpha subcomplex, 4, 9kDa	339600	4024	339720	12012	20000, 27988, 35976, 43964, 51952
3870	NADH dehydrogenase (ubiquinone) 1 beta subcomplex 5 16kDa	471112	4025	419501	12013	20001, 27989, 35977, 43965, 51953
3871	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa	329559	4026	330787	12014	20002, 27990, 35978, 43966, 51954
3872	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa	553377	4027	451293	12015	20003, 27991, 35979, 43967, 51955
3873	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 1, 7kDa	555441	4028	450776	12016	20004, 27992, 35980, 43968, 51956
3874	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	204307	4029	204307	12017	20005, 27993, 35981, 43969, 51957
3875	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	247866	4030	247866	12018	20006, 27994, 35982, 43970, 51958
3876	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	464566	4031	419479	12019	20007, 27995, 35983, 43971, 51959
3877	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	465506	4032	419357	12020	20008, 27996, 35984, 43972, 51960
3878	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2, 8kDa	476279	4033	419087	12021	20009, 27997, 35985, 43973, 51961

3879	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	184266	4034	184266	12022	20010, 27998, 35986, 43974, 51962
3880	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 4, 15kDa	485064	4035	419578	12023	20011, 27999, 35987, 43975, 51963
3881	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	259037	4036	259037	12024	20012, 28000, 35988, 43976, 51964
3882	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 5, 16kDa	493866	4037	419656	12025	20013, 28001, 35989, 43977, 51965
3883	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 6, 17kDa	350021	4038	297983	12026	20014, 28002, 35990, 43978, 51966
3884	NADH dehydrogenase (ubiquinone) 1 subcomplex unknown 2 14.5kDa	525085	4039	434262	12027	20015, 28003, 35991, 43979, 51967
3885	NADH dehydrogenase (ubiquinone) 1 subcomplex unknown 2 14.5kDa	527806	4040	432739	12028	20016, 28004, 35992, 43980, 51968
3886	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa	281031	4041	281031	12029	20017, 28005, 35993, 43981, 51969
3887	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 2, 14.5kDa	324742	4042	316370	12030	20018, 28006, 35994, 43982, 51970
3888	NADH dehydrogenase (ubiquinone) complex I assembly factor 7	336237	4043	337431	12031	20019, 28007, 35995, 43983, 51971
3889	NADPH oxidase activator 1	341349	4044	342848	12032	20020, 28008, 35996, 43984, 51972

3890	NADPH oxidase activator 1	392815	4045	376562	12033	20021, 28009, 35997, 43985, 51973
3891	NADPH oxidase organizer 1	354249	4046	346195	12034	20022, 28010, 35998, 43986, 51974
3892	NADPH oxidase organizer 1	356120	4047	348435	12035	20023, 28011, 35999, 43987, 51975
3893	NADPH oxidase organizer 1	397280	4048	380450	12036	20024, 28012, 36000, 43988, 51976
3894	naked cuticle homolog 1 (Drosophila)	268459	4049	268459	12037	20025, 28013, 36001, 43989, 51977
3895	naked cuticle homolog 2 (Drosophila)	296849	4050	296849	12038	20026, 28014, 36002, 43990, 51978
3896	naked cuticle homolog 2 (Drosophila)	382730	4051	372177	12039	20027, 28015, 36003, 43991, 51979
3897	naked cuticle homolog 2 (Drosophila)	537972	4052	440925	12040	20028, 28016, 36004, 43992, 51980
3898	naked cuticle homolog 2 (Drosophila)	274150	4053	274150	12041	20029, 28017, 36005, 43993, 51981
3899	natural killer cell group 7 sequence	221978	4054	221978	12042	20030, 28018, 36006, 43994, 51982
3900	NCK adaptor protein 1	288986	4055	288986	12043	20031, 28019, 36007, 43995, 51983
3901	NCK adaptor protein 1	476286	4056	418513	12044	20032, 28020, 36008, 43996, 51984
3902	NCK adaptor protein 1	481752	4057	417273	12045	20033, 28021, 36009, 43997, 51985
3903	NCK adaptor protein 1	485096	4058	419677	12046	20034, 28022, 36010, 43998, 51986
3904	NCK adaptor protein 1	491539	4059	419302	12047	20035, 28023, 36011, 43999, 51987
3905	NCK adaptor protein 1	469404	4060	419631	12048	20036, 28024, 36012, 44000, 51988
3906	NCK-associated protein 1-like	293373	4061	293373	12049	20037, 28025, 36013, 44001, 51989
3907	NCK-associated protein 1-like	545638	4062	445596	12050	20038, 28026, 36014, 44002, 51990

3908	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 3	296499	4063	296499	12051	20039, 28027, 36015, 44003, 51991
3909	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 3	433996	4064	396625	12052	20040, 28028, 36016, 44004, 51992
3910	N-deacetylase/N-sulfotransferase (heparan glucosaminyl) 4	264363	4065	264363	12053	20041, 28029, 36017, 44005, 51993
3911	NEDD4 binding protein 3	274605	4066	274605	12054	20042, 28030, 36018, 44006, 51994
3912	N-ethylmaleimide-sensitive factor attachment protein, gamma	322897	4067	324628	12055	20043, 28031, 36019, 44007, 51995
3913	N-ethylmaleimide-sensitive factor attachment protein, gamma	542979	4068	442849	12056	20044, 28032, 36020, 44008, 51996
3914	netrin G2	360670	4069	353888	12057	20045, 28033, 36021, 44009, 51997
3915	netrin G2	372179	4070	361252	12058	20046, 28034, 36022, 44010, 51998
3916	netrin G2	393228	4071	376920	12059	20047, 28035, 36023, 44011, 51999
3917	netrin G2	393229	4072	376921	12060	20048, 28036, 36024, 44012, 52000
3918	neuralized homolog 2 (Drosophila)	372518	4073	361596	12061	20049, 28037, 36025, 44013, 52001
3919	neurensin 1	378475	4074	367736	12062	20050, 28038, 36026, 44014, 52002
3920	neurensin 1	378477	4075	367738	12063	20051, 28039, 36027, 44015, 52003
3921	neurensin 1	378478	4076	367739	12064	20052, 28040, 36028, 44016, 52004
3922	neurensin 1	378491	4077	367752	12065	20053, 28041, 36029, 44017, 52005
3923	neuritin 1-like	339176	4078	342411	12066	20054, 28042, 36030, 44018, 52006

3924	neuroligin 4, X-linked	275857	4079	275857	12067	20055, 28043, 36031, 44019, 52007
3925	neuroligin 4, X-linked	381092	4080	370482	12068	20056, 28044, 36032, 44020, 52008
3926	neuroligin 4, X-linked	381093	4081	370483	12069	20057, 28045, 36033, 44021, 52009
3927	neuroligin 4, X-linked	381095	4082	370485	12070	20058, 28046, 36034, 44022, 52010
3928	neuroligin 4, X-linked	538097	4083	439203	12071	20059, 28047, 36035, 44023, 52011
3929	Neuron-specific protein family member 1	397958	4084	381049	12072	20060, 28048, 36036, 44024, 52012
3930	Neuron-specific protein family member 1	421177	4085	388823	12073	20061, 28049, 36037, 44025, 52013
3931	Neuron-specific protein family member 1	433139	4086	408833	12074	20062, 28050, 36038, 44026, 52014
3932	Neuron-specific protein family member 1	504171	4087	425803	12075	20063, 28051, 36039, 44027, 52015
3933	Neuron-specific protein family member 1	505246	4088	421841	12076	20064, 28052, 36040, 44028, 52016
3934	Neuron-specific protein family member 1	506380	4089	425423	12077	20065, 28053, 36041, 44029, 52017
3935	Neuron-specific protein family member 1	513555	4090	426358	12078	20066, 28054, 36042, 44030, 52018
3936	Neuron-specific protein family member 1	513829	4091	425345	12079	20067, 28055, 36043, 44031, 52019
3937	Neuron-specific protein family member 2	303177	4092	307722	12080	20068, 28056, 36044, 44032, 52020
3938	Neuron-specific protein family member 2	519717	4093	431119	12081	20069, 28057, 36045, 44033, 52021
3939	Neuron-specific protein family member 2	519867	4094	429689	12082	20070, 28058, 36046, 44034, 52022
3940	Neuron-specific protein family member 2	521278	4095	430208	12083	20071, 28059, 36047, 44035, 52023
3941	neuropeptide FF receptor 1	277942	4096	277942	12084	20072, 28060, 36048, 44036, 52024

3942	neuropeptide FF receptor 1	449957	4097	401171	12085	20073, 28061, 36049, 44037, 52025
3943	neuropeptide FF receptor 2	308744	4098	307822	12086	20074, 28062, 36050, 44038, 52026
3944	neuropeptide FF receptor 2	344413	4099	340789	12087	20075, 28063, 36051, 44039, 52027
3945	neuropeptide FF receptor 2	358749	4100	351599	12088	20076, 28064, 36052, 44040, 52028
3946	neuropeptide FF receptor 2	395999	4101	379321	12089	20077, 28065, 36053, 44041, 52029
3947	neuropeptides B/W receptor 2	369768	4102	358783	12090	20078, 28066, 36054, 44042, 52030
3948	neuropilin (NRP) and tolloid (TLL)-like 2	303155	4103	306726	12091	20079, 28067, 36055, 44043, 52031
3949	neuropilin (NRP) and tolloid (TLL)-like 2	562435	4104	455169	12092	20080, 28068, 36056, 44044, 52032
3950	neurotensin receptor 2	306928	4105	303686	12093	20081, 28069, 36057, 44045, 52033
3951	nicalin	246117	4106	246117	12094	20082, 28070, 36058, 44046, 52034
3952	NIPA-like domain containing 1	295461	4107	295461	12095	20083, 28071, 36059, 44047, 52035
3953	NIPA-like domain containing 2	341166	4108	339256	12096	20084, 28072, 36060, 44048, 52036
3954	NIPA-like domain containing 3	3912	4109	3912	12097	20085, 28073, 36061, 44049, 52037, 56088, 56121
3955	NIPA-like domain containing 3	339255	4110	343549	12098	20086, 28074, 36062, 44050, 52038
3956	NIPA-like domain containing 3	358028	4111	350722	12099	20087, 28075, 36063, 44051, 52039
3957	NIPA-like domain containing 3	374399	4112	363520	12100	20088, 28076, 36064, 44052, 52040
3958	NIPA-like domain containing 3	428131	4113	406509	12101	20089, 28077, 36065, 44053, 52041
3959	NIPA-like domain containing 3	432012	4114	392170	12102	20090, 28078, 36066, 44054, 52042

3960	nischarin	345716	4115	339958	12103	20091, 28079, 36067, 44055, 52043
3961	nischarin	414197	4116	410462	12104	20092, 28080, 36068, 44056, 52044
3962	nischarin	433196	4117	398513	12105	20093, 28081, 36069, 44057, 52045
3963	nischarin	479054	4118	418232	12106	20094, 28082, 36070, 44058, 52046
3964	nischarin	488380	4119	417812	12107	20095, 28083, 36071, 44059, 52047
3965	nitric oxide associated 1	264230	4120	264230	12108	20096, 28084, 36072, 44060, 52048
3966	NODAL modulator 1	287667	4121	287667	12109	20097, 28085, 36073, 44061, 52049
3967	NODAL modulator 1	456867	4122	405450	12110	20098, 28086, 36074, 44062, 52050
3968	NODAL modulator 1	536948	4123	441154	12111	20099, 28087, 36075, 44063, 52051
3969	NODAL modulator 2	330537	4124	331851	12112	20100, 28088, 36076, 44064, 52052
3970	NODAL modulator 2	381474	4125	370883	12113	20101, 28089, 36077, 44065, 52053
3971	NODAL modulator 2	543392	4126	439970	12114	20102, 28090, 36078, 44066, 52054
3972	NODAL modulator 3	263012	4127	263012	12115	20103, 28091, 36079, 44067, 52055
3973	NODAL modulator 3	399336	4128	382274	12116	20104, 28092, 36080, 44068, 52056
3974	NODAL modulator 3	538468	4129	443768	12117	20105, 28093, 36081, 44069, 52057
3975	non-SMC condensin I complex, subunit D2	315579	4130	325017	12118	20106, 28094, 36082, 44070, 52058
3976	non-SMC condensin I complex, subunit D2	535602	4131	445103	12119	20107, 28095, 36083, 44071, 52059
3977	non-SMC condensin I complex, subunit D2	545962	4132	444417	12120	20108, 28096, 36084, 44072, 52060

3978	NSFL1 (p97) cofactor (p47)	216879	4133	216879	12121	20109, 28097, 36085, 44073, 52061
3979	NSFL1 (p97) cofactor (p47)	350991	4134	202584	12122	20110, 28098, 36086, 44074, 52062
3980	NSFL1 (p97) cofactor (p47)	353088	4135	338643	12123	20111, 28099, 36087, 44075, 52063
3981	NSFL1 (p97) cofactor (p47)	381658	4136	371074	12124	20112, 28100, 36088, 44076, 52064
3982	NSFL1 (p97) cofactor (p47)	476071	4137	418529	12125	20113, 28101, 36089, 44077, 52065
3983	N-terminal EF-hand calcium binding protein 1	417640	4138	387380	12126	20114, 28102, 36090, 44078, 52066
3984	N-terminal EF-hand calcium binding protein 1	521366	4139	428632	12127	20115, 28103, 36091, 44079, 52067
3985	N-terminal EF-hand calcium binding protein 1	522820	4140	428953	12128	20116, 28104, 36092, 44080, 52068
3986	NTPase, KAP family P-loop domain containing 1	317951	4141	321976	12129	20117, 28105, 36093, 44081, 52069
3987	NTPase, KAP family P-loop domain containing 1	429338	4142	404706	12130	20118, 28106, 36094, 44082, 52070
3988	NTPase, KAP family P-loop domain containing 1	438936	4143	401739	12131	20119, 28107, 36095, 44083, 52071
3989	Nuclear pore complex-interacting protein-like 1	435324	4144	415207	12132	20120, 28108, 36096, 44084, 52072
3990	nuclear protein localization 4 homolog (S. cerevisiae)	331134	4145	331487	12133	20121, 28109, 36097, 44085, 52073
3991	nuclear protein localization 4 homolog (S. cerevisiae)	374747	4146	363879	12134	20122, 28110, 36098, 44086, 52074
3992	nuclear protein localization 4 homolog (S. cerevisiae)	539314	4147	446199	12135	20123, 28111, 36099, 44087, 52075
3993	nuclear transcription factor, X-box binding-like 1	329043	4148	333113	12136	20124, 28112, 36100, 44088, 52076
3994	nuclear transcription factor, X-box binding-like 1	381538	4149	370949	12137	20125, 28113, 36101, 44089, 52077

3995	nuclear transcription factor, X-box binding-like 1	507489	4150	422037	12138	20126, 28114, 36102, 44090, 52078
3996	nucleoporin 210kDa-like	271854	4151	271854	12139	20127, 28115, 36103, 44091, 52079
3997	nucleoporin 210kDa-like	368553	4152	357541	12140	20128, 28116, 36104, 44092, 52080
3998	nucleoporin 210kDa-like	368559	4153	357547	12141	20129, 28117, 36105, 44093, 52081
3999	nucleoredoxin-like 1	301944	4154	305631	12142	20130, 28118, 36106, 44094, 52082
4000	nudix (nucleoside diphosphate linked moiety X)-type motif 8	301490	4155	301490	12143	20131, 28119, 36107, 44095, 52083
4001	nudix (nucleoside diphosphate linked moiety X)-type motif 8	376693	4156	365883	12144	20132, 28120, 36108, 44096, 52084
4002	nudix (nucleoside diphosphate linked moiety X)-type motif 9	302174	4157	303575	12145	20133, 28121, 36109, 44097, 52085
4003	nudix (nucleoside diphosphate linked moiety X)-type motif 9	473942	4158	421811	12146	20134, 28122, 36110, 44098, 52086
4004	nudix (nucleoside diphosphate linked moiety X)-type motif 9	512216	4159	424702	12147	20135, 28123, 36111, 44099, 52087
4005	nurim (nuclear envelope membrane protein)	259953	4160	259953	12148	20136, 28124, 36112, 44100, 52088
4006	nurim (nuclear envelope membrane protein)	376420	4161	365602	12149	20137, 28125, 36113, 44101, 52089
4007	nurim (nuclear envelope membrane protein)	376421	4162	365603	12150	20138, 28126, 36114, 44102, 52090
4008	nurim (nuclear envelope membrane protein)	383570	4163	373064	12151	20139, 28127, 36115, 44103, 52091
4009	nurim (nuclear envelope membrane protein)	383571	4164	373065	12152	20140, 28128, 36116, 44104, 52092
4010	nurim (nuclear envelope membrane protein)	411883	4165	407049	12153	20141, 28129, 36117, 44105, 52093

4011	nurim (nuclear envelope membrane protein)	422181	4166	409285	12154	20142, 28130, 36118, 44106, 52094
4012	nurim (nuclear envelope membrane protein)	422664	4167	394788	12155	20143, 28131, 36119, 44107, 52095
4013	nurim (nuclear envelope membrane protein)	422747	4168	414927	12156	20144, 28132, 36120, 44108, 52096
4014	nurim (nuclear envelope membrane protein)	427944	4169	405789	12157	20145, 28133, 36121, 44109, 52097
4015	nurim (nuclear envelope membrane protein)	430286	4170	408118	12158	20146, 28134, 36122, 44110, 52098
4016	nurim (nuclear envelope membrane protein)	431322	4171	398752	12159	20147, 28135, 36123, 44111, 52099
4017	nurim (nuclear envelope membrane protein)	434776	4172	394862	12160	20148, 28136, 36124, 44112, 52100
4018	nurim (nuclear envelope membrane protein)	436892	4173	412991	12161	20149, 28137, 36125, 44113, 52101
4019	nurim (nuclear envelope membrane protein)	438502	4174	397755	12162	20150, 28138, 36126, 44114, 52102
4020	nurim (nuclear envelope membrane protein)	444096	4175	397892	12163	20151, 28139, 36127, 44115, 52103
4021	nurim (nuclear envelope membrane protein)	444252	4176	407779	12164	20152, 28140, 36128, 44116, 52104
4022	nurim (nuclear envelope membrane protein)	445058	4177	389958	12165	20153, 28141, 36129, 44117, 52105
4023	nurim (nuclear envelope membrane protein)	446443	4178	389894	12166	20154, 28142, 36130, 44118, 52106
4024	nurim (nuclear envelope membrane protein)	449041	4179	399560	12167	20155, 28143, 36131, 44119, 52107
4025	nurim (nuclear envelope membrane protein)	450138	4180	407111	12168	20156, 28144, 36132, 44120, 52108
4026	nurim (nuclear envelope membrane protein)	456720	4181	392502	12169	20157, 28145, 36133, 44121, 52109
4027	NYN domain and retroviral integrase containing	206466	4182	206466	12170	20158, 28146, 36134, 44122, 52110
4028	NYN domain and retroviral integrase containing	382554	4183	371994	12171	20159, 28147, 36135, 44123, 52111

4029	odz, odd Oz/ten-m homolog 2 (Drosophila)	403607	4184	384905	12172	20160, 28148, 36136, 44124, 52112
4030	odz, odd Oz/ten-m homolog 2 (Drosophila)	518659	4185	429430	12173	20161, 28149, 36137, 44125, 52113
4031	odz, odd Oz/ten-m homolog 2 (Drosophila)	545108	4186	438635	12174	20162, 28150, 36138, 44126, 52114
4032	odz, odd Oz/ten-m homolog 3 (Drosophila)	406950	4187	385276	12175	20163, 28151, 36139, 44127, 52115
4033	odz, odd Oz/ten-m homolog 3 (Drosophila)	511685	4188	424226	12176	20164, 28152, 36140, 44128, 52116
4034	odz, odd Oz/ten-m homolog 3 (Drosophila)	512480	4189	421320	12177	20165, 28153, 36141, 44129, 52117
4035	Olfactory receptor 11H12	550708	4190	449002	12178	20166, 28154, 36142, 44130, 52118
4036	olfactory receptor family 7 subfamily A member 5	594432	4191	471977	12179	20167, 28155, 36143, 44131, 52119
4037	olfactory receptor, family 1, subfamily A, member 1	304094	4192	305207	12180	20168, 28156, 36144, 44132, 52120
4038	olfactory receptor, family 1, subfamily A, member 2	381951	4193	371377	12181	20169, 28157, 36145, 44133, 52121
4039	olfactory receptor, family 1, subfamily B, member 1	304833	4194	303151	12182	20170, 28158, 36146, 44134, 52122
4040	olfactory receptor, family 1, subfamily C, member 1	408896	4195	386138	12183	20171, 28159, 36147, 44135, 52123
4041	olfactory receptor, family 1, subfamily E, member 1	322608	4196	313384	12184	20172, 28160, 36148, 44136, 52124
4042	olfactory receptor, family 1, subfamily E, member 2	248384	4197	248384	12185	20173, 28161, 36149, 44137, 52125
4043	olfactory receptor, family 1, subfamily G, member 1	328890	4198	331545	12186	20174, 28162, 36150, 44138, 52126
4044	olfactory receptor, family 1, subfamily I, member 1	209540	4199	209540	12187	20175, 28163, 36151, 44139, 52127
4045	olfactory receptor, family 1, subfamily J, member 1	259357	4200	259357	12188	20176, 28164, 36152, 44140, 52128
4046	olfactory receptor, family 1, subfamily J, member 2	335302	4201	335575	12189	20177, 28165, 36153, 44141, 52129

4047	olfactory receptor, family 1, subfamily J, member 2	444856	4202	407987	12190	20178, 28166, 36154, 44142, 52130
4048	olfactory receptor, family 1, subfamily J, member 4	340750	4203	343521	12191	20179, 28167, 36155, 44143, 52131
4049	olfactory receptor, family 1, subfamily K, member 1	277309	4204	277309	12192	20180, 28168, 36156, 44144, 52132
4050	olfactory receptor, family 1, subfamily L, member 1	309623	4205	310773	12193	20181, 28169, 36157, 44145, 52133
4051	olfactory receptor, family 1, subfamily L, member 1	373686	4206	362790	12194	20182, 28170, 36158, 44146, 52134
4052	olfactory receptor, family 1, subfamily L, member 3	304820	4207	302863	12195	20183, 28171, 36159, 44147, 52135
4053	olfactory receptor, family 1, subfamily L, member 4	259466	4208	259466	12196	20184, 28172, 36160, 44148, 52136
4054	olfactory receptor, family 1, subfamily L, member 6	304720	4209	304235	12197	20185, 28173, 36161, 44149, 52137
4055	olfactory receptor, family 1, subfamily L, member 6	373684	4210	362788	12198	20186, 28174, 36162, 44150, 52138
4056	olfactory receptor, family 1, subfamily L, member 8	304865	4211	306607	12199	20187, 28175, 36163, 44151, 52139
4057	olfactory receptor, family 1, subfamily M, member 1	305465	4212	303195	12200	20188, 28176, 36164, 44152, 52140
4058	olfactory receptor, family 1, subfamily M, member 1	429566	4213	401966	12201	20189, 28177, 36165, 44153, 52141
4059	olfactory receptor, family 1, subfamily N, member 1	304880	4214	306974	12202	20190, 28178, 36166, 44154, 52142
4060	olfactory receptor, family 1, subfamily N, member 2	373688	4215	362792	12203	20191, 28179, 36167, 44155, 52143
4061	olfactory receptor, family 1, subfamily Q, member 1	297913	4216	297913	12204	20192, 28180, 36168, 44156, 52144
4062	olfactory receptor, family 1, subfamily S, member 1	309433	4217	311688	12205	20193, 28181, 36169, 44157, 52145
4063	olfactory receptor, family 1, subfamily S, member 2	302592	4218	305469	12206	20194, 28182, 36170, 44158, 52146
4064	olfactory receptor, family 10, subfamily A, member 2	307322	4219	303862	12207	20195, 28183, 36171, 44159, 52147

4065	olfactory receptor, family 10, subfamily A, member 3	360759	4220	353988	12208	20196, 28184, 36172, 44160, 52148
4066	olfactory receptor, family 10, subfamily A, member 4	379829	4221	369157	12209	20197, 28185, 36173, 44161, 52149
4067	olfactory receptor, family 10, subfamily A, member 5	299454	4222	299454	12210	20198, 28186, 36174, 44162, 52150
4068	olfactory receptor, family 10, subfamily A, member 5	379831	4223	369159	12211	20199, 28187, 36175, 44163, 52151
4069	olfactory receptor, family 10, subfamily A, member 6	309838	4224	312470	12212	20200, 28188, 36176, 44164, 52152
4070	olfactory receptor, family 10, subfamily A, member 7	326258	4225	326718	12213	20201, 28189, 36177, 44165, 52153
4071	olfactory receptor, family 10, subfamily AB, member 1 pseudogene	317359	4226	322295	12214	20202, 28190, 36178, 44166, 52154
4072	olfactory receptor, family 10, subfamily AD, member 1	310248	4227	308689	12215	20203, 28191, 36179, 44167, 52155
4073	olfactory receptor, family 10, subfamily AG, member 1	312345	4228	311477	12216	20204, 28192, 36180, 44168, 52156
4074	olfactory receptor, family 10, subfamily C, member 1	377138	4229	366343	12217	20205, 28193, 36181, 44169, 52157
4075	olfactory receptor, family 10, subfamily C, member 1	391549	4230	375393	12218	20206, 28194, 36182, 44170, 52158
4076	olfactory receptor, family 10, subfamily C, member 1	428644	4231	404869	12219	20207, 28195, 36183, 44171, 52159
4077	olfactory receptor, family 10, subfamily C, member 1	437403	4232	408961	12220	20208, 28196, 36184, 44172, 52160
4078	olfactory receptor, family 10, subfamily C, member 1	444197	4233	419119	12221	20209, 28197, 36185, 44173, 52161
4079	olfactory receptor, family 10, subfamily C, member 1	455234	4234	402486	12222	20210, 28198, 36186, 44174, 52162
4080	olfactory receptor, family 10, subfamily C, member 1	457403	4235	412512	12223	20211, 28199, 36187, 44175, 52163
4081	olfactory receptor, family 10, subfamily C, member 1	503212	4236	425554	12224	20212, 28200, 36188, 44176, 52164
4082	olfactory receptor, family 10, subfamily C, member 1	546473	4237	448774	12225	20213, 28201, 36189, 44177, 52165

4083	olfactory receptor, family 10, subfamily C, member 1	550017	4238	450100	12226	20214, 28202, 36190, 44178, 52166
4084	olfactory receptor, family 10, subfamily C, member 1	550132	4239	449846	12227	20215, 28203, 36191, 44179, 52167
4085	olfactory receptor, family 10, subfamily C, member 1	551349	4240	448262	12228	20216, 28204, 36192, 44180, 52168
4086	olfactory receptor, family 10, subfamily C, member 1	552057	4241	447194	12229	20217, 28205, 36193, 44181, 52169
4087	olfactory receptor, family 10, subfamily C, member 1	552404	4242	448011	12230	20218, 28206, 36194, 44182, 52170
4088	olfactory receptor, family 10, subfamily C, member 1	552782	4243	448371	12231	20219, 28207, 36195, 44183, 52171
4089	olfactory receptor, family 10, subfamily D, member 3 (non-functional)	318666	4244	323895	12232	20220, 28208, 36196, 44184, 52172
4090	olfactory receptor, family 10, subfamily G, member 2	542433	4245	445383	12233	20221, 28209, 36197, 44185, 52173
4091	olfactory receptor, family 10, subfamily G, member 3	303532	4246	302437	12234	20222, 28210, 36198, 44186, 52174
4092	olfactory receptor, family 10, subfamily G, member 4	320891	4247	325076	12235	20223, 28211, 36199, 44187, 52175
4093	olfactory receptor, family 10, subfamily G, member 7	330487	4248	329689	12236	20224, 28212, 36200, 44188, 52176
4094	olfactory receptor, family 10, subfamily G, member 8	431524	4249	389072	12237	20225, 28213, 36201, 44189, 52177
4095	olfactory receptor, family 10, subfamily G, member 9	375024	4250	364164	12238	20226, 28214, 36202, 44190, 52178
4096	olfactory receptor, family 10, subfamily H, member 1	334920	4251	335596	12239	20227, 28215, 36203, 44191, 52179
4097	olfactory receptor, family 10, subfamily H, member 2	305899	4252	306095	12240	20228, 28216, 36204, 44192, 52180
4098	olfactory receptor, family 10, subfamily H, member 3	305892	4253	307130	12241	20229, 28217, 36205, 44193, 52181
4099	olfactory receptor, family 10, subfamily H, member 4	322107	4254	318834	12242	20230, 28218, 36206, 44194, 52182
4100	olfactory receptor, family 10, subfamily H, member 5	308940	4255	310704	12243	20231, 28219, 36207, 44195, 52183

4101	olfactory receptor, family 10, subfamily J, member 1	423932	4256	399078	12244	20232, 28220, 36208, 44196, 52184
4102	olfactory receptor, family 10, subfamily J, member 3	332217	4257	331789	12245	20233, 28221, 36209, 44197, 52185
4103	olfactory receptor, family 10, subfamily J, member 5	334857	4258	334441	12246	20234, 28222, 36210, 44198, 52186
4104	olfactory receptor, family 10, subfamily K, member 1	289451	4259	289451	12247	20235, 28223, 36211, 44199, 52187
4105	olfactory receptor, family 10, subfamily K, member 2	314902	4260	324251	12248	20236, 28224, 36212, 44200, 52188
4106	olfactory receptor, family 10, subfamily P, member 1	309675	4261	308082	12249	20237, 28225, 36213, 44201, 52189
4107	olfactory receptor, family 10, subfamily Q, member 1	316770	4262	314324	12250	20238, 28226, 36214, 44202, 52190
4108	olfactory receptor, family 10, subfamily R, member 2	368152	4263	357134	12251	20239, 28227, 36215, 44203, 52191
4109	olfactory receptor, family 10, subfamily S, member 1	531945	4264	431914	12252	20240, 28228, 36216, 44204, 52192
4110	olfactory receptor, family 10, subfamily T, member 2	334438	4265	334115	12253	20241, 28229, 36217, 44205, 52193
4111	olfactory receptor, family 10, subfamily V, member 1	307552	4266	302199	12254	20242, 28230, 36218, 44206, 52194
4112	olfactory receptor, family 10, subfamily W, member 1	395079	4267	378516	12255	20243, 28231, 36219, 44207, 52195
4113	olfactory receptor, family 10, subfamily X, member 1	368150	4268	357132	12256	20244, 28232, 36220, 44208, 52196
4114	olfactory receptor, family 10, subfamily Z, member 1	361284	4269	354707	12257	20245, 28233, 36221, 44209, 52197
4115	olfactory receptor, family 10, subfamily Z, member 1	539185	4270	443651	12258	20246, 28234, 36222, 44210, 52198
4116	olfactory receptor, family 11, subfamily A, member 1	377147	4271	366352	12259	20247, 28235, 36223, 44211, 52199
4117	olfactory receptor, family 11, subfamily A, member 1	377148	4272	366353	12260	20248, 28236, 36224, 44212, 52200
4118	olfactory receptor, family 11, subfamily A, member 1	377149	4273	366354	12261	20249, 28237, 36225, 44213, 52201

4119	olfactory receptor, family 11, subfamily A, member 1	383551	4274	373043	12262	20250, 28238, 36226, 44214, 52202
4120	olfactory receptor, family 11, subfamily A, member 1	383645	4275	373141	12263	20251, 28239, 36227, 44215, 52203
4121	olfactory receptor, family 11, subfamily A, member 1	400696	4276	383532	12264	20252, 28240, 36228, 44216, 52204
4122	olfactory receptor, family 11, subfamily A, member 1	400715	4277	383550	12265	20253, 28241, 36229, 44217, 52205
4123	olfactory receptor, family 11, subfamily A, member 1	418485	4278	400657	12266	20254, 28242, 36230, 44218, 52206
4124	olfactory receptor, family 11, subfamily A, member 1	419773	4279	399062	12267	20255, 28243, 36231, 44219, 52207
4125	olfactory receptor, family 11, subfamily A, member 1	421634	4280	400331	12268	20256, 28244, 36232, 44220, 52208
4126	olfactory receptor, family 11, subfamily A, member 1	427264	4281	403427	12269	20257, 28245, 36233, 44221, 52209
4127	olfactory receptor, family 11, subfamily A, member 1	428144	4282	399592	12270	20258, 28246, 36234, 44222, 52210
4128	olfactory receptor, family 11, subfamily A, member 1	435232	4283	398659	12271	20259, 28247, 36235, 44223, 52211
4129	olfactory receptor, family 11, subfamily A, member 1	440485	4284	392324	12272	20260, 28248, 36236, 44224, 52212
4130	olfactory receptor, family 11, subfamily A, member 1	444884	4285	412097	12273	20261, 28249, 36237, 44225, 52213
4131	olfactory receptor, family 11, subfamily A, member 1	546665	4286	447956	12274	20262, 28250, 36238, 44226, 52214
4132	olfactory receptor, family 11, subfamily A, member 1	547506	4287	447215	12275	20263, 28251, 36239, 44227, 52215
4133	olfactory receptor, family 11, subfamily A, member 1	547645	4288	450263	12276	20264, 28252, 36240, 44228, 52216
4134	olfactory receptor, family 11, subfamily A, member 1	549749	4289	447745	12277	20265, 28253, 36241, 44229, 52217
4135	olfactory receptor, family 11, subfamily A, member 1	551986	4290	447627	12278	20266, 28254, 36242, 44230, 52218
4136	olfactory receptor, family 11, subfamily A, member 1	552225	4291	447222	12279	20267, 28255, 36243, 44231, 52219

4137	olfactory receptor, family 11, subfamily G, member 2	357366	4292	349930	12280	20268, 28256, 36244, 44232, 52220
4138	olfactory receptor, family 11, subfamily H, member 1	252835	4293	252835	12281	20269, 28257, 36245, 44233, 52221
4139	olfactory receptor, family 11, subfamily H, member 4	315409	4294	318997	12282	20270, 28258, 36246, 44234, 52222
4140	olfactory receptor, family 11, subfamily H, member 6	315519	4295	319071	12283	20271, 28259, 36247, 44235, 52223
4141	olfactory receptor, family 11, subfamily L, member 1	355784	4296	348033	12284	20272, 28260, 36248, 44236, 52224
4142	olfactory receptor, family 12, subfamily D, member 2	383555	4297	373047	12285	20273, 28261, 36249, 44237, 52225
4143	olfactory receptor, family 12, subfamily D, member 2	432767	4298	390448	12286	20274, 28262, 36250, 44238, 52226
4144	olfactory receptor, family 12, subfamily D, member 2	443442	4299	400571	12287	20275, 28263, 36251, 44239, 52227
4145	olfactory receptor, family 12, subfamily D, member 3	377143	4300	366348	12288	20276, 28264, 36252, 44240, 52228
4146	olfactory receptor, family 12, subfamily D, member 3	383556	4301	373048	12289	20277, 28265, 36253, 44241, 52229
4147	olfactory receptor, family 12, subfamily D, member 3	396806	4302	380023	12290	20278, 28266, 36254, 44242, 52230
4148	olfactory receptor, family 12, subfamily D, member 3	430148	4303	393734	12291	20279, 28267, 36255, 44243, 52231
4149	olfactory receptor, family 12, subfamily D, member 3	505384	4304	421215	12292	20280, 28268, 36256, 44244, 52232
4150	olfactory receptor, family 12, subfamily D, member 3	550681	4305	449350	12293	20281, 28269, 36257, 44245, 52233
4151	olfactory receptor, family 12, subfamily D, member 3	550913	4306	447580	12294	20282, 28270, 36258, 44246, 52234
4152	olfactory receptor, family 12, subfamily D, member 3	552446	4307	447204	12295	20283, 28271, 36259, 44247, 52235
4153	olfactory receptor, family 13, subfamily A, member 1	374401	4308	363522	12296	20284, 28272, 36260, 44248, 52236
4154	olfactory receptor, family 13, subfamily A, member 1	536058	4309	438657	12297	20285, 28273, 36261, 44249, 52237

4155	olfactory receptor, family 13, subfamily A, member 1	553795	4310	451950	12298	20286, 28274, 36262, 44250, 52238
4156	olfactory receptor, family 13, subfamily C, member 2	542196	4311	438815	12299	20287, 28275, 36263, 44251, 52239
4157	olfactory receptor, family 13, subfamily C, member 3	374781	4312	363913	12300	20288, 28276, 36264, 44252, 52240
4158	olfactory receptor, family 13, subfamily C, member 4	277216	4313	277216	12301	20289, 28277, 36265, 44253, 52241
4159	olfactory receptor, family 13, subfamily C, member 4	545903	4314	444047	12302	20290, 28278, 36266, 44254, 52242
4160	olfactory receptor, family 13, subfamily C, member 5	374779	4315	363911	12303	20291, 28279, 36267, 44255, 52243
4161	olfactory receptor, family 13, subfamily C, member 8	335040	4316	334068	12304	20292, 28280, 36268, 44256, 52244
4162	olfactory receptor, family 13, subfamily C, member 9	259362	4317	259362	12305	20293, 28281, 36269, 44257, 52245
4163	olfactory receptor, family 13, subfamily D, member 1	318763	4318	317357	12306	20294, 28282, 36270, 44258, 52246
4164	olfactory receptor, family 13, subfamily F, member 1	334726	4319	334452	12307	20295, 28283, 36271, 44259, 52247
4165	olfactory receptor, family 13, subfamily H, member 1	338616	4320	340748	12308	20296, 28284, 36272, 44260, 52248
4166	olfactory receptor, family 13, subfamily J, member 1	377981	4321	367219	12309	20297, 28285, 36273, 44261, 52249
4167	olfactory receptor, family 14, subfamily A, member 16	357627	4322	350248	12310	20298, 28286, 36274, 44262, 52250
4168	olfactory receptor, family 14, subfamily A, member 2	366485	4323	355441	12311	20299, 28287, 36275, 44263, 52251
4169	olfactory receptor, family 14, subfamily C, member 36	317861	4324	324534	12312	20300, 28288, 36276, 44264, 52252
4170	olfactory receptor, family 14, subfamily J, member 1	230221	4325	230221	12313	20301, 28289, 36277, 44265, 52253
4171	olfactory receptor, family 14, subfamily J, member 1	377160	4326	366365	12314	20302, 28290, 36278, 44266, 52254
4172	olfactory receptor, family 14, subfamily J, member 1	434778	4327	398851	12315	20303, 28291, 36279, 44267, 52255

4173	olfactory receptor, family 14, subfamily K, member 1	283225	4328	283225	12316	20304, 28292, 36280, 44268, 52256
4174	olfactory receptor, family 2, subfamily A, member 1	408951	4329	386175	12317	20305, 28293, 36281, 44269, 52257
4175	olfactory receptor, family 2, subfamily A, member 12	408949	4330	386174	12318	20306, 28294, 36282, 44270, 52258
4176	olfactory receptor, family 2, subfamily A, member 14	408899	4331	386137	12319	20307, 28295, 36283, 44271, 52259
4177	olfactory receptor, family 2, subfamily A, member 2	408979	4332	386209	12320	20308, 28296, 36284, 44272, 52260
4178	olfactory receptor, family 2, subfamily A, member 25	408898	4333	386167	12321	20309, 28297, 36285, 44273, 52261
4179	olfactory receptor, family 2, subfamily A, member 4	315453	4334	319546	12322	20310, 28298, 36286, 44274, 52262
4180	olfactory receptor, family 2, subfamily A, member 42	391496	4335	375334	12323	20311, 28299, 36287, 44275, 52263
4181	olfactory receptor, family 2, subfamily A, member 5	408906	4336	386208	12324	20312, 28300, 36288, 44276, 52264
4182	olfactory receptor, family 2, subfamily A, member 7	493325	4337	420502	12325	20313, 28301, 36289, 44277, 52265
4183	olfactory receptor, family 2, subfamily AE, member 1	316368	4338	313936	12326	20314, 28302, 36290, 44278, 52266
4184	olfactory receptor, family 2, subfamily AG, member 1	307401	4339	307447	12327	20315, 28303, 36291, 44279, 52267
4185	olfactory receptor, family 2, subfamily AJ, member 1	318244	4340	325078	12328	20316, 28304, 36292, 44280, 52268
4186	olfactory receptor, family 2, subfamily AK, member 2	366480	4341	355436	12329	20317, 28305, 36293, 44281, 52269
4187	olfactory receptor, family 2, subfamily AP, member 1	321688	4342	323423	12330	20318, 28306, 36294, 44282, 52270
4188	olfactory receptor, family 2, subfamily AT, member 4	305159	4343	304846	12331	20319, 28307, 36295, 44283, 52271
4189	olfactory receptor, family 2, subfamily B, member 11	318749	4344	325682	12332	20320, 28308, 36296, 44284, 52272
4190	olfactory receptor, family 2, subfamily B, member 2	303324	4345	304419	12333	20321, 28309, 36297, 44285, 52273

4191	olfactory receptor, family 2, subfamily B, member 3	377173	4346	366378	12334	20322, 28310, 36298, 44286, 52274
4192	olfactory receptor, family 2, subfamily B, member 3	383653	4347	373149	12335	20323, 28311, 36299, 44287, 52275
4193	olfactory receptor, family 2, subfamily B, member 3	415976	4348	394571	12336	20324, 28312, 36300, 44288, 52276
4194	olfactory receptor, family 2, subfamily B, member 3	419873	4349	394593	12337	20325, 28313, 36301, 44289, 52277
4195	olfactory receptor, family 2, subfamily B, member 3	420178	4350	388604	12338	20326, 28314, 36302, 44290, 52278
4196	olfactory receptor, family 2, subfamily B, member 3	444830	4351	393235	12339	20327, 28315, 36303, 44291, 52279
4197	olfactory receptor, family 2, subfamily B, member 3	450817	4352	399881	12340	20328, 28316, 36304, 44292, 52280
4198	olfactory receptor, family 2, subfamily B, member 3	456140	4353	403571	12341	20329, 28317, 36305, 44293, 52281
4199	olfactory receptor, family 2, subfamily B, member 6	244623	4354	244623	12342	20330, 28318, 36306, 44294, 52282
4200	olfactory receptor, family 2, subfamily C, member 1	304936	4355	307726	12343	20331, 28319, 36307, 44295, 52283
4201	olfactory receptor, family 2, subfamily C, member 3	366487	4356	355443	12344	20332, 28320, 36308, 44296, 52284
4202	olfactory receptor, family 2, subfamily D, member 2	299459	4357	299459	12345	20333, 28321, 36309, 44297, 52285
4203	olfactory receptor, family 2, subfamily D, member 3	317834	4358	320560	12346	20334, 28322, 36310, 44298, 52286
4204	olfactory receptor, family 2, subfamily F, member 1	392899	4359	376633	12347	20335, 28323, 36311, 44299, 52287
4205	olfactory receptor, family 2, subfamily F, member 2	408955	4360	386222	12348	20336, 28324, 36312, 44300, 52288
4206	olfactory receptor, family 2, subfamily G, member 2	320065	4361	326349	12349	20337, 28325, 36313, 44301, 52289
4207	olfactory receptor, family 2, subfamily G, member 3	320002	4362	326301	12350	20338, 28326, 36314, 44302, 52290
4208	olfactory receptor, family 2, subfamily G, member 6	343414	4363	341291	12351	20339, 28327, 36315, 44303, 52291

4209	olfactory receptor, family 2, subfamily H, member 1	377132	4364	366336	12352	20340, 28328, 36316, 44304, 52292
4210	olfactory receptor, family 2, subfamily H, member 1	377133	4365	366337	12353	20341, 28329, 36317, 44305, 52293
4211	olfactory receptor, family 2, subfamily H, member 1	377136	4366	366340	12354	20342, 28330, 36318, 44306, 52294
4212	olfactory receptor, family 2, subfamily H, member 1	383550	4367	373042	12355	20343, 28331, 36319, 44307, 52295
4213	olfactory receptor, family 2, subfamily H, member 1	383644	4368	373140	12356	20344, 28332, 36320, 44308, 52296
4214	olfactory receptor, family 2, subfamily H, member 1	396792	4369	380010	12357	20345, 28333, 36321, 44309, 52297
4215	olfactory receptor, family 2, subfamily H, member 1	400689	4370	383527	12358	20346, 28334, 36322, 44310, 52298
4216	olfactory receptor, family 2, subfamily H, member 1	400693	4371	383529	12359	20347, 28335, 36323, 44311, 52299
4217	olfactory receptor, family 2, subfamily H, member 1	400694	4372	383530	12360	20348, 28336, 36324, 44312, 52300
4218	olfactory receptor, family 2, subfamily H, member 1	400712	4373	383547	12361	20349, 28337, 36325, 44313, 52301
4219	olfactory receptor, family 2, subfamily H, member 1	400713	4374	383548	12362	20350, 28338, 36326, 44314, 52302
4220	olfactory receptor, family 2, subfamily H, member 1	400714	4375	383549	12363	20351, 28339, 36327, 44315, 52303
4221	olfactory receptor, family 2, subfamily H, member 1	412956	4376	407739	12364	20352, 28340, 36328, 44316, 52304
4222	olfactory receptor, family 2, subfamily H, member 1	415581	4377	396944	12365	20353, 28341, 36329, 44317, 52305
4223	olfactory receptor, family 2, subfamily H, member 1	416582	4378	395850	12366	20354, 28342, 36330, 44318, 52306
4224	olfactory receptor, family 2, subfamily H, member 1	418376	4379	395567	12367	20355, 28343, 36331, 44319, 52307
4225	olfactory receptor, family 2, subfamily H, member 1	421808	4380	410401	12368	20356, 28344, 36332, 44320, 52308
4226	olfactory receptor, family 2, subfamily H, member 1	431658	4381	394698	12369	20357, 28345, 36333, 44321, 52309

4227	olfactory receptor, family 2, subfamily H, member 1	435958	4382	397171	12370	20358, 28346, 36334, 44322, 52310
4228	olfactory receptor, family 2, subfamily H, member 1	436167	4383	388844	12371	20359, 28347, 36335, 44323, 52311
4229	olfactory receptor, family 2, subfamily H, member 1	438840	4384	412463	12372	20360, 28348, 36336, 44324, 52312
4230	olfactory receptor, family 2, subfamily H, member 1	439879	4385	409651	12373	20361, 28349, 36337, 44325, 52313
4231	olfactory receptor, family 2, subfamily H, member 1	440557	4386	413910	12374	20362, 28350, 36338, 44326, 52314
4232	olfactory receptor, family 2, subfamily H, member 1	440672	4387	396414	12375	20363, 28351, 36339, 44327, 52315
4233	olfactory receptor, family 2, subfamily H, member 1	442615	4388	393254	12376	20364, 28352, 36340, 44328, 52316
4234	olfactory receptor, family 2, subfamily H, member 1	443407	4389	398695	12377	20365, 28353, 36341, 44329, 52317
4235	olfactory receptor, family 2, subfamily H, member 1	444920	4390	410659	12378	20366, 28354, 36342, 44330, 52318
4236	olfactory receptor, family 2, subfamily H, member 1	446161	4391	389230	12379	20367, 28355, 36343, 44331, 52319
4237	olfactory receptor, family 2, subfamily H, member 1	449826	4392	411617	12380	20368, 28356, 36344, 44332, 52320
4238	olfactory receptor, family 2, subfamily H, member 1	453467	4393	392619	12381	20369, 28357, 36345, 44333, 52321
4239	olfactory receptor, family 2, subfamily H, member 1	454071	4394	395934	12382	20370, 28358, 36346, 44334, 52322
4240	olfactory receptor, family 2, subfamily H, member 1	456657	4395	408584	12383	20371, 28359, 36347, 44335, 52323
4241	olfactory receptor, family 2, subfamily H, member 1	458051	4396	405714	12384	20372, 28360, 36348, 44336, 52324
4242	olfactory receptor, family 2, subfamily H, member 1	546418	4397	449206	12385	20373, 28361, 36349, 44337, 52325
4243	olfactory receptor, family 2, subfamily H, member 1	546570	4398	449512	12386	20374, 28362, 36350, 44338, 52326
4244	olfactory receptor, family 2, subfamily H, member 1	548244	4399	449029	12387	20375, 28363, 36351, 44339, 52327

4245	olfactory receptor, family 2, subfamily H, member 1	550783	4400	447994	12388	20376, 28364, 36352, 44340, 52328
4246	olfactory receptor, family 2, subfamily H, member 1	551060	4401	449069	12389	20377, 28365, 36353, 44341, 52329
4247	olfactory receptor, family 2, subfamily H, member 1	552011	4402	448814	12390	20378, 28366, 36354, 44342, 52330
4248	olfactory receptor, family 2, subfamily H, member 1	552129	4403	450138	12391	20379, 28367, 36355, 44343, 52331
4249	olfactory receptor, family 2, subfamily H, member 2	376947	4404	366146	12392	20380, 28368, 36356, 44344, 52332
4250	olfactory receptor, family 2, subfamily H, member 2	383640	4405	373136	12393	20381, 28369, 36357, 44345, 52333
4251	olfactory receptor, family 2, subfamily H, member 2	411574	4406	410227	12394	20382, 28370, 36358, 44346, 52334
4252	olfactory receptor, family 2, subfamily J, member 1 (gene/pseudogene)	377171	4407	366376	12395	20383, 28371, 36359, 44347, 52335
4253	olfactory receptor, family 2, subfamily J, member 2	415857	4408	392497	12396	20384, 28372, 36360, 44348, 52336
4254	olfactory receptor, family 2, subfamily J, member 2	419605	4409	408988	12397	20385, 28373, 36361, 44349, 52337
4255	olfactory receptor, family 2, subfamily J, member 2	427744	4410	403186	12398	20386, 28374, 36362, 44350, 52338
4256	olfactory receptor, family 2, subfamily J, member 2	440124	4411	398238	12399	20387, 28375, 36363, 44351, 52339
4257	olfactory receptor, family 2, subfamily J, member 2	457762	4412	416299	12400	20388, 28376, 36364, 44352, 52340
4258	olfactory receptor, family 2, subfamily J, member 3	383651	4413	373147	12401	20389, 28377, 36365, 44353, 52341
4259	olfactory receptor, family 2, subfamily J, member 3	414140	4414	390144	12402	20390, 28378, 36366, 44354, 52342
4260	olfactory receptor, family 2, subfamily J, member 3	418630	4415	400546	12403	20391, 28379, 36367, 44355, 52343
4261	olfactory receptor, family 2, subfamily J, member 3	419260	4416	408783	12404	20392, 28380, 36368, 44356, 52344
4262	olfactory receptor, family 2, subfamily J, member 3	422576	4417	393371	12405	20393, 28381, 36369, 44357, 52345

4263	olfactory receptor, family 2, subfamily J, member 3	428081	4418	388392	12406	20394, 28382, 36370, 44358, 52346
4264	olfactory receptor, family 2, subfamily J, member 3	430478	4419	388205	12407	20395, 28383, 36371, 44359, 52347
4265	olfactory receptor, family 2, subfamily K, member 2	302681	4420	305055	12408	20396, 28384, 36372, 44360, 52348
4266	olfactory receptor, family 2, subfamily K, member 2	374428	4421	363550	12409	20397, 28385, 36373, 44361, 52349
4267	olfactory receptor, family 2, subfamily L, member 13	358120	4422	350836	12410	20398, 28386, 36374, 44362, 52350
4268	olfactory receptor, family 2, subfamily L, member 13	366478	4423	355434	12411	20399, 28387, 36375, 44363, 52351
4269	olfactory receptor, family 2, subfamily L, member 2	366479	4424	355435	12412	20400, 28388, 36376, 44364, 52352
4270	olfactory receptor, family 2, subfamily L, member 3	359959	4425	353044	12413	20401, 28389, 36377, 44365, 52353
4271	olfactory receptor, family 2, subfamily L, member 5	355281	4426	347428	12414	20402, 28390, 36378, 44366, 52354
4272	olfactory receptor, family 2, subfamily L, member 8	357191	4427	349719	12415	20403, 28391, 36379, 44367, 52355
4273	olfactory receptor, family 2, subfamily M, member 2	359682	4428	352710	12416	20404, 28392, 36380, 44368, 52356
4274	olfactory receptor, family 2, subfamily M, member 3	456743	4429	389625	12417	20405, 28393, 36381, 44369, 52357
4275	olfactory receptor, family 2, subfamily M, member 4	306687	4430	306688	12418	20406, 28394, 36382, 44370, 52358
4276	olfactory receptor, family 2, subfamily M, member 5	366476	4431	355432	12419	20407, 28395, 36383, 44371, 52359
4277	olfactory receptor, family 2, subfamily M, member 7	317965	4432	324557	12420	20408, 28396, 36384, 44372, 52360
4278	olfactory receptor, family 2, subfamily S, member 2	341959	4433	344040	12421	20409, 28397, 36385, 44373, 52361
4279	olfactory receptor, family 2, subfamily T, member 1	366474	4434	355430	12422	20410, 28398, 36386, 44374, 52362
4280	olfactory receptor, family 2, subfamily T, member 10	330500	4435	329210	12423	20411, 28399, 36387, 44375, 52363

4281	olfactory receptor, family 2, subfamily T, member 11	330803	4436	328934	12424	20412, 28400, 36388, 44376, 52364
4282	olfactory receptor, family 2, subfamily T, member 12	317996	4437	324583	12425	20413, 28401, 36389, 44377, 52365
4283	olfactory receptor, family 2, subfamily T, member 2	342927	4438	343062	12426	20414, 28402, 36390, 44378, 52366
4284	olfactory receptor, family 2, subfamily T, member 27	344889	4439	342008	12427	20415, 28403, 36391, 44379, 52367
4285	olfactory receptor, family 2, subfamily T, member 29	328570	4440	331774	12428	20416, 28404, 36392, 44380, 52368
4286	olfactory receptor, family 2, subfamily T, member 3	359594	4441	352604	12429	20417, 28405, 36393, 44381, 52369
4287	olfactory receptor, family 2, subfamily T, member 33	318021	4442	324687	12430	20418, 28406, 36394, 44382, 52370
4288	olfactory receptor, family 2, subfamily T, member 34	328782	4443	330904	12431	20419, 28407, 36395, 44383, 52371
4289	olfactory receptor, family 2, subfamily T, member 35	317450	4444	324369	12432	20420, 28408, 36396, 44384, 52372
4290	olfactory receptor, family 2, subfamily T, member 4	366475	4445	355431	12433	20421, 28409, 36397, 44385, 52373
4291	olfactory receptor, family 2, subfamily T, member 5	366473	4446	355429	12434	20422, 28410, 36398, 44386, 52374
4292	olfactory receptor, family 2, subfamily T, member 6	355728	4447	347965	12435	20423, 28411, 36399, 44387, 52375
4293	olfactory receptor, family 2, subfamily V, member 1	329365	4448	404102	12436	20424, 28412, 36400, 44388, 52376
4294	olfactory receptor, family 2, subfamily V, member 2	328275	4449	332185	12437	20425, 28413, 36401, 44389, 52377
4295	olfactory receptor, family 2, subfamily W, member 1	377175	4450	366380	12438	20426, 28414, 36402, 44390, 52378
4296	olfactory receptor, family 2, subfamily W, member 1	383654	4451	373150	12439	20427, 28415, 36403, 44391, 52379
4297	olfactory receptor, family 2, subfamily W, member 1	411447	4452	388144	12440	20428, 28416, 36404, 44392, 52380
4298	olfactory receptor, family 2, subfamily W, member 1	420540	4453	392635	12441	20429, 28417, 36405, 44393, 52381

4299	olfactory receptor, family 2, subfamily W, member 1	421027	4454	412537	12442	20430, 28418, 36406, 44394, 52382
4300	olfactory receptor, family 2, subfamily W, member 1	421766	4455	389825	12443	20431, 28419, 36407, 44395, 52383
4301	olfactory receptor, family 2, subfamily W, member 1	439723	4456	401866	12444	20432, 28420, 36408, 44396, 52384
4302	olfactory receptor, family 2, subfamily W, member 1	446776	4457	405025	12445	20433, 28421, 36409, 44397, 52385
4303	olfactory receptor, family 2, subfamily W, member 3	360358	4458	353516	12446	20434, 28422, 36410, 44398, 52386
4304	olfactory receptor, family 2, subfamily W, member 3	537741	4459	445853	12447	20435, 28423, 36411, 44399, 52387
4305	olfactory receptor, family 2, subfamily Y, member 1	307832	4460	312403	12448	20436, 28424, 36412, 44400, 52388
4306	olfactory receptor, family 2, subfamily Z, member 1	324060	4461	316284	12449	20437, 28425, 36413, 44401, 52389
4307	olfactory receptor, family 3, subfamily A, member 1	323404	4462	313803	12450	20438, 28426, 36414, 44402, 52390
4308	olfactory receptor, family 3, subfamily A, member 2	408891	4463	386180	12451	20439, 28427, 36415, 44403, 52391
4309	olfactory receptor, family 3, subfamily A, member 3	291231	4464	291231	12452	20440, 28428, 36416, 44404, 52392
4310	olfactory receptor, family 4, subfamily A, member 15	314706	4465	325065	12453	20441, 28429, 36417, 44405, 52393
4311	olfactory receptor, family 4, subfamily A, member 16	314721	4466	325128	12454	20442, 28430, 36418, 44406, 52394
4312	olfactory receptor, family 4, subfamily A, member 47	446524	4467	412752	12455	20443, 28431, 36419, 44407, 52395
4313	olfactory receptor, family 4, subfamily A, member 5	319760	4468	367664	12456	20444, 28432, 36420, 44408, 52396
4314	olfactory receptor, family 4, subfamily B, member 1	309562	4469	311605	12457	20445, 28433, 36421, 44409, 52397
4315	olfactory receptor, family 4, subfamily C, member 11	302231	4470	306651	12458	20446, 28434, 36422, 44410, 52398
4316	olfactory receptor, family 4, subfamily C, member 12	335238	4471	334418	12459	20447, 28435, 36423, 44411, 52399

4317	olfactory receptor, family 4, subfamily C, member 13	555099	4472	452277	12460	20448, 28436, 36424, 44412, 52400
4318	olfactory receptor, family 4, subfamily C, member 15	314644	4473	324958	12461	20449, 28437, 36425, 44413, 52401
4319	olfactory receptor, family 4, subfamily C, member 16	314634	4474	324913	12462	20450, 28438, 36426, 44414, 52402
4320	olfactory receptor, family 4, subfamily C, member 3	319856	4475	321419	12463	20451, 28439, 36427, 44415, 52403
4321	olfactory receptor, family 4, subfamily C, member 3	395239	4476	378660	12464	20452, 28440, 36428, 44416, 52404
4322	olfactory receptor, family 4, subfamily C, member 5	319813	4477	321338	12465	20453, 28441, 36429, 44417, 52405
4323	olfactory receptor, family 4, subfamily C, member 6	314259	4478	324769	12466	20454, 28442, 36430, 44418, 52406
4324	olfactory receptor, family 4, subfamily D, member 1	268912	4479	365451	12467	20455, 28443, 36431, 44419, 52407
4325	olfactory receptor, family 4, subfamily D, member 10	530162	4480	436424	12468	20456, 28444, 36432, 44420, 52408
4326	olfactory receptor, family 4, subfamily D, member 11	313253	4481	320077	12469	20457, 28445, 36433, 44421, 52409
4327	olfactory receptor, family 4, subfamily D, member 2	545221	4482	441354	12470	20458, 28446, 36434, 44422, 52410
4328	olfactory receptor, family 4, subfamily D, member 5	307033	4483	305970	12471	20459, 28447, 36435, 44423, 52411
4329	olfactory receptor, family 4, subfamily D, member 6	300127	4484	300127	12472	20460, 28448, 36436, 44424, 52412
4330	olfactory receptor, family 4, subfamily D, member 9	329328	4485	328563	12473	20461, 28449, 36437, 44425, 52413
4331	olfactory receptor, family 4, subfamily E, member 2	408935	4486	386195	12474	20462, 28450, 36438, 44426, 52414
4332	olfactory receptor, family 4, subfamily F, member 15	332238	4487	333184	12475	20463, 28451, 36439, 44427, 52415
4333	olfactory receptor, family 4, subfamily F, member 16	332831	4488	329982	12476	20464, 28452, 36440, 44428, 52416
4334	olfactory receptor, family 4, subfamily F, member 17	318050	4489	315047	12477	20465, 28453, 36441, 44429, 52417

4335	olfactory receptor, family 4, subfamily F, member 17	442916	4490	400284	12478	20466, 28454, 36442, 44430, 52418
4336	olfactory receptor, family 4, subfamily F, member 21	320901	4491	318878	12479	20467, 28455, 36443, 44431, 52419
4337	olfactory receptor, family 4, subfamily F, member 29	426406	4492	409316	12480	20468, 28456, 36444, 44432, 52420
4338	olfactory receptor, family 4, subfamily F, member 3	456475	4493	394282	12481	20469, 28457, 36445, 44433, 52421
4339	olfactory receptor, family 4, subfamily F, member 4	326183	4494	317482	12482	20470, 28458, 36446, 44434, 52422
4340	olfactory receptor, family 4, subfamily F, member 5	335137	4495	334393	12483	20471, 28459, 36447, 44435, 52423
4341	olfactory receptor, family 4, subfamily F, member 6	328882	4496	327525	12484	20472, 28460, 36448, 44436, 52424
4342	olfactory receptor, family 4, subfamily K, member 1	285600	4497	285600	12485	20473, 28461, 36449, 44437, 52425
4343	olfactory receptor, family 4, subfamily K, member 13	315693	4498	319322	12486	20474, 28462, 36450, 44438, 52426
4344	olfactory receptor, family 4, subfamily K, member 14	305045	4499	305011	12487	20475, 28463, 36451, 44439, 52427
4345	olfactory receptor, family 4, subfamily K, member 15	305051	4500	304077	12488	20476, 28464, 36452, 44440, 52428
4346	olfactory receptor, family 4, subfamily K, member 17	315543	4501	319197	12489	20477, 28465, 36453, 44441, 52429
4347	olfactory receptor, family 4, subfamily K, member 2	298642	4502	298642	12490	20478, 28466, 36454, 44442, 52430
4348	olfactory receptor, family 4, subfamily K, member 5	315915	4503	319511	12491	20479, 28467, 36455, 44443, 52431
4349	olfactory receptor, family 4, subfamily L, member 1	315683	4504	319217	12492	20480, 28468, 36456, 44444, 52432
4350	olfactory receptor, family 4, subfamily M, member 1	315957	4505	319654	12493	20481, 28469, 36457, 44445, 52433
4351	olfactory receptor, family 4, subfamily M, member 2	332663	4506	329467	12494	20482, 28470, 36458, 44446, 52434
4352	olfactory receptor, family 4, subfamily N, member 2	315947	4507	319601	12495	20483, 28471, 36459, 44447, 52435

4353	olfactory receptor, family 4, subfamily N, member 2	557414	4508	451462	12496	20484, 28472, 36460, 44448, 52436
4354	olfactory receptor, family 4, subfamily N, member 2	557677	4509	452022	12497	20485, 28473, 36461, 44449, 52437
4355	olfactory receptor, family 4, subfamily N, member 4	328795	4510	332500	12498	20486, 28474, 36462, 44450, 52438
4356	olfactory receptor, family 4, subfamily N, member 5	333629	4511	332110	12499	20487, 28475, 36463, 44451, 52439
4357	olfactory receptor, family 4, subfamily P, member 4	314612	4512	324831	12500	20488, 28476, 36464, 44452, 52440
4358	olfactory receptor, family 4, subfamily Q, member 3	331723	4513	330049	12501	20489, 28477, 36465, 44453, 52441
4359	olfactory receptor, family 4, subfamily S, member 1	319988	4514	321447	12502	20490, 28478, 36466, 44454, 52442
4360	olfactory receptor, family 4, subfamily S, member 2	312422	4515	310337	12503	20491, 28479, 36467, 44455, 52443
4361	olfactory receptor, family 4, subfamily X, member 1	320048	4516	321506	12504	20492, 28480, 36468, 44456, 52444
4362	olfactory receptor, family 4, subfamily X, member 2	302329	4517	307751	12505	20493, 28481, 36469, 44457, 52445
4363	olfactory receptor, family 5, subfamily A, member 1	302030	4518	303096	12506	20494, 28482, 36470, 44458, 52446
4364	olfactory receptor, family 5, subfamily A, member 2	302040	4519	303834	12507	20495, 28483, 36471, 44459, 52447
4365	olfactory receptor, family 5, subfamily AC, member 2	358642	4520	351466	12508	20496, 28484, 36472, 44460, 52448
4366	olfactory receptor, family 5, subfamily AK, member 2	326855	4521	322784	12509	20497, 28485, 36473, 44461, 52449
4367	olfactory receptor, family 5, subfamily AN, member 1	313940	4522	320302	12510	20498, 28486, 36474, 44462, 52450
4368	olfactory receptor, family 5, subfamily AP, member 2	302981	4523	303111	12511	20499, 28487, 36475, 44463, 52451
4369	olfactory receptor, family 5, subfamily AP, member 2	544374	4524	442701	12512	20500, 28488, 36476, 44464, 52452
4370	olfactory receptor, family 5, subfamily AR, member 1	302969	4525	302639	12513	20501, 28489, 36477, 44465, 52453

4371	olfactory receptor, family 5, subfamily AS, member 1	313555	4526	324111	12514	20502, 28490, 36478, 44466, 52454
4372	olfactory receptor, family 5, subfamily AU, member 1	304418	4527	302057	12515	20503, 28491, 36479, 44467, 52455
4373	olfactory receptor, family 5, subfamily B, member 12	302572	4528	306657	12516	20504, 28492, 36480, 44468, 52456
4374	olfactory receptor, family 5, subfamily B, member 17	357377	4529	349945	12517	20505, 28493, 36481, 44469, 52457
4375	olfactory receptor, family 5, subfamily B, member 2	302581	4530	303076	12518	20506, 28494, 36482, 44470, 52458
4376	olfactory receptor, family 5, subfamily B, member 3	309403	4531	308270	12519	20507, 28495, 36483, 44471, 52459
4377	olfactory receptor, family 5, subfamily C, member 1	373680	4532	362784	12520	20508, 28496, 36484, 44472, 52460
4378	olfactory receptor, family 5, subfamily D, member 13	361760	4533	354800	12521	20509, 28497, 36485, 44473, 52461
4379	olfactory receptor, family 5, subfamily D, member 14	335605	4534	334456	12522	20510, 28498, 36486, 44474, 52462
4380	olfactory receptor, family 5, subfamily D, member 16	378396	4535	367649	12523	20511, 28499, 36487, 44475, 52463
4381	olfactory receptor, family 5, subfamily D, member 18	333976	4536	335025	12524	20512, 28500, 36488, 44476, 52464
4382	olfactory receptor, family 5, subfamily F, member 1	278409	4537	278409	12525	20513, 28501, 36489, 44477, 52465
4383	olfactory receptor, family 5, subfamily H, member 14	437310	4538	401706	12526	20514, 28502, 36490, 44478, 52466
4384	olfactory receptor, family 5, subfamily H, member 2	355273	4539	347418	12527	20515, 28503, 36491, 44479, 52467
4385	olfactory receptor, family 5, subfamily I, member 1	301532	4540	301532	12528	20516, 28504, 36492, 44480, 52468
4386	olfactory receptor, family 5, subfamily J, member 2	312298	4541	310788	12529	20517, 28505, 36493, 44481, 52469
4387	olfactory receptor, family 5, subfamily K, member 1	332650	4542	373193	12530	20518, 28506, 36494, 44482, 52470
4388	olfactory receptor, family 5, subfamily K, member 2	427338	4543	393889	12531	20519, 28507, 36495, 44483, 52471

4389	olfactory receptor, family 5, subfamily K, member 4	354924	4544	347003	12532	20520, 28508, 36496, 44484, 52472
4390	olfactory receptor, family 5, subfamily L, member 1	333973	4545	335529	12533	20521, 28509, 36497, 44485, 52473
4391	olfactory receptor, family 5, subfamily L, member 2	378397	4546	367650	12534	20522, 28510, 36498, 44486, 52474
4392	olfactory receptor, family 5, subfamily M, member 1	526538	4547	435416	12535	20523, 28511, 36499, 44487, 52475
4393	olfactory receptor, family 5, subfamily M, member 10	526812	4548	436004	12536	20524, 28512, 36500, 44488, 52476
4394	olfactory receptor, family 5, subfamily M, member 11	528616	4549	432417	12537	20525, 28513, 36501, 44489, 52477
4395	olfactory receptor, family 5, subfamily M, member 3	312240	4550	312208	12538	20526, 28514, 36502, 44490, 52478
4396	olfactory receptor, family 5, subfamily M, member 8	327216	4551	323354	12539	20527, 28515, 36503, 44491, 52479
4397	olfactory receptor, family 5, subfamily M, member 9	279791	4552	279791	12540	20528, 28516, 36504, 44492, 52480
4398	olfactory receptor, family 5, subfamily P, member 2	329434	4553	331823	12541	20529, 28517, 36505, 44493, 52481
4399	olfactory receptor, family 5, subfamily P, member 3	328375	4554	332068	12542	20530, 28518, 36506, 44494, 52482
4400	olfactory receptor, family 5, subfamily R, member 1	312253	4555	308595	12543	20531, 28519, 36507, 44495, 52483
4401	olfactory receptor, family 5, subfamily T, member 1	313033	4556	323612	12544	20532, 28520, 36508, 44496, 52484
4402	olfactory receptor, family 5, subfamily T, member 2	313264	4557	323688	12545	20533, 28521, 36509, 44497, 52485
4403	olfactory receptor, family 5, subfamily T, member 3	303059	4558	305403	12546	20534, 28522, 36510, 44498, 52486
4404	olfactory receptor, family 5, subfamily V, member 1	377151	4559	366356	12547	20535, 28523, 36511, 44499, 52487
4405	olfactory receptor, family 5, subfamily V, member 1	377154	4560	366359	12548	20536, 28524, 36512, 44500, 52488
4406	olfactory receptor, family 5, subfamily V, member 1	441440	4561	404163	12549	20537, 28525, 36513, 44501, 52489

4407	olfactory receptor, family 5, subfamily V, member 1	444009	4562	407363	12550	20538, 28526, 36514, 44502, 52490
4408	olfactory receptor, family 5, subfamily V, member 1	446761	4563	404109	12551	20539, 28527, 36515, 44503, 52491
4409	olfactory receptor, family 5, subfamily V, member 1	458372	4564	404990	12552	20540, 28528, 36516, 44504, 52492
4410	olfactory receptor, family 5, subfamily V, member 1	543825	4565	443309	12553	20541, 28529, 36517, 44505, 52493
4411	olfactory receptor, family 5, subfamily V, member 1	549299	4566	450230	12554	20542, 28530, 36518, 44506, 52494
4412	olfactory receptor, family 5, subfamily V, member 1	550240	4567	446579	12555	20543, 28531, 36519, 44507, 52495
4413	olfactory receptor, family 5, subfamily W, member 2	344514	4568	342448	12556	20544, 28532, 36520, 44508, 52496
4414	olfactory receptor, family 51, subfamily A, member 2	380371	4569	369729	12557	20545, 28533, 36521, 44509, 52497
4415	olfactory receptor, family 51, subfamily A, member 4	380373	4570	369731	12558	20546, 28534, 36522, 44510, 52498
4416	olfactory receptor, family 51, subfamily A, member 7	359350	4571	352305	12559	20547, 28535, 36523, 44511, 52499
4417	olfactory receptor, family 51, subfamily A, member 7	544684	4572	445796	12560	20548, 28536, 36524, 44512, 52500
4418	olfactory receptor, family 51, subfamily A, member 7	545959	4573	439834	12561	20549, 28537, 36525, 44513, 52501
4419	olfactory receptor, family 51, subfamily B, member 2	328813	4574	327540	12562	20550, 28538, 36526, 44514, 52502
4420	olfactory receptor, family 51, subfamily B, member 4	380224	4575	369573	12563	20551, 28539, 36527, 44515, 52503
4421	olfactory receptor, family 51, subfamily B, member 5	300773	4576	300773	12564	20552, 28540, 36528, 44516, 52504
4422	olfactory receptor, family 51, subfamily B, member 6	380219	4577	369568	12565	20553, 28541, 36529, 44517, 52505
4423	olfactory receptor, family 51, subfamily B, member 6	537299	4578	441886	12566	20554, 28542, 36530, 44518, 52506
4424	olfactory receptor, family 51, subfamily C, member 1 pseudogene	357764	4579	350408	12567	20555, 28543, 36531, 44519, 52507

4425	olfactory receptor, family 51, subfamily D, member 1	357605	4580	350222	12568	20556, 28544, 36532, 44520, 52508
4426	olfactory receptor, family 51, subfamily E, member 1	396952	4581	380155	12569	20557, 28545, 36533, 44521, 52509
4427	olfactory receptor, family 51, subfamily E, member 2	396950	4582	380153	12570	20558, 28546, 36534, 44522, 52510
4428	olfactory receptor, family 51, subfamily E, member 2	532598	4583	432644	12571	20559, 28547, 36535, 44523, 52511
4429	olfactory receptor, family 51, subfamily F, member 2	322110	4584	323952	12572	20560, 28548, 36536, 44524, 52512
4430	olfactory receptor, family 51, subfamily G, member 1	321961	4585	322546	12573	20561, 28549, 36537, 44525, 52513
4431	olfactory receptor, family 51, subfamily G, member 2	322013	4586	322593	12574	20562, 28550, 36538, 44526, 52514
4432	olfactory receptor, family 51, subfamily H, member 1 pseudogene	322059	4587	322724	12575	20563, 28551, 36539, 44527, 52515
4433	olfactory receptor, family 51, subfamily I, member 1	317283	4588	348350	12576	20564, 28552, 36540, 44528, 52516
4434	olfactory receptor, family 51, subfamily I, member 1	321307	4589	439622	12577	20565, 28553, 36541, 44529, 52517
4435	olfactory receptor, family 51, subfamily I, member 1	380211	4590	369559	12578	20566, 28554, 36542, 44530, 52518
4436	olfactory receptor, family 51, subfamily I, member 2	341449	4591	341987	12579	20567, 28555, 36543, 44531, 52519
4437	olfactory receptor, family 51, subfamily J, member 1 (gene/pseudogene)	332043	4592	332473	12580	20568, 28556, 36544, 44532, 52520
4438	olfactory receptor, family 51, subfamily L, member 1	321543	4593	322156	12581	20569, 28557, 36545, 44533, 52521
4439	olfactory receptor, family 51, subfamily Q, member 1	300778	4594	300778	12582	20570, 28558, 36546, 44534, 52522
4440	olfactory receptor, family 51, subfamily S, member 1	322101	4595	322754	12583	20571, 28559, 36547, 44535, 52523
4441	olfactory receptor, family 51, subfamily T, member 1	322049	4596	322679	12584	20572, 28560, 36548, 44536, 52524

4442	olfactory receptor, family 51, subfamily T, member 1	380378	4597	369738	12585	20573, 28561, 36549, 44537, 52525
4443	olfactory receptor, family 51, subfamily V, member 1	321255	4598	321729	12586	20574, 28562, 36550, 44538, 52526
4444	olfactory receptor, family 52, subfamily A, member 1	328942	4599	333684	12587	20575, 28563, 36551, 44539, 52527
4445	olfactory receptor, family 52, subfamily A, member 1	380367	4600	369725	12588	20576, 28564, 36552, 44540, 52528
4446	olfactory receptor, family 52, subfamily A, member 5	307388	4601	303469	12589	20577, 28565, 36553, 44541, 52529
4447	olfactory receptor, family 52, subfamily B, member 2	530810	4602	432011	12590	20578, 28566, 36554, 44542, 52530
4448	olfactory receptor, family 52, subfamily B, member 4	408920	4603	386160	12591	20579, 28567, 36555, 44543, 52531
4449	olfactory receptor, family 52, subfamily B, member 6	345043	4604	341581	12592	20580, 28568, 36556, 44544, 52532
4450	olfactory receptor, family 52, subfamily D, member 1	322641	4605	326232	12593	20581, 28569, 36557, 44545, 52533
4451	olfactory receptor, family 52, subfamily E, member 2	321522	4606	322088	12594	20582, 28570, 36558, 44546, 52534
4452	olfactory receptor, family 52, subfamily E, member 4	316987	4607	321426	12595	20583, 28571, 36559, 44547, 52535
4453	olfactory receptor, family 52, subfamily E, member 6	329322	4608	328878	12596	20584, 28572, 36560, 44548, 52536
4454	olfactory receptor, family 52, subfamily E, member 6	379946	4609	369279	12597	20585, 28573, 36561, 44549, 52537
4455	olfactory receptor, family 52, subfamily E, member 8	537935	4610	444054	12598	20586, 28574, 36562, 44550, 52538
4456	olfactory receptor, family 52, subfamily H, member 1	322653	4611	326259	12599	20587, 28575, 36563, 44551, 52539
4457	olfactory receptor, family 52, subfamily I, member 1	450052	4612	409094	12600	20588, 28576, 36564, 44552, 52540
4458	olfactory receptor, family 52, subfamily I, member 1	530443	4613	436453	12601	20589, 28577, 36565, 44553, 52541
4459	olfactory receptor, family 52, subfamily I, member 2	312614	4614	308764	12602	20590, 28578, 36566, 44554, 52542

4460	olfactory receptor, family 52, subfamily J, member 3	380370	4615	369728	12603	20591, 28579, 36567, 44555, 52543
4461	olfactory receptor, family 52, subfamily K, member 1	307632	4616	302422	12604	20592, 28580, 36568, 44556, 52544
4462	olfactory receptor, family 52, subfamily K, member 2	325719	4617	318956	12605	20593, 28581, 36569, 44557, 52545
4463	olfactory receptor, family 52, subfamily L, member 1	332249	4618	330338	12606	20594, 28582, 36570, 44558, 52546
4464	olfactory receptor, family 52, subfamily M, member 1	360213	4619	353343	12607	20595, 28583, 36571, 44559, 52547
4465	olfactory receptor, family 52, subfamily N, member 1	317078	4620	322823	12608	20596, 28584, 36572, 44560, 52548
4466	olfactory receptor, family 52, subfamily N, member 2	317037	4621	322801	12609	20597, 28585, 36573, 44561, 52549
4467	olfactory receptor, family 52, subfamily N, member 4	317254	4622	323224	12610	20598, 28586, 36574, 44562, 52550
4468	olfactory receptor, family 52, subfamily N, member 5	317093	4623	322866	12611	20599, 28587, 36575, 44563, 52551
4469	olfactory receptor, family 52, subfamily R, member 1	356069	4624	348368	12612	20600, 28588, 36576, 44564, 52552
4470	olfactory receptor, family 52, subfamily R, member 1	380382	4625	369742	12613	20601, 28589, 36577, 44565, 52553
4471	olfactory receptor, family 52, subfamily W, member 1	311352	4626	309673	12614	20602, 28590, 36578, 44566, 52554
4472	olfactory receptor, family 56, subfamily A, member 1	316650	4627	321246	12615	20603, 28591, 36579, 44567, 52555
4473	olfactory receptor, family 56, subfamily A, member 3	329564	4628	331572	12616	20604, 28592, 36580, 44568, 52556
4474	olfactory receptor, family 56, subfamily A, member 4	330728	4629	328215	12617	20605, 28593, 36581, 44569, 52557
4475	olfactory receptor, family 56, subfamily B, member 1	317121	4630	322939	12618	20606, 28594, 36582, 44570, 52558
4476	olfactory receptor, family 56, subfamily B, member 4	316529	4631	321196	12619	20607, 28595, 36583, 44571, 52559
4477	olfactory receptor, family 6, subfamily A, member 2	332601	4632	330384	12620	20608, 28596, 36584, 44572, 52560

4478	olfactory receptor, family 6, subfamily B, member 1	408922	4633	386151	12621	20609, 28597, 36585, 44573, 52561
4479	olfactory receptor, family 6, subfamily B, member 2	402971	4634	384563	12622	20610, 28598, 36586, 44574, 52562
4480	olfactory receptor, family 6, subfamily B, member 3	319423	4635	322435	12623	20611, 28599, 36587, 44575, 52563
4481	olfactory receptor, family 6, subfamily C, member 1	379668	4636	368990	12624	20612, 28600, 36588, 44576, 52564
4482	olfactory receptor, family 6, subfamily C, member 2	322678	4637	323606	12625	20613, 28601, 36589, 44577, 52565
4483	olfactory receptor, family 6, subfamily C, member 3	379667	4638	368989	12626	20614, 28602, 36590, 44578, 52566
4484	olfactory receptor, family 6, subfamily C, member 4	394256	4639	377799	12627	20615, 28603, 36591, 44579, 52567
4485	olfactory receptor, family 6, subfamily C, member 65	379665	4640	368986	12628	20616, 28604, 36592, 44580, 52568
4486	olfactory receptor, family 6, subfamily C, member 68	379662	4641	368983	12629	20617, 28605, 36593, 44581, 52569
4487	olfactory receptor, family 6, subfamily C, member 68	548615	4642	448811	12630	20618, 28606, 36594, 44582, 52570
4488	olfactory receptor, family 6, subfamily C, member 70	327335	4643	329153	12631	20619, 28607, 36595, 44583, 52571
4489	olfactory receptor, family 6, subfamily C, member 74	343870	4644	342836	12632	20620, 28608, 36596, 44584, 52572
4490	olfactory receptor, family 6, subfamily C, member 75	343399	4645	368987	12633	20621, 28609, 36597, 44585, 52573
4491	olfactory receptor, family 6, subfamily F, member 1	302084	4646	305640	12634	20622, 28610, 36598, 44586, 52574
4492	olfactory receptor, family 6, subfamily J, member 1	540461	4647	437629	12635	20623, 28611, 36599, 44587, 52575
4493	olfactory receptor, family 6, subfamily K, member 2	359610	4648	352626	12636	20624, 28612, 36600, 44588, 52576
4494	olfactory receptor, family 6, subfamily K, member 3	368145	4649	357127	12637	20625, 28613, 36601, 44589, 52577
4495	olfactory receptor, family 6, subfamily K, member 3	368146	4650	357128	12638	20626, 28614, 36602, 44590, 52578

4496	olfactory receptor, family 6, subfamily K, member 6	368144	4651	357126	12639	20627, 28615, 36603, 44591, 52579
4497	olfactory receptor, family 6, subfamily M, member 1	309154	4652	311038	12640	20628, 28616, 36604, 44592, 52580
4498	olfactory receptor, family 6, subfamily N, member 1	335094	4653	335535	12641	20629, 28617, 36605, 44593, 52581
4499	olfactory receptor, family 6, subfamily N, member 2	339258	4654	344101	12642	20630, 28618, 36606, 44594, 52582
4500	olfactory receptor, family 6, subfamily P, member 1	334632	4655	334721	12643	20631, 28619, 36607, 44595, 52583
4501	olfactory receptor, family 6, subfamily Q, member 1	302622	4656	307734	12644	20632, 28620, 36608, 44596, 52584
4502	olfactory receptor, family 6, subfamily S, member 1	320704	4657	313110	12645	20633, 28621, 36609, 44597, 52585
4503	olfactory receptor, family 6, subfamily T, member 1	321252	4658	325203	12646	20634, 28622, 36610, 44598, 52586
4504	olfactory receptor, family 6, subfamily V, member 1	418316	4659	396085	12647	20635, 28623, 36611, 44599, 52587
4505	olfactory receptor, family 6, subfamily X, member 1	327930	4660	333724	12648	20636, 28624, 36612, 44600, 52588
4506	olfactory receptor, family 6, subfamily Y, member 1	302617	4661	304807	12649	20637, 28625, 36613, 44601, 52589
4507	olfactory receptor, family 7, subfamily A, member 10	248058	4662	248058	12650	20638, 28626, 36614, 44602, 52590
4508	olfactory receptor, family 7, subfamily A, member 17	327462	4663	328144	12651	20639, 28627, 36615, 44603, 52591
4509	olfactory receptor, family 7, subfamily A, member 2 pseudogene	304105	4664	307397	12652	20640, 28628, 36616, 44604, 52592
4510	olfactory receptor, family 7, subfamily A, member 5	322301	4665	316955	12653	20641, 28629, 36617, 44605, 52593
4511	olfactory receptor, family 7, subfamily D, member 2	344248	4666	345563	12654	20642, 28630, 36618, 44606, 52594
4512	olfactory receptor, family 7, subfamily E, member 24	456448	4667	387523	12655	20643, 28631, 36619, 44607, 52595
4513	olfactory receptor, family 7, subfamily G, member 1	293614	4668	293614	12656	20644, 28632, 36620, 44608, 52596

4514	olfactory receptor, family 7, subfamily G, member 1	541538	4669	444134	12657	20645, 28633, 36621, 44609, 52597
4515	olfactory receptor, family 7, subfamily G, member 2	305456	4670	303822	12658	20646, 28634, 36622, 44610, 52598
4516	olfactory receptor, family 7, subfamily G, member 3	305444	4671	302867	12659	20647, 28635, 36623, 44611, 52599
4517	olfactory receptor, family 8, subfamily A, member 1	284287	4672	284287	12660	20648, 28636, 36624, 44612, 52600
4518	olfactory receptor, family 8, subfamily B, member 12	306842	4673	307159	12661	20649, 28637, 36625, 44613, 52601
4519	olfactory receptor, family 8, subfamily B, member 2	375013	4674	364152	12662	20650, 28638, 36626, 44614, 52602
4520	olfactory receptor, family 8, subfamily B, member 3	354597	4675	346611	12663	20651, 28639, 36627, 44615, 52603
4521	olfactory receptor, family 8, subfamily B, member 4	356130	4676	348449	12664	20652, 28640, 36628, 44616, 52604
4522	olfactory receptor, family 8, subfamily B, member 8	328064	4677	330280	12665	20653, 28641, 36629, 44617, 52605
4523	olfactory receptor, family 8, subfamily D, member 1	357821	4678	350474	12666	20654, 28642, 36630, 44618, 52606
4524	olfactory receptor, family 8, subfamily D, member 2	357438	4679	350022	12667	20655, 28643, 36631, 44619, 52607
4525	olfactory receptor, family 8, subfamily D, member 4	321355	4680	325381	12668	20656, 28644, 36632, 44620, 52608
4526	olfactory receptor, family 8, subfamily H, member 1	313022	4681	323595	12669	20657, 28645, 36633, 44621, 52609
4527	olfactory receptor, family 8, subfamily H, member 1	395186	4682	378613	12670	20658, 28646, 36634, 44622, 52610
4528	olfactory receptor, family 8, subfamily H, member 2	313503	4683	323982	12671	20659, 28647, 36635, 44623, 52611
4529	olfactory receptor, family 8, subfamily H, member 3	313472	4684	323928	12672	20660, 28648, 36636, 44624, 52612
4530	olfactory receptor, family 8, subfamily I, member 2	302124	4685	303864	12673	20661, 28649, 36637, 44625, 52613
4531	olfactory receptor, family 8, subfamily J, member 1	303039	4686	304060	12674	20662, 28650, 36638, 44626, 52614

4532	olfactory receptor, family 8, subfamily J, member 3	301529	4687	301529	12675	20663, 28651, 36639, 44627, 52615
4533	olfactory receptor, family 8, subfamily K, member 1	279783	4688	279783	12676	20664, 28652, 36640, 44628, 52616
4534	olfactory receptor, family 8, subfamily K, member 3	312711	4689	323555	12677	20665, 28653, 36641, 44629, 52617
4535	olfactory receptor, family 8, subfamily K, member 5	313447	4690	323853	12678	20666, 28654, 36642, 44630, 52618
4536	olfactory receptor, family 8, subfamily S, member 1	310194	4691	310632	12679	20667, 28655, 36643, 44631, 52619
4537	olfactory receptor, family 8, subfamily U, member 1	302270	4692	304188	12680	20668, 28656, 36644, 44632, 52620
4538	olfactory receptor, family 9, subfamily A, member 2	350513	4693	316518	12681	20669, 28657, 36645, 44633, 52621
4539	olfactory receptor, family 9, subfamily A, member 4	548136	4694	448789	12682	20670, 28658, 36646, 44634, 52622
4540	olfactory receptor, family 9, subfamily G, member 1	312153	4695	309012	12683	20671, 28659, 36647, 44635, 52623
4541	olfactory receptor, family 9, subfamily G, member 4	302957	4696	307515	12684	20672, 28660, 36648, 44636, 52624
4542	olfactory receptor, family 9, subfamily I, member 1	302610	4697	302606	12685	20673, 28661, 36649, 44637, 52625
4543	olfactory receptor, family 9, subfamily K, member 2	305377	4698	307598	12686	20674, 28662, 36650, 44638, 52626
4544	olfactory receptor, family 9, subfamily Q, member 1	335397	4699	334934	12687	20675, 28663, 36651, 44639, 52627
4545	olfactory receptor, family 9, subfamily Q, member 2	311591	4700	308714	12688	20676, 28664, 36652, 44640, 52628
4546	oligodendrocytic myelin paranodal and inner loop protein	371172	4701	360214	12689	20677, 28665, 36653, 44641, 52629
4547	oligodendrocytic myelin paranodal and inner loop protein	393870	4702	377448	12690	20678, 28666, 36654, 44642, 52630
4548	oligodendrocytic myelin paranodal and inner loop protein	393871	4703	377449	12691	20679, 28667, 36655, 44643, 52631

4549	oligodendrocytic myelin paranodal and inner loop protein	419479	4704	398025	12692	20680, 28668, 36656, 44644, 52632
4550	oligodendrocytic myelin paranodal and inner loop protein	536387	4705	445125	12693	20681, 28669, 36657, 44645, 52633
4551	oligosaccharyltransferase complex subunit	361564	4706	354676	12694	20682, 28670, 36658, 44646, 52634
4552	oligosaccharyltransferase complex subunit	512478	4707	426167	12695	20683, 28671, 36659, 44647, 52635
4553	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	358603	4708	351417	12696	20684, 28672, 36660, 44648, 52636
4554	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	371226	4709	360270	12697	20685, 28673, 36661, 44649, 52637
4555	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	419242	4710	409589	12698	20686, 28674, 36662, 44650, 52638
4556	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	421528	4711	391941	12699	20687, 28675, 36663, 44651, 52639
4557	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	426139	4712	416495	12700	20688, 28676, 36664, 44652, 52640
4558	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	453710	4713	392978	12701	20689, 28677, 36665, 44653, 52641
4559	OMA1 zinc metallopeptidase homolog (S. cerevisiae)	456980	4714	395053	12702	20690, 28678, 36666, 44654, 52642
4560	omega-3 fatty acid receptor 1	371481	4715	360536	12703	20691, 28679, 36667, 44655, 52643
4561	omega-3 fatty acid receptor 1	371483	4716	360538	12704	20692, 28680, 36668, 44656, 52644
4562	opiate receptor-like 1	336866	4717	336843	12705	20693, 28681, 36669, 44657, 52645
4563	opiate receptor-like 1	349451	4718	336764	12706	20694, 28682, 36670, 44658, 52646

4564	opiate receptor-like 1	355631	4719	347848	12707	20695, 28683, 36671, 44659, 52647
4565	opsin 1 (cone pigments), long-wave-sensitive	442922	4720	402493	12708	20696, 28684, 36672, 44660, 52648
4566	opsin 1 (cone pigments), medium-wave-sensitive 2	369929	4721	358945	12709	20697, 28685, 36673, 44661, 52649
4567	opsin 4	241891	4722	241891	12710	20698, 28686, 36674, 44662, 52650
4568	opsin 4	372071	4723	361141	12711	20699, 28687, 36675, 44663, 52651
4569	opsin 4	443292	4724	393132	12712	20700, 28688, 36676, 44664, 52652
4570	opsin 5	371211	4725	360255	12713	20701, 28689, 36677, 44665, 52653
4571	organic solute carrier partner 1	235532	4726	235532	12714	20702, 28690, 36678, 44666, 52654
4572	organic solute carrier partner 1	315643	4727	314541	12715	20703, 28691, 36679, 44667, 52655
4573	organic solute carrier partner 1	354267	4728	346216	12716	20704, 28692, 36680, 44668, 52656
4574	organic solute carrier partner 1	356637	4729	349052	12717	20705, 28693, 36681, 44669, 52657
4575	Organic solute transporter subunit alpha	296327	4730	296327	12718	20706, 28694, 36682, 44670, 52658
4576	Organic solute transporter subunit beta	334287	4731	335292	12719	20707, 28695, 36683, 44671, 52659
4577	O-sialoglycoprotein endopeptidase-like 1	264151	4732	264151	12720	20708, 28696, 36684, 44672, 52660
4578	O-sialoglycoprotein endopeptidase-like 1	517895	4733	430879	12721	20709, 28697, 36685, 44673, 52661
4579	O-sialoglycoprotein endopeptidase-like 1	521630	4734	429385	12722	20710, 28698, 36686, 44674, 52662
4580	O-sialoglycoprotein endopeptidase-like 1	522700	4735	429697	12723	20711, 28699, 36687, 44675, 52663
4581	otopetrin 2	331427	4736	332528	12724	20712, 28700, 36688, 44676, 52664

4582	otopetrin 3	328801	4737	328090	12725	20713, 28701, 36689, 44677, 52665
4583	oxidoreductase NAD-binding domain containing 1	285083	4738	285083	12726	20714, 28702, 36690, 44678, 52666
4584	oxidoreductase NAD-binding domain containing 1	435829	4739	389872	12727	20715, 28703, 36691, 44679, 52667
4585	oxidoreductase NAD-binding domain containing 1	544043	4740	437967	12728	20716, 28704, 36692, 44680, 52668
4586	oxoeicosanoid (OXE) receptor 1	378661	4741	367930	12729	20717, 28705, 36693, 44681, 52669
4587	oxoglutarate (alpha-ketoglutarate) receptor 1	298440	4742	298440	12730	20718, 28706, 36694, 44682, 52670
4588	oxoglutarate (alpha-ketoglutarate) receptor 1	541038	4743	437356	12731	20719, 28707, 36695, 44683, 52671
4589	oxoglutarate (alpha-ketoglutarate) receptor 1	541518	4744	445269	12732	20720, 28708, 36696, 44684, 52672
4590	oxoglutarate (alpha-ketoglutarate) receptor 1	543457	4745	438800	12733	20721, 28709, 36697, 44685, 52673
4591	oxoglutarate dehydrogenase-like	374103	4746	363216	12734	20722, 28710, 36698, 44686, 52674
4592	oxoglutarate dehydrogenase-like	419399	4747	401356	12735	20723, 28711, 36699, 44687, 52675
4593	oxoglutarate dehydrogenase-like	432695	4748	390240	12736	20724, 28712, 36700, 44688, 52676
4594	p21 protein (Cdc42/Rac)-activated kinase 7	353224	4749	322957	12737	20725, 28713, 36701, 44689, 52677
4595	p21 protein (Cdc42/Rac)-activated kinase 7	378423	4750	367679	12738	20726, 28714, 36702, 44690, 52678
4596	p21 protein (Cdc42/Rac)-activated kinase 7	378429	4751	367686	12739	20727, 28715, 36703, 44691, 52679
4597	p21 protein (Cdc42/Rac)-activated kinase 7	439520	4752	414175	12740	20728, 28716, 36704, 44692, 52680
4598	pannexin 1	227638	4753	227638	12741	20729, 28717, 36705, 44693, 52681
4599	pannexin 1	436171	4754	411461	12742	20730, 28718, 36706, 44694, 52682

4600	pannexin 2	395842	4755	379183	12743	20731, 28719, 36707, 44695, 52683
4601	pannexin 2	401643	4756	385054	12744	20732, 28720, 36708, 44696, 52684
4602	pannexin 3	284288	4757	284288	12745	20733, 28721, 36709, 44697, 52685
4603	PAPPA antisense RNA 1 (non-protein coding)	445861	4758	398729	12746	20734, 28722, 36710, 44698, 52686
4604	par-3 partitioning defective 3 homolog B (C. elegans)	349953	4759	340280	12747	20735, 28723, 36711, 44699, 52687
4605	par-3 partitioning defective 3 homolog B (C. elegans)	351153	4760	317261	12748	20736, 28724, 36712, 44700, 52688
4606	par-3 partitioning defective 3 homolog B (C. elegans)	358768	4761	351618	12749	20737, 28725, 36713, 44701, 52689
4607	par-3 partitioning defective 3 homolog B (C. elegans)	406610	4762	385848	12750	20738, 28726, 36714, 44702, 52690
4608	par-6 partitioning defective 6 homolog alpha (C. elegans)	219255	4763	219255	12751	20739, 28727, 36715, 44703, 52691
4609	par-6 partitioning defective 6 homolog alpha (C. elegans)	458121	4764	392388	12752	20740, 28728, 36716, 44704, 52692
4610	paralemmin	264560	4765	264560	12753	20741, 28729, 36717, 44705, 52693
4611	paralemmin	338448	4766	341911	12754	20742, 28730, 36718, 44706, 52694
4612	paralemmin	538247	4767	446163	12755	20743, 28731, 36719, 44707, 52695
4613	paraneoplastic antigen MA1	316836	4768	318914	12756	20744, 28732, 36720, 44708, 52696
4614	parathyroid hormone 1 receptor	313049	4769	321999	12757	20745, 28733, 36721, 44709, 52697
4615	parathyroid hormone 1 receptor	418619	4770	411424	12758	20746, 28734, 36722, 44710, 52698
4616	parathyroid hormone 1 receptor	427125	4771	400977	12759	20747, 28735, 36723, 44711, 52699
4617	parathyroid hormone 1 receptor	428220	4772	389811	12760	20748, 28736, 36724, 44712, 52700

4618	parathyroid hormone 1 receptor	430002	4773	413774	12761	20749, 28737, 36725, 44713, 52701
4619	parathyroid hormone 1 receptor	449590	4774	402723	12762	20750, 28738, 36726, 44714, 52702
4620	parathyroid hormone 2 receptor	272847	4775	272847	12763	20751, 28739, 36727, 44715, 52703
4621	PDZK1 interacting protein 1	294338	4776	294338	12764	20752, 28740, 36728, 44716, 52704
4622	PDZK1 interacting protein 1	371885	4777	360952	12765	20753, 28741, 36729, 44717, 52705
4623	pecanex homolog (Drosophila)	238570	4778	238570	12766	20754, 28742, 36730, 44718, 52706
4624	pecanex homolog (Drosophila)	304743	4779	304192	12767	20755, 28743, 36731, 44719, 52707
4625	pecanex homolog (Drosophila)	439984	4780	396617	12768	20756, 28744, 36732, 44720, 52708
4626	pecanex homolog (Drosophila)	554691	4781	451016	12769	20757, 28745, 36733, 44721, 52709
4627	pecanex-like 2 (Drosophila)	258229	4782	258229	12770	20758, 28746, 36734, 44722, 52710
4628	pecanex-like 2 (Drosophila)	344698	4783	340759	12771	20759, 28747, 36735, 44723, 52711
4629	pecanex-like 2 (Drosophila)	430153	4784	394703	12772	20760, 28748, 36736, 44724, 52712
4630	pecanex-like 3 (Drosophila)	355703	4785	347931	12773	20761, 28749, 36737, 44725, 52713
4631	pentatricopeptide repeat domain 2	308077	4786	308948	12774	20762, 28750, 36738, 44726, 52714
4632	pentatricopeptide repeat domain 2	380639	4787	370013	12775	20763, 28751, 36739, 44727, 52715
4633	pentatricopeptide repeat domain 2	536805	4788	444772	12776	20764, 28752, 36740, 44728, 52716
4634	pentatricopeptide repeat domain 2	543322	4789	438810	12777	20765, 28753, 36741, 44729, 52717
4635	Pentatricopeptide repeat domain 3	254630	4790	254630	12778	20766, 28754, 36742, 44730, 52718

4636	Pentatricopeptide repeat domain 3	409277	4791	386462	12779	20767, 28755, 36743, 44731, 52719
4637	peptidase (mitochondrial processing) beta	249269	4792	249269	12780	20768, 28756, 36744, 44732, 52720
4638	peptidase (mitochondrial processing) beta	420236	4793	410393	12781	20769, 28757, 36745, 44733, 52721
4639	peptidyl-tRNA hydrolase 1 homolog (S. cerevisiae)	419060	4794	418661	12782	20770, 28758, 36746, 44734, 52722
4640	peptidyl-tRNA hydrolase 1 homolog (S. cerevisiae)	543175	4795	439469	12783	20771, 28759, 36747, 44735, 52723
4641	perilipin 4	301286	4796	301286	12784	20772, 28760, 36748, 44736, 52724
4642	peroxisomal biogenesis factor 11 beta	369306	4797	358312	12785	20773, 28761, 36749, 44737, 52725
4643	peroxisomal biogenesis factor 11 beta	428634	4798	414018	12786	20774, 28762, 36750, 44738, 52726
4644	peroxisomal biogenesis factor 11 beta	537888	4799	437510	12787	20775, 28763, 36751, 44739, 52727
4645	peroxisomal biogenesis factor 12	225873	4800	225873	12788	20776, 28764, 36752, 44740, 52728
4646	peroxisomal biogenesis factor 12	424525	4801	399205	12789	20777, 28765, 36753, 44741, 52729
4647	peroxisomal membrane protein 2, 22kDa	317479	4802	321271	12790	20778, 28766, 36754, 44742, 52730
4648	peroxisomal membrane protein 2, 22kDa	545677	4803	445782	12791	20779, 28767, 36755, 44743, 52731
4649	peroxisomal membrane protein 4, 24kDa	344022	4804	343071	12792	20780, 28768, 36756, 44744, 52732
4650	peroxisomal membrane protein 4, 24kDa	409299	4805	386385	12793	20781, 28769, 36757, 44745, 52733
4651	PERP, TP53 apoptosis effector	265603	4806	265603	12794	20782, 28770, 36758, 44746, 52734
4652	PERP, TP53 apoptosis effector	421351	4807	397157	12795	20783, 28771, 36759, 44747, 52735
4653	PET112 homolog (yeast)	263985	4808	263985	12796	20784, 28772, 36760, 44748, 52736

4654	phosphatidic acid phosphatase type 2 domain containing 1A	369073	4809	358069	12797	20785, 28773, 36761, 44749, 52737
4655	phosphatidic acid phosphatase type 2 domain containing 1A	398248	4810	381300	12798	20786, 28774, 36762, 44750, 52738
4656	phosphatidic acid phosphatase type 2 domain containing 1A	398250	4811	381302	12799	20787, 28775, 36763, 44751, 52739
4657	phosphatidic acid phosphatase type 2 domain containing 1A	427079	4812	407979	12800	20788, 28776, 36764, 44752, 52740
4658	phosphatidic acid phosphatase type 2 domain containing 1A	439221	4813	403508	12801	20789, 28777, 36765, 44753, 52741
4659	phosphatidic acid phosphatase type 2 domain containing 1A	541332	4814	440493	12802	20790, 28778, 36766, 44754, 52742
4660	phosphatidic acid phosphatase type 2 domain containing 3	372261	4815	361335	12803	20791, 28779, 36767, 44755, 52743
4661	phosphatidic acid phosphatase type 2 domain containing 3	372264	4816	361338	12804	20792, 28780, 36768, 44756, 52744
4662	phosphatidic acid phosphatase type 2A	264775	4817	264775	12805	20793, 28781, 36769, 44757, 52745
4663	phosphatidic acid phosphatase type 2A	307259	4818	302229	12806	20794, 28782, 36770, 44758, 52746
4664	phosphatidic acid phosphatase type 2B	371250	4819	360296	12807	20795, 28783, 36771, 44759, 52747
4665	phosphatidic acid phosphatase type 2C	269812	4820	269812	12808	20796, 28784, 36772, 44760, 52748
4666	phosphatidic acid phosphatase type 2C	327790	4821	329697	12809	20797, 28785, 36773, 44761, 52749
4667	phosphatidic acid phosphatase type 2C	434325	4822	388565	12810	20798, 28786, 36774, 44762, 52750
4668	phosphatidylethanolamine N-methyltransferase	255389	4823	255389	12811	20799, 28787, 36775, 44763, 52751
4669	phosphatidylethanolamine N-methyltransferase	395781	4824	379127	12812	20800, 28788, 36776, 44764, 52752

4670	phosphatidylethanolamine N-methyltransferase	395782	4825	379128	12813	20801, 28789, 36777, 44765, 52753
4671	phosphatidylethanolamine N-methyltransferase	395783	4826	379129	12814	20802, 28790, 36778, 44766, 52754
4672	phosphatidylethanolamine N-methyltransferase	421096	4827	398705	12815	20803, 28791, 36779, 44767, 52755
4673	phosphatidylethanolamine N-methyltransferase	435340	4828	391288	12816	20804, 28792, 36780, 44768, 52756
4674	phosphatidylethanolamine-binding protein 4	256404	4829	256404	12817	20805, 28793, 36781, 44769, 52757
4675	phosphatidylglycerophosphate synthase 1	262764	4830	262764	12818	20806, 28794, 36782, 44770, 52758
4676	phosphatidylglycerophosphate synthase 1	329897	4831	330039	12819	20807, 28795, 36783, 44771, 52759
4677	phosphatidylglycerophosphate synthase 1	335081	4832	334151	12820	20808, 28796, 36784, 44772, 52760
4678	phosphatidylinositol glycan anchor biosynthesis, class G	296306	4833	296306	12821	20809, 28797, 36785, 44773, 52761
4679	phosphatidylinositol glycan anchor biosynthesis, class G	310340	4834	311750	12822	20810, 28798, 36786, 44774, 52762
4680	phosphatidylinositol glycan anchor biosynthesis, class G	383028	4835	372494	12823	20811, 28799, 36787, 44775, 52763
4681	phosphatidylinositol glycan anchor biosynthesis, class G	453061	4836	415203	12824	20812, 28800, 36788, 44776, 52764
4682	phosphatidylinositol glycan anchor biosynthesis, class G	453065	4837	394941	12825	20813, 28801, 36789, 44777, 52765
4683	phosphatidylinositol glycan anchor biosynthesis, class G	503111	4838	426002	12826	20814, 28802, 36790, 44778, 52766
4684	phosphatidylinositol glycan anchor biosynthesis, class G	536264	4839	439240	12827	20815, 28803, 36791, 44779, 52767
4685	phosphatidylinositol glycan anchor biosynthesis, class O	298004	4840	298004	12828	20816, 28804, 36792, 44780, 52768
4686	phosphatidylinositol glycan anchor biosynthesis, class O	341666	4841	339382	12829	20817, 28805, 36793, 44781, 52769
4687	phosphatidylinositol glycan anchor biosynthesis, class O	361778	4842	354678	12830	20818, 28806, 36794, 44782, 52770

4688	phosphatidylinositol glycan anchor biosynthesis, class O	378617	4843	367880	12831	20819, 28807, 36795, 44783, 52771
4689	phosphatidylinositol glycan anchor biosynthesis, class Q	26218	4844	26218	12832	20820, 28808, 36796, 44784, 52772, 56089, 56122
4690	phosphatidylinositol glycan anchor biosynthesis, class Q	293874	4845	293874	12833	20821, 28809, 36797, 44785, 52773
4691	phosphatidylinositol glycan anchor biosynthesis, class Q	321878	4846	326674	12834	20822, 28810, 36798, 44786, 52774
4692	phosphatidylinositol glycan anchor biosynthesis, class Q	409439	4847	386554	12835	20823, 28811, 36799, 44787, 52775
4693	phosphatidylinositol glycan anchor biosynthesis, class Q	409527	4848	386760	12836	20824, 28812, 36800, 44788, 52776
4694	phosphatidylinositol glycan anchor biosynthesis, class Q	422307	4849	413753	12837	20825, 28813, 36801, 44789, 52777
4695	phosphatidylinositol glycan anchor biosynthesis, class Q	439574	4850	387820	12838	20826, 28814, 36802, 44790, 52778
4696	phosphatidylinositol glycan anchor biosynthesis, class Q	443147	4851	410434	12839	20827, 28815, 36803, 44791, 52779
4697	phosphatidylinositol glycan anchor biosynthesis, class Q	470411	4852	439650	12840	20828, 28816, 36804, 44792, 52780
4698	phosphatidylinositol glycan anchor biosynthesis, class S	268758	4853	268758	12841	20829, 28817, 36805, 44793, 52781
4699	phosphatidylinositol glycan anchor biosynthesis, class S	308360	4854	309430	12842	20830, 28818, 36806, 44794, 52782
4700	phosphatidylinositol glycan anchor biosynthesis, class S	395346	4855	378755	12843	20831, 28819, 36807, 44795, 52783
4701	phosphatidylinositol glycan anchor biosynthesis, class S	543734	4856	438447	12844	20832, 28820, 36808, 44796, 52784
4702	phosphatidylinositol glycan anchor biosynthesis, class T	279035	4857	279035	12845	20833, 28821, 36809, 44797, 52785
4703	phosphatidylinositol glycan anchor biosynthesis, class T	279036	4858	279036	12846	20834, 28822, 36810, 44798, 52786
4704	phosphatidylinositol glycan anchor biosynthesis, class T	341555	4859	343783	12847	20835, 28823, 36811, 44799, 52787
4705	phosphatidylinositol glycan anchor biosynthesis, class T	372689	4860	361774	12848	20836, 28824, 36812, 44800, 52788

4706	phosphatidylinositol glycan anchor biosynthesis, class T	535404	4861	440528	12849	20837, 28825, 36813, 44801, 52789
4707	phosphatidylinositol glycan anchor biosynthesis, class T	543458	4862	441577	12850	20838, 28826, 36814, 44802, 52790
4708	phosphatidylinositol glycan anchor biosynthesis, class T	545755	4863	443963	12851	20839, 28827, 36815, 44803, 52791
4709	phosphatidylinositol glycan anchor biosynthesis, class Y	273968	4864	273968	12852	20840, 28828, 36816, 44804, 52792
4710	Phosphatidylinositol N-acetylglucosaminyltransferase subunit Y	527353	4865	432688	12853	20841, 28829, 36817, 44805, 52793
4711	phosphatidylinositol transfer protein, membrane-associated 2	280562	4866	280562	12854	20842, 28830, 36818, 44806, 52794
4712	phosphatidylinositol transfer protein, membrane-associated 2	320201	4867	322218	12855	20843, 28831, 36819, 44807, 52795
4713	phosphatidylinositol transfer protein, membrane-associated 2	392428	4868	376223	12856	20844, 28832, 36820, 44808, 52796
4714	phosphatidylinositol transfer protein, membrane-associated 2	541244	4869	445399	12857	20845, 28833, 36821, 44809, 52797
4715	phosphatidylinositol transfer protein, membrane-associated 2	542210	4870	437869	12858	20846, 28834, 36822, 44810, 52798
4716	phosphatidylinositol transfer protein, membrane-associated 2	542749	4871	437611	12859	20847, 28835, 36823, 44811, 52799
4717	phosphatidylinositol -5-phosphate 4-kinase, type II, beta	269554	4872	269554	12860	20848, 28836, 36824, 44812, 52800
4718	phosphatidylinositol -5-phosphate 4-kinase, type II, beta	311500	4873	311210	12861	20849, 28837, 36825, 44813, 52801
4719	phosphodiesterase 12	311180	4874	309142	12862	20850, 28838, 36826, 44814, 52802
4720	phosphodiesterase 12	487257	4875	420626	12863	20851, 28839, 36827, 44815, 52803
4721	phosphodiesterase 2A, cGMP-stimulated	334456	4876	334910	12864	20852, 28840, 36828, 44816, 52804

4722	phosphodiesterase 2A, cGMP-stimulated	376450	4877	365633	12865	20853, 28841, 36829, 44817, 52805
4723	phosphodiesterase 2A, cGMP-stimulated	429363	4878	401006	12866	20854, 28842, 36830, 44818, 52806
4724	phosphodiesterase 2A, cGMP-stimulated	444035	4879	411657	12867	20855, 28843, 36831, 44819, 52807
4725	phosphodiesterase 2A, cGMP-stimulated	544570	4880	442256	12868	20856, 28844, 36832, 44820, 52808
4726	phosphodiesterase 3A, cGMP-inhibited	359062	4881	351957	12869	20857, 28845, 36833, 44821, 52809
4727	phosphofurin acidic cluster sorting protein 2	325438	4882	321834	12870	20858, 28846, 36834, 44822, 52810
4728	phosphofurin acidic cluster sorting protein 2	447393	4883	393559	12871	20859, 28847, 36835, 44823, 52811
4729	phosphofurin acidic cluster sorting protein 2	458164	4884	399732	12872	20860, 28848, 36836, 44824, 52812
4730	phosphoglycerate mutase family member 5	317555	4885	321503	12873	20861, 28849, 36837, 44825, 52813
4731	phosphoglycerate mutase family member 5	498926	4886	438465	12874	20862, 28850, 36838, 44826, 52814
4732	phosphoinositide-3-kinase adaptor protein 1	339364	4887	339826	12875	20863, 28851, 36839, 44827, 52815
4733	phosphoinositide-3-kinase adaptor protein 1	371109	4888	360150	12876	20864, 28852, 36840, 44828, 52816
4734	phosphoinositide-3-kinase adaptor protein 1	371110	4889	360151	12877	20865, 28853, 36841, 44829, 52817
4735	phosphoinositide-3-kinase interacting protein 1	215912	4890	215912	12878	20866, 28854, 36842, 44830, 52818
4736	phosphoinositide-3-kinase interacting protein 1	402249	4891	385204	12879	20867, 28855, 36843, 44831, 52819
4737	phosphoinositide-3-kinase interacting protein 1	416925	4892	403641	12880	20868, 28856, 36844, 44832, 52820
4738	phosphoinositide-3-kinase interacting protein 1	441972	4893	415608	12881	20869, 28857, 36845, 44833, 52821
4739	phosphoinositide-3-kinase interacting protein 1	487265	4894	441361	12882	20870, 28858, 36846, 44834, 52822

4740	phospholipase A2, group IVF	290497	4895	290497	12883	20871, 28859, 36847, 44835, 52823
4741	phospholipase A2, group IVF	357924	4896	350604	12884	20872, 28860, 36848, 44836, 52824
4742	phospholipase A2, group IVF	382396	4897	371833	12885	20873, 28861, 36849, 44837, 52825
4743	phospholipase A2, group IVF	397272	4898	380442	12886	20874, 28862, 36850, 44838, 52826
4744	phospholipase A2, group IVF	443825	4899	400843	12887	20875, 28863, 36851, 44839, 52827
4745	phospholipase B domain containing 2	280800	4900	280800	12888	20876, 28864, 36852, 44840, 52828
4746	phospholipase B domain containing 2	545182	4901	443463	12889	20877, 28865, 36853, 44841, 52829
4747	phospholipase D family, member 3	356508	4902	348901	12890	20878, 28866, 36854, 44842, 52830
4748	phospholipase D family, member 3	359274	4903	352220	12891	20879, 28867, 36855, 44843, 52831
4749	phospholipase D family, member 3	392032	4904	375886	12892	20880, 28868, 36856, 44844, 52832
4750	phospholipase D family, member 3	409281	4905	387022	12893	20881, 28869, 36857, 44845, 52833
4751	phospholipase D family, member 3	409419	4906	386293	12894	20882, 28870, 36858, 44846, 52834
4752	phospholipase D family, member 3	409587	4907	387050	12895	20883, 28871, 36859, 44847, 52835
4753	phospholipase D family, member 3	409735	4908	386938	12896	20884, 28872, 36860, 44848, 52836
4754	phospholipase D family, member 3	536031	4909	445216	12897	20885, 28873, 36861, 44849, 52837
4755	phospholipase D family, member 4	392593	4910	376372	12898	20886, 28874, 36862, 44850, 52838
4756	phospholipase D family, member 4	540372	4911	438677	12899	20887, 28875, 36863, 44851, 52839
4757	phospholipase D family, member 5	427495	4912	401285	12900	20888, 28876, 36864, 44852, 52840

4758	phospholipase D family, member 5	442594	4913	414188	12901	20889, 28877, 36865, 44853, 52841
4759	phospholipase D family, member 5	536534	4914	440896	12902	20890, 28878, 36866, 44854, 52842
4760	phospholipase D family, member 6	321560	4915	317177	12903	20891, 28879, 36867, 44855, 52843
4761	phospholipase D family, member 6	427497	4916	394249	12904	20892, 28880, 36868, 44856, 52844
4762	phosphoserine phosphatase	275605	4917	275605	12905	20893, 28881, 36869, 44857, 52845
4763	phosphoserine phosphatase	395471	4918	378854	12906	20894, 28882, 36870, 44858, 52846
4764	phosphoserine phosphatase	413218	4919	404674	12907	20895, 28883, 36871, 44859, 52847
4765	phosphoserine phosphatase	416592	4920	405538	12908	20896, 28884, 36872, 44860, 52848
4766	phosphoserine phosphatase	419984	4921	399660	12909	20897, 28885, 36873, 44861, 52849
4767	phosphoserine phosphatase	421312	4922	390952	12910	20898, 28886, 36874, 44862, 52850
4768	phosphoserine phosphatase	421626	4923	398653	12911	20899, 28887, 36875, 44863, 52851
4769	phosphoserine phosphatase	424596	4924	390452	12912	20900, 28888, 36876, 44864, 52852
4770	phosphoserine phosphatase	437355	4925	401639	12913	20901, 28889, 36877, 44865, 52853
4771	phosphoseryl-tRNA kinase	368887	4926	357882	12914	20902, 28890, 36878, 44866, 52854
4772	phosphoseryl-tRNA kinase	405485	4927	384764	12915	20903, 28891, 36879, 44867, 52855
4773	phosphoseryl-tRNA kinase	406217	4928	384653	12916	20904, 28892, 36880, 44868, 52856
4774	piezo-type mechanosensitive ion channel component 1	301015	4929	301015	12917	20905, 28893, 36881, 44869, 52857
4775	piezo-type mechanosensitive ion channel	327397	4930	333704	12918	20906, 28894, 36882, 44870, 52858

	component 1					
4776	piezo-type mechanosensitive ion channel component 1	451779	4931	408244	12919	20907, 28895, 36883, 44871, 52859
4777	piggyBac transposable element derived 5	321327	4932	322530	12920	20908, 28896, 36884, 44872, 52860
4778	piggyBac transposable element derived 5	525115	4933	431404	12921	20909, 28897, 36885, 44873, 52861
4779	platelet endothelial aggregation receptor 1	292357	4934	292357	12922	20910, 28898, 36886, 44874, 52862
4780	platelet endothelial aggregation receptor 1	338302	4935	344465	12923	20911, 28899, 36887, 44875, 52863
4781	platelet endothelial aggregation receptor 1	455314	4936	389742	12924	20912, 28900, 36888, 44876, 52864
4782	pleckstrin and Sec7 domain containing 2	274710	4937	274710	12925	20913, 28901, 36889, 44877, 52865
4783	pleckstrin homology-like domain, family B, member 2	359729	4938	352764	12926	20914, 28902, 36890, 44878, 52866
4784	pleckstrin homology-like domain, family B, member 2	393923	4939	377500	12927	20915, 28903, 36891, 44879, 52867
4785	pleckstrin homology-like domain, family B, member 2	393925	4940	377502	12928	20916, 28904, 36892, 44880, 52868
4786	pleckstrin homology-like domain, family B, member 2	412622	4941	405292	12929	20917, 28905, 36893, 44881, 52869
4787	pleckstrin homology-like domain, family B, member 2	431670	4942	405405	12930	20918, 28906, 36894, 44882, 52870
4788	pleckstrin homology-like domain, family B, member 2	481953	4943	418319	12931	20919, 28907, 36895, 44883, 52871
4789	pleckstrin homology-like domain, family B, member 2	498699	4944	418296	12932	20920, 28908, 36896, 44884, 52872
4790	plexin A3	369682	4945	358696	12933	20921, 28909, 36897, 44885,

						52873
4791	plexin C1	258526	4946	258526	12934	20922, 28910, 36898, 44886, 52874
4792	plexin C1	547057	4947	446720	12935	20923, 28911, 36899, 44887, 52875
4793	podocalyxin-like 2	302192	4948	304498	12936	20924, 28912, 36900, 44888, 52876
4794	podocalyxin-like 2	342480	4949	345359	12937	20925, 28913, 36901, 44889, 52877
4795	podoplanin	294489	4950	294489	12938	20926, 28914, 36902, 44890, 52878
4796	podoplanin	376057	4951	365225	12939	20927, 28915, 36903, 44891, 52879
4797	podoplanin	376061	4952	365229	12940	20928, 28916, 36904, 44892, 52880
4798	podoplanin	475043	4953	426063	12941	20929, 28917, 36905, 44893, 52881
4799	podoplanin	487038	4954	427537	12942	20930, 28918, 36906, 44894, 52882
4800	podoplanin	513143	4955	425304	12943	20931, 28919, 36907, 44895, 52883
4801	poliovirus receptor related immunoglobulin domain containing	317271	4956	316675	12944	20932, 28920, 36908, 44896, 52884
4802	poly (ADP-ribose) polymerase family, member 16	261888	4957	261888	12945	20933, 28921, 36909, 44897, 52885
4803	poly(A)-specific ribonuclease (PARN)-like domain containing 1	275275	4958	275275	12946	20934, 28922, 36910, 44898, 52886
4804	polymerase (RNA) II (DNA directed) polypeptide J3	379357	4959	368662	12947	20935, 28923, 36911, 44899, 52887
4805	polyribonucleotide nucleotidyltransferase 1	415374	4960	393953	12948	20936, 28924, 36912, 44900, 52888
4806	polyribonucleotide nucleotidyltransferase 1	447944	4961	400646	12949	20937, 28925, 36913, 44901, 52889
4807	POM121 membrane glycoprotein	257622	4962	257622	12950	20938, 28926, 36914, 44902,

						52890
4808	POM121 membrane glycoprotein	358357	4963	351124	12951	20939, 28927, 36915, 44903, 52891
4809	POM121 membrane glycoprotein	395270	4964	378687	12952	20940, 28928, 36916, 44904, 52892
4810	POM121 membrane glycoprotein	434423	4965	405562	12953	20941, 28929, 36917, 44905, 52893
4811	POM121 membrane glycoprotein	446813	4966	393020	12954	20942, 28930, 36918, 44906, 52894
4812	POM121 membrane glycoprotein C	257665	4967	257665	12955	20943, 28931, 36919, 44907, 52895
4813	POM121 membrane glycoprotein C	398379	4968	381415	12956	20944, 28932, 36920, 44908, 52896
4814	POM121 membrane glycoprotein C	453279	4969	414208	12957	20945, 28933, 36921, 44909, 52897
4815	post-GPI attachment to proteins 2	278243	4970	278243	12958	20946, 28934, 36922, 44910, 52898
4816	post-GPI attachment to proteins 2	300730	4971	300730	12959	20947, 28935, 36923, 44911, 52899
4817	post-GPI attachment to proteins 2	396991	4972	380188	12960	20948, 28936, 36924, 44912, 52900
4818	post-GPI attachment to proteins 2	396993	4973	380190	12961	20949, 28937, 36925, 44913, 52901
4819	post-GPI attachment to proteins 2	463452	4974	435223	12962	20950, 28938, 36926, 44914, 52902
4820	post-GPI attachment to proteins 2	464906	4975	434631	12963	20951, 28939, 36927, 44915, 52903
4821	post-GPI attachment to proteins 2	502872	4976	445541	12964	20952, 28940, 36928, 44916, 52904
4822	post-GPI attachment to proteins 2	396986	4977	380183	12965	20953, 28941, 36929, 44917, 52905
4823	post-GPI attachment to proteins 2	493547	4978	431851	12966	20954, 28942, 36930, 44918, 52906
4824	post-GPI attachment to proteins 2	528216	4979	432215	12967	20955, 28943, 36931, 44919, 52907

4825	post-GPI attachment to proteins 3	300658	4980	300658	12968	20956, 28944, 36932, 44920, 52908
4826	post-GPI attachment to proteins 3	309862	4981	310218	12969	20957, 28945, 36933, 44921, 52909
4827	post-GPI attachment to proteins 3	378011	4982	367250	12970	20958, 28946, 36934, 44922, 52910
4828	post-GPI attachment to proteins 3	429199	4983	415765	12971	20959, 28947, 36935, 44923, 52911
4829	potassium channel regulator	312942	4984	324191	12972	20960, 28948, 36936, 44924, 52912
4830	potassium channel regulator	360473	4985	353661	12973	20961, 28949, 36937, 44925, 52913
4831	potassium channel tetramerisation domain containing 12	317765	4986	317141	12974	20962, 28950, 36938, 44926, 52914
4832	potassium channel tetramerisation domain containing 12	377474	4987	366694	12975	20963, 28951, 36939, 44927, 52915
4833	potassium channel tetramerisation domain containing 14	353172	4988	316482	12976	20964, 28952, 36940, 44928, 52916
4834	potassium channel tetramerisation domain containing 14	533144	4989	431155	12977	20965, 28953, 36941, 44929, 52917
4835	potassium channel tetramerisation domain containing 15	422820	4990	389293	12978	20966, 28954, 36942, 44930, 52918
4836	potassium channel tetramerisation domain containing 15	430256	4991	394390	12979	20967, 28955, 36943, 44931, 52919
4837	potassium channel tetramerisation domain containing 17	402077	4992	384391	12980	20968, 28956, 36944, 44932, 52920
4838	potassium channel tetramerisation domain containing 17	403888	4993	385096	12981	20969, 28957, 36945, 44933, 52921
4839	potassium channel tetramerisation domain containing 17	431531	4994	402434	12982	20970, 28958, 36946, 44934, 52922

4840	potassium channel tetramerisation domain containing 17	456470	4995	409638	12983	20971, 28959, 36947, 44935, 52923
4841	potassium channel tetramerisation domain containing 18	359878	4996	352941	12984	20972, 28960, 36948, 44936, 52924
4842	potassium channel tetramerisation domain containing 18	409157	4997	386751	12985	20973, 28961, 36949, 44937, 52925
4843	potassium channel tetramerisation domain containing 19	304372	4998	305702	12986	20974, 28962, 36950, 44938, 52926
4844	potassium channel tetramerisation domain containing 20	373731	4999	362836	12987	20975, 28963, 36951, 44939, 52927
4845	potassium channel tetramerisation domain containing 20	449081	5000	412205	12988	20976, 28964, 36952, 44940, 52928
4846	potassium channel tetramerisation domain containing 20	460983	5001	417126	12989	20977, 28965, 36953, 44941, 52929
4847	potassium channel tetramerisation domain containing 20	483557	5002	419943	12990	20978, 28966, 36954, 44942, 52930
4848	potassium channel tetramerisation domain containing 20	498267	5003	418459	12991	20979, 28967, 36955, 44943, 52931
4849	potassium channel tetramerisation domain containing 20	536244	5004	439118	12992	20980, 28968, 36956, 44944, 52932
4850	potassium channel tetramerisation domain containing 20	544295	5005	440150	12993	20981, 28969, 36957, 44945, 52933
4851	potassium channel tetramerisation domain containing 21	340067	5006	339340	12994	20982, 28970, 36958, 44946, 52934
4852	potassium channel tetramerisation domain containing 21	525447	5007	434174	12995	20983, 28971, 36959, 44947, 52935
4853	potassium channel tetramerisation domain containing 4	379108	5008	368402	12996	20984, 28972, 36960, 44948, 52936

4854	potassium channel tetramerisation domain containing 4	405872	5009	385144	12997	20985, 28973, 36961, 44949, 52937
4855	potassium channel tetramerisation domain containing 5	301738	5010	301738	12998	20986, 28974, 36962, 44950, 52938
4856	potassium channel tetramerisation domain containing 6	355076	5011	347188	12999	20987, 28975, 36963, 44951, 52939
4857	potassium channel tetramerisation domain containing 6	404589	5012	384948	13000	20988, 28976, 36964, 44952, 52940
4858	potassium channel tetramerisation domain containing 6	479179	5013	418999	13001	20989, 28977, 36965, 44953, 52941
4859	potassium channel tetramerisation domain containing 6	490264	5014	417490	13002	20990, 28978, 36966, 44954, 52942
4860	potassium channel tetramerisation domain containing 8	360029	5015	353129	13003	20991, 28979, 36967, 44955, 52943
4861	potassium channel tetramerisation domain containing 9	221200	5016	221200	13004	20992, 28980, 36968, 44956, 52944
4862	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1	222249	5017	222249	13005	20993, 28981, 36969, 44957, 52945
4863	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1	536713	5018	437873	13006	20994, 28982, 36970, 44958, 52946
4864	potassium inwardly-rectifying channel, subfamily J, member 14	342291	5019	341479	13007	20995, 28983, 36971, 44959, 52947
4865	potassium inwardly-rectifying channel, subfamily J, member 14	391884	5020	375756	13008	20996, 28984, 36972, 44960, 52948
4866	potassium inwardly-rectifying channel, subfamily J, member 9	368088	5021	357067	13009	20997, 28985, 36973, 44961, 52949
4867	potassium large conductance calcium-activated channel, subfamily M, beta member 2	358316	5022	351068	13010	20998, 28986, 36974, 44962, 52950

4868	potassium large conductance calcium-activated channel, subfamily M, beta member 2	420517	5023	408252	13011	20999, 28987, 36975, 44963, 52951
4869	potassium large conductance calcium-activated channel, subfamily M, beta member 2	432997	5024	407592	13012	21000, 28988, 36976, 44964, 52952
4870	potassium large conductance calcium-activated channel, subfamily M, beta member 2	437510	5025	395807	13013	21001, 28989, 36977, 44965, 52953
4871	potassium large conductance calcium-activated channel, subfamily M, beta member 2	452583	5026	397483	13014	21002, 28990, 36978, 44966, 52954
4872	potassium large conductance calcium-activated channel, subfamily M, beta member 2	455865	5027	399100	13015	21003, 28991, 36979, 44967, 52955
4873	potassium large conductance calcium-activated channel, subfamily M, beta member 2	457763	5028	395918	13016	21004, 28992, 36980, 44968, 52956
4874	potassium voltage-gated channel subfamily H (eag-related) member 6	581784	5029	463830	13017	21005, 28993, 36981, 44969, 52957
4875	potassium voltage-gated channel subfamily H (eag-related) member 6	583023	5030	463533	13018	21006, 28994, 36982, 44970, 52958
4876	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 1	306117	5031	307694	13019	21007, 28995, 36983, 44971, 52959
4877	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 1	537075	5032	445595	13020	21008, 28996, 36984, 44972, 52960
4878	potassium voltage-gated channel, shaker-related subfamily, member 2	316361	5033	314520	13021	21009, 28997, 36985, 44973, 52961

4879	potassium voltage-gated channel, shaker-related subfamily, member 2	369770	5034	358785	13022	21010, 28998, 36986, 44974, 52962
4880	potassium voltage-gated channel, shaker-related subfamily, member 2	440270	5035	415257	13023	21011, 28999, 36987, 44975, 52963
4881	potassium voltage-gated channel, shaker-related subfamily, member 2	485317	5036	433109	13024	21012, 29000, 36988, 44976, 52964
4882	potassium voltage-gated channel, shaker-related subfamily, member 6	280684	5037	280684	13025	21013, 29001, 36989, 44977, 52965
4883	potassium voltage-gated channel, shaker-related subfamily, member 6	433855	5038	408321	13026	21014, 29002, 36990, 44978, 52966
4884	potassium voltage-gated channel, Shal-related subfamily, member 1	218176	5039	218176	13027	21015, 29003, 36991, 44979, 52967
4885	potassium voltage-gated channel, Shal-related subfamily, member 1	376477	5040	365660	13028	21016, 29004, 36992, 44980, 52968
4886	potassium voltage-gated channel, Shal-related subfamily, member 1	419374	5041	413989	13029	21017, 29005, 36993, 44981, 52969
4887	potassium voltage-gated channel, subfamily G, member 2	316249	5042	315654	13030	21018, 29006, 36994, 44982, 52970
4888	potassium voltage-gated channel, subfamily H (eag-related), member 4	264661	5043	264661	13031	21019, 29007, 36995, 44983, 52971
4889	potassium voltage-gated channel, subfamily H (eag-related), member 6	314672	5044	318212	13032	21020, 29008, 36996, 44984, 52972
4890	potassium voltage-gated channel, subfamily H (eag-related), member 6	456941	5045	396900	13033	21021, 29009, 36997, 44985, 52973

4891	potassium voltage-gated channel, subfamily H (eag-related), member 8	328405	5046	328813	13034	21022, 29010, 36998, 44986, 52974
4892	potassium voltage-gated channel, subfamily H (eag-related), member 8	537696	5047	446294	13035	21023, 29011, 36999, 44987, 52975
4893	PQ loop repeat containing 1	351365	5048	315627	13036	21024, 29012, 37000, 44988, 52976
4894	PQ loop repeat containing 1	357575	5049	350188	13037	21025, 29013, 37001, 44989, 52977
4895	PQ loop repeat containing 1	397778	5050	380880	13038	21026, 29014, 37002, 44990, 52978
4896	PQ loop repeat containing 1	590381	5051	465546	13039	21027, 29015, 37003, 44991, 52979
4897	PQ loop repeat containing 2	375153	5052	364295	13040	21028, 29016, 37004, 44992, 52980
4898	PQ loop repeat containing 2	375155	5053	364297	13041	21029, 29017, 37005, 44993, 52981
4899	PQ loop repeat containing 2	400548	5054	383395	13042	21030, 29018, 37006, 44994, 52982
4900	PQ loop repeat containing 3	295083	5055	295083	13043	21031, 29019, 37007, 44995, 52983
4901	PQ loop repeat containing 3	441908	5056	406148	13044	21032, 29020, 37008, 44996, 52984
4902	praja ring finger 2	361189	5057	354775	13045	21033, 29021, 37009, 44997, 52985
4903	praja ring finger 2	361557	5058	355284	13046	21034, 29022, 37010, 44998, 52986
4904	PRELI domain containing 2	334744	5059	335675	13047	21035, 29023, 37011, 44999, 52987
4905	PRELI domain containing 2	358004	5060	350694	13048	21036, 29024, 37012, 45000, 52988
4906	PRELI domain containing 2	394450	5061	377965	13049	21037, 29025, 37013, 45001, 52989
4907	progestin and adipoQ receptor family member III	295462	5062	295462	13050	21038, 29026, 37014, 45002, 52990

4908	progestin and adipoQ receptor family member III	380645	5063	370019	13051	21039, 29027, 37015, 45003, 52991
4909	progestin and adipoQ receptor family member III	511594	5064	425080	13052	21040, 29028, 37016, 45004, 52992
4910	progestin and adipoQ receptor family member III	512733	5065	421981	13053	21041, 29029, 37017, 45005, 52993
4911	progestin and adipoQ receptor family member IV	293978	5066	293978	13054	21042, 29030, 37018, 45006, 52994
4912	progestin and adipoQ receptor family member IV	318782	5067	321804	13055	21043, 29031, 37019, 45007, 52995
4913	progestin and adipoQ receptor family member IX	340634	5068	341564	13056	21044, 29032, 37020, 45008, 52996
4914	progestin and adipoQ receptor family member V	340965	5069	343877	13057	21045, 29033, 37021, 45009, 52997
4915	progestin and adipoQ receptor family member V	395407	5070	378803	13058	21046, 29034, 37022, 45010, 52998
4916	progestin and adipoQ receptor family member V	561153	5071	453526	13059	21047, 29035, 37023, 45011, 52999
4917	progestin and adipoQ receptor family member VI	292291	5072	292291	13060	21048, 29036, 37024, 45012, 53000
4918	progestin and adipoQ receptor family member VI	335852	5073	338330	13061	21049, 29037, 37025, 45013, 53001
4919	progestin and adipoQ receptor family member VI	340183	5074	341926	13062	21050, 29038, 37026, 45014, 53002
4920	progestin and adipoQ receptor family member VI	356983	5075	349474	13063	21051, 29039, 37027, 45015, 53003
4921	progestin and adipoQ receptor family member VI	360733	5076	353961	13064	21052, 29040, 37028, 45016, 53004
4922	progestin and adipoQ receptor family member VI	368270	5077	357253	13065	21053, 29041, 37029, 45017, 53005
4923	progestin and adipoQ receptor family member VI	368271	5078	357254	13066	21054, 29042, 37030, 45018, 53006
4924	progestin and adipoQ receptor family member VI	540423	5079	443167	13067	21055, 29043, 37031, 45019, 53007
4925	progestin and adipoQ receptor family member VIII	360726	5080	353953	13068	21056, 29044, 37032, 45020, 53008

4926	progestin and adipoQ receptor family member VIII	442253	5081	406197	13069	21057, 29045, 37033, 45021, 53009
4927	progestin and adipoQ receptor family member VIII	512121	5082	427161	13070	21058, 29046, 37034, 45022, 53010
4928	programmed cell death 6	264933	5083	264933	13071	21059, 29047, 37035, 45023, 53011
4929	programmed cell death 6	505221	5084	422085	13072	21060, 29048, 37036, 45024, 53012
4930	programmed cell death 6	506909	5085	426003	13073	21061, 29049, 37037, 45025, 53013
4931	programmed cell death 6	507528	5086	423815	13074	21062, 29050, 37038, 45026, 53014
4932	programmed cell death 6	509581	5087	422691	13075	21063, 29051, 37039, 45027, 53015
4933	prokineticin receptor 1	303786	5088	303775	13076	21064, 29052, 37040, 45028, 53016
4934	prokineticin receptor 1	394342	5089	377874	13077	21065, 29053, 37041, 45029, 53017
4935	prolactin releasing hormone receptor	239032	5090	239032	13078	21066, 29054, 37042, 45030, 53018
4936	prolactin releasing hormone receptor	369169	5091	358167	13079	21067, 29055, 37043, 45031, 53019
4937	proline rich 18	322583	5092	319590	13080	21068, 29056, 37044, 45032, 53020
4938	proline rich 18	529616	5093	433381	13081	21069, 29057, 37045, 45033, 53021
4939	proline rich 5 like	311599	5094	310103	13082	21070, 29058, 37046, 45034, 53022
4940	proline rich 5 like	378867	5095	368144	13083	21071, 29059, 37047, 45035, 53023
4941	proline rich 5 like	524380	5096	433305	13084	21072, 29060, 37048, 45036, 53024
4942	proline rich 5 like	526679	5097	436402	13085	21073, 29061, 37049, 45037, 53025
4943	proline rich 5 like	526682	5098	436485	13086	21074, 29062, 37050, 45038, 53026

4944	proline rich 5 like	526728	5099	431610	13087	21075, 29063, 37051, 45039, 53027
4945	proline rich 5 like	527172	5100	433708	13088	21076, 29064, 37052, 45040, 53028
4946	proline rich 5 like	530050	5101	432203	13089	21077, 29065, 37053, 45041, 53029
4947	proline rich 5 like	530252	5102	431475	13090	21078, 29066, 37054, 45042, 53030
4948	proline rich 5 like	530639	5103	435050	13091	21079, 29067, 37055, 45043, 53031
4949	proline rich 5 like	532121	5104	433893	13092	21080, 29068, 37056, 45044, 53032
4950	proline rich 5 like	527487	5105	435241	13093	21081, 29069, 37057, 45045, 53033
4951	proline rich 7 (synaptic)	323249	5106	327168	13094	21082, 29070, 37058, 45046, 53034
4952	proline rich 7 (synaptic)	355386	5107	347547	13095	21083, 29071, 37059, 45047, 53035
4953	proline rich 7 (synaptic)	502922	5108	420872	13096	21084, 29072, 37060, 45048, 53036
4954	proline rich 7 (synaptic)	507881	5109	426601	13097	21085, 29073, 37061, 45049, 53037
4955	proline rich 7 (synaptic)	510492	5110	421039	13098	21086, 29074, 37062, 45050, 53038
4956	proline-rich coiled-coil 1	296666	5111	296666	13099	21087, 29075, 37063, 45051, 53039
4957	proline-rich coiled-coil 1	330542	5112	332855	13100	21088, 29076, 37064, 45052, 53040
4958	proline-rich coiled-coil 1	414018	5113	414586	13101	21089, 29077, 37065, 45053, 53041
4959	proline-rich coiled-coil 1	442138	5114	392873	13102	21090, 29078, 37066, 45054, 53042
4960	proline-rich coiled-coil 1	512535	5115	426785	13103	21091, 29079, 37067, 45055, 53043
4961	proline-rich coiled-coil 1	512635	5116	421965	13104	21092, 29080, 37068, 45056, 53044

4962	proline-rich transmembrane protein 1	211413	5117	211413	13105	21093, 29081, 37069, 45057, 53045
4963	proline-rich transmembrane protein 1	375150	5118	364292	13106	21094, 29082, 37070, 45058, 53046
4964	proline-rich transmembrane protein 1	375152	5119	364294	13107	21095, 29083, 37071, 45059, 53047
4965	proline-rich transmembrane protein 1	383309	5120	372799	13108	21096, 29084, 37072, 45060, 53048
4966	proline-rich transmembrane protein 1	414687	5121	414711	13109	21097, 29085, 37073, 45061, 53049
4967	proline-rich transmembrane protein 1	418753	5122	411544	13110	21098, 29086, 37074, 45062, 53050
4968	proline-rich transmembrane protein 1	419655	5123	396427	13111	21099, 29087, 37075, 45063, 53051
4969	proline-rich transmembrane protein 1	419839	5124	395695	13112	21100, 29088, 37076, 45064, 53052
4970	proline-rich transmembrane protein 1	423003	5125	413784	13113	21101, 29089, 37077, 45065, 53053
4971	proline-rich transmembrane protein 1	423671	5126	411183	13114	21102, 29090, 37078, 45066, 53054
4972	proline-rich transmembrane protein 1	425067	5127	393852	13115	21103, 29091, 37079, 45067, 53055
4973	proline-rich transmembrane protein 1	425739	5128	416064	13116	21104, 29092, 37080, 45068, 53056
4974	proline-rich transmembrane protein 1	428778	5129	396077	13117	21105, 29093, 37081, 45069, 53057
4975	proline-rich transmembrane protein 1	437574	5130	416602	13118	21106, 29094, 37082, 45070, 53058
4976	proline-rich transmembrane protein 1	439937	5131	389727	13119	21107, 29095, 37083, 45071, 53059
4977	proline-rich transmembrane protein 1	441129	5132	411596	13120	21108, 29096, 37084, 45072, 53060
4978	proline-rich transmembrane protein 1	444218	5133	415611	13121	21109, 29097, 37085, 45073, 53061
4979	proline-rich transmembrane protein 1	444466	5134	405389	13122	21110, 29098, 37086, 45074, 53062

4980	proline-rich transmembrane protein 1	445122	5135	396426	13123	21111, 29099, 37087, 45075, 53063
4981	proline-rich transmembrane protein 1	451329	5136	398756	13124	21112, 29100, 37088, 45076, 53064
4982	proline-rich transmembrane protein 1	452030	5137	394808	13125	21113, 29101, 37089, 45077, 53065
4983	proline-rich transmembrane protein 1	454112	5138	389058	13126	21114, 29102, 37090, 45078, 53066
4984	proline-rich transmembrane protein 1	456814	5139	397896	13127	21115, 29103, 37091, 45079, 53067
4985	proline-rich transmembrane protein 1	457819	5140	390214	13128	21116, 29104, 37092, 45080, 53068
4986	proline-rich transmembrane protein 1	458719	5141	398252	13129	21117, 29105, 37093, 45081, 53069
4987	proline-rich transmembrane protein 1	547412	5142	449685	13130	21118, 29106, 37094, 45082, 53070
4988	proline-rich transmembrane protein 1	548904	5143	449975	13131	21119, 29107, 37095, 45083, 53071
4989	proline-rich transmembrane protein 1	549696	5144	447380	13132	21120, 29108, 37096, 45084, 53072
4990	proline-rich transmembrane protein 1	551213	5145	449638	13133	21121, 29109, 37097, 45085, 53073
4991	proline-rich transmembrane protein 1	551958	5146	450235	13134	21122, 29110, 37098, 45086, 53074
4992	proline-rich transmembrane protein 1	552325	5147	449065	13135	21123, 29111, 37099, 45087, 53075
4993	proline-rich transmembrane protein 1	552684	5148	448469	13136	21124, 29112, 37100, 45088, 53076
4994	proline-rich transmembrane protein 3	295984	5149	295984	13137	21125, 29113, 37101, 45089, 53077
4995	proline-rich transmembrane protein 3	412055	5150	392511	13138	21126, 29114, 37102, 45090, 53078
4996	proline-rich transmembrane protein 4	435512	5151	410779	13139	21127, 29115, 37103, 45091, 53079
4997	proline-rich transmembrane protein 4	446477	5152	415026	13140	21128, 29116, 37104, 45092, 53080

4998	proline-rich transmembrane protein 4	535159	5153	445239	13141	21129, 29117, 37105, 45093, 53081
4999	proline-rich transmembrane protein 4	489835	5154	419296	13142	21130, 29118, 37106, 45094, 53082
5000	prolyl 4-hydroxylase, transmembrane (endoplasmic reticulum)	343546	5155	341422	13143	21131, 29119, 37107, 45095, 53083
5001	prolyl 4-hydroxylase, transmembrane (endoplasmic reticulum)	383729	5156	373235	13144	21132, 29120, 37108, 45096, 53084
5002	proprotein convertase subtilisin/kexin type 7	320934	5157	325917	13145	21133, 29121, 37109, 45097, 53085
5003	proprotein convertase subtilisin/kexin type 7	524507	5158	433841	13146	21134, 29122, 37110, 45098, 53086
5004	proprotein convertase subtilisin/kexin type 7	530269	5159	433252	13147	21135, 29123, 37111, 45099, 53087
5005	proprotein convertase subtilisin/kexin type 7	532301	5160	436459	13148	21136, 29124, 37112, 45100, 53088
5006	proprotein convertase subtilisin/kexin type 7	540028	5161	441944	13149	21137, 29125, 37113, 45101, 53089
5007	proprotein convertase subtilisin/kexin type 7	543900	5162	445538	13150	21138, 29126, 37114, 45102, 53090
5008	ProSAP-interacting protein 1	329152	5163	332123	13151	21139, 29127, 37115, 45103, 53091
5009	ProSAP-interacting protein 1	337576	5164	338166	13152	21140, 29128, 37116, 45104, 53092
5010	ProSAP-interacting protein 1	360342	5165	353496	13153	21141, 29129, 37117, 45105, 53093
5011	prostaglandin D2 receptor 2	332539	5166	332812	13154	21142, 29130, 37118, 45106, 53094
5012	prostate androgen-regulated mucin-like protein 1	307428	5167	370224	13155	21143, 29131, 37119, 45107, 53095

5013	prostate tumor overexpressed 1	221557	5168	221557	13156	21144, 29132, 37120, 45108, 53096
5014	prostate tumor overexpressed 1	391842	5169	375717	13157	21145, 29133, 37121, 45109, 53097
5015	protease serine 55	522210	5170	430459	13158	21146, 29134, 37122, 45110, 53098
5016	protease, serine, 55	328655	5171	333003	13159	21147, 29135, 37123, 45111, 53099
5017	protein arginine methyltransferase 8	382622	5172	372067	13160	21148, 29136, 37124, 45112, 53100
5018	protein arginine methyltransferase 8	452611	5173	414507	13161	21149, 29137, 37125, 45113, 53101
5019	Protein Coding	251879	5174	251879	13162	21150, 29138, 37126, 45114, 53102
5020	Protein Coding	297625	5175	297625	13163	21151, 29139, 37127, 45115, 53103
5021	Protein Coding	356068	5176	364329	13164	21152, 29140, 37128, 45116, 53104
5022	Protein Coding	358422	5177	351198	13165	21153, 29141, 37129, 45117, 53105
5023	Protein Coding	367706	5178	356679	13166	21154, 29142, 37130, 45118, 53106
5024	Protein Coding	373258	5179	362355	13167	21155, 29143, 37131, 45119, 53107
5025	Protein Coding	375199	5180	364345	13168	21156, 29144, 37132, 45120, 53108
5026	Protein Coding	375208	5181	364354	13169	21157, 29145, 37133, 45121, 53109
5027	Protein Coding	375248	5182	364397	13170	21158, 29146, 37134, 45122, 53110
5028	Protein Coding	376576	5183	365760	13171	21159, 29147, 37135, 45123, 53111
5029	Protein Coding	379142	5184	368437	13172	21160, 29148, 37136, 45124, 53112
5030	Protein Coding	381532	5185	370943	13173	21161, 29149, 37137, 45125, 53113

5031	Protein Coding	392412	5186	376212	13174	21162, 29150, 37138, 45126, 53114
5032	Protein Coding	392413	5187	376213	13175	21163, 29151, 37139, 45127, 53115
5033	Protein Coding	409959	5188	386787	13176	21164, 29152, 37140, 45128, 53116
5034	Protein Coding	411671	5189	393122	13177	21165, 29153, 37141, 45129, 53117
5035	Protein Coding	414202	5190	416696	13178	21166, 29154, 37142, 45130, 53118
5036	Protein Coding	418622	5191	402240	13179	21167, 29155, 37143, 45131, 53119
5037	Protein Coding	426982	5192	395883	13180	21168, 29156, 37144, 45132, 53120
5038	Protein Coding	427634	5193	404501	13181	21169, 29157, 37145, 45133, 53121
5039	Protein Coding	440579	5194	407576	13182	21170, 29158, 37146, 45134, 53122
5040	Protein Coding	440693	5195	409663	13183	21171, 29159, 37147, 45135, 53123
5041	Protein Coding	449720	5196	398823	13184	21172, 29160, 37148, 45136, 53124
5042	Protein Coding	469892	5197	419396	13185	21173, 29161, 37149, 45137, 53125
5043	Protein Coding	494948	5198	420226	13186	21174, 29162, 37150, 45138, 53126
5044	Protein Coding	526264	5199	435066	13187	21175, 29163, 37151, 45139, 53127
5045	Protein Coding	529753	5200	434595	13188	21176, 29164, 37152, 45140, 53128
5046	Protein Coding	531664	5201	431349	13189	21177, 29165, 37153, 45141, 53129
5047	Protein Coding	533147	5202	431134	13190	21178, 29166, 37154, 45142, 53130
5048	Protein Coding	534476	5203	432164	13191	21179, 29167, 37155, 45143, 53131

5049	Protein Coding	543377	5204	444648	13192	21180, 29168, 37156, 45144, 53132
5050	Protein Coding	555249	5205	450458	13193	21181, 29169, 37157, 45145, 53133
5051	Protein coding	194118	5206	194118	13194	21182, 29170, 37158, 45146, 53134
5052	Protein coding	432126	5207	396225	13195	21183, 29171, 37159, 45147, 53135
5053	Protein Coding	507481	5208	426138	13196	21184, 29172, 37160, 45148, 53136
5054	protein disulfide isomerase family A, member 5	316218	5209	323313	13197	21185, 29173, 37161, 45149, 53137
5055	protein disulfide isomerase-like, testis expressed	302451	5210	305465	13198	21186, 29174, 37162, 45150, 53138
5056	protein kinase, AMP-activated, beta 2 non-catalytic subunit	254101	5211	254101	13199	21187, 29175, 37163, 45151, 53139
5057	protein kinase, AMP-activated, beta 2 non-catalytic subunit	425272	5212	415469	13200	21188, 29176, 37164, 45152, 53140
5058	Protein kinase-like protein SgK196	331373	5213	331258	13201	21189, 29177, 37165, 45153, 53141
5059	protein O-fucosyltransferase 1	375730	5214	364882	13202	21190, 29178, 37166, 45154, 53142
5060	protein O-fucosyltransferase 1	375749	5215	364902	13203	21191, 29179, 37167, 45155, 53143
5061	protein O-fucosyltransferase 1	539210	5216	446154	13204	21192, 29180, 37168, 45156, 53144
5062	protein O-fucosyltransferase 2	331343	5217	329682	13205	21193, 29181, 37169, 45157, 53145
5063	protein O-fucosyltransferase 2	349485	5218	339613	13206	21194, 29182, 37170, 45158, 53146
5064	protein O-glucosyltransferase 1	295588	5219	295588	13207	21195, 29183, 37171, 45159, 53147
5065	protein phosphatase 1, regulatory subunit 13B	202556	5220	202556	13208	21196, 29184, 37172, 45160, 53148

5066	protein phosphatase 1, regulatory subunit 13B	380023	5221	369362	13209	21197, 29185, 37173, 45161, 53149
5067	protein phosphatase 1, regulatory subunit 13B	423488	5222	395213	13210	21198, 29186, 37174, 45162, 53150
5068	protein phosphatase 1, regulatory subunit 13B	556597	5223	451739	13211	21199, 29187, 37175, 45163, 53151
5069	protein phosphatase 1, regulatory subunit 16A	292539	5224	292539	13212	21200, 29188, 37176, 45164, 53152
5070	protein phosphatase 1, regulatory subunit 16A	435887	5225	391126	13213	21201, 29189, 37177, 45165, 53153
5071	protein phosphatase 1, regulatory subunit 3E	452015	5226	408288	13214	21202, 29190, 37178, 45166, 53154
5072	protein phosphatase 1, regulatory subunit 3E	558058	5227	453175	13215	21203, 29191, 37179, 45167, 53155
5073	protein phosphatase 1, regulatory subunit 3E	559314	5228	454106	13216	21204, 29192, 37180, 45168, 53156
5074	protein phosphatase 1, regulatory subunit 3E	559942	5229	453437	13217	21205, 29193, 37181, 45169, 53157
5075	protein phosphatase 1, regulatory subunit 3E	560913	5230	453543	13218	21206, 29194, 37182, 45170, 53158
5076	protein phosphatase 1, regulatory subunit 3E	561437	5231	453726	13219	21207, 29195, 37183, 45171, 53159
5077	protein phosphatase 1, regulatory subunit 3F	55335	5232	55335	13220	21208, 29196, 37184, 45172, 53160, 56090, 56123
5078	protein phosphatase 1, regulatory subunit 3F	438316	5233	415548	13221	21209, 29197, 37185, 45173, 53161
5079	protein phosphatase, Mg2+/Mn2+ dependent, 1A	325642	5234	327255	13222	21210, 29198, 37186, 45174, 53162
5080	protein phosphatase, Mg2+/Mn2+ dependent, 1A	325658	5235	314850	13223	21211, 29199, 37187, 45175, 53163
5081	protein phosphatase, Mg2+/Mn2+ dependent, 1A	395076	5236	378514	13224	21212, 29200, 37188, 45176, 53164
5082	protein phosphatase, Mg2+/Mn2+ dependent, 1A	525399	5237	435398	13225	21213, 29201, 37189, 45177, 53165
5083	protein phosphatase, Mg2+/Mn2+ dependent, 1A	528241	5238	431453	13226	21214, 29202, 37190, 45178, 53166

5084	protein phosphatase, Mg2+/Mn2+ dependent, 1A	529574	5239	432966	13227	21215, 29203, 37191, 45179, 53167
5085	protein phosphatase, Mg2+/Mn2+ dependent, 1A	531937	5240	435575	13228	21216, 29204, 37192, 45180, 53168
5086	Protein transport protein Sec16B	239472	5241	239472	13229	21217, 29205, 37193, 45181, 53169
5087	Protein transport protein Sec16B	308284	5242	308339	13230	21218, 29206, 37194, 45182, 53170
5088	Protein transport protein Sec16B	414025	5243	408171	13231	21219, 29207, 37195, 45183, 53171
5089	protein tyrosine phosphatase mitochondrial 1	426530	5244	410272	13232	21220, 29208, 37196, 45184, 53172
5090	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	443686	5245	388373	13233	21221, 29209, 37197, 45185, 53173
5091	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	541570	5246	438337	13234	21222, 29210, 37198, 45186, 53174
5092	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	548586	5247	449338	13235	21223, 29211, 37199, 45187, 53175
5093	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	549325	5248	450298	13236	21224, 29212, 37200, 45188, 53176
5094	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	550584	5249	449558	13237	21225, 29213, 37201, 45189, 53177
5095	protein tyrosine phosphatase receptor type f polypeptide (PTPRF) interacting protein (liprin) alpha 2	552948	5250	447868	13238	21226, 29214, 37202, 45190, 53178

5096	protein tyrosine phosphatase receptor type R	342084	5251	339605	13239	21227, 29215, 37203, 45191, 53179
5097	protein tyrosine phosphatase, mitochondrial 1	326674	5252	325958	13240	21228, 29216, 37204, 45192, 53180
5098	protein tyrosine phosphatase, non-receptor type 3	262539	5253	262539	13241	21229, 29217, 37205, 45193, 53181
5099	protein tyrosine phosphatase, non-receptor type 3	374541	5254	363667	13242	21230, 29218, 37206, 45194, 53182
5100	protein tyrosine phosphatase, non-receptor type 3	394827	5255	378304	13243	21231, 29219, 37207, 45195, 53183
5101	protein tyrosine phosphatase, non-receptor type 3	394831	5256	378308	13244	21232, 29220, 37208, 45196, 53184
5102	protein tyrosine phosphatase, non-receptor type 3	412145	5257	416654	13245	21233, 29221, 37209, 45197, 53185
5103	protein tyrosine phosphatase, non-receptor type 3	446349	5258	395384	13246	21234, 29222, 37210, 45198, 53186
5104	protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)	263708	5259	263708	13247	21235, 29223, 37211, 45199, 53187
5105	protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)	420482	5260	405763	13248	21236, 29224, 37212, 45200, 53188
5106	protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)	488279	5261	438445	13249	21237, 29225, 37213, 45201, 53189
5107	protein tyrosine phosphatase, non-receptor type 4 (megakaryocyte)	544261	5262	445841	13250	21238, 29226, 37214, 45202, 53190
5108	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	333447	5263	327416	13251	21239, 29227, 37215, 45203, 53191
5109	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	407050	5264	385093	13252	21240, 29228, 37216, 45204, 53192

5110	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	541017	5265	445532	13253	21241, 29229, 37217, 45205, 53193
5111	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	541501	5266	439748	13254	21242, 29230, 37218, 45206, 53194
5112	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	547623	5267	447918	13255	21243, 29231, 37219, 45207, 53195
5113	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2	549396	5268	450337	13256	21244, 29232, 37220, 45208, 53196
5114	protein tyrosine phosphatase, receptor type, R	283228	5269	283228	13257	21245, 29233, 37221, 45209, 53197
5115	protein tyrosine phosphatase, receptor type, R	378778	5270	368054	13258	21246, 29234, 37222, 45210, 53198
5116	protein tyrosine phosphatase, receptor type, R	440835	5271	391750	13259	21247, 29235, 37223, 45211, 53199
5117	protein tyrosine phosphatase, receptor type, R	549308	5272	446943	13260	21248, 29236, 37224, 45212, 53200
5118	protein tyrosine phosphatase, receptor type, R	550661	5273	449616	13261	21249, 29237, 37225, 45213, 53201
5119	protein tyrosine phosphatase, receptor type, T	356100	5274	348408	13262	21250, 29238, 37226, 45214, 53202
5120	protein tyrosine phosphatase, receptor type, T	373184	5275	362280	13263	21251, 29239, 37227, 45215, 53203
5121	protein tyrosine phosphatase, receptor type, T	373187	5276	362283	13264	21252, 29240, 37228, 45216, 53204
5122	protein tyrosine phosphatase, receptor type, T	373190	5277	362286	13265	21253, 29241, 37229, 45217, 53205

5123	protein tyrosine phosphatase, receptor type, T	373193	5278	362289	13266	21254, 29242, 37230, 45218, 53206
5124	protein tyrosine phosphatase, receptor type, T	373198	5279	362294	13267	21255, 29243, 37231, 45219, 53207
5125	protein tyrosine phosphatase, receptor type, T	373201	5280	362297	13268	21256, 29244, 37232, 45220, 53208
5126	protein tyrosine phosphatase-like (proline instead of catalytic arginine), member b	383657	5281	373153	13269	21257, 29245, 37233, 45221, 53209
5127	protein tyrosine phosphatase-like A domain containing 1	261875	5282	261875	13270	21258, 29246, 37234, 45222, 53210
5128	protein tyrosine phosphatase-like A domain containing 2	495827	5283	419503	13271	21259, 29247, 37235, 45223, 53211
5129	protein tyrosine phosphatase-like A domain containing 2	513293	5284	426475	13272	21260, 29248, 37236, 45224, 53212
5130	protocadherin alpha 4	356878	5285	349344	13273	21261, 29249, 37237, 45225, 53213
5131	protocadherin alpha 4	512229	5286	423470	13274	21262, 29250, 37238, 45226, 53214
5132	protocadherin alpha 4	530339	5287	435300	13275	21263, 29251, 37239, 45227, 53215
5133	protocadherin beta 10	239446	5288	239446	13276	21264, 29252, 37240, 45228, 53216
5134	Protocadherin-psi1Uncharacterized protein	539533	5289	438685	13277	21265, 29253, 37241, 45229, 53217
5135	prune homolog (Drosophila)	271619	5290	271619	13278	21266, 29254, 37242, 45230, 53218
5136	prune homolog (Drosophila)	271620	5291	271620	13279	21267, 29255, 37243, 45231, 53219
5137	prune homolog (Drosophila)	302413	5292	302092	13280	21268, 29256, 37244, 45232, 53220
5138	prune homolog (Drosophila)	368934	5293	357930	13281	21269, 29257, 37245, 45233, 53221
5139	prune homolog (Drosophila)	368935	5294	357931	13282	21270, 29258, 37246, 45234, 53222

5140	prune homolog (Drosophila)	368936	5295	357932	13283	21271, 29259, 37247, 45235, 53223
5141	prune homolog (Drosophila)	368937	5296	357933	13284	21272, 29260, 37248, 45236, 53224
5142	prune homolog (Drosophila)	431193	5297	392632	13285	21273, 29261, 37249, 45237, 53225
5143	prune homolog (Drosophila)	450884	5298	387696	13286	21274, 29262, 37250, 45238, 53226
5144	Pseudopodium-enriched atypical kinase 1	312493	5299	309230	13287	21275, 29263, 37251, 45239, 53227
5145	Pseudopodium-enriched atypical kinase 1	560626	5300	452796	13288	21276, 29264, 37252, 45240, 53228
5146	PTPRF interacting protein, binding protein 1 (liprin beta 1)	228425	5301	228425	13289	21277, 29265, 37253, 45241, 53229
5147	PTPRF interacting protein, binding protein 1 (liprin beta 1)	318304	5302	314724	13290	21278, 29266, 37254, 45242, 53230
5148	PTPRF interacting protein, binding protein 1 (liprin beta 1)	535047	5303	444046	13291	21279, 29267, 37255, 45243, 53231
5149	PTPRF interacting protein, binding protein 1 (liprin beta 1)	535575	5304	437438	13292	21280, 29268, 37256, 45244, 53232
5150	PTPRF interacting protein, binding protein 1 (liprin beta 1)	537927	5305	445425	13293	21281, 29269, 37257, 45245, 53233
5151	PTPRF interacting protein, binding protein 1 (liprin beta 1)	538433	5306	442462	13294	21282, 29270, 37258, 45246, 53234
5152	PTPRF interacting protein, binding protein 1 (liprin beta 1)	542629	5307	443442	13295	21283, 29271, 37259, 45247, 53235
5153	PTPRF interacting protein, binding protein 1 (liprin beta 1)	543820	5308	440806	13296	21284, 29272, 37260, 45248, 53236
5154	PTPRF interacting protein, binding protein 1 (liprin beta 1)	545381	5309	445822	13297	21285, 29273, 37261, 45249, 53237

5155	purinergic receptor P2X ligand-gated ion channel 5	345901	5310	342161	13298	21286, 29274, 37262, 45250, 53238
5156	purinergic receptor P2X ligand-gated ion channel 6	401443	5311	385309	13299	21287, 29275, 37263, 45251, 53239
5157	purinergic receptor P2X, ligand-gated ion channel, 2	343948	5312	343339	13300	21288, 29276, 37264, 45252, 53240
5158	purinergic receptor P2X, ligand-gated ion channel, 2	348800	5313	345095	13301	21289, 29277, 37265, 45253, 53241
5159	purinergic receptor P2X, ligand-gated ion channel, 2	350048	5314	343904	13302	21290, 29278, 37266, 45254, 53242
5160	purinergic receptor P2X, ligand-gated ion channel, 2	351222	5315	344502	13303	21291, 29279, 37267, 45255, 53243
5161	purinergic receptor P2X, ligand-gated ion channel, 2	352418	5316	341419	13304	21292, 29280, 37268, 45256, 53244
5162	purinergic receptor P2X, ligand-gated ion channel, 2	389110	5317	373762	13305	21293, 29281, 37269, 45257, 53245
5163	purinergic receptor P2X, ligand-gated ion channel, 2	449132	5318	405531	13306	21294, 29282, 37270, 45258, 53246
5164	purinergic receptor P2X, ligand-gated ion channel, 5	225328	5319	225328	13307	21295, 29283, 37271, 45259, 53247
5165	purinergic receptor P2X, ligand-gated ion channel, 5	435558	5320	415370	13308	21296, 29284, 37272, 45260, 53248
5166	purinergic receptor P2X, ligand-gated ion channel, 5	547178	5321	448355	13309	21297, 29285, 37273, 45261, 53249
5167	purinergic receptor P2X, ligand-gated ion channel, 5	551178	5322	447545	13310	21298, 29286, 37274, 45262, 53250
5168	purinergic receptor P2X, ligand-gated ion channel, 5	552050	5323	450006	13311	21299, 29287, 37275, 45263, 53251
5169	purinergic receptor P2X, ligand-gated ion channel, 6	336296	5324	338797	13312	21300, 29288, 37276, 45264, 53252
5170	purinergic receptor P2X, ligand-gated ion channel, 6	402329	5325	383997	13313	21301, 29289, 37277, 45265, 53253
5171	purinergic receptor P2X, ligand-gated ion channel, 6	413302	5326	416193	13314	21302, 29290, 37278, 45266, 53254
5172	purinergic receptor P2X, ligand-gated ion channel, 6	442475	5327	401192	13315	21303, 29291, 37279, 45267, 53255

5173	purinergic receptor P2X, ligand-gated ion channel, 6	443995	5328	408088	13316	21304, 29292, 37280, 45268, 53256
5174	purinergic receptor P2Y, G-protein coupled, 10	171757	5329	171757	13317	21305, 29293, 37281, 45269, 53257
5175	purinergic receptor P2Y, G-protein coupled, 10	544091	5330	443138	13318	21306, 29294, 37282, 45270, 53258
5176	purinergic receptor P2Y, G-protein coupled, 13	325602	5331	320376	13319	21307, 29295, 37283, 45271, 53259
5177	purinergic receptor P2Y, G-protein coupled, 14	309170	5332	308361	13320	21308, 29296, 37284, 45272, 53260
5178	purinergic receptor P2Y, G-protein coupled, 14	424796	5333	408733	13321	21309, 29297, 37285, 45273, 53261
5179	purinergic receptor P2Y, G-protein coupled, 14	494668	5334	418065	13322	21310, 29298, 37286, 45274, 53262
5180	putative homeodomain transcription factor 2	248550	5335	248550	13323	21311, 29299, 37287, 45275, 53263
5181	putative homeodomain transcription factor 2	275575	5336	275575	13324	21312, 29300, 37288, 45276, 53264
5182	putative homeodomain transcription factor 2	307305	5337	307699	13325	21313, 29301, 37289, 45277, 53265
5183	putative homeodomain transcription factor 2	416283	5338	400958	13326	21314, 29302, 37290, 45278, 53266
5184	putative homeodomain transcription factor 2	422959	5339	403042	13327	21315, 29303, 37291, 45279, 53267
5185	putative homeodomain transcription factor 2	427986	5340	415496	13328	21316, 29304, 37292, 45280, 53268
5186	putative homeodomain transcription factor 2	415251	5341	408035	13329	21317, 29305, 37293, 45281, 53269
5187	putative homeodomain transcription factor 2	450574	5342	387355	13330	21318, 29306, 37294, 45282, 53270
5188	Putative maltase-glucoamylase-like protein LOC93432	550469	5343	447431	13331	21319, 29307, 37295, 45283, 53271
5189	Putative maltase-glucoamylase-like protein LOC93432	550494	5344	448551	13332	21320, 29308, 37296, 45284, 53272
5190	Putative NPIP-like protein LOC100132247	342168	5345	441680	13333	21321, 29309, 37297, 45285, 53273

5191	Putative NPIP-like protein LOC100132247	344223	5346	440432	13334	21322, 29310, 37298, 45286, 53274
5192	Putative NPIP-like protein LOC100132247	424340	5347	440703	13335	21323, 29311, 37299, 45287, 53275
5193	Putative NPIP-like protein LOC100132247	446615	5348	437919	13336	21324, 29312, 37300, 45288, 53276
5194	Putative NPIP-like protein LOC100132247	457705	5349	446325	13337	21325, 29313, 37301, 45289, 53277
5195	Putative NPIP-like protein LOC100132247	503072	5350	426452	13338	21326, 29314, 37302, 45290, 53278
5196	Putative NPIP-like protein LOC100132247	517539	5351	430633	13339	21327, 29315, 37303, 45291, 53279
5197	Putative transmembrane protein C8orfK29	398633	5352	381630	13340	21328, 29316, 37304, 45292, 53280
5198	Putative transmembrane protein C8orfK29	531225	5353	436572	13341	21329, 29317, 37305, 45293, 53281
5199	Putative transmembrane protein LOC401397	397764	5354	380871	13342	21330, 29318, 37306, 45294, 53282
5200	Putative transmembrane protein LOC401397	413744	5355	410731	13343	21331, 29319, 37307, 45295, 53283
5201	Putative transmembrane protein LOC401397	441359	5356	405021	13344	21332, 29320, 37308, 45296, 53284
5202	pyridoxal (pyridoxine, vitamin B6) phosphatase	215904	5357	215904	13345	21333, 29321, 37309, 45297, 53285
5203	pyridoxal (pyridoxine, vitamin B6) phosphatase	403251	5358	385336	13346	21334, 29322, 37310, 45298, 53286
5204	pyroglutamylated RFamide peptide receptor	394427	5359	377948	13347	21335, 29323, 37311, 45299, 53287
5205	pyruvate dehydrogenase complex component X	430469	5360	415695	13348	21336, 29324, 37312, 45300, 53288
5206	pyruvate dehydrogenase complex, component X	227868	5361	227868	13349	21337, 29325, 37313, 45301, 53289
5207	pyruvate dehydrogenase complex, component X	448838	5362	389404	13350	21338, 29326, 37314, 45302, 53290

5208	pyruvate dehydrogenase kinase, isozyme 3	379162	5363	368460	13351	21339, 29327, 37315, 45303, 53291
5209	pyruvate dehydrogenase kinase, isozyme 3	441463	5364	387536	13352	21340, 29328, 37316, 45304, 53292
5210	pyruvate dehyrogenase phosphatase catalytic subunit 2	311765	5365	309548	13353	21341, 29329, 37317, 45305, 53293
5211	QKI, KH domain containing, RNA binding	275262	5366	275262	13354	21342, 29330, 37318, 45306, 53294
5212	QKI, KH domain containing, RNA binding	361195	5367	354867	13355	21343, 29331, 37319, 45307, 53295
5213	QKI, KH domain containing, RNA binding	361752	5368	355094	13356	21344, 29332, 37320, 45308, 53296
5214	QKI, KH domain containing, RNA binding	392127	5369	375973	13357	21345, 29333, 37321, 45309, 53297
5215	QKI, KH domain containing, RNA binding	453779	5370	408775	13358	21346, 29334, 37322, 45310, 53298
5216	Rab acceptor 1 (prenylated)	222008	5371	222008	13359	21347, 29335, 37323, 45311, 53299
5217	RAB11 family interacting protein 5 (class I)	258098	5372	258098	13360	21348, 29336, 37324, 45312, 53300
5218	RAB11B, member RAS oncogene family	328024	5373	333547	13361	21349, 29337, 37325, 45313, 53301
5219	RAB15, member RAS onocogene family	267512	5374	267512	13362	21350, 29338, 37326, 45314, 53302
5220	RAB15, member RAS onocogene family	533601	5375	434103	13363	21351, 29339, 37327, 45315, 53303
5221	RAB19, member RAS oncogene family	275874	5376	275874	13364	21352, 29340, 37328, 45316, 53304
5222	RAB19, member RAS oncogene family	356407	5377	348778	13365	21353, 29341, 37329, 45317, 53305
5223	RAB19, member RAS oncogene family	495590	5378	420782	13366	21354, 29342, 37330, 45318, 53306
5224	RAB19, member RAS oncogene family	537763	5379	440167	13367	21355, 29343, 37331, 45319, 53307
5225	RAB20, member RAS oncogene family	267328	5380	267328	13368	21356, 29344, 37332, 45320, 53308

5226	RAB27B, member RAS oncogene family	262094	5381	262094	13369	21357, 29345, 37333, 45321, 53309
5227	RAB39A, member RAS oncogene family	320578	5382	322594	13370	21358, 29346, 37334, 45322, 53310
5228	RAB3D, member RAS oncogene family	222120	5383	222120	13371	21359, 29347, 37335, 45323, 53311
5229	RAB40A, member RAS oncogene family	304236	5384	305648	13372	21360, 29348, 37336, 45324, 53312
5230	RAB40A, member RAS oncogene family	372633	5385	361716	13373	21361, 29349, 37337, 45325, 53313
5231	RAB40B member RAS oncogene family	571995	5386	461785	13374	21362, 29350, 37338, 45326, 53314
5232	RAB40B, member RAS oncogene family	269347	5387	269347	13375	21363, 29351, 37339, 45327, 53315
5233	RAB40B, member RAS oncogene family	538809	5388	438897	13376	21364, 29352, 37340, 45328, 53316
5234	RAB40C, member RAS oncogene family	248139	5389	248139	13377	21365, 29353, 37341, 45329, 53317
5235	RAB40C, member RAS oncogene family	535977	5390	438492	13378	21366, 29354, 37342, 45330, 53318
5236	RAB40C, member RAS oncogene family	538492	5391	438382	13379	21367, 29355, 37343, 45331, 53319
5237	RAB40C, member RAS oncogene family	539661	5392	445050	13380	21368, 29356, 37344, 45332, 53320
5238	RAB43 member RAS oncogene family	476465	5393	427632	13381	21369, 29357, 37345, 45333, 53321
5239	RAB43, member RAS oncogene family	315150	5394	319781	13382	21370, 29358, 37346, 45334, 53322
5240	RAB43, member RAS oncogene family	393304	5395	376981	13383	21371, 29359, 37347, 45335, 53323
5241	RAB43, member RAS oncogene family	393305	5396	376982	13384	21372, 29360, 37348, 45336, 53324
5242	RAB43, member RAS oncogene family	393307	5397	376984	13385	21373, 29361, 37349, 45337, 53325
5243	RAB43, member RAS oncogene family	393308	5398	376985	13386	21374, 29362, 37350, 45338, 53326

5244	RAB43, member RAS oncogene family	457077	5399	390782	13387	21375, 29363, 37351, 45339, 53327
5245	RAB8B, member RAS oncogene family	321437	5400	312734	13388	21376, 29364, 37352, 45340, 53328
5246	RAB8B, member RAS oncogene family	448330	5401	405463	13389	21377, 29365, 37353, 45341, 53329
5247	Rab9 effector protein with kelch motifs	259460	5402	259460	13390	21378, 29366, 37354, 45342, 53330
5248	Rab9 effector protein with kelch motifs	373538	5403	362639	13391	21379, 29367, 37355, 45343, 53331
5249	Rab9 effector protein with kelch motifs	373544	5404	362645	13392	21380, 29368, 37356, 45344, 53332
5250	Rab9 effector protein with kelch motifs	394124	5405	377682	13393	21381, 29369, 37357, 45345, 53333
5251	Rab9 effector protein with kelch motifs	394125	5406	377683	13394	21382, 29370, 37358, 45346, 53334
5252	Rab9 effector protein with kelch motifs	416065	5407	402234	13395	21383, 29371, 37359, 45347, 53335
5253	RAB9A, member RAS oncogene family	464506	5408	420127	13396	21384, 29372, 37360, 45348, 53336
5254	raftlin family member 2	295049	5409	295049	13397	21385, 29373, 37361, 45349, 53337
5255	raftlin, lipid raft linker 1	334133	5410	334153	13398	21386, 29374, 37362, 45350, 53338
5256	raftlin, lipid raft linker 1	431547	5411	393216	13399	21387, 29375, 37363, 45351, 53339
5257	raftlin, lipid raft linker 1	441460	5412	388718	13400	21388, 29376, 37364, 45352, 53340
5258	raftlin, lipid raft linker 1	449415	5413	409427	13401	21389, 29377, 37365, 45353, 53341
5259	raftlin, lipid raft linker 1	451036	5414	403997	13402	21390, 29378, 37366, 45354, 53342
5260	Ral GEF with PH domain and SH3 binding motif 2	324778	5415	313613	13403	21391, 29379, 37367, 45355, 53343
5261	Ral GEF with PH domain and SH3 binding motif 2	367634	5416	356606	13404	21392, 29380, 37368, 45356, 53344

5262	Ral GEF with PH domain and SH3 binding motif 2	367635	5417	356607	13405	21393, 29381, 37369, 45357, 53345
5263	Ral GEF with PH domain and SH3 binding motif 2	535251	5418	445104	13406	21394, 29382, 37370, 45358, 53346
5264	RALBP1 associated Eps domain containing 1	258062	5419	258062	13407	21395, 29383, 37371, 45359, 53347
5265	RALBP1 associated Eps domain containing 1	367663	5420	356635	13408	21396, 29384, 37372, 45360, 53348
5266	RALBP1 associated Eps domain containing 1	367668	5421	356640	13409	21397, 29385, 37373, 45361, 53349
5267	RALBP1 associated Eps domain containing 1	409812	5422	386699	13410	21398, 29386, 37374, 45362, 53350
5268	RALBP1 associated Eps domain containing 1	450536	5423	392065	13411	21399, 29387, 37375, 45363, 53351
5269	RALBP1 associated Eps domain containing 1	530255	5424	435131	13412	21400, 29388, 37376, 45364, 53352
5270	RAN binding protein 3-like	296604	5425	296604	13413	21401, 29389, 37377, 45365, 53353
5271	RAN binding protein 3-like	505865	5426	427147	13414	21402, 29390, 37378, 45366, 53354
5272	RAN binding protein 3-like	502994	5427	421853	13415	21403, 29391, 37379, 45367, 53355
5273	Rap guanine nucleotide exchange factor (GEF) 2	264431	5428	264431	13416	21404, 29392, 37380, 45368, 53356
5274	Rap guanine nucleotide exchange factor (GEF) 3	171000	5429	171000	13417	21405, 29393, 37381, 45369, 53357
5275	Rap guanine nucleotide exchange factor (GEF) 3	389211	5430	373863	13418	21406, 29394, 37382, 45370, 53358
5276	Rap guanine nucleotide exchange factor (GEF) 3	389212	5431	373864	13419	21407, 29395, 37383, 45371, 53359
5277	Rap guanine nucleotide exchange factor (GEF) 3	395358	5432	378764	13420	21408, 29396, 37384, 45372, 53360
5278	Rap guanine nucleotide exchange factor (GEF) 3	397089	5433	380278	13421	21409, 29397, 37385, 45373, 53361
5279	Rap guanine nucleotide exchange factor (GEF) 3	405493	5434	384521	13422	21410, 29398, 37386, 45374, 53362

5280	Rap guanine nucleotide exchange factor (GEF) 3	449771	5435	395708	13423	21411, 29399, 37387, 45375, 53363
5281	Rap guanine nucleotide exchange factor (GEF) 3	466322	5436	446731	13424	21412, 29400, 37388, 45376, 53364
5282	Rap guanine nucleotide exchange factor (GEF) 3	495953	5437	448804	13425	21413, 29401, 37389, 45377, 53365
5283	Rap guanine nucleotide exchange factor (GEF) 3	541821	5438	438798	13426	21414, 29402, 37390, 45378, 53366
5284	Rap guanine nucleotide exchange factor (GEF) 3	549151	5439	448619	13427	21415, 29403, 37391, 45379, 53367
5285	Rap guanine nucleotide exchange factor (GEF) 4	264111	5440	264111	13428	21416, 29404, 37392, 45380, 53368
5286	Rap guanine nucleotide exchange factor (GEF) 4	397081	5441	380271	13429	21417, 29405, 37393, 45381, 53369
5287	Rap guanine nucleotide exchange factor (GEF) 4	397087	5442	380276	13430	21418, 29406, 37394, 45382, 53370
5288	Rap guanine nucleotide exchange factor (GEF) 4	409036	5443	387104	13431	21419, 29407, 37395, 45383, 53371
5289	Rap guanine nucleotide exchange factor (GEF) 4	535187	5444	438011	13432	21420, 29408, 37396, 45384, 53372
5290	Rap guanine nucleotide exchange factor (GEF) 4	538974	5445	440135	13433	21421, 29409, 37397, 45385, 53373
5291	Rap guanine nucleotide exchange factor (GEF) 4	539331	5446	437384	13434	21422, 29410, 37398, 45386, 53374
5292	Rap guanine nucleotide exchange factor (GEF) 4	539767	5447	443231	13435	21423, 29411, 37399, 45387, 53375
5293	Rap guanine nucleotide exchange factor (GEF) 4	540783	5448	440250	13436	21424, 29412, 37400, 45388, 53376
5294	RAP2B, member of RAS oncogene family	323534	5449	319096	13437	21425, 29413, 37401, 45389, 53377
5295	RAP2C, member of RAS oncogene family	342983	5450	340274	13438	21426, 29414, 37402, 45390, 53378
5296	RAP2C, member of RAS oncogene family	370874	5451	359911	13439	21427, 29415, 37403, 45391, 53379
5297	RAS (RAD and GEM)-like GTP binding 2	267396	5452	267396	13440	21428, 29416, 37404, 45392, 53380

5298	RAS (RAD and GEM)-like GTP binding 2	536884	5453	442774	13441	21429, 29417, 37405, 45393, 53381
5299	RAS (RAD and GEM)-like GTP-binding 1	201979	5454	201979	13442	21430, 29418, 37406, 45394, 53382
5300	Ras and Rab interactor 1	311320	5455	310406	13443	21431, 29419, 37407, 45395, 53383
5301	Ras and Rab interactor 1	424433	5456	400560	13444	21432, 29420, 37408, 45396, 53384
5302	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	308091	5457	311293	13445	21433, 29421, 37409, 45397, 53385
5303	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	319170	5458	316543	13446	21434, 29422, 37410, 45398, 53386
5304	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	374488	5459	363612	13447	21435, 29423, 37411, 45399, 53387
5305	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	374489	5460	363613	13448	21436, 29424, 37412, 45400, 53388
5306	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	374493	5461	363617	13449	21437, 29425, 37413, 45401, 53389
5307	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	413201	5462	394454	13450	21438, 29426, 37414, 45402, 53390
5308	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	418114	5463	396711	13451	21439, 29427, 37415, 45403, 53391
5309	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	419464	5464	390578	13452	21440, 29428, 37416, 45404, 53392
5310	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	420371	5465	412241	13453	21441, 29429, 37417, 45405, 53393
5311	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	423104	5466	397751	13454	21442, 29430, 37418, 45406, 53394
5312	Ras association (RalGDS/AF-6) and pleckstrin homology	428637	5467	414430	13455	21443, 29431, 37419, 45407, 53395

	domains 1					
5313	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	432342	5468	415364	13456	21444, 29432, 37420, 45408, 53396
5314	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	439222	5469	411138	13457	21445, 29433, 37421, 45409, 53397
5315	Ras association (RalGDS/AF-6) and pleckstrin homology domains 1	453034	5470	406662	13458	21446, 29434, 37422, 45410, 53398
5316	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	402538	5471	385886	13459	21447, 29435, 37423, 45411, 53399
5317	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	403687	5472	384192	13460	21448, 29436, 37424, 45412, 53400
5318	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	407811	5473	383917	13461	21449, 29437, 37425, 45413, 53401
5319	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	423159	5474	388139	13462	21450, 29438, 37426, 45414, 53402
5320	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	425210	5475	401974	13463	21451, 29439, 37427, 45415, 53403
5321	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	437184	5476	393866	13464	21452, 29440, 37428, 45416, 53404
5322	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	442390	5477	405648	13465	21453, 29441, 37429, 45417, 53405
5323	RAS guanyl releasing protein 3 (calcium and DAG-regulated)	444784	5478	400602	13466	21454, 29442, 37430, 45418, 53406
5324	Ras homolog enriched in brain like 1	301068	5479	301068	13467	21455, 29443, 37431, 45419, 53407
5325	ras homolog gene family, member D	308831	5480	308576	13468	21456, 29444, 37432, 45420, 53408
5326	ras homolog gene family, member F	267205	5481	267205	13469	21457, 29445, 37433, 45421,

	(in filopodia)					53409
5327	ras homolog gene family, member F (in filopodia)	535560	5482	440397	13470	21458, 29446, 37434, 45422, 53410
5328	ras homolog gene family, member G (rho G)	351018	5483	339467	13471	21459, 29447, 37435, 45423, 53411
5329	ras homolog gene family, member G (rho G)	396978	5484	380175	13472	21460, 29448, 37436, 45424, 53412
5330	ras homolog gene family, member G (rho G)	396979	5485	380176	13473	21461, 29449, 37437, 45425, 53413
5331	ras homolog gene family, member G (rho G)	533217	5486	436932	13474	21462, 29450, 37438, 45426, 53414
5332	ras homolog gene family, member H	381799	5487	371219	13475	21463, 29451, 37439, 45427, 53415
5333	ras homolog gene family, member H	503941	5488	426439	13476	21464, 29452, 37440, 45428, 53416
5334	ras homolog gene family, member H	505618	5489	425010	13477	21465, 29453, 37441, 45429, 53417
5335	ras homolog gene family, member H	507851	5490	423384	13478	21466, 29454, 37442, 45430, 53418
5336	ras homolog gene family, member H	508513	5491	422241	13479	21467, 29455, 37443, 45431, 53419
5337	ras homolog gene family, member H	511121	5492	420866	13480	21468, 29456, 37444, 45432, 53420
5338	ras homolog gene family, member J	316754	5493	316729	13481	21469, 29457, 37445, 45433, 53421
5339	ras homolog gene family, member Q	238738	5494	238738	13482	21470, 29458, 37446, 45434, 53422
5340	ras homolog gene family, member V	220507	5495	220507	13483	21471, 29459, 37447, 45435, 53423
5341	RAS protein activator like 2	367647	5496	356619	13484	21472, 29460, 37448, 45436, 53424
5342	RAS protein activator like 2	367649	5497	356621	13485	21473, 29461, 37449, 45437, 53425
5343	RAS protein activator like 2	433130	5498	402897	13486	21474, 29462, 37450, 45438, 53426

5344	RAS protein activator like 2	448150	5499	407768	13487	21475, 29463, 37451, 45439, 53427
5345	RAS protein activator like 2	462775	5500	420558	13488	21476, 29464, 37452, 45440, 53428
5346	RAS protein activator like 3	343625	5501	341905	13489	21477, 29465, 37453, 45441, 53429
5347	Ras-like without CAAX 1	368322	5502	357305	13490	21478, 29466, 37454, 45442, 53430
5348	Ras-like without CAAX 1	368323	5503	357306	13491	21479, 29467, 37455, 45443, 53431
5349	Ras-like without CAAX 1	539040	5504	441950	13492	21480, 29468, 37456, 45444, 53432
5350	Ras-like without CAAX 2	282028	5505	282028	13493	21481, 29469, 37457, 45445, 53433
5351	Ras-like without CAAX 2	326695	5506	321805	13494	21482, 29470, 37458, 45446, 53434
5352	reactive oxygen species modulator 1	336695	5507	338293	13495	21483, 29471, 37459, 45447, 53435
5353	reactive oxygen species modulator 1	374077	5508	363190	13496	21484, 29472, 37460, 45448, 53436
5354	reactive oxygen species modulator 1	374078	5509	363191	13497	21485, 29473, 37461, 45449, 53437
5355	reactive oxygen species modulator 1	397416	5510	380561	13498	21486, 29474, 37462, 45450, 53438
5356	receptor (chemosensory) transporter protein 1	312295	5511	311712	13499	21487, 29475, 37463, 45451, 53439
5357	receptor (chemosensory) transporter protein 2	358241	5512	350976	13500	21488, 29476, 37464, 45452, 53440
5358	receptor (TNFRSF)-interacting serine-threonine kinase 1	259808	5513	259808	13501	21489, 29477, 37465, 45453, 53441
5359	receptor (TNFRSF)-interacting serine-threonine kinase 1	380409	5514	369773	13502	21490, 29478, 37466, 45454, 53442
5360	receptor (TNFRSF)-interacting serine-threonine kinase 1	453483	5515	415981	13503	21491, 29479, 37467, 45455, 53443
5361	receptor (TNFRSF)-interacting serine-threonine kinase 1	541791	5516	442294	13504	21492, 29480, 37468, 45456, 53444

5362	regulator of G-protein signaling 10	369101	5517	358097	13505	21493, 29481, 37469, 45457, 53445
5363	regulator of G-protein signaling 10	369103	5518	358099	13506	21494, 29482, 37470, 45458, 53446
5364	regulator of G-protein signaling 10	392865	5519	376605	13507	21495, 29483, 37471, 45459, 53447
5365	regulator of G-protein signaling 11	316163	5520	319069	13508	21496, 29484, 37472, 45460, 53448
5366	regulator of G-protein signaling 11	397768	5521	380874	13509	21497, 29485, 37473, 45461, 53449
5367	regulator of G-protein signaling 11	397770	5522	380876	13510	21498, 29486, 37474, 45462, 53450
5368	regulator of G-protein signaling 11	431291	5523	411215	13511	21499, 29487, 37475, 45463, 53451
5369	regulator of G-protein signaling 13	391995	5524	375853	13512	21500, 29488, 37476, 45464, 53452
5370	regulator of G-protein signaling 13	543215	5525	442837	13513	21501, 29489, 37477, 45465, 53453
5371	regulator of G-protein signaling 17	206262	5526	206262	13514	21502, 29490, 37478, 45466, 53454
5372	regulator of G-protein signaling 17	367225	5527	356194	13515	21503, 29491, 37479, 45467, 53455
5373	regulator of G-protein signaling 18	367460	5528	356430	13516	21504, 29492, 37480, 45468, 53456
5374	regulator of G-protein signaling 19	332298	5529	333194	13517	21505, 29493, 37481, 45469, 53457
5375	regulator of G-protein signaling 19	395042	5530	378483	13518	21506, 29494, 37482, 45470, 53458
5376	regulator of G-protein signaling 20	276500	5531	276500	13519	21507, 29495, 37483, 45471, 53459
5377	regulator of G-protein signaling 20	297313	5532	297313	13520	21508, 29496, 37484, 45472, 53460
5378	regulator of G-protein signaling 22	360863	5533	354109	13521	21509, 29497, 37485, 45473, 53461
5379	regulator of G-protein signaling 22	427793	5534	389751	13522	21510, 29498, 37486, 45474, 53462

5380	regulator of G-protein signaling 8	258302	5535	258302	13523	21511, 29499, 37487, 45475, 53463
5381	regulator of G-protein signaling 8	367556	5536	356527	13524	21512, 29500, 37488, 45476, 53464
5382	regulator of G-protein signaling 8	367557	5537	356528	13525	21513, 29501, 37489, 45477, 53465
5383	regulator of G-protein signaling 8	483095	5538	426289	13526	21514, 29502, 37490, 45478, 53466
5384	regulator of G-protein signaling 8	508450	5539	427076	13527	21515, 29503, 37491, 45479, 53467
5385	relaxin/insulin-like family peptide receptor 1	307765	5540	303248	13528	21516, 29504, 37492, 45480, 53468
5386	relaxin/insulin-like family peptide receptor 1	423548	5541	405841	13529	21517, 29505, 37493, 45481, 53469
5387	relaxin/insulin-like family peptide receptor 1	440678	5542	402226	13530	21518, 29506, 37494, 45482, 53470
5388	relaxin/insulin-like family peptide receptor 1	448688	5543	414885	13531	21519, 29507, 37495, 45483, 53471
5389	relaxin/insulin-like family peptide receptor 1	342048	5544	432036	13532	21520, 29508, 37496, 45484, 53472
5390	relaxin/insulin-like family peptide receptor 2	298386	5545	298386	13533	21521, 29509, 37497, 45485, 53473
5391	relaxin/insulin-like family peptide receptor 2	380314	5546	369670	13534	21522, 29510, 37498, 45486, 53474
5392	relaxin/insulin-like family peptide receptor 3	330120	5547	328708	13535	21523, 29511, 37499, 45487, 53475
5393	relaxin/insulin-like family peptide receptor 4	368318	5548	357301	13536	21524, 29512, 37500, 45488, 53476
5394	RELT-like 1	314117	5549	313385	13537	21525, 29513, 37501, 45489, 53477
5395	RELT-like 1	454158	5550	398778	13538	21526, 29514, 37502, 45490, 53478
5396	reprimo-like	322329	5551	318032	13539	21527, 29515, 37503, 45491, 53479
5397	required for meiotic nuclear division 1 homolog (S. cerevisiae)	336451	5552	336683	13540	21528, 29516, 37504, 45492, 53480

5398	required for meiotic nuclear division 1 homolog (S. cerevisiae)	367299	5553	356268	13541	21529, 29517, 37505, 45493, 53481
5399	required for meiotic nuclear division 1 homolog (S. cerevisiae)	367303	5554	356272	13542	21530, 29518, 37506, 45494, 53482
5400	required for meiotic nuclear division 1 homolog (S. cerevisiae)	444024	5555	412708	13543	21531, 29519, 37507, 45495, 53483
5401	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	306256	5556	302088	13544	21532, 29520, 37508, 45496, 53484
5402	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	378512	5557	367773	13545	21533, 29521, 37509, 45497, 53485
5403	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	378513	5558	367774	13546	21534, 29522, 37510, 45498, 53486
5404	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	378518	5559	367779	13547	21535, 29523, 37511, 45499, 53487
5405	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	434662	5560	396797	13548	21536, 29524, 37512, 45500, 53488
5406	RER1 retention in endoplasmic reticulum 1 homolog (S. cerevisiae)	443438	5561	417000	13549	21537, 29525, 37513, 45501, 53489
5407	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	309737	5562	308820	13550	21538, 29526, 37514, 45502, 53490
5408	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	335425	5563	333988	13551	21539, 29527, 37515, 45503, 53491
5409	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	343202	5564	344904	13552	21540, 29528, 37516, 45504, 53492
5410	resistance to inhibitors of cholinesterase 3 homolog (C.	396677	5565	379910	13553	21541, 29529, 37517, 45505, 53493

	elegans)					
5411	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	419822	5566	404415	13554	21542, 29530, 37518, 45506, 53494
5412	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	539720	5567	443871	13555	21543, 29531, 37519, 45507, 53495
5413	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	543346	5568	442352	13556	21544, 29532, 37520, 45508, 53496
5414	resistance to inhibitors of cholinesterase 3 homolog (C. elegans)	425599	5569	395320	13557	21545, 29533, 37521, 45509, 53497
5415	resistance to inhibitors of cholinesterase 8 homolog A (C. elegans)	325207	5570	325941	13558	21546, 29534, 37522, 45510, 53498
5416	resistance to inhibitors of cholinesterase 8 homolog A (C. elegans)	526104	5571	432008	13559	21547, 29535, 37523, 45511, 53499
5417	resistance to inhibitors of cholinesterase 8 homolog B (C. elegans)	355478	5572	347662	13560	21548, 29536, 37524, 45512, 53500
5418	resistance to inhibitors of cholinesterase 8 homolog B (C. elegans)	392837	5573	376582	13561	21549, 29537, 37525, 45513, 53501
5419	resistance to inhibitors of cholinesterase 8 homolog B (C. elegans)	392839	5574	376583	13562	21550, 29538, 37526, 45514, 53502
5420	reticulocalbin 3, EF-hand calcium binding domain	270645	5575	270645	13563	21551, 29539, 37527, 45515, 53503
5421	reticulon 4 receptor-like 1	331238	5576	330631	13564	21552, 29540, 37528, 45516, 53504

5422	reticulon 4 receptor-like 2	335099	5577	335397	13565	21553, 29541, 37529, 45517, 53505
5423	retinal pigment epithelium-derived rhodopsin homolog	317735	5578	314992	13566	21554, 29542, 37530, 45518, 53506
5424	retinoic acid early transcript 1E	357183	5579	349709	13567	21555, 29543, 37531, 45519, 53507
5425	retinoic acid early transcript 1E	367363	5580	356332	13568	21556, 29544, 37532, 45520, 53508
5426	retinoic acid early transcript 1E	392270	5581	376096	13569	21557, 29545, 37533, 45521, 53509
5427	retinoic acid early transcript 1E	529948	5582	432366	13570	21558, 29546, 37534, 45522, 53510
5428	retinoic acid early transcript 1E	531073	5583	433489	13571	21559, 29547, 37535, 45523, 53511
5429	retinoic acid early transcript 1E	532335	5584	437067	13572	21560, 29548, 37536, 45524, 53512
5430	retinoic acid early transcript 1G	367360	5585	356329	13573	21561, 29549, 37537, 45525, 53513
5431	retinol dehydrogenase 13 (all-trans/9-cis)	291892	5586	291892	13574	21562, 29550, 37538, 45526, 53514
5432	retinol dehydrogenase 13 (all-trans/9-cis)	396247	5587	379547	13575	21563, 29551, 37539, 45527, 53515
5433	retinol dehydrogenase 13 (all-trans/9-cis)	415061	5588	391121	13576	21564, 29552, 37540, 45528, 53516
5434	retinol dehydrogenase 14 (all-trans/9-cis/11-cis)	381249	5589	370648	13577	21565, 29553, 37541, 45529, 53517
5435	retinol dehydrogenase 16 (all-trans)	398138	5590	381206	13578	21566, 29554, 37542, 45530, 53518
5436	retinol saturase (all-trans-retinol 13,14-reductase)	263854	5591	263854	13579	21567, 29555, 37543, 45531, 53519
5437	retinol saturase (all-trans-retinol 13,14-reductase)	295802	5592	295802	13580	21568, 29556, 37544, 45532, 53520
5438	retinol saturase (all-trans-retinol 13,14-reductase)	457495	5593	405040	13581	21569, 29557, 37545, 45533, 53521
5439	Rho family GTPase 1	309739	5594	308461	13582	21570, 29558, 37546, 45534, 53522

5440	Rho family GTPase 1	550607	5595	447059	13583	21571, 29559, 37547, 45535, 53523
5441	Rho family GTPase 2	225973	5596	225973	13584	21572, 29560, 37548, 45536, 53524
5442	Rho family GTPase 2	544533	5597	439328	13585	21573, 29561, 37549, 45537, 53525
5443	Rho family GTPase 2	587250	5598	466680	13586	21574, 29562, 37550, 45538, 53526
5444	Rho GTPase activating protein 32	310343	5599	310561	13587	21575, 29563, 37551, 45539, 53527
5445	Rho GTPase activating protein 32	356092	5600	348396	13588	21576, 29564, 37552, 45540, 53528
5446	Rho GTPase activating protein 32	457677	5601	416571	13589	21577, 29565, 37553, 45541, 53529
5447	Rho GTPase activating protein 32	527272	5602	432862	13590	21578, 29566, 37554, 45542, 53530
5448	Rho GTPase activating protein 4	350060	5603	203786	13591	21579, 29567, 37555, 45543, 53531
5449	Rho GTPase activating protein 4	370016	5604	359033	13592	21580, 29568, 37556, 45544, 53532
5450	Rho GTPase activating protein 4	370028	5605	359045	13593	21581, 29569, 37557, 45545, 53533
5451	Rho GTPase activating protein 4	393721	5606	377322	13594	21582, 29570, 37558, 45546, 53534
5452	Rho GTPase activating protein 4	537206	5607	444169	13595	21583, 29571, 37559, 45547, 53535
5453	Rho guanine nucleotide exchange factor (GEF) 11	315174	5608	313470	13596	21584, 29572, 37560, 45548, 53536
5454	Rho guanine nucleotide exchange factor (GEF) 11	361409	5609	354644	13597	21585, 29573, 37561, 45549, 53537
5455	Rho guanine nucleotide exchange factor (GEF) 11	368194	5610	357177	13598	21586, 29574, 37562, 45550, 53538
5456	Rho guanine nucleotide exchange factor (GEF) 25	286494	5611	286494	13599	21587, 29575, 37563, 45551, 53539
5457	Rho guanine nucleotide exchange factor (GEF) 25	300189	5612	300189	13600	21588, 29576, 37564, 45552, 53540

5458	Rho guanine nucleotide exchange factor (GEF) 25	333972	5613	335560	13601	21589, 29577, 37565, 45553, 53541
5459	Rho-guanine nucleotide exchange factor	287898	5614	287898	13602	21590, 29578, 37566, 45554, 53542
5460	Rho-guanine nucleotide exchange factor	296794	5615	296794	13603	21591, 29579, 37567, 45555, 53543
5461	Rho-guanine nucleotide exchange factor	426542	5616	412175	13604	21592, 29580, 37568, 45556, 53544
5462	Rho-guanine nucleotide exchange factor	509848	5617	421859	13605	21593, 29581, 37569, 45557, 53545
5463	Rho-guanine nucleotide exchange factor	513042	5618	441436	13606	21594, 29582, 37570, 45558, 53546
5464	Rho-guanine nucleotide exchange factor	545377	5619	441913	13607	21595, 29583, 37571, 45559, 53547
5465	rhomboid domain containing 1	341329	5620	344779	13608	21596, 29584, 37572, 45560, 53548
5466	rhomboid domain containing 1	392062	5621	375914	13609	21597, 29585, 37573, 45561, 53549
5467	rhomboid domain containing 1	423616	5622	399694	13610	21598, 29586, 37574, 45562, 53550
5468	rhomboid domain containing 1	424132	5623	400765	13611	21599, 29587, 37575, 45563, 53551
5469	rhomboid domain containing 1	436481	5624	397298	13612	21600, 29588, 37576, 45564, 53552
5470	rhomboid domain containing 1	437454	5625	410384	13613	21601, 29589, 37577, 45565, 53553
5471	rhomboid domain containing 1	443477	5626	414801	13614	21602, 29590, 37578, 45566, 53554
5472	rhomboid domain containing 1	448992	5627	388847	13615	21603, 29591, 37579, 45567, 53555
5473	rhomboid domain containing 2	6777	5628	6777	13616	21604, 29592, 37580, 45568, 53556, 56091, 56124
5474	rhomboid domain containing 2	318622	5629	314144	13617	21605, 29593, 37581, 45569, 53557
5475	rhomboid domain containing 2	413229	5630	407074	13618	21606, 29594, 37582, 45570, 53558

5476	rhomboid domain containing 2	428119	5631	391232	13619	21607, 29595, 37583, 45571, 53559
5477	rhomboid domain containing 3	216085	5632	216085	13620	21608, 29596, 37584, 45572, 53560
5478	rhomboid domain containing 3	406335	5633	384113	13621	21609, 29597, 37585, 45573, 53561
5479	rhomboid domain containing 3	414672	5634	413128	13622	21610, 29598, 37586, 45574, 53562
5480	rhomboid, veinlet-like 1 (Drosophila)	219551	5635	219551	13623	21611, 29599, 37587, 45575, 53563
5481	rhomboid, veinlet-like 1 (Drosophila)	352681	5636	344206	13624	21612, 29600, 37588, 45576, 53564
5482	rhomboid, veinlet-like 1 (Drosophila)	450775	5637	401752	13625	21613, 29601, 37589, 45577, 53565
5483	rhomboid, veinlet-like 2 (Drosophila)	289248	5638	289248	13626	21614, 29602, 37590, 45578, 53566
5484	rhomboid, veinlet-like 2 (Drosophila)	372985	5639	362076	13627	21615, 29603, 37591, 45579, 53567
5485	rhomboid, veinlet-like 2 (Drosophila)	372990	5640	362081	13628	21616, 29604, 37592, 45580, 53568
5486	rhomboid, veinlet-like 2 (Drosophila)	538156	5641	439227	13629	21617, 29605, 37593, 45581, 53569
5487	rhomboid, veinlet-like 3 (Drosophila)	269051	5642	269051	13630	21618, 29606, 37594, 45582, 53570
5488	rhomboid, veinlet-like 3 (Drosophila)	431505	5643	394849	13631	21619, 29607, 37595, 45583, 53571
5489	rhomboid, veinlet-like 3 (Drosophila)	536287	5644	442289	13632	21620, 29608, 37596, 45584, 53572
5490	rhomboid, veinlet-like 3 (Drosophila)	538145	5645	442092	13633	21621, 29609, 37597, 45585, 53573
5491	rhotekin 2	315289	5646	325379	13634	21622, 29610, 37598, 45586, 53574
5492	rhotekin 2	373789	5647	362894	13635	21623, 29611, 37599, 45587, 53575
5493	rhotekin 2	395260	5648	378678	13636	21624, 29612, 37600, 45588, 53576

5494	rhotekin 2	395265	5649	378682	13637	21625, 29613, 37601, 45589, 53577
5495	ribonuclease, RNase K	402093	5650	385440	13638	21626, 29614, 37602, 45590, 53578
5496	ribonuclease, RNase K	548577	5651	449500	13639	21627, 29615, 37603, 45591, 53579
5497	ribosomal protein S27a	272317	5652	272317	13640	21628, 29616, 37604, 45592, 53580
5498	ribosomal protein S27a	402285	5653	383981	13641	21629, 29617, 37605, 45593, 53581
5499	ribosomal protein S27a	404735	5654	385659	13642	21630, 29618, 37606, 45594, 53582
5500	ribosomal protein S27a	449323	5655	408482	13643	21631, 29619, 37607, 45595, 53583
5501	ribosomal RNA adenine dimethylase domain containing 1	368216	5656	357199	13644	21632, 29620, 37608, 45596, 53584
5502	ribosomal RNA adenine dimethylase domain containing 1	368218	5657	357201	13645	21633, 29621, 37609, 45597, 53585
5503	ribosomal RNA processing 12 homolog (S. cerevisiae)	315563	5658	324315	13646	21634, 29622, 37610, 45598, 53586
5504	ribosomal RNA processing 12 homolog (S. cerevisiae)	370992	5659	360031	13647	21635, 29623, 37611, 45599, 53587
5505	ribosomal RNA processing 12 homolog (S. cerevisiae)	414986	5660	414863	13648	21636, 29624, 37612, 45600, 53588
5506	ribosomal RNA processing 12 homolog (S. cerevisiae)	536831	5661	446184	13649	21637, 29625, 37613, 45601, 53589
5507	ribosomal RNA processing 15 homolog (S. cerevisiae)	366932	5662	355899	13650	21638, 29626, 37614, 45602, 53590
5508	ribosome binding factor A (putative)	262197	5663	262197	13651	21639, 29627, 37615, 45603, 53591
5509	ribosome binding factor A (putative)	306735	5664	305696	13652	21640, 29628, 37616, 45604, 53592

5510	ring finger protein 103	237455	5665	237455	13653	21641, 29629, 37617, 45605, 53593
5511	ring finger protein 121	361756	5666	354571	13654	21642, 29630, 37618, 45606, 53594
5512	ring finger protein 121	545854	5667	443799	13655	21643, 29631, 37619, 45607, 53595
5513	ring finger protein 122	256257	5668	256257	13656	21644, 29632, 37620, 45608, 53596
5514	ring finger protein 13	344229	5669	341361	13657	21645, 29633, 37621, 45609, 53597
5515	ring finger protein 13	392894	5670	376628	13658	21646, 29634, 37622, 45610, 53598
5516	ring finger protein 13	459632	5671	419069	13659	21647, 29635, 37623, 45611, 53599
5517	ring finger protein 13	466478	5672	419508	13660	21648, 29636, 37624, 45612, 53600
5518	ring finger protein 13	466795	5673	417655	13661	21649, 29637, 37625, 45613, 53601
5519	ring finger protein 13	468648	5674	420067	13662	21650, 29638, 37626, 45614, 53602
5520	ring finger protein 13	470151	5675	419836	13663	21651, 29639, 37627, 45615, 53603
5521	ring finger protein 13	482539	5676	420691	13664	21652, 29640, 37628, 45616, 53604
5522	ring finger protein 13	543506	5677	442599	13665	21653, 29641, 37629, 45617, 53605
5523	ring finger protein 130	521389	5678	430237	13666	21654, 29642, 37630, 45618, 53606
5524	ring finger protein 133	340112	5679	344489	13667	21655, 29643, 37631, 45619, 53607
5525	ring finger protein 144A	320892	5680	321330	13668	21656, 29644, 37632, 45620, 53608
5526	ring finger protein 144A	416587	5681	414420	13669	21657, 29645, 37633, 45621, 53609
5527	ring finger protein 144A	427092	5682	389017	13670	21658, 29646, 37634, 45622, 53610

5528	ring finger protein 144A	433456	5683	402645	13671	21659, 29647, 37635, 45623, 53611
5529	ring finger protein 144B	259939	5684	259939	13672	21660, 29648, 37636, 45624, 53612
5530	ring finger protein 144B	429054	5685	411270	13673	21661, 29649, 37637, 45625, 53613
5531	ring finger protein 145	274542	5686	274542	13674	21662, 29650, 37638, 45626, 53614
5532	ring finger protein 145	413445	5687	445115	13675	21663, 29651, 37639, 45627, 53615
5533	ring finger protein 145	424310	5688	409064	13676	21664, 29652, 37640, 45628, 53616
5534	ring finger protein 145	518802	5689	430955	13677	21665, 29653, 37641, 45629, 53617
5535	ring finger protein 145	519865	5690	430397	13678	21666, 29654, 37642, 45630, 53618
5536	ring finger protein 145	520638	5691	429071	13679	21667, 29655, 37643, 45631, 53619
5537	ring finger protein 145	521606	5692	430753	13680	21668, 29656, 37644, 45632, 53620
5538	ring finger protein 145	535312	5693	442941	13681	21669, 29657, 37645, 45633, 53621
5539	ring finger protein 148	434824	5694	388207	13682	21670, 29658, 37646, 45634, 53622
5540	ring finger protein 149	295317	5695	295317	13683	21671, 29659, 37647, 45635, 53623
5541	ring finger protein 150	306799	5696	304321	13684	21672, 29660, 37648, 45636, 53624
5542	ring finger protein 150	379512	5697	368827	13685	21673, 29661, 37649, 45637, 53625
5543	ring finger protein 150	420921	5698	394581	13686	21674, 29662, 37650, 45638, 53626
5544	ring finger protein 150	507500	5699	425568	13687	21675, 29663, 37651, 45639, 53627
5545	ring finger protein 150	515673	5700	425840	13688	21676, 29664, 37652, 45640, 53628

5546	ring finger protein 152	312828	5701	316628	13689	21677, 29665, 37653, 45641, 53629
5547	ring finger protein 167	262482	5702	262482	13690	21678, 29666, 37654, 45642, 53630
5548	ring finger protein 170	319073	5703	325969	13691	21679, 29667, 37655, 45643, 53631
5549	ring finger protein 170	319104	5704	326138	13692	21680, 29668, 37656, 45644, 53632
5550	ring finger protein 170	524954	5705	437146	13693	21681, 29669, 37657, 45645, 53633
5551	ring finger protein 170	527424	5706	434797	13694	21682, 29670, 37658, 45646, 53634
5552	ring finger protein 170	531440	5707	436416	13695	21683, 29671, 37659, 45647, 53635
5553	ring finger protein 170	534961	5708	445725	13696	21684, 29672, 37660, 45648, 53636
5554	ring finger protein 170	526349	5709	435782	13697	21685, 29673, 37661, 45649, 53637
5555	ring finger protein 175	274068	5710	274068	13698	21686, 29674, 37662, 45650, 53638
5556	ring finger protein 175	347063	5711	340979	13699	21687, 29675, 37663, 45651, 53639
5557	ring finger protein 180	296615	5712	296615	13700	21688, 29676, 37664, 45652, 53640
5558	ring finger protein 180	381081	5713	370471	13701	21689, 29677, 37665, 45653, 53641
5559	ring finger protein 180	389100	5714	373752	13702	21690, 29678, 37666, 45654, 53642
5560	ring finger protein 180	504296	5715	426884	13703	21691, 29679, 37667, 45655, 53643
5561	ring finger protein 182	420478	5716	419329	13704	21692, 29680, 37668, 45656, 53644
5562	ring finger protein 182	423553	5717	418717	13705	21693, 29681, 37669, 45657, 53645
5563	ring finger protein 182	471906	5718	417514	13706	21694, 29682, 37670, 45658, 53646

5564	ring finger protein 182	488300	5719	420465	13707	21695, 29683, 37671, 45659, 53647
5565	ring finger protein 182	488763	5720	417500	13708	21696, 29684, 37672, 45660, 53648
5566	ring finger protein 182	537388	5721	441271	13709	21697, 29685, 37673, 45661, 53649
5567	ring finger protein 182	537663	5722	443228	13710	21698, 29686, 37674, 45662, 53650
5568	ring finger protein 182	544682	5723	442021	13711	21699, 29687, 37675, 45663, 53651
5569	ring finger protein 185	326132	5724	320508	13712	21700, 29688, 37676, 45664, 53652
5570	ring finger protein 185	426256	5725	410916	13713	21701, 29689, 37677, 45665, 53653
5571	ring finger protein 185	436825	5726	404601	13714	21702, 29690, 37678, 45666, 53654
5572	ring finger protein 185	518626	5727	427755	13715	21703, 29691, 37679, 45667, 53655
5573	ring finger protein 185	266252	5728	266252	13716	21704, 29692, 37680, 45668, 53656
5574	ring finger protein 19A	341084	5729	342667	13717	21705, 29693, 37681, 45669, 53657
5575	ring finger protein 19A	432381	5730	397305	13718	21706, 29694, 37682, 45670, 53658
5576	ring finger protein 19A	519449	5731	428968	13719	21707, 29695, 37683, 45671, 53659
5577	ring finger protein 19A	519527	5732	431077	13720	21708, 29696, 37684, 45672, 53660
5578	ring finger protein 19A	522369	5733	429841	13721	21709, 29697, 37685, 45673, 53661
5579	ring finger protein 19A	523167	5734	429549	13722	21710, 29698, 37686, 45674, 53662
5580	ring finger protein 19A	523481	5735	430553	13723	21711, 29699, 37687, 45675, 53663
5581	ring finger protein 19B	235150	5736	235150	13724	21712, 29700, 37688, 45676, 53664

5582	ring finger protein 19B	356990	5737	349482	13725	21713, 29701, 37689, 45677, 53665
5583	ring finger protein 19B	373456	5738	362555	13726	21714, 29702, 37690, 45678, 53666
5584	ring finger protein 19B	405457	5739	385924	13727	21715, 29703, 37691, 45679, 53667
5585	ring finger protein 215	382363	5740	371800	13728	21716, 29704, 37692, 45680, 53668
5586	ring finger protein 217	275184	5741	275184	13729	21717, 29705, 37693, 45681, 53669
5587	ring finger protein 217	359704	5742	352734	13730	21718, 29706, 37694, 45682, 53670
5588	ring finger protein 217	519799	5743	427711	13731	21719, 29707, 37695, 45683, 53671
5589	ring finger protein 217	560949	5744	452812	13732	21720, 29708, 37696, 45684, 53672
5590	ring finger protein 223	453464	5745	410533	13733	21721, 29709, 37697, 45685, 53673
5591	ring finger protein 40	324685	5746	325677	13734	21722, 29710, 37698, 45686, 53674
5592	ring finger protein 40	357890	5747	350563	13735	21723, 29711, 37699, 45687, 53675
5593	ring finger protein 40	402121	5748	384942	13736	21724, 29712, 37700, 45688, 53676
5594	ring finger protein 40	452273	5749	397150	13737	21725, 29713, 37701, 45689, 53677
5595	ring finger protein 40	538323	5750	445060	13738	21726, 29714, 37702, 45690, 53678
5596	ring finger protein, transmembrane 1	305783	5751	304670	13739	21727, 29715, 37703, 45691, 53679
5597	ring finger protein, transmembrane 1	442346	5752	389049	13740	21728, 29716, 37704, 45692, 53680
5598	ring finger protein, transmembrane 2	257575	5753	257575	13741	21729, 29717, 37705, 45693, 53681
5599	ring finger protein, transmembrane 2	392549	5754	376332	13742	21730, 29718, 37706, 45694, 53682

5600	ring finger protein, transmembrane 2	407967	5755	385669	13743	21731, 29719, 37707, 45695, 53683
5601	RNA (guanine-9-) methyltransferase domain containing 1	309922	5756	312356	13744	21732, 29720, 37708, 45696, 53684
5602	RNA (guanine-9-) methyltransferase domain containing 1	495642	5757	419389	13745	21733, 29721, 37709, 45697, 53685
5603	RNA pseudouridylate synthase domain containing 4	298317	5758	298317	13746	21734, 29722, 37710, 45698, 53686
5604	RNA pseudouridylate synthase domain containing 4	533628	5759	433065	13747	21735, 29723, 37711, 45699, 53687
5605	RRS1 ribosome biogenesis regulator homolog (S. cerevisiae)	320270	5760	322396	13748	21736, 29724, 37712, 45700, 53688
5606	RUN and FYVE domain containing 1	319449	5761	325594	13749	21737, 29725, 37713, 45701, 53689
5607	RUN and FYVE domain containing 1	360569	5762	353773	13750	21738, 29726, 37714, 45702, 53690
5608	RUN and FYVE domain containing 1	377001	5763	366200	13751	21739, 29727, 37715, 45703, 53691
5609	RUN and FYVE domain containing 1	393438	5764	377087	13752	21740, 29728, 37716, 45704, 53692
5610	RUN and FYVE domain containing 1	437570	5765	390025	13753	21741, 29729, 37717, 45705, 53693
5611	RYK receptor-like tyrosine kinase	296084	5766	296084	13754	21742, 29730, 37718, 45706, 53694
5612	RYK receptor-like tyrosine kinase	427044	5767	399527	13755	21743, 29731, 37719, 45707, 53695
5613	RYK receptor-like tyrosine kinase	460933	5768	419122	13756	21744, 29732, 37720, 45708, 53696
5614	S100 calcium binding protein G	380200	5769	369547	13757	21745, 29733, 37721, 45709, 53697
5615	saccharopine dehydrogenase (putative)	366509	5770	355466	13758	21746, 29734, 37722, 45710, 53698
5616	saccharopine dehydrogenase	366510	5771	355467	13759	21747, 29735, 37723, 45711,

	(putative)					53699
5617	Sad1 and UNC84 domain containing 3	297325	5772	297325	13760	21748, 29736, 37724, 45712, 53700
5618	Sad1 and UNC84 domain containing 3	395572	5773	378939	13761	21749, 29737, 37725, 45713, 53701
5619	Sad1 and UNC84 domain containing 3	412142	5774	410204	13762	21750, 29738, 37726, 45714, 53702
5620	Sad1 and UNC84 domain containing 3	438771	5775	409077	13763	21751, 29739, 37727, 45715, 53703
5621	Sad1 and UNC84 domain containing 3	453071	5776	388627	13764	21752, 29740, 37728, 45716, 53704
5622	Sad1 and UNC84 domain containing 3	453192	5777	387525	13765	21753, 29741, 37729, 45717, 53705
5623	sarcoglycan, zeta	382080	5778	371512	13766	21754, 29742, 37730, 45718, 53706
5624	sarcoglycan, zeta	421524	5779	405224	13767	21755, 29743, 37731, 45719, 53707
5625	sarcolemma associated protein	295951	5780	295951	13768	21756, 29744, 37732, 45720, 53708
5626	sarcolemma associated protein	295952	5781	295952	13769	21757, 29745, 37733, 45721, 53709
5627	sarcolemma associated protein	383718	5782	373224	13770	21758, 29746, 37734, 45722, 53710
5628	sarcolemma associated protein	416870	5783	412342	13771	21759, 29747, 37735, 45723, 53711
5629	sarcolemma associated protein	417128	5784	412829	13772	21760, 29748, 37736, 45724, 53712
5630	sarcolemma associated protein	428312	5785	398661	13773	21761, 29749, 37737, 45725, 53713
5631	sarcolemma associated protein	438794	5786	391886	13774	21762, 29750, 37738, 45726, 53714
5632	sarcolemma associated protein	442599	5787	388978	13775	21763, 29751, 37739, 45727, 53715
5633	sarcolemma associated protein	449503	5788	412945	13776	21764, 29752, 37740, 45728, 53716

5634	sarcolemma associated protein	494088	5789	418218	13777	21765, 29753, 37741, 45729, 53717
5635	sarcolemma associated protein	495364	5790	419543	13778	21766, 29754, 37742, 45730, 53718
5636	sarcolemma associated protein	537224	5791	437995	13779	21767, 29755, 37743, 45731, 53719
5637	SAYSVFN motif domain containing 1	229903	5792	229903	13780	21768, 29756, 37744, 45732, 53720
5638	SAYSVFN motif domain containing 1	373249	5793	362346	13781	21769, 29757, 37745, 45733, 53721
5639	scavenger receptor class A, member 5 (putative)	301906	5794	301906	13782	21770, 29758, 37746, 45734, 53722
5640	scavenger receptor class A, member 5 (putative)	354914	5795	346990	13783	21771, 29759, 37747, 45735, 53723
5641	scavenger receptor class A, member 5 (putative)	380385	5796	369746	13784	21772, 29760, 37748, 45736, 53724
5642	scavenger receptor class A, member 5 (putative)	518030	5797	430713	13785	21773, 29761, 37749, 45737, 53725
5643	scavenger receptor class A, member 5 (putative)	524352	5798	428663	13786	21774, 29762, 37750, 45738, 53726
5644	SCY1-like 2 (S. cerevisiae)	258506	5799	258506	13787	21775, 29763, 37751, 45739, 53727
5645	SCY1-like 2 (S. cerevisiae)	360820	5800	354061	13788	21776, 29764, 37752, 45740, 53728
5646	SCY1-like 2 (S. cerevisiae)	549687	5801	448366	13789	21777, 29765, 37753, 45741, 53729
5647	sec1 family domain containing 1	396629	5802	379870	13790	21778, 29766, 37754, 45742, 53730
5648	sec1 family domain containing 1	421551	5803	388078	13791	21779, 29767, 37755, 45743, 53731
5649	sec1 family domain containing 1	458591	5804	390783	13792	21780, 29768, 37756, 45744, 53732
5650	sec1 family domain containing 1	541123	5805	443537	13793	21781, 29769, 37757, 45745, 53733
5651	sec1 family domain containing 1	544052	5806	443010	13794	21782, 29770, 37758, 45746, 53734

5652	SEC11 homolog A (S. cerevisiae)	268220	5807	268220	13795	21783, 29771, 37759, 45747, 53735
5653	SEC11 homolog A (S. cerevisiae)	455959	5808	413121	13796	21784, 29772, 37760, 45748, 53736
5654	SEC11 homolog C (S. cerevisiae)	299714	5809	299714	13797	21785, 29773, 37761, 45749, 53737
5655	SEC11 homolog C (S. cerevisiae)	509791	5810	443624	13798	21786, 29774, 37762, 45750, 53738
5656	SEC11 homolog C (S. cerevisiae)	587834	5811	468633	13799	21787, 29775, 37763, 45751, 53739
5657	SEC14 and spectrin domains 1	428443	5812	415332	13800	21788, 29776, 37764, 45752, 53740
5658	SEC14 and spectrin domains 1	435047	5813	410286	13801	21789, 29777, 37765, 45753, 53741
5659	SEC14 and spectrin domains 1	440010	5814	416164	13802	21790, 29778, 37766, 45754, 53742
5660	SEC14-like 1 (S. cerevisiae)	392476	5815	376268	13803	21791, 29779, 37767, 45755, 53743
5661	SEC14-like 1 (S. cerevisiae)	413679	5816	394716	13804	21792, 29780, 37768, 45756, 53744
5662	SEC14-like 1 (S. cerevisiae)	430767	5817	408169	13805	21793, 29781, 37769, 45757, 53745
5663	SEC14-like 1 (S. cerevisiae)	431431	5818	389838	13806	21794, 29782, 37770, 45758, 53746
5664	SEC14-like 1 (S. cerevisiae)	436233	5819	390392	13807	21795, 29783, 37771, 45759, 53747
5665	SEC14-like 1 (S. cerevisiae)	443798	5820	406030	13808	21796, 29784, 37772, 45760, 53748
5666	SEC14-like 5 (S. cerevisiae)	251170	5821	251170	13809	21797, 29785, 37773, 45761, 53749
5667	SEC22 vesicle trafficking protein homolog C (S. cerevisiae)	264454	5822	264454	13810	21798, 29786, 37774, 45762, 53750
5668	SEC22 vesicle trafficking protein homolog C (S. cerevisiae)	273156	5823	273156	13811	21799, 29787, 37775, 45763, 53751

5669	SEC22 vesicle trafficking protein homolog C (S. cerevisiae)	417572	5824	407564	13812	21800, 29788, 37776, 45764, 53752
5670	SEC22 vesicle trafficking protein homolog C (S. cerevisiae)	423701	5825	414576	13813	21801, 29789, 37777, 45765, 53753
5671	SEC22 vesicle trafficking protein homolog C (S. cerevisiae)	536332	5826	439845	13814	21802, 29790, 37778, 45766, 53754
5672	SEC24 family member A (S. cerevisiae)	322887	5827	321749	13815	21803, 29791, 37779, 45767, 53755
5673	SEC24 family, member A (S. cerevisiae)	398844	5828	381823	13816	21804, 29792, 37780, 45768, 53756
5674	SEC24 family, member B (S. cerevisiae)	265175	5829	265175	13817	21805, 29793, 37781, 45769, 53757
5675	SEC24 family, member B (S. cerevisiae)	399100	5830	382051	13818	21806, 29794, 37782, 45770, 53758
5676	SEC24 family, member B (S. cerevisiae)	504968	5831	428564	13819	21807, 29795, 37783, 45771, 53759
5677	SEC24 family, member C (S. cerevisiae)	339365	5832	343405	13820	21808, 29796, 37784, 45772, 53760
5678	SEC24 family, member C (S. cerevisiae)	345254	5833	321845	13821	21809, 29797, 37785, 45773, 53761
5679	SEC24 family, member C (S. cerevisiae)	411652	5834	402913	13822	21810, 29798, 37786, 45774, 53762
5680	SEC24 family, member C (S. cerevisiae)	535742	5835	446174	13823	21811, 29799, 37787, 45775, 53763
5681	SEC24 family, member C (S. cerevisiae)	540668	5836	445023	13824	21812, 29800, 37788, 45776, 53764
5682	SEC24 family, member D (S. cerevisiae)	280551	5837	280551	13825	21813, 29801, 37789, 45777, 53765
5683	SEC24 family, member D (S. cerevisiae)	379735	5838	369059	13826	21814, 29802, 37790, 45778, 53766
5684	SEC24 family, member D (S. cerevisiae)	419654	5839	388324	13827	21815, 29803, 37791, 45779, 53767
5685	SEC24 family, member D (S. cerevisiae)	429811	5840	409775	13828	21816, 29804, 37792, 45780, 53768

5686	SEC31 homolog A (S. cerevisiae)	264405	5841	264405	13829	21817, 29805, 37793, 45781, 53769
5687	SEC31 homolog A (S. cerevisiae)	311785	5842	309070	13830	21818, 29806, 37794, 45782, 53770
5688	SEC31 homolog A (S. cerevisiae)	326950	5843	325087	13831	21819, 29807, 37795, 45783, 53771
5689	SEC31 homolog A (S. cerevisiae)	348405	5844	337602	13832	21820, 29808, 37796, 45784, 53772
5690	SEC31 homolog A (S. cerevisiae)	355196	5845	347329	13833	21821, 29809, 37797, 45785, 53773
5691	SEC31 homolog A (S. cerevisiae)	395310	5846	378721	13834	21822, 29810, 37798, 45786, 53774
5692	SEC31 homolog A (S. cerevisiae)	432794	5847	407944	13835	21823, 29811, 37799, 45787, 53775
5693	SEC31 homolog A (S. cerevisiae)	448323	5848	400926	13836	21824, 29812, 37800, 45788, 53776
5694	SEC31 homolog A (S. cerevisiae)	500777	5849	421464	13837	21825, 29813, 37801, 45789, 53777
5695	SEC31 homolog A (S. cerevisiae)	503210	5850	422563	13838	21826, 29814, 37802, 45790, 53778
5696	SEC31 homolog A (S. cerevisiae)	505434	5851	425095	13839	21827, 29815, 37803, 45791, 53779
5697	SEC31 homolog A (S. cerevisiae)	505984	5852	424451	13840	21828, 29816, 37804, 45792, 53780
5698	SEC31 homolog A (S. cerevisiae)	506495	5853	425064	13841	21829, 29817, 37805, 45793, 53781
5699	SEC31 homolog A (S. cerevisiae)	508502	5854	424635	13842	21830, 29818, 37806, 45794, 53782
5700	SEC31 homolog A (S. cerevisiae)	509142	5855	426569	13843	21831, 29819, 37807, 45795, 53783
5701	SEC31 homolog A (S. cerevisiae)	513323	5856	426950	13844	21832, 29820, 37808, 45796, 53784
5702	SEC31 homolog A (S. cerevisiae)	514326	5857	425555	13845	21833, 29821, 37809, 45797, 53785
5703	SEC31 homolog A (S. cerevisiae)	443462	5858	408027	13846	21834, 29822, 37810, 45798, 53786

5704	Sec61 alpha 1 subunit (S. cerevisiae)	243253	5859	243253	13847	21835, 29823, 37811, 45799, 53787
5705	Sec61 alpha 1 subunit (S. cerevisiae)	424880	5860	411445	13848	21836, 29824, 37812, 45800, 53788
5706	Sec61 alpha 1 subunit (S. cerevisiae)	464451	5861	418493	13849	21837, 29825, 37813, 45801, 53789
5707	Sec61 alpha 2 subunit (S. cerevisiae)	298428	5862	298428	13850	21838, 29826, 37814, 45802, 53790
5708	Sec61 alpha 2 subunit (S. cerevisiae)	304267	5863	302048	13851	21839, 29827, 37815, 45803, 53791
5709	Sec61 alpha 2 subunit (S. cerevisiae)	379017	5864	368302	13852	21840, 29828, 37816, 45804, 53792
5710	Sec61 alpha 2 subunit (S. cerevisiae)	379020	5865	368306	13853	21841, 29829, 37817, 45805, 53793
5711	Sec61 alpha 2 subunit (S. cerevisiae)	379033	5866	368319	13854	21842, 29830, 37818, 45806, 53794
5712	Sec61 alpha 2 subunit (S. cerevisiae)	379051	5867	368339	13855	21843, 29831, 37819, 45807, 53795
5713	Sec61 alpha 2 subunit (S. cerevisiae)	418772	5868	393214	13856	21844, 29832, 37820, 45808, 53796
5714	Sec61 alpha 2 subunit (S. cerevisiae)	419021	5869	402124	13857	21845, 29833, 37821, 45809, 53797
5715	Sec61 alpha 2 subunit (S. cerevisiae)	426560	5870	404563	13858	21846, 29834, 37822, 45810, 53798
5716	Sec61 alpha 2 subunit (S. cerevisiae)	441368	5871	404959	13859	21847, 29835, 37823, 45811, 53799
5717	Sec61 alpha 2 subunit (S. cerevisiae)	457034	5872	401731	13860	21848, 29836, 37824, 45812, 53800
5718	Sec61 alpha 2 subunit (S. cerevisiae)	475268	5873	436749	13861	21849, 29837, 37825, 45813, 53801
5719	Sec61 beta subunit	223641	5874	223641	13862	21850, 29838, 37826, 45814, 53802
5720	Sec61 gamma subunit	352861	5875	341538	13863	21851, 29839, 37827, 45815, 53803
5721	Sec61 gamma subunit	395535	5876	378906	13864	21852, 29840, 37828, 45816, 53804

5722	Sec61 gamma subunit	415949	5877	388337	13865	21853, 29841, 37829, 45817, 53805
5723	Sec61 gamma subunit	450622	5878	409884	13866	21854, 29842, 37830, 45818, 53806
5724	seizure related 6 homolog (mouse)	317338	5879	312942	13867	21855, 29843, 37831, 45819, 53807
5725	seizure related 6 homolog (mouse)	335960	5880	337407	13868	21856, 29844, 37832, 45820, 53808
5726	seizure related 6 homolog (mouse)	360295	5881	353440	13869	21857, 29845, 37833, 45821, 53809
5727	seizure related 6 homolog (mouse)	442608	5882	403784	13870	21858, 29846, 37834, 45822, 53810
5728	seizure related 6 homolog (mouse)-like 2	308713	5883	312550	13871	21859, 29847, 37835, 45823, 53811
5729	seizure related 6 homolog (mouse)-like 2	346932	5884	319215	13872	21860, 29848, 37836, 45824, 53812
5730	seizure related 6 homolog (mouse)-like 2	350527	5885	310206	13873	21861, 29849, 37837, 45825, 53813
5731	seizure related 6 homolog (mouse)-like 2	537485	5886	439412	13874	21862, 29850, 37838, 45826, 53814
5732	sel-1 suppressor of lin-12-like 3 (C. elegans)	264868	5887	264868	13875	21863, 29851, 37839, 45827, 53815
5733	sel-1 suppressor of lin-12-like 3 (C. elegans)	399878	5888	382767	13876	21864, 29852, 37840, 45828, 53816
5734	sel-1 suppressor of lin-12-like 3 (C. elegans)	502949	5889	425438	13877	21865, 29853, 37841, 45829, 53817
5735	sel-1 suppressor of lin-12-like 3 (C. elegans)	510880	5890	423743	13878	21866, 29854, 37842, 45830, 53818
5736	sel-1 suppressor of lin-12-like 3 (C. elegans)	513691	5891	421567	13879	21867, 29855, 37843, 45831, 53819
5737	sel-1 suppressor of lin-12-like 3 (C. elegans)	514872	5892	420951	13880	21868, 29856, 37844, 45832, 53820
5738	Selenoprotein S	398226	5893	381282	13881	21869, 29857, 37845, 45833, 53821
5739	Selenoprotein S	526049	5894	433541	13882	21870, 29858, 37846, 45834, 53822

5740	Selenoprotein S	537379	5895	437381	13883	21871, 29859, 37847, 45835, 53823
5741	sema domain transmembrane domain (TM) and cytoplasmic domain (semaphorin) 6B	586582	5896	467290	13884	21872, 29860, 37848, 45836, 53824
5742	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	2829	5897	2829	13885	21873, 29861, 37849, 45837, 53825, 56092, 56125
5743	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	414301	5898	392588	13886	21874, 29862, 37850, 45838, 53826
5744	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	426511	5899	400549	13887	21875, 29863, 37851, 45839, 53827
5745	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	434342	5900	409859	13888	21876, 29864, 37852, 45840, 53828
5746	sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3F	450338	5901	398399	13889	21877, 29865, 37853, 45841, 53829
5747	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	332496	5902	332204	13890	21878, 29866, 37854, 45842, 53830
5748	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	379122	5903	368417	13891	21879, 29867, 37855, 45843, 53831

5749	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	411539	5904	394720	13892	21880, 29868, 37856, 45844, 53832
5750	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	558895	5905	453705	13893	21881, 29869, 37857, 45845, 53833
5751	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	559322	5906	453272	13894	21882, 29870, 37858, 45846, 53834
5752	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4B	559792	5907	453563	13895	21883, 29871, 37859, 45847, 53835
5753	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	305476	5908	306844	13896	21884, 29872, 37860, 45848, 53836
5754	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4C	442264	5909	393498	13897	21885, 29873, 37861, 45849, 53837
5755	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain,	449330	5910	391094	13898	21886, 29874, 37862, 45850, 53838

	(semaphorin) 4C					
5756	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	343780	5911	343418	13899	21887, 29875, 37863, 45851, 53839
5757	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	356444	5912	348822	13900	21888, 29876, 37864, 45852, 53840
5758	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	418828	5913	416747	13901	21889, 29877, 37865, 45853, 53841
5759	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	420101	5914	399948	13902	21890, 29878, 37866, 45854, 53842
5760	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	420670	5915	405652	13903	21891, 29879, 37867, 45855, 53843
5761	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	420681	5916	390754	13904	21892, 29880, 37868, 45856, 53844

5762	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	420987	5917	391733	13905	21893, 29881, 37869, 45857, 53845
5763	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	422704	5918	388768	13906	21894, 29882, 37870, 45858, 53846
5764	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	433650	5919	413352	13907	21895, 29883, 37871, 45859, 53847
5765	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	438547	5920	405102	13908	21896, 29884, 37872, 45860, 53848
5766	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	450295	5921	416523	13909	21897, 29885, 37873, 45861, 53849
5767	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	540475	5922	438389	13910	21898, 29886, 37874, 45862, 53850
5768	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain,	357877	5923	350547	13911	21899, 29887, 37875, 45863, 53851

	(semaphorin) 4F					
5769	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4F	446927	5924	413916	13912	21900, 29888, 37876, 45864, 53852
5770	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	210633	5925	210633	13913	21901, 29889, 37877, 45865, 53853
5771	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	370250	5926	359270	13914	21902, 29890, 37878, 45866, 53854
5772	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	457585	5927	405616	13915	21903, 29891, 37879, 45867, 53855
5773	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	517724	5928	430175	13916	21904, 29892, 37880, 45868, 53856
5774	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	518124	5929	430103	13917	21905, 29893, 37881, 45869, 53857

5775	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	519649	5930	428896	13918	21906, 29894, 37882, 45870, 53858
5776	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4G	521006	5931	430881	13919	21907, 29895, 37883, 45871, 53859
5777	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	195173	5932	195173	13920	21908, 29896, 37884, 45872, 53860
5778	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	357599	5933	350215	13921	21909, 29897, 37885, 45873, 53861
5779	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	393583	5934	377208	13922	21910, 29898, 37886, 45874, 53862
5780	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	418793	5935	413917	13923	21911, 29899, 37887, 45875, 53863

5781	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	421053	5936	401056	13924	21912, 29900, 37888, 45876, 53864
5782	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	449546	5937	401038	13925	21913, 29901, 37889, 45877, 53865
5783	sema domain, seven thrombospondin repeats (type 1 and type 1-like), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 5B	451055	5938	389588	13926	21914, 29902, 37890, 45878, 53866
5784	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	257414	5939	257414	13927	21915, 29903, 37891, 45879, 53867
5785	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	282394	5940	282394	13928	21916, 29904, 37892, 45880, 53868
5786	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	343348	5941	345512	13929	21917, 29905, 37893, 45881, 53869
5787	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	503865	5942	425364	13930	21918, 29906, 37894, 45882, 53870
5788	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	509665	5943	425553	13931	21919, 29907, 37895, 45883, 53871

5789	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	510263	5944	424388	13932	21920, 29908, 37896, 45884, 53872
5790	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	513137	5945	422997	13933	21921, 29909, 37897, 45885, 53873
5791	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A	515009	5946	421935	13934	21922, 29910, 37898, 45886, 53874
5792	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6B	301292	5947	301292	13935	21923, 29911, 37899, 45887, 53875
5793	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6B	301293	5948	301293	13936	21924, 29912, 37900, 45888, 53876
5794	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	341697	5949	344148	13937	21925, 29913, 37901, 45889, 53877
5795	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	368912	5950	357908	13938	21926, 29914, 37902, 45890, 53878
5796	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	368913	5951	357909	13939	21927, 29915, 37903, 45891, 53879
5797	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	368914	5952	357910	13940	21928, 29916, 37904, 45892, 53880
5798	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6C	392792	5953	376542	13941	21929, 29917, 37905, 45893, 53881
5799	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	316364	5954	324857	13942	21930, 29918, 37906, 45894, 53882

5800	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	354744	5955	346786	13943	21931, 29919, 37907, 45895, 53883
5801	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	355997	5956	348276	13944	21932, 29920, 37908, 45896, 53884
5802	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	358066	5957	350770	13945	21933, 29921, 37909, 45897, 53885
5803	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	389425	5958	374076	13946	21934, 29922, 37910, 45898, 53886
5804	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	389428	5959	374079	13947	21935, 29923, 37911, 45899, 53887
5805	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	389432	5960	374083	13948	21936, 29924, 37912, 45900, 53888
5806	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	389433	5961	374084	13949	21937, 29925, 37913, 45901, 53889
5807	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	536845	5962	446152	13950	21938, 29926, 37914, 45902, 53890
5808	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	537942	5963	442040	13951	21939, 29927, 37915, 45903, 53891
5809	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	558014	5964	452815	13952	21940, 29928, 37916, 45904, 53892
5810	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	558816	5965	453661	13953	21941, 29929, 37917, 45905, 53893

5811	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	559184	5966	453097	13954	21942, 29930, 37918, 45906, 53894
5812	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	559196	5967	453755	13955	21943, 29931, 37919, 45907, 53895
5813	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	560636	5968	453420	13956	21944, 29932, 37920, 45908, 53896
5814	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6D	561133	5969	453530	13957	21945, 29933, 37921, 45909, 53897
5815	serine dehydratase-like	345635	5970	341117	13958	21946, 29934, 37922, 45910, 53898
5816	serine dehydratase-like	403593	5971	385790	13959	21947, 29935, 37923, 45911, 53899
5817	serine dehydratase-like	547802	5972	446867	13960	21948, 29936, 37924, 45912, 53900
5818	serine incorporator 1	339697	5973	342962	13961	21949, 29937, 37925, 45913, 53901
5819	serine incorporator 1	368454	5974	357439	13962	21950, 29938, 37926, 45914, 53902
5820	serine incorporator 2	373709	5975	362813	13963	21951, 29939, 37927, 45915, 53903
5821	serine incorporator 2	373710	5976	362814	13964	21952, 29940, 37928, 45916, 53904
5822	serine incorporator 2	536384	5977	439048	13965	21953, 29941, 37929, 45917, 53905
5823	serine incorporator 2	536859	5978	444307	13966	21954, 29942, 37930, 45918, 53906
5824	serine incorporator 4	249714	5979	249714	13967	21955, 29943, 37931, 45919, 53907
5825	serine incorporator 4	319327	5980	319796	13968	21956, 29944, 37932, 45920, 53908

5826	serine incorporator 4	457418	5981	402868	13969	21957, 29945, 37933, 45921, 53909
5827	serine incorporator 5	329637	5982	327542	13970	21958, 29946, 37934, 45922, 53910
5828	serine incorporator 5	507668	5983	426237	13971	21959, 29947, 37935, 45923, 53911
5829	serine incorporator 5	509193	5984	426134	13972	21960, 29948, 37936, 45924, 53912
5830	serine incorporator 5	512721	5985	420863	13973	21961, 29949, 37937, 45925, 53913
5831	serine palmitoyltransferase, small subunit A	298130	5986	298130	13974	21962, 29950, 37938, 45926, 53914
5832	serine palmitoyltransferase, small subunit B	359175	5987	352097	13975	21963, 29951, 37939, 45927, 53915
5833	serine palmitoyltransferase, small subunit B	497137	5988	420115	13976	21964, 29952, 37940, 45928, 53916
5834	serine/threonine kinase 16	396738	5989	379964	13977	21965, 29953, 37941, 45929, 53917
5835	serine/threonine kinase 16	409638	5990	386928	13978	21966, 29954, 37942, 45930, 53918
5836	serine/threonine/tyrosine kinase 1	75503	5991	75503	13979	21967, 29955, 37943, 45931, 53919, 56093, 56126
5837	serine/threonine/tyrosine kinase 1	535345	5992	444488	13980	21968, 29956, 37944, 45932, 53920
5838	serine/threonine/tyrosine kinase 1	538867	5993	445391	13981	21969, 29957, 37945, 45933, 53921
5839	serine/threonine/tyrosine kinase 1	541561	5994	444942	13982	21970, 29958, 37946, 45934, 53922
5840	serine/threonine/tyrosine kinase 1	542562	5995	446241	13983	21971, 29959, 37947, 45935, 53923
5841	serine-rich and transmembrane domain containing 1	315190	5996	325776	13984	21972, 29960, 37948, 45936, 53924
5842	SERPINE1 mRNA binding protein 1	361219	5997	354591	13985	21973, 29961, 37949, 45937, 53925
5843	SERPINE1 mRNA binding protein 1	370990	5998	360029	13986	21974, 29962, 37950, 45938, 53926

5844	SERPINE1 mRNA binding protein 1	370994	5999	360033	13987	21975, 29963, 37951, 45939, 53927
5845	SERPINE1 mRNA binding protein 1	370995	6000	360034	13988	21976, 29964, 37952, 45940, 53928
5846	Seven transmembrane helix receptorUncharacterized protein	316506	6001	321133	13989	21977, 29965, 37953, 45941, 53929
5847	Seven transmembrane helix receptorUncharacterized protein	344049	6002	340453	13990	21978, 29966, 37954, 45942, 53930
5848	SFT2 domain containing 1	361731	6003	354590	13991	21979, 29967, 37955, 45943, 53931
5849	SFT2 domain containing 2	271375	6004	271375	13992	21980, 29968, 37956, 45944, 53932
5850	SFT2 domain containing 2	367825	6005	356799	13993	21981, 29969, 37957, 45945, 53933
5851	SFT2 domain containing 2	367829	6006	356803	13994	21982, 29970, 37958, 45946, 53934
5852	SFT2 domain containing 3	310981	6007	310803	13995	21983, 29971, 37959, 45947, 53935
5853	SH3 and multiple ankyrin repeat domains 1	293441	6008	293441	13996	21984, 29972, 37960, 45948, 53936
5854	SH3 and multiple ankyrin repeat domains 1	359082	6009	351984	13997	21985, 29973, 37961, 45949, 53937
5855	SH3 and multiple ankyrin repeat domains 1	391813	6010	375689	13998	21986, 29974, 37962, 45950, 53938
5856	SH3 and multiple ankyrin repeat domains 1	391814	6011	375690	13999	21987, 29975, 37963, 45951, 53939
5857	SH3-domain GRB2-like endophilin B1	212369	6012	212369	14000	21988, 29976, 37964, 45952, 53940
5858	SH3-domain GRB2-like endophilin B1	482504	6013	418744	14001	21989, 29977, 37965, 45953, 53941
5859	SH3-domain GRB2-like endophilin B1	535010	6014	441355	14002	21990, 29978, 37966, 45954, 53942
5860	SH3KBP1 binding protein 1	291842	6015	291842	14003	21991, 29979, 37967, 45955, 53943

5861	SH3KBP1 binding protein 1	446701	6016	410670	14004	21992, 29980, 37968, 45956, 53944
5862	SHC (Src homology 2 domain containing) family, member 4	332408	6017	329668	14005	21993, 29981, 37969, 45957, 53945
5863	SHC (Src homology 2 domain containing) family, member 4	396535	6018	379786	14006	21994, 29982, 37970, 45958, 53946
5864	shisa homolog 2 (Xenopus laevis)	319420	6019	313079	14007	21995, 29983, 37971, 45959, 53947
5865	shisa homolog 3 (Xenopus laevis)	319234	6020	326445	14008	21996, 29984, 37972, 45960, 53948
5866	shisa homolog 4 (Xenopus laevis)	362011	6021	355064	14009	21997, 29985, 37973, 45961, 53949
5867	shisa homolog 6 (Xenopus laevis)	409168	6022	387157	14010	21998, 29986, 37974, 45962, 53950
5868	shisa homolog 6 (Xenopus laevis)	432116	6023	388659	14011	21999, 29987, 37975, 45963, 53951
5869	shisa homolog 6 (Xenopus laevis)	441885	6024	390084	14012	22000, 29988, 37976, 45964, 53952
5870	short chain dehydrogenase/reductase family 16C, member 5	303749	6025	307607	14013	22001, 29989, 37977, 45965, 53953
5871	short chain dehydrogenase/reductase family 16C, member 5	396721	6026	379947	14014	22002, 29990, 37978, 45966, 53954
5872	short chain dehydrogenase/reductase family 16C, member 5	538514	6027	440545	14015	22003, 29991, 37979, 45967, 53955
5873	short chain dehydrogenase/reductase family 42E, member 1	328945	6028	332407	14016	22004, 29992, 37980, 45968, 53956
5874	short coiled-coil protein	338517	6029	345262	14017	22005, 29993, 37981, 45969, 53957
5875	short coiled-coil protein	394201	6030	377751	14018	22006, 29994, 37982, 45970, 53958
5876	short coiled-coil protein	394203	6031	377753	14019	22007, 29995, 37983, 45971, 53959

5877	short coiled-coil protein	394205	6032	377755	14020	22008, 29996, 37984, 45972, 53960
5878	short coiled-coil protein	506597	6033	426649	14021	22009, 29997, 37985, 45973, 53961
5879	sialic acid binding Ig-like lectin 14	360844	6034	354090	14022	22010, 29998, 37986, 45974, 53962
5880	sialic acid binding Ig-like lectin 15	389474	6035	374125	14023	22011, 29999, 37987, 45975, 53963
5881	sialic acid binding Ig-like lectin 15	546268	6036	443509	14024	22012, 30000, 37988, 45976, 53964
5882	sialidase 4	325935	6037	320318	14025	22013, 30001, 37989, 45977, 53965
5883	sialidase 4	391969	6038	375830	14026	22014, 30002, 37990, 45978, 53966
5884	sialidase 4	404257	6039	385149	14027	22015, 30003, 37991, 45979, 53967
5885	sialidase 4	405370	6040	384804	14028	22016, 30004, 37992, 45980, 53968
5886	sialidase 4	407683	6041	385402	14029	22017, 30005, 37993, 45981, 53969
5887	sialidase 4	420288	6042	388707	14030	22018, 30006, 37994, 45982, 53970
5888	sialidase 4	423583	6043	397860	14031	22019, 30007, 37995, 45983, 53971
5889	sialidase 4	472793	6044	441629	14032	22020, 30008, 37996, 45984, 53972
5890	SID1 transmembrane family, member 1	264852	6045	264852	14033	22021, 30009, 37997, 45985, 53973
5891	SID1 transmembrane family, member 1	393830	6046	377416	14034	22022, 30010, 37998, 45986, 53974
5892	SID1 transmembrane family, member 2	278951	6047	278951	14035	22023, 30011, 37999, 45987, 53975
5893	SID1 transmembrane family, member 2	324225	6048	314023	14036	22024, 30012, 38000, 45988, 53976
5894	SID1 transmembrane family, member 2	392956	6049	376683	14037	22025, 30013, 38001, 45989, 53977

5895	SID1 transmembrane family, member 2	431081	6050	399635	14038	22026, 30014, 38002, 45990, 53978
5896	SID1 transmembrane family, member 2	525347	6051	432058	14039	22027, 30015, 38003, 45991, 53979
5897	SID1 transmembrane family, member 2	532960	6052	431176	14040	22028, 30016, 38004, 45992, 53980
5898	sidekick cell adhesion molecule 1	404826	6053	385899	14041	22029, 30017, 38005, 45993, 53981
5899	sidekick cell adhesion molecule 1	446104	6054	393517	14042	22030, 30018, 38006, 45994, 53982
5900	sidekick cell adhesion molecule 2	316893	6055	324967	14043	22031, 30019, 38007, 45995, 53983
5901	sidekick cell adhesion molecule 2	388726	6056	373378	14044	22032, 30020, 38008, 45996, 53984
5902	sidekick cell adhesion molecule 2	392650	6057	376421	14045	22033, 30021, 38009, 45997, 53985
5903	sideroflexin 1	321442	6058	316905	14046	22034, 30022, 38010, 45998, 53986
5904	sideroflexin 1	506963	6059	421467	14047	22035, 30023, 38011, 45999, 53987
5905	sideroflexin 1	507017	6060	420961	14048	22036, 30024, 38012, 46000, 53988
5906	sideroflexin 2	369893	6061	358909	14049	22037, 30025, 38013, 46001, 53989
5907	sideroflexin 3	224807	6062	224807	14050	22038, 30026, 38014, 46002, 53990
5908	sideroflexin 3	393459	6063	377103	14051	22039, 30027, 38015, 46003, 53991
5909	sideroflexin 4	330036	6064	333200	14052	22040, 30028, 38016, 46004, 53992
5910	sideroflexin 4	355697	6065	347924	14053	22041, 30029, 38017, 46005, 53993
5911	sideroflexin 4	369131	6066	358127	14054	22042, 30030, 38018, 46006, 53994
5912	sideroflexin 4	392875	6067	376614	14055	22043, 30031, 38019, 46007, 53995

5913	sideroflexin 4	419372	6068	414193	14056	22044, 30032, 38020, 46008, 53996
5914	sideroflexin 5	272433	6069	272433	14057	22045, 30033, 38021, 46009, 53997
5915	signal peptidase complex subunit 1 homolog (S. cerevisiae)	233025	6070	233025	14058	22046, 30034, 38022, 46010, 53998
5916	signal peptidase complex subunit 2 homolog (S. cerevisiae)	263672	6071	263672	14059	22047, 30035, 38023, 46011, 53999
5917	signal peptidase complex subunit 3 homolog (S. cerevisiae)	503362	6072	427463	14060	22048, 30036, 38024, 46012, 54000
5918	Signal peptide peptidase-like 2A	261854	6073	261854	14061	22049, 30037, 38025, 46013, 54001
5919	Signal peptide peptidase-like 2C	329196	6074	332488	14062	22050, 30038, 38026, 46014, 54002
5920	Signal peptide peptidase-like 3	353487	6075	288680	14063	22051, 30039, 38027, 46015, 54003
5921	Signal peptide peptidase-like 3	405631	6076	385950	14064	22052, 30040, 38028, 46016, 54004
5922	signal recognition particle receptor, B subunit	466490	6077	418401	14065	22053, 30041, 38029, 46017, 54005
5923	signal recognition particle receptor, B subunit	484684	6078	417096	14066	22054, 30042, 38030, 46018, 54006
5924	signal sequence receptor, alpha	244763	6079	244763	14067	22055, 30043, 38031, 46019, 54007
5925	signal sequence receptor, alpha	534851	6080	443020	14068	22056, 30044, 38032, 46020, 54008
5926	signal sequence receptor, gamma (translocon-associated protein gamma)	265044	6081	265044	14069	22057, 30045, 38033, 46021, 54009
5927	signal sequence receptor, gamma (translocon-associated protein gamma)	467789	6082	420641	14070	22058, 30046, 38034, 46022, 54010
5928	signal-induced proliferation-associated 1 like 1	381232	6083	370630	14071	22059, 30047, 38035, 46023, 54011

5929	signal-induced proliferation-associated 1 like 1	537413	6084	440682	14072	22060, 30048, 38036, 46024, 54012
5930	signal-induced proliferation-associated 1 like 1	555818	6085	450832	14073	22061, 30049, 38037, 46025, 54013
5931	signaling threshold regulating transmembrane adaptor 1	259608	6086	259608	14074	22062, 30050, 38038, 46026, 54014
5932	signal-regulatory protein alpha	356025	6087	348307	14075	22063, 30051, 38039, 46027, 54015
5933	signal-regulatory protein alpha	358771	6088	351621	14076	22064, 30052, 38040, 46028, 54016
5934	signal-regulatory protein alpha	400068	6089	382941	14077	22065, 30053, 38041, 46029, 54017
5935	signal-regulatory protein beta 1	262929	6090	262929	14078	22066, 30054, 38042, 46030, 54018
5936	signal-regulatory protein beta 1	279477	6091	279477	14079	22067, 30055, 38043, 46031, 54019
5937	signal-regulatory protein beta 1	381596	6092	371009	14080	22068, 30056, 38044, 46032, 54020
5938	signal-regulatory protein beta 1	381603	6093	371016	14081	22069, 30057, 38045, 46033, 54021
5939	signal-regulatory protein beta 1	381605	6094	371018	14082	22070, 30058, 38046, 46034, 54022
5940	Sin3A-associated protein, 18kDa	382533	6095	371973	14083	22071, 30059, 38047, 46035, 54023
5941	six transmembrane epithelial antigen of the prostate 1	297205	6096	297205	14084	22072, 30060, 38048, 46036, 54024
5942	SLAM family member 9	368092	6097	357071	14085	22073, 30061, 38049, 46037, 54025
5943	SLAM family member 9	368093	6098	357072	14086	22074, 30062, 38050, 46038, 54026
5944	slowmo homolog 1 (Drosophila)	336990	6099	338988	14087	22075, 30063, 38051, 46039, 54027
5945	slowmo homolog 1 (Drosophila)	440960	6100	404700	14088	22076, 30064, 38052, 46040, 54028
5946	slowmo homolog 2 (Drosophila)	355937	6101	348206	14089	22077, 30065, 38053, 46041, 54029

5947	SMAD specific E3 ubiquitin protein ligase 2	262435	6102	262435	14090	22078, 30066, 38054, 46042, 54030
5948	small cell adhesion glycoprotein	380103	6103	369446	14091	22079, 30067, 38055, 46043, 54031
5949	small cell adhesion glycoprotein	398453	6104	381471	14092	22080, 30068, 38056, 46044, 54032
5950	small G protein signaling modulator 1	400358	6105	383211	14093	22081, 30069, 38057, 46045, 54033
5951	small G protein signaling modulator 1	400359	6106	383212	14094	22082, 30070, 38058, 46046, 54034
5952	small G protein signaling modulator 1	403206	6107	385854	14095	22083, 30071, 38059, 46047, 54035
5953	small VCP/p97-interacting protein	354193	6108	346130	14096	22084, 30072, 38060, 46048, 54036
5954	Smith-Magenis syndrome chromosome region, candidate 7	323019	6109	323591	14097	22085, 30073, 38061, 46049, 54037
5955	Smith-Magenis syndrome chromosome region, candidate 7	395703	6110	379055	14098	22086, 30074, 38062, 46050, 54038
5956	Smith-Magenis syndrome chromosome region, candidate 7	395704	6111	379056	14099	22087, 30075, 38063, 46051, 54039
5957	Smith-Magenis syndrome chromosome region, candidate 7	395706	6112	379057	14100	22088, 30076, 38064, 46052, 54040
5958	Smith-Magenis syndrome chromosome region, candidate 7-like	325301	6113	327124	14101	22089, 30077, 38065, 46053, 54041
5959	Smith-Magenis syndrome chromosome region, candidate 7-like	402881	6114	385110	14102	22090, 30078, 38066, 46054, 54042
5960	Smith-Magenis syndrome chromosome region, candidate 7-like	404569	6115	385191	14103	22091, 30079, 38067, 46055, 54043
5961	Smith-Magenis syndrome chromosome region, candidate 7-like	428069	6116	413730	14104	22092, 30080, 38068, 46056, 54044

5962	Smith-Magenis syndrome chromosome region, candidate 7-like	433117	6117	404096	14105	22093, 30081, 38069, 46057, 54045
5963	Smith-Magenis syndrome chromosome region, candidate 7-like	434364	6118	390029	14106	22094, 30082, 38070, 46058, 54046
5964	sodium channel and clathrin linker 1	281142	6119	281142	14107	22095, 30083, 38071, 46059, 54047
5965	sodium channel and clathrin linker 1	434680	6120	401539	14108	22096, 30084, 38072, 46060, 54048
5966	sodium channel and clathrin linker 1	439369	6121	395292	14109	22097, 30085, 38073, 46061, 54049
5967	sodium channel and clathrin linker 1	511426	6122	420861	14110	22098, 30086, 38074, 46062, 54050
5968	sodium channel, nonvoltage-gated 1 alpha	338748	6123	345028	14111	22099, 30087, 38075, 46063, 54051
5969	sodium channel, nonvoltage-gated 1 alpha	360168	6124	353292	14112	22100, 30088, 38076, 46064, 54052
5970	sodium channel, nonvoltage-gated 1 alpha	543768	6125	438739	14113	22101, 30089, 38077, 46065, 54053
5971	solute carrier family 1 (glutamate transporter), member 7	371491	6126	360546	14114	22102, 30090, 38078, 46066, 54054
5972	solute carrier family 1 (glutamate transporter), member 7	371494	6127	360549	14115	22103, 30091, 38079, 46067, 54055
5973	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	221742	6128	221742	14116	22104, 30092, 38080, 46068, 54056
5974	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	430939	6129	409386	14117	22105, 30093, 38081, 46069, 54057
5975	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	542610	6130	442673	14118	22106, 30094, 38082, 46070, 54058

5976	solute carrier family 1 (high affinity aspartate/glutamate transporter), member 6	544886	6131	446175	14119	22107, 30095, 38083, 46071, 54059
5977	solute carrier family 10 (sodium/bile acid cotransporter family), member 5	518568	6132	428612	14120	22108, 30096, 38084, 46072, 54060
5978	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	264986	6133	264986	14121	22109, 30097, 38085, 46073, 54061
5979	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	335472	6134	334594	14122	22110, 30098, 38086, 46074, 54062
5980	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	394059	6135	377623	14123	22111, 30099, 38087, 46075, 54063
5981	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	394062	6136	377626	14124	22112, 30100, 38088, 46076, 54064
5982	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	432059	6137	411297	14125	22113, 30101, 38089, 46077, 54065
5983	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	502607	6138	422577	14126	22114, 30102, 38090, 46078, 54066
5984	solute carrier family 10 (sodium/bile acid cotransporter family), member 7	507030	6139	421275	14127	22115, 30103, 38091, 46079, 54067
5985	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	262051	6140	262051	14128	22116, 30104, 38092, 46080, 54068
5986	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	262052	6141	262052	14129	22117, 30105, 38093, 46081, 54069
5987	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	394904	6142	378364	14130	22118, 30106, 38094, 46082, 54070

5988	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	541174	6143	444542	14131	22119, 30107, 38095, 46083, 54071
5989	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	545993	6144	442810	14132	22120, 30108, 38096, 46084, 54072
5990	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	546636	6145	449008	14133	22121, 30109, 38097, 46085, 54073
5991	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	546743	6146	446914	14134	22122, 30110, 38098, 46086, 54074
5992	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	547198	6147	446769	14135	22123, 30111, 38099, 46087, 54075
5993	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	547688	6148	449200	14136	22124, 30112, 38100, 46088, 54076
5994	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	548150	6149	448273	14137	22125, 30113, 38101, 46089, 54077
5995	solute carrier family 11 (proton-coupled divalent metal ion transporters), member 2	548193	6150	449209	14138	22126, 30114, 38102, 46090, 54078
5996	solute carrier family 12 (potassium/chloride transporters), member 8	393469	6151	377112	14139	22127, 30115, 38103, 46091, 54079
5997	solute carrier family 12 (potassium/chloride transporters), member 8	469902	6152	418783	14140	22128, 30116, 38104, 46092, 54080
5998	solute carrier family 12 (potassium/chloride transporters), member 9	275729	6153	275729	14141	22129, 30117, 38105, 46093, 54081

5999	solute carrier family 12 (potassium/chloride transporters), member 9	354161	6154	275730	14142	22130, 30118, 38106, 46094, 54082
6000	solute carrier family 12 (potassium/chloride transporters), member 9	415287	6155	413796	14143	22131, 30119, 38107, 46095, 54083
6001	solute carrier family 12 (potassium/chloride transporters), member 9	428758	6156	408301	14144	22132, 30120, 38108, 46096, 54084
6002	solute carrier family 12 (potassium/chloride transporters), member 9	434158	6157	408571	14145	22133, 30121, 38109, 46097, 54085
6003	solute carrier family 12 (potassium/chloride transporters), member 9	539308	6158	442859	14146	22134, 30122, 38110, 46098, 54086
6004	solute carrier family 12 (potassium/chloride transporters), member 9	540482	6159	443702	14147	22135, 30123, 38111, 46099, 54087
6005	solute carrier family 15 (H+/peptide transporter), member 2	295605	6160	295605	14148	22136, 30124, 38112, 46100, 54088
6006	solute carrier family 15 (H+/peptide transporter), member 2	489711	6161	417085	14149	22137, 30125, 38113, 46101, 54089
6007	solute carrier family 15 (H+/peptide transporter), member 2	542599	6162	444920	14150	22138, 30126, 38114, 46102, 54090
6008	solute carrier family 15, member 3	227880	6163	227880	14151	22139, 30127, 38115, 46103, 54091
6009	solute carrier family 15, member 3	442626	6164	403318	14152	22140, 30128, 38116, 46104, 54092
6010	solute carrier family 15, member 4	266771	6165	266771	14153	22141, 30129, 38117, 46105, 54093
6011	solute carrier family 16 member 4 (monocarboxylic acid transporter 5)	472422	6166	432495	14154	22142, 30130, 38118, 46106, 54094

6012	solute carrier family 16, member 11 (monocarboxylic acid transporter 11)	308009	6167	310490	14155	22143, 30131, 38119, 46107, 54095
6013	solute carrier family 16, member 11 (monocarboxylic acid transporter 11)	447225	6168	394449	14156	22144, 30132, 38120, 46108, 54096
6014	solute carrier family 16, member 13 (monocarboxylic acid transporter 13)	308027	6169	309751	14157	22145, 30133, 38121, 46109, 54097
6015	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	295190	6170	295190	14158	22146, 30134, 38122, 46110, 54098
6016	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	412034	6171	395775	14159	22147, 30135, 38123, 46111, 54099
6017	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	425822	6172	389726	14160	22148, 30136, 38124, 46112, 54100
6018	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	436869	6173	396834	14161	22149, 30137, 38125, 46113, 54101
6019	solute carrier family 16, member 14 (monocarboxylic acid transporter 14)	457406	6174	400352	14162	22150, 30138, 38126, 46114, 54102
6020	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	369779	6175	358794	14163	22151, 30139, 38127, 46115, 54103
6021	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	369781	6176	358796	14164	22152, 30140, 38128, 46116, 54104
6022	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	437429	6177	394790	14165	22153, 30141, 38129, 46117, 54105
6023	solute carrier family 16, member 4 (monocarboxylic acid transporter 5)	541986	6178	446087	14166	22154, 30142, 38130, 46118, 54106
6024	solute carrier family 16, member 5 (monocarboxylic acid transporter 6)	329783	6179	330141	14167	22155, 30143, 38131, 46119, 54107

6025	solute carrier family 16, member 5 (monocarboxylic acid transporter 6)	450736	6180	390564	14168	22156, 30144, 38132, 46120, 54108
6026	solute carrier family 16, member 5 (monocarboxylic acid transporter 6)	538213	6181	440212	14169	22157, 30145, 38133, 46121, 54109
6027	solute carrier family 16, member 6 (monocarboxylic acid transporter 7)	327268	6182	319991	14170	22158, 30146, 38134, 46122, 54110
6028	solute carrier family 16, member 8 (monocarboxylic acid transporter 3)	320521	6183	321735	14171	22159, 30147, 38135, 46123, 54111
6029	solute carrier family 16, member 8 (monocarboxylic acid transporter 3)	427592	6184	409547	14172	22160, 30148, 38136, 46124, 54112
6030	solute carrier family 2 (facilitated glucose transporter), member 11	316185	6185	326748	14173	22161, 30149, 38137, 46125, 54113
6031	solute carrier family 2 (facilitated glucose transporter), member 11	345044	6186	342542	14174	22162, 30150, 38138, 46126, 54114
6032	solute carrier family 2 (facilitated glucose transporter), member 11	398356	6187	381399	14175	22163, 30151, 38139, 46127, 54115
6033	solute carrier family 2 (facilitated glucose transporter), member 11	398359	6188	381400	14176	22164, 30152, 38140, 46128, 54116
6034	solute carrier family 2 (facilitated glucose transporter), member 11	398363	6189	381404	14177	22165, 30153, 38141, 46129, 54117
6035	solute carrier family 2 (facilitated glucose transporter), member 11	407566	6190	386027	14178	22166, 30154, 38142, 46130, 54118
6036	solute carrier family 2 (facilitated glucose transporter), member 12	275230	6191	275230	14179	22167, 30155, 38143, 46131, 54119
6037	solute carrier family 22 (organic anion transporter), member 13	311856	6192	310241	14180	22168, 30156, 38144, 46132, 54120
6038	solute carrier family 22 (organic anion transporter), member	450935	6193	406929	14181	22169, 30157, 38145, 46133, 54121

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6039	solute carrier family 22 (organic anion transporter), member 9	279178	6194	279178	14182	22170, 30158, 38146, 46134, 54122
6040	solute carrier family 22 (organic anion transporter), member 9	310969	6195	311527	14183	22171, 30159, 38147, 46135, 54123
6041	solute carrier family 22, member 10	332793	6196	327569	14184	22172, 30160, 38148, 46136, 54124
6042	solute carrier family 22, member 10	533483	6197	433048	14185	22173, 30161, 38149, 46137, 54125
6043	solute carrier family 22, member 10	535888	6198	444602	14186	22174, 30162, 38150, 46138, 54126
6044	solute carrier family 22, member 10	544661	6199	445667	14187	22175, 30163, 38151, 46139, 54127
6045	solute carrier family 22, member 14	273173	6200	273173	14188	22176, 30164, 38152, 46140, 54128
6046	solute carrier family 22, member 14	448498	6201	396283	14189	22177, 30165, 38153, 46141, 54129
6047	solute carrier family 22, member 18	312221	6202	311139	14190	22178, 30166, 38154, 46142, 54130
6048	solute carrier family 22, member 18	347936	6203	307859	14191	22179, 30167, 38155, 46143, 54131
6049	solute carrier family 22, member 18	380574	6204	369948	14192	22180, 30168, 38156, 46144, 54132
6050	solute carrier family 22, member 18	449793	6205	392072	14193	22181, 30169, 38157, 46145, 54133
6051	solute carrier family 22, member 18	485423	6206	433019	14194	22182, 30170, 38158, 46146, 54134
6052	solute carrier family 22, member 25	306494	6207	307443	14195	22183, 30171, 38159, 46147, 54135
6053	solute carrier family 22, member 25	403374	6208	384208	14196	22184, 30172, 38160, 46148, 54136
6054	solute carrier family 22, member 25	451441	6209	398848	14197	22185, 30173, 38161, 46149, 54137
6055	solute carrier family 22, member 25	527057	6210	432242	14198	22186, 30174, 38162, 46150,

						54138
6056	solute carrier family 23 (nucleobase transporters), member 3	295738	6211	295738	14199	22187, 30175, 38163, 46151, 54139
6057	solute carrier family 23 (nucleobase transporters), member 3	396775	6212	379996	14200	22188, 30176, 38164, 46152, 54140
6058	solute carrier family 23 (nucleobase transporters), member 3	409878	6213	386473	14201	22189, 30177, 38165, 46153, 54141
6059	solute carrier family 23 (nucleobase transporters), member 3	455516	6214	406546	14202	22190, 30178, 38166, 46154, 54142
6060	solute carrier family 25 (mitochondrial carrier; phosphate carrier) member 24	565488	6215	457733	14203	22191, 30179, 38167, 46155, 54143
6061	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 23	264088	6216	264088	14204	22192, 30180, 38168, 46156, 54144
6062	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 23	301454	6217	301454	14205	22193, 30181, 38169, 46157, 54145
6063	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 23	334510	6218	334537	14206	22194, 30182, 38170, 46158, 54146
6064	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 23	414491	6219	408814	14207	22195, 30183, 38171, 46159, 54147
6065	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 23	422102	6220	390524	14208	22196, 30184, 38172, 46160, 54148
6066	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 24	264128	6221	264128	14209	22197, 30185, 38173, 46161, 54149
6067	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 24	370041	6222	359058	14210	22198, 30186, 38174, 46162, 54150
6068	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	373064	6223	362155	14211	22199, 30187, 38175, 46163, 54151

6069	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	373066	6224	362157	14212	22200, 30188, 38176, 46164, 54152
6070	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	373068	6225	362159	14213	22201, 30189, 38177, 46165, 54153
6071	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	373069	6226	362160	14214	22202, 30190, 38178, 46166, 54154
6072	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	432073	6227	410053	14215	22203, 30191, 38179, 46167, 54155
6073	solute carrier family 25 (mitochondrial carrier; phosphate carrier), member 25	433501	6228	401672	14216	22204, 30192, 38180, 46168, 54156
6074	solute carrier family 25 member 52	579441	6229	462754	14217	22205, 30193, 38181, 46169, 54157
6075	solute carrier family 25, member 29	359232	6230	352167	14218	22206, 30194, 38182, 46170, 54158
6076	solute carrier family 25, member 29	539621	6231	442985	14219	22207, 30195, 38183, 46171, 54159
6077	solute carrier family 25, member 29	554912	6232	450913	14220	22208, 30196, 38184, 46172, 54160
6078	solute carrier family 25, member 29	555927	6233	452078	14221	22209, 30197, 38185, 46173, 54161
6079	solute carrier family 25, member 29	556505	6234	452446	14222	22210, 30198, 38186, 46174, 54162
6080	solute carrier family 25, member 36	324194	6235	320688	14223	22211, 30199, 38187, 46175, 54163
6081	solute carrier family 25, member 36	446041	6236	401938	14224	22212, 30200, 38188, 46176, 54164
6082	solute carrier family 25, member 47	361529	6237	354886	14225	22213, 30201, 38189, 46177, 54165
6083	solute carrier family 25, member 48	274513	6238	274513	14226	22214, 30202, 38190, 46178, 54166
6084	solute carrier family 25, member 48	412661	6239	413049	14227	22215, 30203, 38191, 46179, 54167

6085	solute carrier family 25, member 48	420621	6240	407973	14228	22216, 30204, 38192, 46180, 54168
6086	solute carrier family 25, member 48	433282	6241	399834	14229	22217, 30205, 38193, 46181, 54169
6087	solute carrier family 26 (sulfate transporter), member 1	361661	6242	354721	14230	22218, 30206, 38194, 46182, 54170
6088	solute carrier family 26 (sulfate transporter), member 1	398516	6243	381528	14231	22219, 30207, 38195, 46183, 54171
6089	solute carrier family 26 (sulfate transporter), member 1	398520	6244	381532	14232	22220, 30208, 38196, 46184, 54172
6090	solute carrier family 26, member 10	379218	6245	368520	14233	22221, 30209, 38197, 46185, 54173
6091	solute carrier family 26, member 11	361193	6246	355384	14234	22222, 30210, 38198, 46186, 54174
6092	solute carrier family 26, member 11	411502	6247	403998	14235	22223, 30211, 38199, 46187, 54175
6093	solute carrier family 26, member 11	546047	6248	440724	14236	22224, 30212, 38200, 46188, 54176
6094	solute carrier family 26, member 7	276609	6249	276609	14237	22225, 30213, 38201, 46189, 54177
6095	solute carrier family 26, member 7	309536	6250	309504	14238	22226, 30214, 38202, 46190, 54178
6096	solute carrier family 26, member 7	522862	6251	428881	14239	22227, 30215, 38203, 46191, 54179
6097	solute carrier family 26, member 7	523719	6252	428849	14240	22228, 30216, 38204, 46192, 54180
6098	solute carrier family 26, member 8	355574	6253	347778	14241	22229, 30217, 38205, 46193, 54181
6099	solute carrier family 26, member 8	394602	6254	378100	14242	22230, 30218, 38206, 46194, 54182
6100	solute carrier family 26, member 8	490799	6255	417638	14243	22231, 30219, 38207, 46195, 54183
6101	solute carrier family 26, member 9	340781	6256	341682	14244	22232, 30220, 38208, 46196, 54184

6102	solute carrier family 26, member 9	367134	6257	356102	14245	22233, 30221, 38209, 46197, 54185
6103	solute carrier family 26, member 9	367135	6258	356103	14246	22234, 30222, 38210, 46198, 54186
6104	solute carrier family 27 (fatty acid transporter), member 6	262462	6259	262462	14247	22235, 30223, 38211, 46199, 54187
6105	solute carrier family 27 (fatty acid transporter), member 6	395266	6260	378684	14248	22236, 30224, 38212, 46200, 54188
6106	solute carrier family 27 (fatty acid transporter), member 6	506176	6261	421024	14249	22237, 30225, 38213, 46201, 54189
6107	solute carrier family 29 (nucleoside transporters), member 4	297195	6262	297195	14250	22238, 30226, 38214, 46202, 54190
6108	solute carrier family 29 (nucleoside transporters), member 4	396872	6263	380081	14251	22239, 30227, 38215, 46203, 54191
6109	solute carrier family 29 (nucleoside transporters), member 4	434816	6264	406803	14252	22240, 30228, 38216, 46204, 54192
6110	solute carrier family 30 (zinc transporter), member 9	264451	6265	264451	14253	22241, 30229, 38217, 46205, 54193
6111	solute carrier family 30 (zinc transporter), member 9	536881	6266	445151	14254	22242, 30230, 38218, 46206, 54194
6112	solute carrier family 32 (GABA vesicular transporter), member 1	217420	6267	217420	14255	22243, 30231, 38219, 46207, 54195
6113	solute carrier family 35 member E1	595753	6268	470652	14256	22244, 30232, 38220, 46208, 54196
6114	solute carrier family 35 member F4	556826	6269	452086	14257	22245, 30233, 38221, 46209, 54197
6115	solute carrier family 35, member A4	323146	6270	327133	14258	22246, 30234, 38222, 46210, 54198
6116	solute carrier family 35, member A4	432254	6271	415133	14259	22247, 30235, 38223, 46211, 54199
6117	solute carrier family 35, member A4	514199	6272	424566	14260	22248, 30236, 38224, 46212, 54200

6118	solute carrier family 35, member A5	468642	6273	418265	14261	22249, 30237, 38225, 46213, 54201
6119	solute carrier family 35, member A5	484995	6274	419958	14262	22250, 30238, 38226, 46214, 54202
6120	solute carrier family 35, member A5	492406	6275	417654	14263	22251, 30239, 38227, 46215, 54203
6121	solute carrier family 35, member C2	243896	6276	243896	14264	22252, 30240, 38228, 46216, 54204
6122	solute carrier family 35, member C2	317734	6277	318960	14265	22253, 30241, 38229, 46217, 54205
6123	solute carrier family 35, member C2	372223	6278	361297	14266	22254, 30242, 38230, 46218, 54206
6124	solute carrier family 35, member C2	372225	6279	361299	14267	22255, 30243, 38231, 46219, 54207
6125	solute carrier family 35, member C2	372227	6280	361301	14268	22256, 30244, 38232, 46220, 54208
6126	solute carrier family 35, member C2	372229	6281	361303	14269	22257, 30245, 38233, 46221, 54209
6127	solute carrier family 35, member C2	372230	6282	361304	14270	22258, 30246, 38234, 46222, 54210
6128	solute carrier family 35, member C2	420518	6283	397142	14271	22259, 30247, 38235, 46223, 54211
6129	solute carrier family 35, member C2	424568	6284	415736	14272	22260, 30248, 38236, 46224, 54212
6130	solute carrier family 35, member C2	543605	6285	439974	14273	22261, 30249, 38237, 46225, 54213
6131	solute carrier family 35, member E1	409648	6286	387152	14274	22262, 30250, 38238, 46226, 54214
6132	solute carrier family 35, member E1	431408	6287	397670	14275	22263, 30251, 38239, 46227, 54215
6133	solute carrier family 35, member E2	246421	6288	246421	14276	22264, 30252, 38240, 46228, 54216
6134	solute carrier family 35, member E2	355439	6289	347614	14277	22265, 30253, 38241, 46229, 54217
6135	solute carrier family 35, member E2	400924	6290	383714	14278	22266, 30254, 38242, 46230, 54218

6136	solute carrier family 35, member E2B	234800	6291	234800	14279	22267, 30255, 38243, 46231, 54219
6137	solute carrier family 35, member E2B	378662	6292	367931	14280	22268, 30256, 38244, 46232, 54220
6138	solute carrier family 35, member E3	398004	6293	381089	14281	22269, 30257, 38245, 46233, 54221
6139	solute carrier family 35, member E4	300385	6294	300385	14282	22270, 30258, 38246, 46234, 54222
6140	solute carrier family 35, member E4	343605	6295	339626	14283	22271, 30259, 38247, 46235, 54223
6141	solute carrier family 35, member E4	406566	6296	384377	14284	22272, 30260, 38248, 46236, 54224
6142	solute carrier family 35, member F1	360388	6297	353557	14285	22273, 30261, 38249, 46237, 54225
6143	solute carrier family 35, member F2	265836	6298	265836	14286	22274, 30262, 38250, 46238, 54226
6144	solute carrier family 35, member F2	375682	6299	364834	14287	22275, 30263, 38251, 46239, 54227
6145	solute carrier family 35, member F2	429869	6300	393571	14288	22276, 30264, 38252, 46240, 54228
6146	solute carrier family 35, member F2	525071	6301	434307	14289	22277, 30265, 38253, 46241, 54229
6147	solute carrier family 35, member F2	525815	6302	436785	14290	22278, 30266, 38254, 46242, 54230
6148	solute carrier family 35, member F3	366617	6303	355576	14291	22279, 30267, 38255, 46243, 54231
6149	solute carrier family 35, member F3	366618	6304	355577	14292	22280, 30268, 38256, 46244, 54232
6150	solute carrier family 35, member F4	339762	6305	342518	14293	22281, 30269, 38257, 46245, 54233
6151	solute carrier family 35, member F5	245680	6306	245680	14294	22282, 30270, 38258, 46246, 54234
6152	solute carrier family 35, member F5	409106	6307	386754	14295	22283, 30271, 38259, 46247, 54235
6153	solute carrier family 35, member G1	371408	6308	360462	14296	22284, 30272, 38260, 46248, 54236

6154	solute carrier family 35, member G1	427197	6309	400932	14297	22285, 30273, 38261, 46249, 54237
6155	solute carrier family 35, member G3	297307	6310	297307	14298	22286, 30274, 38262, 46250, 54238
6156	solute carrier family 35, member G5	382435	6311	371872	14299	22287, 30275, 38263, 46251, 54239
6157	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	298280	6312	298280	14300	22288, 30276, 38264, 46252, 54240
6158	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	308074	6313	311833	14301	22289, 30277, 38265, 46253, 54241
6159	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	403796	6314	384407	14302	22290, 30278, 38266, 46254, 54242
6160	solute carrier family 37 (glycerol-3-phosphate transporter), member 2	407458	6315	385126	14303	22291, 30279, 38267, 46255, 54243
6161	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	326232	6316	321498	14304	22292, 30280, 38268, 46256, 54244
6162	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	340308	6317	343358	14305	22293, 30281, 38269, 46257, 54245
6163	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	429996	6318	412208	14306	22294, 30282, 38270, 46258, 54246
6164	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	447932	6319	397481	14307	22295, 30283, 38271, 46259, 54247
6165	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	491505	6320	417181	14308	22296, 30284, 38272, 46260, 54248

6166	solute carrier family 37 (glycerol-3-phosphate transporter), member 3	539816	6321	442808	14309	22297, 30285, 38273, 46261, 54249
6167	solute carrier family 38, member 10	288439	6322	288439	14310	22298, 30286, 38274, 46262, 54250
6168	solute carrier family 38, member 10	374759	6323	363891	14311	22299, 30287, 38275, 46263, 54251
6169	solute carrier family 38, member 11	303735	6324	306178	14312	22300, 30288, 38276, 46264, 54252
6170	solute carrier family 38, member 11	409149	6325	386272	14313	22301, 30289, 38277, 46265, 54253
6171	solute carrier family 38, member 11	409662	6326	386774	14314	22302, 30290, 38278, 46266, 54254
6172	solute carrier family 38, member 6	267488	6327	267488	14315	22303, 30291, 38279, 46267, 54255
6173	solute carrier family 38, member 6	354886	6328	346959	14316	22304, 30292, 38280, 46268, 54256
6174	solute carrier family 38, member 6	451406	6329	395851	14317	22305, 30293, 38281, 46269, 54257
6175	solute carrier family 38, member 6	456840	6330	413863	14318	22306, 30294, 38282, 46270, 54258
6176	solute carrier family 38, member 9	318672	6331	316596	14319	22307, 30295, 38283, 46271, 54259
6177	solute carrier family 38, member 9	396865	6332	380074	14320	22308, 30296, 38284, 46272, 54260
6178	solute carrier family 38, member 9	416547	6333	397429	14321	22309, 30297, 38285, 46273, 54261
6179	solute carrier family 38, member 9	503891	6334	425055	14322	22310, 30298, 38286, 46274, 54262
6180	solute carrier family 38, member 9	506624	6335	425259	14323	22311, 30299, 38287, 46275, 54263
6181	solute carrier family 38, member 9	507109	6336	420950	14324	22312, 30300, 38288, 46276, 54264
6182	solute carrier family 38, member 9	512595	6337	427335	14325	22313, 30301, 38289, 46277, 54265

6183	solute carrier family 38, member 9	513275	6338	425842	14326	22314, 30302, 38290, 46278, 54266
6184	solute carrier family 38, member 9	513993	6339	422843	14327	22315, 30303, 38291, 46279, 54267
6185	solute carrier family 38, member 9	515629	6340	420934	14328	22316, 30304, 38292, 46280, 54268
6186	solute carrier family 38, member 9	539768	6341	437771	14329	22317, 30305, 38293, 46281, 54269
6187	solute carrier family 39 (metal ion transporter), member 11	255559	6342	255559	14330	22318, 30306, 38294, 46282, 54270
6188	solute carrier family 39 (metal ion transporter), member 11	542342	6343	445829	14331	22319, 30307, 38295, 46283, 54271
6189	solute carrier family 39 (metal ion transporter), member 5	266980	6344	266980	14332	22320, 30308, 38296, 46284, 54272
6190	solute carrier family 39 (metal ion transporter), member 5	417965	6345	414868	14333	22321, 30309, 38297, 46285, 54273
6191	solute carrier family 39 (metal ion transporter), member 5	419753	6346	402891	14334	22322, 30310, 38298, 46286, 54274
6192	solute carrier family 39 (metal ion transporter), member 5	424625	6347	404155	14335	22323, 30311, 38299, 46287, 54275
6193	solute carrier family 39 (metal ion transporter), member 5	437277	6348	407399	14336	22324, 30312, 38300, 46288, 54276
6194	solute carrier family 39 (metal ion transporter), member 5	454355	6349	405360	14337	22325, 30313, 38301, 46289, 54277
6195	solute carrier family 39 (zinc transporter) member 9	556605	6350	452385	14338	22326, 30314, 38302, 46290, 54278
6196	solute carrier family 39 (zinc transporter), member 10	359634	6351	352655	14339	22327, 30315, 38303, 46291, 54279
6197	solute carrier family 39 (zinc transporter), member 10	409086	6352	386766	14340	22328, 30316, 38304, 46292, 54280

6198	solute carrier family 39 (zinc transporter), member 10	412905	6353	406590	14341	22329, 30317, 38305, 46293, 54281
6199	solute carrier family 39 (zinc transporter), member 10	418005	6354	409272	14342	22330, 30318, 38306, 46294, 54282
6200	solute carrier family 39 (zinc transporter), member 10	458054	6355	389640	14343	22331, 30319, 38307, 46295, 54283
6201	solute carrier family 39 (zinc transporter), member 10	541054	6356	437787	14344	22332, 30320, 38308, 46296, 54284
6202	solute carrier family 39 (zinc transporter), member 12	377369	6357	366586	14345	22333, 30321, 38309, 46297, 54285
6203	solute carrier family 39 (zinc transporter), member 12	377371	6358	366588	14346	22334, 30322, 38310, 46298, 54286
6204	solute carrier family 39 (zinc transporter), member 12	377374	6359	366591	14347	22335, 30323, 38311, 46299, 54287
6205	solute carrier family 39 (zinc transporter), member 12	425219	6360	395382	14348	22336, 30324, 38312, 46300, 54288
6206	solute carrier family 39 (zinc transporter), member 12	539911	6361	440445	14349	22337, 30325, 38313, 46301, 54289
6207	solute carrier family 39 (zinc transporter), member 14	240095	6362	240095	14350	22338, 30326, 38314, 46302, 54290
6208	solute carrier family 39 (zinc transporter), member 14	289952	6363	289952	14351	22339, 30327, 38315, 46303, 54291
6209	solute carrier family 39 (zinc transporter), member 14	359741	6364	352779	14352	22340, 30328, 38316, 46304, 54292
6210	solute carrier family 39 (zinc transporter), member 14	381237	6365	370635	14353	22341, 30329, 38317, 46305, 54293
6211	solute carrier family 39 (zinc transporter), member 8	356736	6366	349174	14354	22342, 30330, 38318, 46306, 54294
6212	solute carrier family 39 (zinc transporter), member 8	394833	6367	378310	14355	22343, 30331, 38319, 46307, 54295
6213	solute carrier family 39 (zinc transporter), member 8	424970	6368	394548	14356	22344, 30332, 38320, 46308, 54296
6214	solute carrier family 39 (zinc transporter), member 9	336643	6369	336887	14357	22345, 30333, 38321, 46309, 54297
6215	solute carrier family 39 (zinc transporter), member 9	555840	6370	450639	14358	22346, 30334, 38322, 46310, 54298

6216	solute carrier family 4 sodium bicarbonate cotransporter member 9	506545	6371	422855	14359	22347, 30335, 38323, 46311, 54299
6217	solute carrier family 4, anion exchanger, member 3	273063	6372	273063	14360	22348, 30336, 38324, 46312, 54300
6218	solute carrier family 4, anion exchanger, member 3	317151	6373	314006	14361	22349, 30337, 38325, 46313, 54301
6219	solute carrier family 4, anion exchanger, member 3	356251	6374	348586	14362	22350, 30338, 38326, 46314, 54302
6220	solute carrier family 4, anion exchanger, member 3	358055	6375	350756	14363	22351, 30339, 38327, 46315, 54303
6221	solute carrier family 4, anion exchanger, member 3	373760	6376	362865	14364	22352, 30340, 38328, 46316, 54304
6222	solute carrier family 4, anion exchanger, member 3	373762	6377	362867	14365	22353, 30341, 38329, 46317, 54305
6223	solute carrier family 4, anion exchanger, member 3	413743	6378	414722	14366	22354, 30342, 38330, 46318, 54306
6224	solute carrier family 4, sodium bicarbonate cotransporter, member 9	230993	6379	230993	14367	22355, 30343, 38331, 46319, 54307
6225	solute carrier family 4, sodium bicarbonate cotransporter, member 9	432095	6380	410056	14368	22356, 30344, 38332, 46320, 54308
6226	solute carrier family 4, sodium bicarbonate cotransporter, member 9	506757	6381	424424	14369	22357, 30345, 38333, 46321, 54309
6227	solute carrier family 4, sodium bicarbonate cotransporter, member 9	507527	6382	427661	14370	22358, 30346, 38334, 46322, 54310
6228	solute carrier family 43, member 3	352187	6383	337561	14371	22359, 30347, 38335, 46323, 54311
6229	solute carrier family 43, member 3	395123	6384	378555	14372	22360, 30348, 38336, 46324, 54312
6230	solute carrier family 43, member 3	395124	6385	378556	14373	22361, 30349, 38337, 46325, 54313

6231	solute carrier family 43, member 3	524863	6386	434569	14374	22362, 30350, 38338, 46326, 54314
6232	solute carrier family 43, member 3	525474	6387	436055	14375	22363, 30351, 38339, 46327, 54315
6233	solute carrier family 43, member 3	526621	6388	434710	14376	22364, 30352, 38340, 46328, 54316
6234	solute carrier family 43, member 3	529112	6389	434913	14377	22365, 30353, 38341, 46329, 54317
6235	solute carrier family 43, member 3	529494	6390	433974	14378	22366, 30354, 38342, 46330, 54318
6236	solute carrier family 43, member 3	529554	6391	436254	14379	22367, 30355, 38343, 46331, 54319
6237	solute carrier family 43, member 3	529748	6392	433393	14380	22368, 30356, 38344, 46332, 54320
6238	solute carrier family 43, member 3	530005	6393	435893	14381	22369, 30357, 38345, 46333, 54321
6239	solute carrier family 43, member 3	530316	6394	431765	14382	22370, 30358, 38346, 46334, 54322
6240	solute carrier family 43, member 3	532278	6395	434371	14383	22371, 30359, 38347, 46335, 54323
6241	solute carrier family 43, member 3	532795	6396	435109	14384	22372, 30360, 38348, 46336, 54324
6242	solute carrier family 43, member 3	533051	6397	435490	14385	22373, 30361, 38349, 46337, 54325
6243	solute carrier family 43, member 3	533235	6398	435156	14386	22374, 30362, 38350, 46338, 54326
6244	solute carrier family 43, member 3	533245	6399	431762	14387	22375, 30363, 38351, 46339, 54327
6245	solute carrier family 44 member 3	527077	6400	433641	14388	22376, 30364, 38352, 46340, 54328
6246	solute carrier family 44 member 3	529450	6401	431836	14389	22377, 30365, 38353, 46341, 54329
6247	solute carrier family 44, member 3	271227	6402	271227	14390	22378, 30366, 38354, 46342, 54330
6248	solute carrier family 44, member 3	422520	6403	410832	14391	22379, 30367, 38355, 46343, 54331

6249	solute carrier family 44, member 3	446120	6404	389143	14392	22380, 30368, 38356, 46344, 54332
6250	solute carrier family 44, member 3	467909	6405	432789	14393	22381, 30369, 38357, 46345, 54333
6251	solute carrier family 44, member 5	370855	6406	359892	14394	22382, 30370, 38358, 46346, 54334
6252	solute carrier family 44, member 5	370859	6407	359896	14395	22383, 30371, 38359, 46347, 54335
6253	solute carrier family 44, member 5	535611	6408	443090	14396	22384, 30372, 38360, 46348, 54336
6254	solute carrier family 44, member 5	535790	6409	442685	14397	22385, 30373, 38361, 46349, 54337
6255	solute carrier family 44, member 5	536707	6410	440581	14398	22386, 30374, 38362, 46350, 54338
6256	solute carrier family 46, member 3	266943	6411	266943	14399	22387, 30375, 38363, 46351, 54339
6257	solute carrier family 46, member 3	380814	6412	370192	14400	22388, 30376, 38364, 46352, 54340
6258	solute carrier family 48 (heme transporter), member 1	432662	6413	389956	14401	22389, 30377, 38365, 46353, 54341
6259	solute carrier family 48 (heme transporter), member 1	442218	6414	415998	14402	22390, 30378, 38366, 46354, 54342
6260	solute carrier family 48 (heme transporter), member 1	442892	6415	410134	14403	22391, 30379, 38367, 46355, 54343
6261	solute carrier family 48 (heme transporter), member 1	547002	6416	446739	14404	22392, 30380, 38368, 46356, 54344
6262	solute carrier family 48 (heme transporter), member 1	548498	6417	450234	14405	22393, 30381, 38369, 46357, 54345
6263	solute carrier family 48 (heme transporter), member 1	549243	6418	446686	14406	22394, 30382, 38370, 46358, 54346
6264	solute carrier family 5 (choline transporter), member 7	264047	6419	264047	14407	22395, 30383, 38371, 46359, 54347

6265	solute carrier family 5 (choline transporter), member 7	409059	6420	387346	14408	22396, 30384, 38372, 46360, 54348
6266	solute carrier family 5 (choline transporter), member 7	540517	6421	445351	14409	22397, 30385, 38373, 46361, 54349
6267	solute carrier family 5 (low affinity glucose cotransporter), member 4	266086	6422	266086	14410	22398, 30386, 38374, 46362, 54350
6268	solute carrier family 5 (sodium/glucose cotransporter) member 11	565769	6423	457179	14411	22399, 30387, 38375, 46363, 54351
6269	solute carrier family 5 (sodium/glucose cotransporter), member 10	317977	6424	324346	14412	22400, 30388, 38376, 46364, 54352
6270	solute carrier family 5 (sodium/glucose cotransporter), member 10	395642	6425	379004	14413	22401, 30389, 38377, 46365, 54353
6271	solute carrier family 5 (sodium/glucose cotransporter), member 10	395643	6426	379005	14414	22402, 30390, 38378, 46366, 54354
6272	solute carrier family 5 (sodium/glucose cotransporter), member 10	395645	6427	379007	14415	22403, 30391, 38379, 46367, 54355
6273	solute carrier family 5 (sodium/glucose cotransporter), member 10	395647	6428	379008	14416	22404, 30392, 38380, 46368, 54356
6274	solute carrier family 5 (sodium/glucose cotransporter), member 10	417251	6429	401875	14417	22405, 30393, 38381, 46369, 54357
6275	solute carrier family 5 (sodium/glucose cotransporter), member 11	347898	6430	289932	14418	22406, 30394, 38382, 46370, 54358
6276	solute carrier family 5 (sodium/glucose cotransporter), member 11	424767	6431	416782	14419	22407, 30395, 38383, 46371, 54359
6277	solute carrier family 5 (sodium/glucose cotransporter), member 11	449109	6432	389606	14420	22408, 30396, 38384, 46372, 54360

6278	solute carrier family 5 (sodium/glucose cotransporter), member 11	539472	6433	441018	14421	22409, 30397, 38385, 46373, 54361
6279	solute carrier family 5 (sodium/glucose cotransporter), member 11	545376	6434	441384	14422	22410, 30398, 38386, 46374, 54362
6280	solute carrier family 5 (sodium/glucose cotransporter), member 9	236495	6435	236495	14423	22411, 30399, 38387, 46375, 54363
6281	solute carrier family 5 (sodium/glucose cotransporter), member 9	420136	6436	408881	14424	22412, 30400, 38388, 46376, 54364
6282	solute carrier family 5 (sodium/glucose cotransporter), member 9	438567	6437	401730	14425	22413, 30401, 38389, 46377, 54365
6283	solute carrier family 5 (sodium/glucose cotransporter), member 9	441260	6438	399991	14426	22414, 30402, 38390, 46378, 54366
6284	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	310574	6439	310208	14427	22415, 30403, 38391, 46379, 54367
6285	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	401463	6440	384265	14428	22416, 30404, 38392, 46380, 54368
6286	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	408041	6441	384853	14429	22417, 30405, 38393, 46381, 54369
6287	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	412471	6442	403851	14430	22418, 30406, 38394, 46382, 54370
6288	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	414408	6443	404032	14431	22419, 30407, 38395, 46383, 54371
6289	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	426119	6444	401347	14432	22420, 30408, 38396, 46384, 54372

6290	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	428518	6445	402903	14433	22421, 30409, 38397, 46385, 54373
6291	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	430186	6446	399299	14434	22422, 30410, 38398, 46386, 54374
6292	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	432106	6447	411536	14435	22423, 30411, 38399, 46387, 54375
6293	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	442731	6448	412115	14436	22424, 30412, 38400, 46388, 54376
6294	solute carrier family 5 (sodium-dependent vitamin transporter), member 6	445802	6449	411361	14437	22425, 30413, 38401, 46389, 54377
6295	solute carrier family 6 (neurotransmitter transporter, GABA), member 13	313154	6450	318097	14438	22426, 30414, 38402, 46390, 54378
6296	solute carrier family 6 (neurotransmitter transporter, GABA), member 13	343164	6451	339260	14439	22427, 30415, 38403, 46391, 54379
6297	solute carrier family 6 (neurotransmitter transporter, GABA), member 13	436453	6452	389316	14440	22428, 30416, 38404, 46392, 54380
6298	solute carrier family 6 (neurotransmitter transporter, GABA), member 13	445055	6453	407104	14441	22429, 30417, 38405, 46393, 54381
6299	solute carrier family 6 (neutral amino acid transporter), member 15	266682	6454	266682	14442	22430, 30418, 38406, 46394, 54382
6300	solute carrier family 6 (neutral amino acid transporter), member 15	318721	6455	317711	14443	22431, 30419, 38407, 46395, 54383
6301	solute carrier family 6 (neutral amino acid transporter), member 15	450363	6456	390706	14444	22432, 30420, 38408, 46396, 54384

6302	solute carrier family 6 (neutral amino acid transporter), member 15	549540	6457	448308	14445	22433, 30421, 38409, 46397, 54385
6303	solute carrier family 6 (neutral amino acid transporter), member 15	552192	6458	450145	14446	22434, 30422, 38410, 46398, 54386
6304	solute carrier family 6, member 16	335875	6459	338627	14447	22435, 30423, 38411, 46399, 54387
6305	solute carrier family 6, member 16	454748	6460	404022	14448	22436, 30424, 38412, 46400, 54388
6306	solute carrier family 6, member 17	331565	6461	330199	14449	22437, 30425, 38413, 46401, 54389
6307	solute carrier family 6, member 17	450985	6462	405461	14450	22438, 30426, 38414, 46402, 54390
6308	solute carrier family 7 (anionic amino acid transporter light chain, xc- system), member 11	280612	6463	280612	14451	22439, 30427, 38415, 46403, 54391
6309	solute carrier family 7 (anionic amino acid transporter), member 13	297524	6464	297524	14452	22440, 30428, 38416, 46404, 54392
6310	solute carrier family 7 (anionic amino acid transporter), member 13	419776	6465	410982	14453	22441, 30429, 38417, 46405, 54393
6311	solute carrier family 7 (cationic amino acid transporter, y+ system), member 3	298085	6466	298085	14454	22442, 30430, 38418, 46406, 54394
6312	solute carrier family 7 (cationic amino acid transporter, y+ system), member 3	374299	6467	363417	14455	22443, 30431, 38419, 46407, 54395
6313	solute carrier family 7 (neutral amino acid transporter light chain, asc system), member 10	253188	6468	253188	14456	22444, 30432, 38420, 46408, 54396
6314	solute carrier family 7 (orphan transporter), member 14	231706	6469	231706	14457	22445, 30433, 38421, 46409, 54397
6315	solute carrier family 8 (sodium/calcium exchanger), member 3	216568	6470	216568	14458	22446, 30434, 38422, 46410, 54398

6316	solute carrier family 8 (sodium/calcium exchanger), member 3	356921	6471	349392	14459	22447, 30435, 38423, 46411, 54399
6317	solute carrier family 8 (sodium/calcium exchanger), member 3	357887	6472	350560	14460	22448, 30436, 38424, 46412, 54400
6318	solute carrier family 8 (sodium/calcium exchanger), member 3	381269	6473	370669	14461	22449, 30437, 38425, 46413, 54401
6319	solute carrier family 8 (sodium/calcium exchanger), member 3	394330	6474	377863	14462	22450, 30438, 38426, 46414, 54402
6320	solute carrier family 8 (sodium/calcium exchanger), member 3	494208	6475	436332	14463	22451, 30439, 38427, 46415, 54403
6321	solute carrier family 8 (sodium/calcium exchanger), member 3	528359	6476	433531	14464	22452, 30440, 38428, 46416, 54404
6322	solute carrier family 8 (sodium/calcium exchanger), member 3	534137	6477	436688	14465	22453, 30441, 38429, 46417, 54405
6323	solute carrier family 9, member 11	367714	6478	356687	14466	22454, 30442, 38430, 46418, 54406
6324	solute carrier family 9, member 11	536496	6479	445437	14467	22455, 30443, 38431, 46419, 54407
6325	solute carrier family 9, subfamily B (cation proton antiporter 2), member 1	296422	6480	296422	14468	22456, 30444, 38432, 46420, 54408
6326	solute carrier family 9, subfamily B (cation proton antiporter 2), member 1	394789	6481	378269	14469	22457, 30445, 38433, 46421, 54409
6327	solute carrier family 9, subfamily B (cation proton antiporter 2), member 1	452285	6482	387772	14470	22458, 30446, 38434, 46422, 54410
6328	solute carrier family 9, subfamily B (cation proton antiporter 2), member 1	510559	6483	426325	14471	22459, 30447, 38435, 46423, 54411

6329	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	339611	6484	345241	14472	22460, 30448, 38436, 46424, 54412
6330	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	362026	6485	354574	14473	22461, 30449, 38437, 46425, 54413
6331	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	394785	6486	378265	14474	22462, 30450, 38438, 46426, 54414
6332	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	503103	6487	425385	14475	22463, 30451, 38439, 46427, 54415
6333	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	503230	6488	422477	14476	22464, 30452, 38440, 46428, 54416
6334	solute carrier family 9, subfamily B (cation proton antiporter 2), member 2	503818	6489	426305	14477	22465, 30453, 38441, 46429, 54417
6335	solute carrier organic anion transporter family member 5A1	524945	6490	434422	14478	22466, 30454, 38442, 46430, 54418
6336	solute carrier organic anion transporter family, member 1A2	307378	6491	305974	14479	22467, 30455, 38443, 46431, 54419
6337	solute carrier organic anion transporter family, member 1A2	390670	6492	375088	14480	22468, 30456, 38444, 46432, 54420
6338	solute carrier organic anion transporter family, member 1A2	416627	6493	392124	14481	22469, 30457, 38445, 46433, 54421
6339	solute carrier organic anion transporter family, member 1A2	421287	6494	390672	14482	22470, 30458, 38446, 46434, 54422
6340	solute carrier organic anion transporter family, member 1A2	421294	6495	390572	14483	22471, 30459, 38447, 46435, 54423

6341	solute carrier organic anion transporter family, member 1A2	422327	6496	416190	14484	22472, 30460, 38448, 46436, 54424
6342	solute carrier organic anion transporter family, member 1A2	430803	6497	410338	14485	22473, 30461, 38449, 46437, 54425
6343	solute carrier organic anion transporter family, member 1A2	435179	6498	401195	14486	22474, 30462, 38450, 46438, 54426
6344	solute carrier organic anion transporter family, member 1A2	450590	6499	407462	14487	22475, 30463, 38451, 46439, 54427
6345	solute carrier organic anion transporter family, member 1A2	452078	6500	393973	14488	22476, 30464, 38452, 46440, 54428
6346	solute carrier organic anion transporter family, member 1A2	453443	6501	409314	14489	22477, 30465, 38453, 46441, 54429
6347	solute carrier organic anion transporter family, member 1A2	458504	6502	394854	14490	22478, 30466, 38454, 46442, 54430
6348	solute carrier organic anion transporter family, member 1A2	537524	6503	439401	14491	22479, 30467, 38455, 46443, 54431
6349	solute carrier organic anion transporter family, member 2A1	493729	6504	418893	14492	22480, 30468, 38456, 46444, 54432
6350	solute carrier organic anion transporter family, member 2B1	289575	6505	289575	14493	22481, 30469, 38457, 46445, 54433
6351	solute carrier organic anion transporter family, member 2B1	341411	6506	341286	14494	22482, 30470, 38458, 46446, 54434
6352	solute carrier organic anion transporter family, member 2B1	428359	6507	388912	14495	22483, 30471, 38459, 46447, 54435
6353	solute carrier organic anion transporter family, member 2B1	454962	6508	389653	14496	22484, 30472, 38460, 46448, 54436
6354	solute carrier organic anion transporter family,	525650	6509	436324	14497	22485, 30473, 38461, 46449, 54437

	member 2B1					
6355	solute carrier organic anion transporter family, member 2B1	525845	6510	431324	14498	22486, 30474, 38462, 46450, 54438
6356	solute carrier organic anion transporter family, member 2B1	527180	6511	436513	14499	22487, 30475, 38463, 46451, 54439
6357	solute carrier organic anion transporter family, member 2B1	530556	6512	435384	14500	22488, 30476, 38464, 46452, 54440
6358	solute carrier organic anion transporter family, member 2B1	531713	6513	432889	14501	22489, 30477, 38465, 46453, 54441
6359	solute carrier organic anion transporter family, member 2B1	532236	6514	434112	14502	22490, 30478, 38466, 46454, 54442
6360	solute carrier organic anion transporter family, member 2B1	534004	6515	431192	14503	22491, 30479, 38467, 46455, 54443
6361	solute carrier organic anion transporter family, member 2B1	534186	6516	433872	14504	22492, 30480, 38468, 46456, 54444
6362	solute carrier organic anion transporter family, member 4C1	310954	6517	309741	14505	22493, 30481, 38469, 46457, 54445
6363	solute carrier organic anion transporter family, member 5A1	260126	6518	260126	14506	22494, 30482, 38470, 46458, 54446
6364	solute carrier organic anion transporter family, member 5A1	530307	6519	431611	14507	22495, 30483, 38471, 46459, 54447
6365	sorting nexin 10	338523	6520	343709	14508	22496, 30484, 38472, 46460, 54448
6366	sorting nexin 10	396376	6521	379661	14509	22497, 30485, 38473, 46461, 54449
6367	sorting nexin 10	446848	6522	395474	14510	22498, 30486, 38474, 46462, 54450
6368	sorting nexin 10	409838	6523	386540	14511	22499, 30487, 38475, 46463, 54451

6369	sorting nexin 14	314673	6524	313121	14512	22500, 30488, 38476, 46464, 54452
6370	sorting nexin 14	346348	6525	257769	14513	22501, 30489, 38477, 46465, 54453
6371	sorting nexin 14	369627	6526	358641	14514	22502, 30490, 38478, 46466, 54454
6372	sorting nexin 14	369628	6527	358642	14515	22503, 30491, 38479, 46467, 54455
6373	sorting nexin 14	505648	6528	427380	14516	22504, 30492, 38480, 46468, 54456
6374	sorting nexin 16	345957	6529	322652	14517	22505, 30493, 38481, 46469, 54457
6375	sorting nexin 16	353788	6530	322631	14518	22506, 30494, 38482, 46470, 54458
6376	sorting nexin 16	396330	6531	379621	14519	22507, 30495, 38483, 46471, 54459
6377	sorting nexin 16	518183	6532	428289	14520	22508, 30496, 38484, 46472, 54460
6378	sorting nexin 16	519817	6533	428591	14521	22509, 30497, 38485, 46473, 54461
6379	sorting nexin 16	521773	6534	430585	14522	22510, 30498, 38486, 46474, 54462
6380	sorting nexin 16	521810	6535	428734	14523	22511, 30499, 38487, 46475, 54463
6381	sorting nexin 18	326277	6536	317332	14524	22512, 30500, 38488, 46476, 54464
6382	sorting nexin 18	343017	6537	342276	14525	22513, 30501, 38489, 46477, 54465
6383	sorting nexin 18	381410	6538	370817	14526	22514, 30502, 38490, 46478, 54466
6384	sorting nexin 19	265909	6539	265909	14527	22515, 30503, 38491, 46479, 54467
6385	sorting nexin 19	539184	6540	443480	14528	22516, 30504, 38492, 46480, 54468
6386	sorting nexin 19	545537	6541	437982	14529	22517, 30505, 38493, 46481, 54469

6387	sorting nexin 22	325881	6542	323435	14530	22518, 30506, 38494, 46482, 54470
6388	sorting nexin 22	380278	6543	369631	14531	22519, 30507, 38495, 46483, 54471
6389	sorting nexin 24	261369	6544	261369	14532	22520, 30508, 38496, 46484, 54472
6390	sorting nexin 24	506996	6545	422535	14533	22521, 30509, 38497, 46485, 54473
6391	sorting nexin 24	513881	6546	424149	14534	22522, 30510, 38498, 46486, 54474
6392	sorting nexin 25	264693	6547	264693	14535	22523, 30511, 38499, 46487, 54475
6393	sorting nexin 25	264694	6548	264694	14536	22524, 30512, 38500, 46488, 54476
6394	sorting nexin 25	504273	6549	426255	14537	22525, 30513, 38501, 46489, 54477
6395	sorting nexin 7	306121	6550	304429	14538	22526, 30514, 38502, 46490, 54478
6396	sorting nexin 7	370189	6551	359208	14539	22527, 30515, 38503, 46491, 54479
6397	sorting nexin 7	529992	6552	434731	14540	22528, 30516, 38504, 46492, 54480
6398	sorting nexin 8	222990	6553	222990	14541	22529, 30517, 38505, 46493, 54481
6399	sorting nexin 8	419693	6554	399127	14542	22530, 30518, 38506, 46494, 54482
6400	sorting nexin 8	457286	6555	406954	14543	22531, 30519, 38507, 46495, 54483
6401	sorting nexin family member 21	342644	6556	344586	14544	22532, 30520, 38508, 46496, 54484
6402	sorting nexin family member 21	372545	6557	361624	14545	22533, 30521, 38509, 46497, 54485
6403	sorting nexin family member 21	462307	6558	420169	14546	22534, 30522, 38510, 46498, 54486
6404	sorting nexin family member 21	491381	6559	418593	14547	22535, 30523, 38511, 46499, 54487

6405	SPANX family, member D	370515	6560	359546	14548	22536, 30524, 38512, 46500, 54488
6406	sperm specific antigen 2	320370	6561	314669	14549	22537, 30525, 38513, 46501, 54489
6407	sperm specific antigen 2	428267	6562	409867	14550	22538, 30526, 38514, 46502, 54490
6408	sperm specific antigen 2	431877	6563	388731	14551	22539, 30527, 38515, 46503, 54491
6409	spermatid maturation 1	323383	6564	315511	14552	22540, 30528, 38516, 46504, 54492
6410	spermatid maturation 1	323675	6565	315554	14553	22541, 30529, 38517, 46505, 54493
6411	spermatogenesis and oogenesis specific basic helix-loop-helix 1	298466	6566	298466	14554	22542, 30530, 38518, 46506, 54494
6412	spermatogenesis and oogenesis specific basic helix-loop-helix 1	425225	6567	404438	14555	22543, 30531, 38519, 46507, 54495
6413	spermatogenesis associated 25	372519	6568	361597	14556	22544, 30532, 38520, 46508, 54496
6414	spermatogenesis associated 9	274432	6569	274432	14557	22545, 30533, 38521, 46509, 54497
6415	spermatogenesis associated 9	316087	6570	325491	14558	22546, 30534, 38522, 46510, 54498
6416	spermatogenesis associated 9	395899	6571	379236	14559	22547, 30535, 38523, 46511, 54499
6417	sphingomyelin phosphodiesterase 2, neutral membrane (neutral sphingomyelinase)	258052	6572	258052	14560	22548, 30536, 38524, 46512, 54500
6418	sphingomyelin phosphodiesterase 3, neutral membrane (neutral sphingomyelinase II)	219334	6573	219334	14561	22549, 30537, 38525, 46513, 54501
6419	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	339679	6574	339721	14562	22550, 30538, 38526, 46514, 54502

6420	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	351288	6575	259217	14563	22551, 30539, 38527, 46515, 54503
6421	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	409031	6576	386531	14564	22552, 30540, 38528, 46516, 54504
6422	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	426662	6577	397479	14565	22553, 30541, 38529, 46517, 54505
6423	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	431183	6578	405187	14566	22554, 30542, 38530, 46518, 54506
6424	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	443958	6579	391896	14567	22555, 30543, 38531, 46519, 54507
6425	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	452225	6580	387762	14568	22556, 30544, 38532, 46520, 54508
6426	sphingomyelin phosphodiesterase 4, neutral membrane (neutral sphingomyelinase-3)	453750	6581	394313	14569	22557, 30545, 38533, 46521, 54509
6427	sphingosine-1-phosphate lyase 1	299297	6582	299297	14570	22558, 30546, 38534, 46522, 54510
6428	sphingosine-1-phosphate lyase 1	373202	6583	362298	14571	22559, 30547, 38535, 46523, 54511
6429	sphingosine-1-phosphate lyase 1	409118	6584	386549	14572	22560, 30548, 38536, 46524, 54512
6430	spire homolog 1 (Drosophila)	309836	6585	309661	14573	22561, 30549, 38537, 46525, 54513
6431	spire homolog 1 (Drosophila)	383356	6586	372847	14574	22562, 30550, 38538, 46526, 54514
6432	spire homolog 1 (Drosophila)	409402	6587	387266	14575	22563, 30551, 38539, 46527, 54515
6433	spire homolog 1 (Drosophila)	410092	6588	387226	14576	22564, 30552, 38540, 46528,

						54516
6434	spire homolog 1 (Drosophila)	453447	6589	407050	14577	22565, 30553, 38541, 46529, 54517
6435	SPRY domain containing 4	338146	6590	338034	14578	22566, 30554, 38542, 46530, 54518
6436	SPRY domain containing 4	543121	6591	444305	14579	22567, 30555, 38543, 46531, 54519
6437	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	377332	6592	366549	14580	22568, 30556, 38544, 46532, 54520
6438	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	393803	6593	377392	14581	22569, 30557, 38545, 46533, 54521
6439	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	393805	6594	377394	14582	22570, 30558, 38546, 46534, 54522
6440	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	393808	6595	377397	14583	22571, 30559, 38547, 46535, 54523
6441	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	455892	6596	401375	14584	22572, 30560, 38548, 46536, 54524
6442	ST3 beta-galactoside alpha-2,3-sialyltransferase 5	525834	6597	433607	14585	22573, 30561, 38549, 46537, 54525
6443	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1	156626	6598	156626	14586	22574, 30562, 38550, 46538, 54526, 56094, 56127
6444	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 1	359088	6599	351991	14587	22575, 30563, 38551, 46539, 54527
6445	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 2	225276	6600	225276	14588	22576, 30564, 38552, 46540, 54528

6446	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	328299	6601	329214	14589	22577, 30565, 38553, 46541, 54529
6447	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	394993	6602	378444	14590	22578, 30566, 38554, 46542, 54530
6448	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	394994	6603	378445	14591	22579, 30567, 38555, 46543, 54531
6449	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 3	415813	6604	395887	14592	22580, 30568, 38556, 46544, 54532
6450	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	335791	6605	336733	14593	22581, 30569, 38557, 46545, 54533
6451	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	343609	6606	340382	14594	22582, 30570, 38558, 46546, 54534
6452	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 4	361444	6607	355130	14595	22583, 30571, 38559, 46547, 54535
6453	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-	541933	6608	439786	14596	22584, 30572, 38560, 46548, 54536

	sialyltransferase 4					
6454	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	291839	6609	291839	14597	22585, 30573, 38561, 46549, 54537
6455	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	373141	6610	362234	14598	22586, 30574, 38562, 46550, 54538
6456	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	373142	6611	362235	14599	22587, 30575, 38563, 46551, 54539
6457	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	373144	6612	362237	14600	22588, 30576, 38564, 46552, 54540
6458	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	373146	6613	362239	14601	22589, 30577, 38565, 46553, 54541
6459	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	447681	6614	405326	14602	22590, 30578, 38566, 46554, 54542
6460	ST6 (alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 6	542456	6615	438109	14603	22591, 30579, 38567, 46555, 54543

6461	ST6 beta-galactosamide alpha-2,6-sialyltranferase 2	361686	6616	355273	14604	22592, 30580, 38568, 46556, 54544
6462	ST6 beta-galactosamide alpha-2,6-sialyltranferase 2	361803	6617	355386	14605	22593, 30581, 38569, 46557, 54545
6463	ST6 beta-galactosamide alpha-2,6-sialyltranferase 2	409087	6618	387332	14606	22594, 30582, 38570, 46558, 54546
6464	ST6 beta-galactosamide alpha-2,6-sialyltranferase 2	409382	6619	386942	14607	22595, 30583, 38571, 46559, 54547
6465	ST6 beta-galactosamide alpha-2,6-sialyltranferase 2	419159	6620	395581	14608	22596, 30584, 38572, 46560, 54548
6466	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1	396037	6621	379353	14609	22597, 30585, 38573, 46561, 54549
6467	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 1	539510	6622	446363	14610	22598, 30586, 38574, 46562, 54550
6468	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2	268164	6623	268164	14611	22599, 30587, 38575, 46563, 54551
6469	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 2	539113	6624	437382	14612	22600, 30588, 38576, 46564, 54552
6470	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 3	324000	6625	320431	14613	22601, 30589, 38577, 46565, 54553
6471	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 3	541833	6626	438901	14614	22602, 30590, 38578, 46566, 54554
6472	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	231461	6627	231461	14615	22603, 30591, 38579, 46567, 54555
6473	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	451528	6628	428914	14616	22604, 30592, 38580, 46568, 54556
6474	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase	315087	6629	321343	14617	22605, 30593, 38581, 46569, 54557

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6475	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 5	536490	6630	443683	14618	22606, 30594, 38582, 46570, 54558
6476	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 5	538168	6631	445492	14619	22607, 30595, 38583, 46571, 54559
6477	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 6	377602	6632	366827	14620	22608, 30596, 38584, 46572, 54560
6478	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 6	377610	6633	366835	14621	22609, 30597, 38585, 46573, 54561
6479	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 6	440449	6634	388343	14622	22610, 30598, 38586, 46574, 54562
6480	stabilin 1	321725	6635	312946	14623	22611, 30599, 38587, 46575, 54563
6481	stabilin 2	258495	6636	258495	14624	22612, 30600, 38588, 46576, 54564
6482	stabilin 2	388887	6637	373539	14625	22613, 30601, 38589, 46577, 54565
6483	starch binding domain 1	237642	6638	237642	14626	22614, 30602, 38590, 46578, 54566
6484	starch binding domain 1	539752	6639	442265	14627	22615, 30603, 38591, 46579, 54567
6485	StAR-related lipid transfer (START) domain containing 7	337288	6640	338030	14628	22616, 30604, 38592, 46580, 54568
6486	STEAP family member 1B	406890	6641	385239	14629	22617, 30605, 38593, 46581, 54569
6487	STEAP family member 1B	424363	6642	416608	14630	22618, 30606, 38594, 46582, 54570
6488	STEAP family member 1B	404369	6643	384370	14631	22619, 30607, 38595, 46583, 54571
6489	stearoyl-CoA desaturase 5	273908	6644	273908	14632	22620, 30608, 38596, 46584, 54572
6490	stearoyl-CoA desaturase 5	282709	6645	282709	14633	22621, 30609, 38597, 46585,

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6491	stearoyl-CoA desaturase 5	319540	6646	316329	14634	22622, 30610, 38598, 46586, 54574
6492	stomatin	286713	6647	286713	14635	22623, 30611, 38599, 46587, 54575
6493	stomatin	347359	6648	339607	14636	22624, 30612, 38600, 46588, 54576
6494	stomatin	538954	6649	445764	14637	22625, 30613, 38601, 46589, 54577
6495	STON1-GTF2A1L readthrough	309827	6650	311493	14638	22626, 30614, 38602, 46590, 54578
6496	STON1-GTF2A1L readthrough	394749	6651	378232	14639	22627, 30615, 38603, 46591, 54579
6497	STON1-GTF2A1L readthrough	394751	6652	378234	14640	22628, 30616, 38604, 46592, 54580
6498	STON1-GTF2A1L readthrough	394754	6653	378236	14641	22629, 30617, 38605, 46593, 54581
6499	STON1-GTF2A1L readthrough	405008	6654	385499	14642	22630, 30618, 38606, 46594, 54582
6500	STON1-GTF2A1L readthrough	402114	6655	385701	14643	22631, 30619, 38607, 46595, 54583
6501	stonin 1	309835	6656	310969	14644	22632, 30620, 38608, 46596, 54584
6502	stonin 1	404752	6657	385273	14645	22633, 30621, 38609, 46597, 54585
6503	stonin 1	406226	6658	384615	14646	22634, 30622, 38610, 46598, 54586
6504	stonin 2	267540	6659	267540	14647	22635, 30623, 38611, 46599, 54587
6505	stonin 2	546306	6660	438942	14648	22636, 30624, 38612, 46600, 54588
6506	stonin 2	554710	6661	451383	14649	22637, 30625, 38613, 46601, 54589
6507	stonin 2	557055	6662	450990	14650	22638, 30626, 38614, 46602, 54590

6508	stonin 2	555447	6663	450857	14651	22639, 30627, 38615, 46603, 54591
6509	stress responsive DNAJB4 interacting membrane protein 1	545867	6664	441459	14652	22640, 30628, 38616, 46604, 54592
6510	stress-associated endoplasmic reticulum protein 1	239944	6665	239944	14653	22641, 30629, 38617, 46605, 54593
6511	stress-associated endoplasmic reticulum protein 1	479209	6666	420076	14654	22642, 30630, 38618, 46606, 54594
6512	stress-associated endoplasmic reticulum protein family member 2	379179	6667	368477	14655	22643, 30631, 38619, 46607, 54595
6513	striatin, calmodulin binding protein	263918	6668	263918	14656	22644, 30632, 38620, 46608, 54596
6514	striatin, calmodulin binding protein	379213	6669	368513	14657	22645, 30633, 38621, 46609, 54597
6515	striatin, calmodulin binding protein	538092	6670	442338	14658	22646, 30634, 38622, 46610, 54598
6516	striatin, calmodulin binding protein 3	355683	6671	347909	14659	22647, 30635, 38623, 46611, 54599
6517	striatin, calmodulin binding protein 3	357479	6672	350071	14660	22648, 30636, 38624, 46612, 54600
6518	STT3, subunit of the oligosaccharyltransferase complex, homolog A (S. cerevisiae)	392708	6673	376472	14661	22649, 30637, 38625, 46613, 54601
6519	STT3, subunit of the oligosaccharyltransferase complex, homolog A (S. cerevisiae)	529196	6674	436962	14662	22650, 30638, 38626, 46614, 54602
6520	STT3, subunit of the oligosaccharyltransferase complex, homolog B (S. cerevisiae)	295770	6675	295770	14663	22651, 30639, 38627, 46615, 54603
6521	succinate receptor 1	362032	6676	355156	14664	22652, 30640, 38628, 46616, 54604
6522	succinate-CoA ligase GDP-forming beta subunit	493112	6677	419325	14665	22653, 30641, 38629, 46617, 54605
6523	succinate-CoA ligase, GDP-forming, beta	307227	6678	307432	14666	22654, 30642, 38630, 46618, 54606

	subunit					
6524	succinate-CoA ligase, GDP-forming, beta subunit	541608	6679	439995	14667	22655, 30643, 38631, 46619, 54607
6525	sulfatase modifying factor 2	275607	6680	275607	14668	22656, 30644, 38632, 46620, 54608
6526	sulfatase modifying factor 2	342190	6681	341938	14669	22657, 30645, 38633, 46621, 54609
6527	sulfatase modifying factor 2	395435	6682	378823	14670	22658, 30646, 38634, 46622, 54610
6528	sulfatase modifying factor 2	395436	6683	378824	14671	22659, 30647, 38635, 46623, 54611
6529	sulfatase modifying factor 2	413952	6684	414434	14672	22660, 30648, 38636, 46624, 54612
6530	sulfatase modifying factor 2	434526	6685	400922	14673	22661, 30649, 38637, 46625, 54613
6531	suppressor of cancer cell invasion	336505	6686	336756	14674	22662, 30650, 38638, 46626, 54614
6532	suppressor of cancer cell invasion	373549	6687	362650	14675	22663, 30651, 38639, 46627, 54615
6533	suppressor of cytokine signaling 7	331159	6688	330659	14676	22664, 30652, 38640, 46628, 54616
6534	suppressor of cytokine signaling 7	577233	6689	464034	14677	22665, 30653, 38641, 46629, 54617
6535	sushi domain containing 1	374263	6690	363381	14678	22666, 30654, 38642, 46630, 54618
6536	sushi domain containing 1	374264	6691	363382	14679	22667, 30655, 38643, 46631, 54619
6537	sushi domain containing 1	374270	6692	363388	14680	22668, 30656, 38644, 46632, 54620
6538	sushi domain containing 2	358321	6693	351075	14681	22669, 30657, 38645, 46633, 54621
6539	sushi domain containing 3	375469	6694	364618	14682	22670, 30658, 38646, 46634, 54622
6540	sushi domain containing 3	375472	6695	364621	14683	22671, 30659, 38647, 46635, 54623

6541	sushi domain containing 4	271787	6696	271787	14684	22672, 30660, 38648, 46636, 54624
6542	sushi domain containing 4	342943	6697	340917	14685	22673, 30661, 38649, 46637, 54625
6543	sushi domain containing 4	343846	6698	344219	14686	22674, 30662, 38650, 46638, 54626
6544	sushi domain containing 4	344029	6699	339926	14687	22675, 30663, 38651, 46639, 54627
6545	sushi domain containing 4	366877	6700	355842	14688	22676, 30664, 38652, 46640, 54628
6546	sushi domain containing 4	366878	6701	355843	14689	22677, 30665, 38653, 46641, 54629
6547	sushi domain containing 4	454695	6702	399288	14690	22678, 30666, 38654, 46642, 54630
6548	sushi domain containing 4	542750	6703	438822	14691	22679, 30667, 38655, 46643, 54631
6549	sushi domain containing 5	309558	6704	308727	14692	22680, 30668, 38656, 46644, 54632
6550	symplekin	245934	6705	245934	14693	22681, 30669, 38657, 46645, 54633
6551	symplekin	340643	6706	343851	14694	22682, 30670, 38658, 46646, 54634
6552	synaptic Ras GTPase activating protein 1	293748	6707	293748	14695	22683, 30671, 38659, 46647, 54635
6553	synaptic Ras GTPase activating protein 1	355818	6708	348072	14696	22684, 30672, 38660, 46648, 54636
6554	synaptic Ras GTPase activating protein 1	395071	6709	378509	14697	22685, 30673, 38661, 46649, 54637
6555	synaptic Ras GTPase activating protein 1	414753	6710	407995	14698	22686, 30674, 38662, 46650, 54638
6556	synaptic Ras GTPase activating protein 1	418600	6711	403636	14699	22687, 30675, 38663, 46651, 54639
6557	synaptic Ras GTPase activating protein 1	449372	6712	416519	14700	22688, 30676, 38664, 46652, 54640
6558	synaptic Ras GTPase activating protein 1	455687	6713	414259	14701	22689, 30677, 38665, 46653, 54641

6559	synaptic Ras GTPase activating protein 1	551507	6714	446753	14702	22690, 30678, 38666, 46654, 54642
6560	synaptic vesicle glycoprotein 2A	369145	6715	358141	14703	22691, 30679, 38667, 46655, 54643
6561	synaptic vesicle glycoprotein 2A	369146	6716	358142	14704	22692, 30680, 38668, 46656, 54644
6562	synaptic vesicle glycoprotein 2B	330276	6717	332818	14705	22693, 30681, 38669, 46657, 54645
6563	synaptic vesicle glycoprotein 2B	394232	6718	377779	14706	22694, 30682, 38670, 46658, 54646
6564	synaptic vesicle glycoprotein 2B	545111	6719	443243	14707	22695, 30683, 38671, 46659, 54647
6565	synaptic vesicle glycoprotein 2B	557410	6720	450992	14708	22696, 30684, 38672, 46660, 54648
6566	synaptic vesicle glycoprotein 2C	322285	6721	316983	14709	22697, 30685, 38673, 46661, 54649
6567	synaptic vesicle glycoprotein 2C	502798	6722	423541	14710	22698, 30686, 38674, 46662, 54650
6568	synaptophysin-like 1	11473	6723	11473	14711	22699, 30687, 38675, 46663, 54651, 56095, 56128
6569	synaptophysin-like 1	455385	6724	388336	14712	22700, 30688, 38676, 46664, 54652
6570	synaptophysin-like 2	369872	6725	358888	14713	22701, 30689, 38677, 46665, 54653
6571	synaptophysin-like 2	401021	6726	383805	14714	22702, 30690, 38678, 46666, 54654
6572	synaptoporin	295894	6727	295894	14715	22703, 30691, 38679, 46667, 54655
6573	synaptoporin	460711	6728	418701	14716	22704, 30692, 38680, 46668, 54656
6574	synaptoporin	478300	6729	418994	14717	22705, 30693, 38681, 46669, 54657
6575	synaptosomal-associated protein 91kDa homolog (mouse)	518312	6730	429937	14718	22706, 30694, 38682, 46670, 54658

6576	synaptosomal-associated protein 91kDa homolog (mouse)	520302	6731	428511	14719	22707, 30695, 38683, 46671, 54659
6577	synaptosomal-associated protein, 91kDa homolog (mouse)	195649	6732	195649	14720	22708, 30696, 38684, 46672, 54660
6578	synaptosomal-associated protein, 91kDa homolog (mouse)	369690	6733	358704	14721	22709, 30697, 38685, 46673, 54661
6579	synaptosomal-associated protein, 91kDa homolog (mouse)	369694	6734	358708	14722	22710, 30698, 38686, 46674, 54662
6580	synaptosomal-associated protein, 91kDa homolog (mouse)	428679	6735	412492	14723	22711, 30699, 38687, 46675, 54663
6581	synaptosomal-associated protein, 91kDa homolog (mouse)	437520	6736	413277	14724	22712, 30700, 38688, 46676, 54664
6582	synaptosomal-associated protein, 91kDa homolog (mouse)	439399	6737	400459	14725	22713, 30701, 38689, 46677, 54665
6583	synaptosomal-associated protein, 91kDa homolog (mouse)	447888	6738	403742	14726	22714, 30702, 38690, 46678, 54666
6584	synaptosomal-associated protein, 91kDa homolog (mouse)	518309	6739	430441	14727	22715, 30703, 38691, 46679, 54667
6585	synaptosomal-associated protein, 91kDa homolog (mouse)	519779	6740	429429	14728	22716, 30704, 38692, 46680, 54668
6586	synaptosomal-associated protein, 91kDa homolog (mouse)	519825	6741	431055	14729	22717, 30705, 38693, 46681, 54669
6587	synaptosomal-associated protein, 91kDa homolog (mouse)	520213	6742	428026	14730	22718, 30706, 38694, 46682, 54670
6588	synaptosomal-associated protein, 91kDa homolog (mouse)	521485	6743	429776	14731	22719, 30707, 38695, 46683, 54671
6589	synaptosomal-associated protein, 91kDa homolog	521743	6744	428215	14732	22720, 30708, 38696, 46684, 54672

	(mouse)					
6590	synaptosomal-associated protein, 91kDa homolog (mouse)	523484	6745	427959	14733	22721, 30709, 38697, 46685, 54673
6591	synaptotagmin binding, cytoplasmic RNA interacting protein	355238	6746	347380	14734	22722, 30710, 38698, 46686, 54674
6592	synaptotagmin binding, cytoplasmic RNA interacting protein	369622	6747	358635	14735	22723, 30711, 38699, 46687, 54675
6593	synaptotagmin binding, cytoplasmic RNA interacting protein	444272	6748	397782	14736	22724, 30712, 38700, 46688, 54676
6594	synaptotagmin II	367267	6749	356236	14737	22725, 30713, 38701, 46689, 54677
6595	synaptotagmin II	367268	6750	356237	14738	22726, 30714, 38702, 46690, 54678
6596	synaptotagmin VIII	381968	6751	371394	14739	22727, 30715, 38703, 46691, 54679
6597	synaptotagmin VIII	436964	6752	414626	14740	22728, 30716, 38704, 46692, 54680
6598	synaptotagmin VIII	535046	6753	443325	14741	22729, 30717, 38705, 46693, 54681
6599	synaptotagmin X	228567	6754	228567	14742	22730, 30718, 38706, 46694, 54682
6600	synaptotagmin X	535526	6755	438691	14743	22731, 30719, 38707, 46695, 54683
6601	synaptotagmin XI	368324	6756	357307	14744	22732, 30720, 38708, 46696, 54684
6602	synaptotagmin XI	539162	6757	441657	14745	22733, 30721, 38709, 46697, 54685
6603	synaptotagmin XVII	355377	6758	347538	14746	22734, 30722, 38710, 46698, 54686
6604	syncoilin, intermediate filament protein	373484	6759	362583	14747	22735, 30723, 38711, 46699, 54687
6605	syncoilin, intermediate filament protein	409190	6760	386439	14748	22736, 30724, 38712, 46700, 54688

6606	syncoilin, intermediate filament protein	417633	6761	401975	14749	22737, 30725, 38713, 46701, 54689
6607	syncoilin, intermediate filament protein	426909	6762	387594	14750	22738, 30726, 38714, 46702, 54690
6608	syncollin	318438	6763	325564	14751	22739, 30727, 38715, 46703, 54691
6609	syndecan binding protein (syntenin)	260130	6764	260130	14752	22740, 30728, 38716, 46704, 54692
6610	syndecan binding protein (syntenin)	413219	6765	411771	14753	22741, 30729, 38717, 46705, 54693
6611	syndecan binding protein (syntenin)	422546	6766	391687	14754	22742, 30730, 38718, 46706, 54694
6612	syndecan binding protein (syntenin)	424270	6767	395351	14755	22743, 30731, 38719, 46707, 54695
6613	syndecan binding protein (syntenin)	447182	6768	409288	14756	22744, 30732, 38720, 46708, 54696
6614	syndecan binding protein (syntenin) 2	339987	6769	342935	14757	22745, 30733, 38721, 46709, 54697
6615	syndecan binding protein (syntenin) 2	360779	6770	354013	14758	22746, 30734, 38722, 46710, 54698
6616	syndecan binding protein (syntenin) 2	381808	6771	371229	14759	22747, 30735, 38723, 46711, 54699
6617	syndecan binding protein (syntenin) 2	381812	6772	371233	14760	22748, 30736, 38724, 46712, 54700
6618	syntaxin 10	242770	6773	242770	14761	22749, 30737, 38725, 46713, 54701
6619	syntaxin 10	343587	6774	339350	14762	22750, 30738, 38726, 46714, 54702
6620	syntaxin 10	440593	6775	415176	14763	22751, 30739, 38727, 46715, 54703
6621	syntaxin 10	587230	6776	466298	14764	22752, 30740, 38728, 46716, 54704
6622	syntaxin 10	589083	6777	465398	14765	22753, 30741, 38729, 46717, 54705
6623	syntaxin 12	373943	6778	363054	14766	22754, 30742, 38730, 46718, 54706

6624	syntaxin 12	440806	6779	392577	14767	22755, 30743, 38731, 46719, 54707
6625	syntaxin 18	306200	6780	305810	14768	22756, 30744, 38732, 46720, 54708
6626	syntaxin 6	258301	6781	258301	14769	22757, 30745, 38733, 46721, 54709
6627	syntaxin 6	542060	6782	440188	14770	22758, 30746, 38734, 46722, 54710
6628	syntaxin binding protein 3	370008	6783	359025	14771	22759, 30747, 38735, 46723, 54711
6629	syntrophin, alpha 1 (dystrophin-associated protein A1, 59kDa, acidic component)	217381	6784	217381	14772	22760, 30748, 38736, 46724, 54712
6630	syntrophin, gamma 2	308624	6785	311837	14773	22761, 30749, 38737, 46725, 54713
6631	T cell receptor beta constant 2	466254	6786	417300	14774	22762, 30750, 38738, 46726, 54714
6632	T cell receptor delta constant	390477	6787	451468	14775	22763, 30751, 38739, 46727, 54715
6633	T cell receptor gamma variable 3	390346	6788	374869	14776	22764, 30752, 38740, 46728, 54716
6634	T cell-interacting, activating receptor on myeloid cells 1	432826	6789	439454	14777	22765, 30753, 38741, 46729, 54717
6635	T cell-interacting, activating receptor on myeloid cells 1	446034	6790	441055	14778	22766, 30754, 38742, 46730, 54718
6636	TAM41, mitochondrial translocator assembly and maintenance protein, homolog (S. cerevisiae)	273037	6791	273037	14779	22767, 30755, 38743, 46731, 54719
6637	TANK-binding kinase 1	331710	6792	329967	14780	22768, 30756, 38744, 46732, 54720
6638	TANK-binding kinase 1	538890	6793	445834	14781	22769, 30757, 38745, 46733, 54721
6639	TANK-binding kinase 1	540417	6794	445628	14782	22770, 30758, 38746, 46734, 54722

6640	TAO kinase 3	359811	6795	352863	14783	22771, 30759, 38747, 46735, 54723
6641	TAO kinase 3	392533	6796	376317	14784	22772, 30760, 38748, 46736, 54724
6642	TAO kinase 3	419821	6797	416374	14785	22773, 30761, 38749, 46737, 54725
6643	TAO kinase 3	535570	6798	443465	14786	22774, 30762, 38750, 46738, 54726
6644	TAO kinase 3	539872	6799	438766	14787	22775, 30763, 38751, 46739, 54727
6645	TAO kinase 3	541186	6800	438820	14788	22776, 30764, 38752, 46740, 54728
6646	TAO kinase 3	541786	6801	442541	14789	22777, 30765, 38753, 46741, 54729
6647	TAO kinase 3	541878	6802	444057	14790	22778, 30766, 38754, 46742, 54730
6648	TAO kinase 3	542532	6803	441071	14791	22779, 30767, 38755, 46743, 54731
6649	TAO kinase 3	542902	6804	440315	14792	22780, 30768, 38756, 46744, 54732
6650	TAP binding protein-like	266556	6805	266556	14793	22781, 30769, 38757, 46745, 54733
6651	target of myb1 (chicken)-like 1	348161	6806	343901	14794	22782, 30770, 38758, 46746, 54734
6652	target of myb1 (chicken)-like 1	445275	6807	408958	14795	22783, 30771, 38759, 46747, 54735
6653	target of myb1 (chicken)-like 1	536554	6808	443099	14796	22784, 30772, 38760, 46748, 54736
6654	target of myb1 (chicken)-like 1	540336	6809	441242	14797	22785, 30773, 38761, 46749, 54737
6655	target of myb1 (chicken)-like 1	575882	6810	460823	14798	22786, 30774, 38762, 46750, 54738
6656	taste receptor, type 2, member 1	382492	6811	371932	14799	22787, 30775, 38763, 46751, 54739
6657	taste receptor, type 2, member 10	240619	6812	240619	14800	22788, 30776, 38764, 46752, 54740

6658	taste receptor, type 2, member 13	390677	6813	375095	14801	22789, 30777, 38765, 46753, 54741
6659	taste receptor, type 2, member 14	537503	6814	441949	14802	22790, 30778, 38766, 46754, 54742
6660	taste receptor, type 2, member 39	446620	6815	405095	14803	22791, 30779, 38767, 46755, 54743
6661	taste receptor, type 2, member 7	240687	6816	240687	14804	22792, 30780, 38768, 46756, 54744
6662	taste receptor, type 2, member 8	240615	6817	240615	14805	22793, 30781, 38769, 46757, 54745
6663	taste receptor, type 2, member 9	240691	6818	240691	14806	22794, 30782, 38770, 46758, 54746
6664	TBC1 domain family, member 9B (with GRAM domain)	355235	6819	347375	14807	22795, 30783, 38771, 46759, 54747
6665	TBC1 domain family, member 9B (with GRAM domain)	356834	6820	349291	14808	22796, 30784, 38772, 46760, 54748
6666	TBC1 domain family, member 9B (with GRAM domain)	444477	6821	401585	14809	22797, 30785, 38773, 46761, 54749
6667	TBC1 domain family, member 9B (with GRAM domain)	544438	6822	443503	14810	22798, 30786, 38774, 46762, 54750
6668	T-cell immunoglobulin and mucin domain containing 4	274532	6823	274532	14811	22799, 30787, 38775, 46763, 54751
6669	T-cell immunoglobulin and mucin domain containing 4	407087	6824	385973	14812	22800, 30788, 38776, 46764, 54752
6670	tectonin beta-propeller repeat containing 1	379795	6825	369121	14813	22801, 30789, 38777, 46765, 54753
6671	tectonin beta-propeller repeat containing 1	423128	6826	407471	14814	22802, 30790, 38778, 46766, 54754
6672	tectonin beta-propeller repeat containing 1	447648	6827	404923	14815	22803, 30791, 38779, 46767, 54755
6673	tectonin beta-propeller repeat containing 1	542604	6828	441121	14816	22804, 30792, 38780, 46768, 54756

6674	tektin 2 (testicular)	207457	6829	207457	14817	22805, 30793, 38781, 46769, 54757
6675	testis expressed 10	374902	6830	364037	14818	22806, 30794, 38782, 46770, 54758
6676	testis expressed 10	429235	6831	399872	14819	22807, 30795, 38783, 46771, 54759
6677	testis expressed 10	444730	6832	413273	14820	22808, 30796, 38784, 46772, 54760
6678	testis expressed 10	535814	6833	444555	14821	22809, 30797, 38785, 46773, 54761
6679	testis expressed 10	537512	6834	438120	14822	22810, 30798, 38786, 46774, 54762
6680	testis expressed 2	258991	6835	258991	14823	22811, 30799, 38787, 46775, 54763
6681	testis expressed 261	272438	6836	272438	14824	22812, 30800, 38788, 46776, 54764
6682	testis expressed 28 pseudogene 1	369932	6837	358948	14825	22813, 30801, 38789, 46777, 54765
6683	testis expressed 28 pseudogene 2	369941	6838	358957	14826	22814, 30802, 38790, 46778, 54766
6684	tetraspanin 10	328585	6839	331620	14827	22815, 30803, 38791, 46779, 54767
6685	tetraspanin 10	540189	6840	444144	14828	22816, 30804, 38792, 46780, 54768
6686	tetraspanin 11	261177	6841	261177	14829	22817, 30805, 38793, 46781, 54769
6687	tetraspanin 11	544427	6842	439895	14830	22818, 30806, 38794, 46782, 54770
6688	tetraspanin 11	546076	6843	437403	14831	22819, 30807, 38795, 46783, 54771
6689	tetraspanin 14	341863	6844	344076	14832	22820, 30808, 38796, 46784, 54772
6690	tetraspanin 14	372156	6845	361229	14833	22821, 30809, 38797, 46785, 54773
6691	tetraspanin 14	372157	6846	361230	14834	22822, 30810, 38798, 46786, 54774

6692	tetraspanin 14	372158	6847	361231	14835	22823, 30811, 38799, 46787, 54775
6693	tetraspanin 14	372160	6848	361233	14836	22824, 30812, 38800, 46788, 54776
6694	tetraspanin 14	372164	6849	361237	14837	22825, 30813, 38801, 46789, 54777
6695	tetraspanin 14	429989	6850	396270	14838	22826, 30814, 38802, 46790, 54778
6696	tetraspanin 14	481124	6851	418195	14839	22827, 30815, 38803, 46791, 54779
6697	tetraspanin 16	316737	6852	319486	14840	22828, 30816, 38804, 46792, 54780
6698	tetraspanin 16	337994	6853	338759	14841	22829, 30817, 38805, 46793, 54781
6699	tetraspanin 17	310032	6854	309036	14842	22830, 30818, 38806, 46794, 54782
6700	tetraspanin 17	405525	6855	385665	14843	22831, 30819, 38807, 46795, 54783
6701	tetraspanin 17	508164	6856	422053	14844	22832, 30820, 38808, 46796, 54784
6702	tetraspanin 17	515708	6857	426650	14845	22833, 30821, 38809, 46797, 54785
6703	tetraspanin 18	340160	6858	339820	14846	22834, 30822, 38810, 46798, 54786
6704	tetraspanin 18	518429	6859	429020	14847	22835, 30823, 38811, 46799, 54787
6705	tetraspanin 18	520358	6860	429993	14848	22836, 30824, 38812, 46800, 54788
6706	tetraspanin 18	533202	6861	434625	14849	22837, 30825, 38813, 46801, 54789
6707	tetraspanin 18	533786	6862	433592	14850	22838, 30826, 38814, 46802, 54790
6708	tetraspanin 33	289407	6863	289407	14851	22839, 30827, 38815, 46803, 54791
6709	tetratricopeptide repeat domain 35	220853	6864	220853	14852	22840, 30828, 38816, 46804, 54792

6710	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1	263635	6865	263635	14853	22841, 30829, 38817, 46805, 54793
6711	tetratricopeptide repeat, ankyrin repeat and coiled-coil containing 1	454300	6866	396339	14854	22842, 30830, 38818, 46806, 54794
6712	TGF-beta activated kinase 1/MAP3K7 binding protein 3	288422	6867	288422	14855	22843, 30831, 38819, 46807, 54795
6713	TGF-beta activated kinase 1/MAP3K7 binding protein 3	378928	6868	368210	14856	22844, 30832, 38820, 46808, 54796
6714	TGF-beta activated kinase 1/MAP3K7 binding protein 3	378930	6869	368212	14857	22845, 30833, 38821, 46809, 54797
6715	TGF-beta activated kinase 1/MAP3K7 binding protein 3	378932	6870	368214	14858	22846, 30834, 38822, 46810, 54798
6716	TGF-beta activated kinase 1/MAP3K7 binding protein 3	378933	6871	368215	14859	22847, 30835, 38823, 46811, 54799
6717	thioesterase superfamily member 4	368814	6872	357804	14860	22848, 30836, 38824, 46812, 54800
6718	thioesterase superfamily member 5	368817	6873	357807	14861	22849, 30837, 38825, 46813, 54801
6719	thioredoxin 2	216185	6874	216185	14862	22850, 30838, 38826, 46814, 54802
6720	thioredoxin 2	403313	6875	385393	14863	22851, 30839, 38827, 46815, 54803
6721	thioredoxin domain containing 11	283033	6876	283033	14864	22852, 30840, 38828, 46816, 54804
6722	thioredoxin domain containing 11	356957	6877	349439	14865	22853, 30841, 38829, 46817, 54805
6723	thioredoxin domain containing 11	436567	6878	397407	14866	22854, 30842, 38830, 46818, 54806
6724	thioredoxin domain containing 15	358387	6879	351157	14867	22855, 30843, 38831, 46819, 54807
6725	thioredoxin domain containing 15	441965	6880	399854	14868	22856, 30844, 38832, 46820, 54808
6726	thioredoxin domain containing 15	546290	6881	443942	14869	22857, 30845, 38833, 46821, 54809

6727	thioredoxin domain containing 5 (endoplasmic reticulum)	379757	6882	369081	14870	22858, 30846, 38834, 46822, 54810
6728	thioredoxin domain containing 5 (endoplasmic reticulum)	473453	6883	420784	14871	22859, 30847, 38835, 46823, 54811
6729	thioredoxin domain containing 5 (endoplasmic reticulum)	539054	6884	442453	14872	22860, 30848, 38836, 46824, 54812
6730	thioredoxin-related transmembrane protein 1	457354	6885	393316	14873	22861, 30849, 38837, 46825, 54813
6731	thioredoxin-related transmembrane protein 2	278422	6886	278422	14874	22862, 30850, 38838, 46826, 54814
6732	thioredoxin-related transmembrane protein 2	378312	6887	367562	14875	22863, 30851, 38839, 46827, 54815
6733	thioredoxin-related transmembrane protein 3	299608	6888	299608	14876	22864, 30852, 38840, 46828, 54816
6734	thioredoxin-related transmembrane protein 3	443099	6889	402605	14877	22865, 30853, 38841, 46829, 54817
6735	thioredoxin-related transmembrane protein 3	544714	6890	444954	14878	22866, 30854, 38842, 46830, 54818
6736	thioredoxin-related transmembrane protein 4	246024	6891	246024	14879	22867, 30855, 38843, 46831, 54819
6737	thyroid hormone receptor interactor 10	313244	6892	320117	14880	22868, 30856, 38844, 46832, 54820
6738	thyroid hormone receptor interactor 10	313285	6893	320493	14881	22869, 30857, 38845, 46833, 54821
6739	thyroid hormone receptor interactor 10	420690	6894	415493	14882	22870, 30858, 38846, 46834, 54822
6740	thyroid hormone receptor interactor 13	166345	6895	166345	14883	22871, 30859, 38847, 46835, 54823, 56096, 56129
6741	thyroid hormone receptor interactor 13	354240	6896	346185	14884	22872, 30860, 38848, 46836, 54824
6742	TLC domain containing 1	292090	6897	292090	14885	22873, 30861, 38849, 46837, 54825
6743	TLC domain containing 1	394933	6898	378391	14886	22874, 30862, 38850, 46838, 54826

6744	TM2 domain containing 1	294613	6899	294613	14887	22875, 30863, 38851, 46839, 54827
6745	TM2 domain containing 1	371177	6900	360219	14888	22876, 30864, 38852, 46840, 54828
6746	TM2 domain containing 1	371178	6901	360220	14889	22877, 30865, 38853, 46841, 54829
6747	TM2 domain containing 1	371180	6902	360222	14890	22878, 30866, 38854, 46842, 54830
6748	TM2 domain containing 2	397070	6903	380260	14891	22879, 30867, 38855, 46843, 54831
6749	TM2 domain containing 2	412303	6904	402964	14892	22880, 30868, 38856, 46844, 54832
6750	TM2 domain containing 2	456397	6905	416050	14893	22881, 30869, 38857, 46845, 54833
6751	TM2 domain containing 2	456845	6906	391674	14894	22882, 30870, 38858, 46846, 54834
6752	TM2 domain containing 2	517872	6907	430685	14895	22883, 30871, 38859, 46847, 54835
6753	TM2 domain containing 2	520152	6908	428203	14896	22884, 30872, 38860, 46848, 54836
6754	TM2 domain containing 2	522142	6909	428394	14897	22885, 30873, 38861, 46849, 54837
6755	TMED7-TICAM2 readthrough	282382	6910	282382	14898	22886, 30874, 38862, 46850, 54838
6756	TMED7-TICAM2 readthrough	333314	6911	333650	14899	22887, 30875, 38863, 46851, 54839
6757	TMEM9 domain family, member B	309134	6912	311842	14900	22888, 30876, 38864, 46852, 54840
6758	TMEM9 domain family, member B	525069	6913	431487	14901	22889, 30877, 38865, 46853, 54841
6759	TMEM9 domain family, member B	534025	6914	433361	14902	22890, 30878, 38866, 46854, 54842
6760	TMPRSS11B N terminal-like	432593	6915	391149	14903	22891, 30879, 38867, 46855, 54843
6761	TNF receptor-associated factor 4	262395	6916	262395	14904	22892, 30880, 38868, 46856, 54844

6762	TNF receptor-associated factor 4	262396	6917	262396	14905	22893, 30881, 38869, 46857, 54845
6763	TNF receptor-associated factor 4	394924	6918	378382	14906	22894, 30882, 38870, 46858, 54846
6764	TNF receptor-associated factor 4	394925	6919	378383	14907	22895, 30883, 38871, 46859, 54847
6765	TNF receptor-associated factor 4	422344	6920	415789	14908	22896, 30884, 38872, 46860, 54848
6766	TNF receptor-associated factor 4	444415	6921	438154	14909	22897, 30885, 38873, 46861, 54849
6767	TNF receptor-associated factor 4	454852	6922	396602	14910	22898, 30886, 38874, 46862, 54850
6768	toll-like receptor 10	308973	6923	308925	14911	22899, 30887, 38875, 46863, 54851
6769	toll-like receptor 10	361424	6924	354459	14912	22900, 30888, 38876, 46864, 54852
6770	toll-like receptor 10	506111	6925	421483	14913	22901, 30889, 38877, 46865, 54853
6771	toll-like receptor 10	508334	6926	424923	14914	22902, 30890, 38878, 46866, 54854
6772	toll-like receptor adaptor molecule 2	408996	6927	386341	14915	22903, 30891, 38879, 46867, 54855
6773	toll-like receptor adaptor molecule 2	427199	6928	415139	14916	22904, 30892, 38880, 46868, 54856
6774	torsin A interacting protein 1	325993	6929	326753	14917	22905, 30893, 38881, 46869, 54857
6775	torsin A interacting protein 1	435319	6930	393292	14918	22906, 30894, 38882, 46870, 54858
6776	torsin A interacting protein 2	367612	6931	356584	14919	22907, 30895, 38883, 46871, 54859
6777	trace amine associated receptor 5	258034	6932	258034	14920	22908, 30896, 38884, 46872, 54860
6778	trace amine associated receptor 8	275200	6933	275200	14921	22909, 30897, 38885, 46873, 54861
6779	trafficking protein particle complex 10	291574	6934	291574	14922	22910, 30898, 38886, 46874, 54862

6780	trafficking protein particle complex 10	542855	6935	438781	14923	22911, 30899, 38887, 46875, 54863
6781	trafficking protein particle complex 2 pseudogene 1	543226	6936	442778	14924	22912, 30900, 38888, 46876, 54864
6782	trafficking protein particle complex 5	317378	6937	316990	14925	22913, 30901, 38889, 46877, 54865
6783	trafficking protein particle complex 5	426877	6938	399025	14926	22914, 30902, 38890, 46878, 54866
6784	trafficking protein particle complex 5	596148	6939	470262	14927	22915, 30903, 38891, 46879, 54867
6785	trafficking protein particle complex 6A	6275	6940	6275	14928	22916, 30904, 38892, 46880, 54868, 56097, 56130
6786	trafficking protein particle complex 6A	585934	6941	468612	14929	22917, 30905, 38893, 46881, 54869
6787	trafficking protein particle complex 6A	588062	6942	468363	14930	22918, 30906, 38894, 46882, 54870
6788	trafficking protein particle complex 6B	330149	6943	330289	14931	22919, 30907, 38895, 46883, 54871
6789	trafficking protein particle complex 6B	347691	6944	335171	14932	22920, 30908, 38896, 46884, 54872
6790	trans-2,3-enoyl-CoA reductase-like	381210	6945	370607	14933	22921, 30909, 38897, 46885, 54873
6791	transcription elongation factor B polypeptide 3B (elongin A2)	332567	6946	331302	14934	22922, 30910, 38898, 46886, 54874
6792	transcription elongation factor B polypeptide 3C (elongin A3)	330682	6947	328232	14935	22923, 30911, 38899, 46887, 54875
6793	transcription elongation factor B polypeptide 3C-like	451265	6948	409932	14936	22924, 30912, 38900, 46888, 54876
6794	transcription elongation factor mitochondrial	581216	6949	462963	14937	22925, 30913, 38901, 46889, 54877
6795	transcription elongation factor, mitochondrial	306049	6950	306574	14938	22926, 30914, 38902, 46890, 54878
6796	transcription elongation factor, mitochondrial	541382	6951	445311	14939	22927, 30915, 38903, 46891, 54879

6797	transcription factor B2, mitochondrial	366514	6952	355471	14940	22928, 30916, 38904, 46892, 54880
6798	transcription factor B2, mitochondrial	544618	6953	442426	14941	22929, 30917, 38905, 46893, 54881
6799	transforming growth factor beta regulator 4	258770	6954	258770	14942	22930, 30918, 38906, 46894, 54882
6800	transforming growth factor beta regulator 4	361278	6955	354992	14943	22931, 30919, 38907, 46895, 54883
6801	transforming growth factor beta regulator 4	395655	6956	379016	14944	22932, 30920, 38908, 46896, 54884
6802	transforming growth factor beta regulator 4	475893	6957	417324	14945	22933, 30921, 38909, 46897, 54885
6803	transforming growth factor beta regulator 4	482285	6958	417967	14946	22934, 30922, 38910, 46898, 54886
6804	transforming growth factor beta regulator 4	494076	6959	420597	14947	22935, 30923, 38911, 46899, 54887
6805	transforming growth factor beta regulator 4	495078	6960	417071	14948	22936, 30924, 38912, 46900, 54888
6806	transient receptor potential cation channel, subfamily C, member 3	264811	6961	264811	14949	22937, 30925, 38913, 46901, 54889
6807	transient receptor potential cation channel, subfamily C, member 3	379645	6962	368966	14950	22938, 30926, 38914, 46902, 54890
6808	transient receptor potential cation channel, subfamily C, member 3	502968	6963	422214	14951	22939, 30927, 38915, 46903, 54891
6809	transient receptor potential cation channel, subfamily C, member 3	513531	6964	426899	14952	22940, 30928, 38916, 46904, 54892
6810	translocase of inner mitochondrial membrane 21 homolog (yeast)	169551	6965	169551	14953	22941, 30929, 38917, 46905, 54893, 56098, 56131
6811	translocase of inner mitochondrial membrane 23 homolog B (yeast)	374097	6966	363210	14954	22942, 30930, 38918, 46906, 54894
6812	translocase of inner mitochondrial membrane 23 homolog B (yeast)	374098	6967	363211	14955	22943, 30931, 38919, 46907, 54895

6813	translocase of inner mitochondrial membrane 23 homolog B (yeast)	429265	6968	409439	14956	22944, 30932, 38920, 46908, 54896
6814	translocase of inner mitochondrial membrane 23 homolog B (yeast)	451577	6969	389331	14957	22945, 30933, 38921, 46909, 54897
6815	translocase of inner mitochondrial membrane 50 homolog (S. cerevisiae)	314349	6970	318115	14958	22946, 30934, 38922, 46910, 54898
6816	translocase of inner mitochondrial membrane 50 homolog (S. cerevisiae)	544017	6971	445806	14959	22947, 30935, 38923, 46911, 54899
6817	translocase of inner mitochondrial membrane 8 homolog B (yeast)	504148	6972	422122	14960	22948, 30936, 38924, 46912, 54900
6818	translocase of inner mitochondrial membrane 8 homolog B (yeast)	541231	6973	438455	14961	22949, 30937, 38925, 46913, 54901
6819	translocase of inner mitochondrial membrane domain containing 1	494664	6974	418803	14962	22950, 30938, 38926, 46914, 54902
6820	translocase of outer mitochondrial membrane 20 homolog (yeast)	366607	6975	355566	14963	22951, 30939, 38927, 46915, 54903
6821	translocase of outer mitochondrial membrane 20 homolog (yeast)-like	360945	6976	354204	14964	22952, 30940, 38928, 46916, 54904
6822	translocase of outer mitochondrial membrane 34	372813	6977	361900	14965	22953, 30941, 38929, 46917, 54905
6823	translocase of outer mitochondrial membrane 40 homolog (yeast)-like	367987	6978	356966	14966	22954, 30942, 38930, 46918, 54906
6824	translocase of outer mitochondrial membrane 40 homolog (yeast)-like	367988	6979	356967	14967	22955, 30943, 38931, 46919, 54907
6825	translocase of outer mitochondrial membrane 40 homolog (yeast)-like	542686	6980	438722	14968	22956, 30944, 38932, 46920, 54908
6826	translocase of outer mitochondrial	545897	6981	443233	14969	22957, 30945, 38933, 46921,

	membrane 40 homolog (yeast)-like					54909
6827	translocase of outer mitochondrial membrane 5 homolog (yeast)	321301	6982	313584	14970	22958, 30946, 38934, 46922, 54910
6828	translocase of outer mitochondrial membrane 5 homolog (yeast)	377773	6983	367004	14971	22959, 30947, 38935, 46923, 54911
6829	translocase of outer mitochondrial membrane 5 homolog (yeast)	544379	6984	438204	14972	22960, 30948, 38936, 46924, 54912
6830	translocase of outer mitochondrial membrane 6 homolog (yeast)	398881	6985	381856	14973	22961, 30949, 38937, 46925, 54913
6831	translocase of outer mitochondrial membrane 6 homolog (yeast)	398884	6986	381859	14974	22962, 30950, 38938, 46926, 54914
6832	translocase of outer mitochondrial membrane 7 homolog (yeast)	358435	6987	351214	14975	22963, 30951, 38939, 46927, 54915
6833	translocase of outer mitochondrial membrane 70 homolog A (S. cerevisiae)	284320	6988	284320	14976	22964, 30952, 38940, 46928, 54916
6834	translocase of outer mitochondrial membrane 70 homolog A (S. cerevisiae)	544924	6989	445730	14977	22965, 30953, 38941, 46929, 54917
6835	translocation associated membrane protein 1	262213	6990	262213	14978	22966, 30954, 38942, 46930, 54918
6836	translocation associated membrane protein 1	536748	6991	439359	14979	22967, 30955, 38943, 46931, 54919
6837	translocation associated membrane protein 1-like 1	310754	6992	309402	14980	22968, 30956, 38944, 46932, 54920
6838	translocation associated membrane protein 2	182527	6993	182527	14981	22969, 30957, 38945, 46933, 54921
6839	translocator protein 2	373161	6994	362255	14982	22970, 30958, 38946, 46934, 54922
6840	translocator protein 2	470917	6995	419985	14983	22971, 30959, 38947, 46935,

						54923
6841	transmembrane (C-terminal) protease, serine 12	398458	6996	381476	14984	22972, 30960, 38948, 46936, 54924
6842	transmembrane 4 L six family member 18	296059	6997	296059	14985	22973, 30961, 38949, 46937, 54925
6843	transmembrane 4 L six family member 18	470080	6998	419278	14986	22974, 30962, 38950, 46938, 54926
6844	transmembrane 4 L six family member 18	474754	6999	418372	14987	22975, 30963, 38951, 46939, 54927
6845	transmembrane 4 L six family member 19	273695	7000	273695	14988	22976, 30964, 38952, 46940, 54928
6846	transmembrane 4 L six family member 19	442633	7001	405973	14989	22977, 30965, 38953, 46941, 54929
6847	transmembrane 4 L six family member 19	454715	7002	387728	14990	22978, 30966, 38954, 46942, 54930
6848	transmembrane 4 L six family member 20	304568	7003	303028	14991	22979, 30967, 38955, 46943, 54931
6849	transmembrane 4 L six family member 20	449706	7004	416565	14992	22980, 30968, 38956, 46944, 54932
6850	transmembrane 9 superfamily member 1	261789	7005	261789	14993	22981, 30969, 38957, 46945, 54933
6851	transmembrane 9 superfamily member 1	396854	7006	380063	14994	22982, 30970, 38958, 46946, 54934
6852	transmembrane 9 superfamily member 1	525592	7007	432435	14995	22983, 30971, 38959, 46947, 54935
6853	transmembrane 9 superfamily member 1	528010	7008	433792	14996	22984, 30972, 38960, 46948, 54936
6854	transmembrane 9 superfamily member 1	528895	7009	431447	14997	22985, 30973, 38961, 46949, 54937
6855	transmembrane 9 superfamily member 1	530468	7010	435857	14998	22986, 30974, 38962, 46950, 54938
6856	transmembrane 9 superfamily member 1	556387	7011	451949	14999	22987, 30975, 38963, 46951, 54939
6857	transmembrane 9 superfamily member 1 isoform a precursor	530611	7012	433967	15000	22988, 30976, 38964, 46952, 54940

6858	transmembrane 9 superfamily member 2	376387	7013	365567	15001	22989, 30977, 38965, 46953, 54941
6859	transmembrane 9 superfamily member 3	371142	7014	360184	15002	22990, 30978, 38966, 46954, 54942
6860	transmembrane 9 superfamily member 3	443638	7015	401152	15003	22991, 30979, 38967, 46955, 54943
6861	transmembrane 9 superfamily protein member 4	217315	7016	217315	15004	22992, 30980, 38968, 46956, 54944
6862	transmembrane 9 superfamily protein member 4	398022	7017	381104	15005	22993, 30981, 38969, 46957, 54945
6863	transmembrane 9 superfamily protein member 4	421148	7018	403254	15006	22994, 30982, 38970, 46958, 54946
6864	transmembrane and coiled-coil domain family 1	329333	7019	327349	15007	22995, 30983, 38971, 46959, 54947
6865	transmembrane and coiled-coil domain family 1	393238	7020	376930	15008	22996, 30984, 38972, 46960, 54948
6866	transmembrane and coiled-coil domain family 1	426664	7021	389892	15009	22997, 30985, 38973, 46961, 54949
6867	transmembrane and coiled-coil domain family 1	432054	7022	404711	15010	22998, 30986, 38974, 46962, 54950
6868	transmembrane and coiled-coil domain family 2	329800	7023	329436	15011	22999, 30987, 38975, 46963, 54951
6869	transmembrane and coiled-coil domain family 2	330675	7024	331842	15012	23000, 30988, 38976, 46964, 54952
6870	transmembrane and coiled-coil domain family 2	358024	7025	350718	15013	23001, 30989, 38977, 46965, 54953
6871	transmembrane and coiled-coil domain family 2	367159	7026	356127	15014	23002, 30990, 38978, 46966, 54954
6872	transmembrane and coiled-coil domain family 2	545499	7027	437943	15015	23003, 30991, 38979, 46967, 54955
6873	transmembrane and coiled-coil domain family 3	261226	7028	261226	15016	23004, 30992, 38980, 46968, 54956
6874	transmembrane and coiled-coil domains 2	372766	7029	361852	15017	23005, 30993, 38981, 46969, 54957
6875	transmembrane and coiled-coil domains 3	434316	7030	389399	15018	23006, 30994, 38982, 46970, 54958

6876	transmembrane and coiled-coil domains 4	294543	7031	294543	15019	23007, 30995, 38983, 46971, 54959
6877	transmembrane and coiled-coil domains 4	375122	7032	364264	15020	23008, 30996, 38984, 46972, 54960
6878	transmembrane and coiled-coil domains 4	375127	7033	364269	15021	23009, 30997, 38985, 46973, 54961
6879	transmembrane and coiled-coil domains 5A	319669	7034	327234	15022	23010, 30998, 38986, 46974, 54962
6880	transmembrane and coiled-coil domains 5A	540944	7035	445914	15023	23011, 30999, 38987, 46975, 54963
6881	transmembrane and coiled-coil domains 5A	558148	7036	453369	15024	23012, 31000, 38988, 46976, 54964
6882	transmembrane and coiled-coil domains 5A	558625	7037	453271	15025	23013, 31001, 38989, 46977, 54965
6883	transmembrane and coiled-coil domains 5A	559502	7038	454112	15026	23014, 31002, 38990, 46978, 54966
6884	transmembrane and coiled-coil domains 5A	560841	7039	453162	15027	23015, 31003, 38991, 46979, 54967
6885	transmembrane and coiled-coil domains 7	261778	7040	261778	15028	23016, 31004, 38992, 46980, 54968
6886	transmembrane and immunoglobulin domain containing 1	328886	7041	332404	15029	23017, 31005, 38993, 46981, 54969
6887	transmembrane and immunoglobulin domain containing 1	538566	7042	446118	15030	23018, 31006, 38994, 46982, 54970
6888	transmembrane and immunoglobulin domain containing 2	301272	7043	301272	15031	23019, 31007, 38995, 46983, 54971
6889	transmembrane and tetratricopeptide repeat containing 1	256062	7044	256062	15032	23020, 31008, 38996, 46984, 54972
6890	transmembrane and tetratricopeptide repeat containing 1	381224	7045	370622	15033	23021, 31009, 38997, 46985, 54973
6891	transmembrane and tetratricopeptide repeat containing 1	539277	7046	442046	15034	23022, 31010, 38998, 46986, 54974

6892	transmembrane and tetratricopeptide repeat containing 1	540901	7047	446123	15035	23023, 31011, 38999, 46987, 54975
6893	transmembrane and tetratricopeptide repeat containing 1	551659	7048	448112	15036	23024, 31012, 39000, 46988, 54976
6894	transmembrane and tetratricopeptide repeat containing 2	321196	7049	322300	15037	23025, 31013, 39001, 46989, 54977
6895	transmembrane and tetratricopeptide repeat containing 3	266712	7050	266712	15038	23026, 31014, 39002, 46990, 54978
6896	transmembrane and tetratricopeptide repeat containing 3	549011	7051	447640	15039	23027, 31015, 39003, 46991, 54979
6897	transmembrane and tetratricopeptide repeat containing 4	328767	7052	365409	15040	23028, 31016, 39004, 46992, 54980
6898	transmembrane and tetratricopeptide repeat containing 4	342624	7053	343871	15041	23029, 31017, 39005, 46993, 54981
6899	transmembrane and tetratricopeptide repeat containing 4	376234	7054	365408	15042	23030, 31018, 39006, 46994, 54982
6900	transmembrane and tetratricopeptide repeat containing 4	423847	7055	398400	15043	23031, 31019, 39007, 46995, 54983
6901	transmembrane and tetratricopeptide repeat containing 4	475272	7056	419613	15044	23032, 31020, 39008, 46996, 54984
6902	transmembrane and ubiquitin-like domain containing 1	297533	7057	297533	15045	23033, 31021, 39009, 46997, 54985
6903	transmembrane and ubiquitin-like domain containing 1	392818	7058	376565	15046	23034, 31022, 39010, 46998, 54986
6904	transmembrane and ubiquitin-like domain containing 1	462940	7059	417519	15047	23035, 31023, 39011, 46999, 54987
6905	transmembrane and ubiquitin-like domain containing 1	476627	7060	419214	15048	23036, 31024, 39012, 47000, 54988
6906	transmembrane and ubiquitin-like domain containing 1	482202	7061	418709	15049	23037, 31025, 39013, 47001, 54989

6907	transmembrane and ubiquitin-like domain containing 1	488752	7062	420692	15050	23038, 31026, 39014, 47002, 54990
6908	transmembrane and ubiquitin-like domain containing 1	492838	7063	420516	15051	23039, 31027, 39015, 47003, 54991
6909	transmembrane and ubiquitin-like domain containing 2	319511	7064	313214	15052	23040, 31028, 39016, 47004, 54992
6910	transmembrane and ubiquitin-like domain containing 2	357984	7065	350672	15053	23041, 31029, 39017, 47005, 54993
6911	transmembrane and ubiquitin-like domain containing 2	446571	7066	413127	15054	23042, 31030, 39018, 47006, 54994
6912	transmembrane and ubiquitin-like domain containing 2	538716	7067	444565	15055	23043, 31031, 39019, 47007, 54995
6913	transmembrane BAX inhibitor motif containing 1	258412	7068	258412	15056	23044, 31032, 39020, 47008, 54996
6914	transmembrane BAX inhibitor motif containing 1	396809	7069	380025	15057	23045, 31033, 39021, 47009, 54997
6915	transmembrane BAX inhibitor motif containing 1	413976	7070	408729	15058	23046, 31034, 39022, 47010, 54998
6916	transmembrane BAX inhibitor motif containing 1	418569	7071	406744	15059	23047, 31035, 39023, 47011, 54999
6917	transmembrane BAX inhibitor motif containing 1	420341	7072	413624	15060	23048, 31036, 39024, 47012, 55000
6918	transmembrane BAX inhibitor motif containing 1	425694	7073	399345	15061	23049, 31037, 39025, 47013, 55001
6919	transmembrane BAX inhibitor motif containing 1	429501	7074	399987	15062	23050, 31038, 39026, 47014, 55002
6920	transmembrane BAX inhibitor motif containing 1	434015	7075	405516	15063	23051, 31039, 39027, 47015, 55003
6921	transmembrane BAX inhibitor motif containing 1	437694	7076	404709	15064	23052, 31040, 39028, 47016, 55004
6922	transmembrane BAX inhibitor motif containing 1	440422	7077	412518	15065	23053, 31041, 39029, 47017, 55005
6923	transmembrane BAX inhibitor motif containing 1	444000	7078	403462	15066	23054, 31042, 39030, 47018, 55006
6924	transmembrane BAX inhibitor motif containing 1	444183	7079	410136	15067	23055, 31043, 39031, 47019, 55007

6925	transmembrane BAX inhibitor motif containing 1	444881	7080	409738	15068	23056, 31044, 39032, 47020, 55008
6926	transmembrane BAX inhibitor motif containing 1	445635	7081	401491	15069	23057, 31045, 39033, 47021, 55009
6927	transmembrane BAX inhibitor motif containing 1	451181	7082	394946	15070	23058, 31046, 39034, 47022, 55010
6928	transmembrane BAX inhibitor motif containing 1	453281	7083	395614	15071	23059, 31047, 39035, 47023, 55011
6929	transmembrane BAX inhibitor motif containing 1	453776	7084	410771	15072	23060, 31048, 39036, 47024, 55012
6930	transmembrane BAX inhibitor motif containing 1	543441	7085	437408	15073	23061, 31049, 39037, 47025, 55013
6931	transmembrane BAX inhibitor motif containing 4	358230	7086	350965	15074	23062, 31050, 39038, 47026, 55014
6932	transmembrane BAX inhibitor motif containing 4	539043	7087	437888	15075	23063, 31051, 39039, 47027, 55015
6933	transmembrane BAX inhibitor motif containing 4	539427	7088	444023	15076	23064, 31052, 39040, 47028, 55016
6934	transmembrane BAX inhibitor motif containing 4	556010	7089	451688	15077	23065, 31053, 39041, 47029, 55017
6935	transmembrane BAX inhibitor motif containing 6	267115	7090	267115	15078	23066, 31054, 39042, 47030, 55018
6936	transmembrane BAX inhibitor motif containing 6	395006	7091	378454	15079	23067, 31055, 39043, 47031, 55019
6937	transmembrane BAX inhibitor motif containing 6	423828	7092	389277	15080	23068, 31056, 39044, 47032, 55020
6938	transmembrane BAX inhibitor motif containing 6	541612	7093	440808	15081	23069, 31057, 39045, 47033, 55021
6939	transmembrane BAX inhibitor motif containing 6	542631	7094	445903	15082	23070, 31058, 39046, 47034, 55022
6940	transmembrane BAX inhibitor motif containing 6	546796	7095	450159	15083	23071, 31059, 39047, 47035, 55023
6941	transmembrane BAX inhibitor motif containing 6	546914	7096	448612	15084	23072, 31060, 39048, 47036, 55024
6942	transmembrane BAX inhibitor motif containing 6	547187	7097	447400	15085	23073, 31061, 39049, 47037, 55025

6943	transmembrane BAX inhibitor motif containing 6	547832	7098	448269	15086	23074, 31062, 39050, 47038, 55026
6944	transmembrane BAX inhibitor motif containing 6	548201	7099	450265	15087	23075, 31063, 39051, 47039, 55027
6945	transmembrane BAX inhibitor motif containing 6	548713	7100	447888	15088	23076, 31064, 39052, 47040, 55028
6946	transmembrane BAX inhibitor motif containing 6	548809	7101	449000	15089	23077, 31065, 39053, 47041, 55029
6947	transmembrane BAX inhibitor motif containing 6	548894	7102	447074	15090	23078, 31066, 39054, 47042, 55030
6948	transmembrane BAX inhibitor motif containing 6	549130	7103	450305	15091	23079, 31067, 39055, 47043, 55031
6949	transmembrane BAX inhibitor motif containing 6	549385	7104	448036	15092	23080, 31068, 39056, 47044, 55032
6950	transmembrane BAX inhibitor motif containing 6	549445	7105	449904	15093	23081, 31069, 39057, 47045, 55033
6951	transmembrane BAX inhibitor motif containing 6	549966	7106	446668	15094	23082, 31070, 39058, 47046, 55034
6952	transmembrane BAX inhibitor motif containing 6	550445	7107	449907	15095	23083, 31071, 39059, 47047, 55035
6953	transmembrane BAX inhibitor motif containing 6	550951	7108	449421	15096	23084, 31072, 39060, 47048, 55036
6954	transmembrane BAX inhibitor motif containing 6	551154	7109	450417	15097	23085, 31073, 39061, 47049, 55037
6955	transmembrane BAX inhibitor motif containing 6	552370	7110	450158	15098	23086, 31074, 39062, 47050, 55038
6956	transmembrane BAX inhibitor motif containing 6	552699	7111	446734	15099	23087, 31075, 39063, 47051, 55039
6957	transmembrane channel-like 3	359440	7112	352413	15100	23088, 31076, 39064, 47052, 55040
6958	transmembrane channel-like 3	558726	7113	452681	15101	23089, 31077, 39065, 47053, 55041
6959	transmembrane channel-like 4	301187	7114	301187	15102	23090, 31078, 39066, 47054, 55042
6960	transmembrane channel-like 4	376591	7115	365776	15103	23091, 31079, 39067, 47055, 55043

6961	transmembrane channel-like 4	416963	7116	405023	15104	23092, 31080, 39068, 47056, 55044
6962	transmembrane channel-like 5	219821	7117	219821	15105	23093, 31081, 39069, 47057, 55045
6963	transmembrane channel-like 5	381414	7118	370822	15106	23094, 31082, 39070, 47058, 55046
6964	transmembrane channel-like 5	396229	7119	379531	15107	23095, 31083, 39071, 47059, 55047
6965	transmembrane channel-like 5	440743	7120	395658	15108	23096, 31084, 39072, 47060, 55048
6966	transmembrane channel-like 5	541464	7121	441227	15109	23097, 31085, 39073, 47061, 55049
6967	transmembrane channel-like 5	542583	7122	446274	15110	23098, 31086, 39074, 47062, 55050
6968	transmembrane channel-like 7	304381	7123	304710	15111	23099, 31087, 39075, 47063, 55051
6969	transmembrane channel-like 7	421369	7124	397081	15112	23100, 31088, 39076, 47064, 55052
6970	transmembrane emp24 domain trafficking protein 2	262225	7125	262225	15113	23101, 31089, 39077, 47065, 55053
6971	transmembrane emp24 domain trafficking protein 2	432022	7126	388691	15114	23102, 31090, 39078, 47066, 55054
6972	transmembrane emp24 domain trafficking protein 2	541504	7127	439546	15115	23103, 31091, 39079, 47067, 55055
6973	transmembrane emp24 protein transport domain containing 3	299705	7128	299705	15116	23104, 31092, 39080, 47068, 55056
6974	transmembrane emp24 protein transport domain containing 3	424155	7129	414983	15117	23105, 31093, 39081, 47069, 55057
6975	transmembrane emp24 protein transport domain containing 5	370280	7130	359303	15118	23106, 31094, 39082, 47070, 55058
6976	transmembrane emp24 protein transport domain containing 5	370282	7131	359305	15119	23107, 31095, 39083, 47071, 55059
6977	transmembrane emp24 protein transport domain	479918	7132	418992	15120	23108, 31096, 39084, 47072, 55060

	containing 5					
6978	transmembrane emp24 protein transport domain containing 5	535517	7133	438246	15121	23109, 31097, 39085, 47073, 55061
6979	transmembrane emp24 protein transport domain containing 6	288025	7134	288025	15122	23110, 31098, 39086, 47074, 55062
6980	transmembrane emp24 protein transport domain containing 7	456936	7135	405926	15123	23111, 31099, 39087, 47075, 55063
6981	transmembrane emp24 protein transport domain containing 7	508420	7136	450928	15124	23112, 31100, 39088, 47076, 55064
6982	transmembrane emp24 protein transport domain containing 8	216468	7137	216468	15125	23113, 31101, 39089, 47077, 55065
6983	transmembrane emp24 protein transport domain containing 9	332598	7138	330945	15126	23114, 31102, 39090, 47078, 55066
6984	transmembrane epididymal protein 1	367565	7139	356536	15127	23115, 31103, 39091, 47079, 55067
6985	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	255310	7140	255310	15128	23116, 31104, 39092, 47080, 55068
6986	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	343548	7141	343109	15129	23117, 31105, 39093, 47081, 55069
6987	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	382975	7142	372435	15130	23118, 31106, 39094, 47082, 55070
6988	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	382977	7143	372437	15131	23119, 31107, 39095, 47083, 55071
6989	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	390680	7144	375098	15132	23120, 31108, 39096, 47084, 55072
6990	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	400103	7145	382974	15133	23121, 31109, 39097, 47085, 55073

6991	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	400230	7146	383089	15134	23122, 31110, 39098, 47086, 55074
6992	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	419256	7147	438339	15135	23123, 31111, 39099, 47087, 55075
6993	transmembrane phosphoinositide 3-phosphatase and tensin homolog 2	457266	7148	442218	15136	23124, 31112, 39100, 47088, 55076
6994	transmembrane protease, serine 11D	283916	7149	283916	15137	23125, 31113, 39101, 47089, 55077, 56099, 56132
6995	transmembrane protease, serine 11D	545541	7150	442045	15138	23126, 31114, 39102, 47090, 55078, 56100, 56133
6996	transmembrane protease, serine 15	284885	7151	284885	15139	23127, 31115, 39103, 47091, 55079
6997	transmembrane protease, serine 7	419127	7152	411645	15140	23128, 31116, 39104, 47092, 55080
6998	transmembrane protease, serine 7	437906	7153	411595	15141	23129, 31117, 39105, 47093, 55081
6999	transmembrane protease, serine 7	443106	7154	389163	15142	23130, 31118, 39106, 47094, 55082
7000	transmembrane protease, serine 7	452346	7155	398236	15143	23131, 31119, 39107, 47095, 55083
7001	transmembrane protease, serine 9	332578	7156	330264	15144	23132, 31120, 39108, 47096, 55084
7002	transmembrane protease, serine 9	395264	7157	378681	15145	23133, 31121, 39109, 47097, 55085
7003	transmembrane protein 100	299377	7158	299377	15146	23134, 31122, 39110, 47098, 55086
7004	transmembrane protein 100	424486	7159	395328	15147	23135, 31123, 39111, 47099, 55087
7005	transmembrane protein 100	575734	7160	465638	15148	23136, 31124, 39112, 47100, 55088
7006	transmembrane protein 101	206380	7161	206380	15149	23137, 31125, 39113, 47101, 55089

7007	transmembrane protein 101	542039	7162	442994	15150	23138, 31126, 39114, 47102, 55090
7008	transmembrane protein 101	589334	7163	468025	15151	23139, 31127, 39115, 47103, 55091
7009	transmembrane protein 104	335464	7164	334849	15152	23140, 31128, 39116, 47104, 55092
7010	transmembrane protein 104	417024	7165	397676	15153	23141, 31129, 39117, 47105, 55093
7011	transmembrane protein 105	332900	7166	329795	15154	23142, 31130, 39118, 47106, 55094
7012	transmembrane protein 106A	331615	7167	330774	15155	23143, 31131, 39119, 47107, 55095
7013	transmembrane protein 106A	536052	7168	439835	15156	23144, 31132, 39120, 47108, 55096
7014	transmembrane protein 106A	541594	7169	439844	15157	23145, 31133, 39121, 47109, 55097
7015	transmembrane protein 106C	256686	7170	256686	15158	23146, 31134, 39122, 47110, 55098
7016	transmembrane protein 106C	429772	7171	400471	15159	23147, 31135, 39123, 47111, 55099
7017	transmembrane protein 106C	449758	7172	402705	15160	23148, 31136, 39124, 47112, 55100
7018	transmembrane protein 106C	552561	7173	446657	15161	23149, 31137, 39125, 47113, 55101
7019	transmembrane protein 107	316425	7174	314116	15162	23150, 31138, 39126, 47114, 55102
7020	transmembrane protein 107	415860	7175	392476	15163	23151, 31139, 39127, 47115, 55103
7021	transmembrane protein 107	437139	7176	402732	15164	23152, 31140, 39128, 47116, 55104
7022	transmembrane protein 107	533070	7177	436674	15165	23153, 31141, 39129, 47117, 55105
7023	transmembrane protein 108	321871	7178	324651	15166	23154, 31142, 39130, 47118, 55106
7024	transmembrane protein 108	393130	7179	376838	15167	23155, 31143, 39131, 47119, 55107

7025	transmembrane protein 108	508711	7180	424897	15168	23156, 31144, 39132, 47120, 55108
7026	transmembrane protein 108	510183	7181	421486	15169	23157, 31145, 39133, 47121, 55109
7027	transmembrane protein 108	511555	7182	422196	15170	23158, 31146, 39134, 47122, 55110
7028	transmembrane protein 108	512137	7183	426301	15171	23159, 31147, 39135, 47123, 55111
7029	transmembrane protein 108	515826	7184	423338	15172	23160, 31148, 39136, 47124, 55112
7030	transmembrane protein 109	227525	7185	227525	15173	23161, 31149, 39137, 47125, 55113
7031	transmembrane protein 109	446886	7186	403489	15174	23162, 31150, 39138, 47126, 55114
7032	transmembrane protein 109	536171	7187	443990	15175	23163, 31151, 39139, 47127, 55115
7033	transmembrane protein 11	317635	7188	319992	15176	23164, 31152, 39140, 47128, 55116
7034	transmembrane protein 110	355083	7189	347195	15177	23165, 31153, 39141, 47129, 55117
7035	transmembrane protein 111	245046	7190	245046	15178	23166, 31154, 39142, 47130, 55118
7036	transmembrane protein 111	429759	7191	408803	15179	23167, 31155, 39143, 47131, 55119
7037	transmembrane protein 115	266025	7192	266025	15180	23168, 31156, 39144, 47132, 55120
7038	transmembrane protein 116	354825	7193	346883	15181	23169, 31157, 39145, 47133, 55121
7039	transmembrane protein 116	437003	7194	395861	15182	23170, 31158, 39146, 47134, 55122
7040	transmembrane protein 116	546962	7195	446766	15183	23171, 31159, 39147, 47135, 55123
7041	transmembrane protein 116	549425	7196	449774	15184	23172, 31160, 39148, 47136, 55124
7042	transmembrane protein 116	550037	7197	446516	15185	23173, 31161, 39149, 47137, 55125

7043	transmembrane protein 116	550233	7198	450060	15186	23174, 31162, 39150, 47138, 55126
7044	transmembrane protein 116	550831	7199	450377	15187	23175, 31163, 39151, 47139, 55127
7045	transmembrane protein 116	552374	7200	447731	15188	23176, 31164, 39152, 47140, 55128
7046	transmembrane protein 116	355445	7201	347620	15189	23177, 31165, 39153, 47141, 55129
7047	transmembrane protein 117	266534	7202	266534	15190	23178, 31166, 39154, 47142, 55130
7048	transmembrane protein 117	417623	7203	405508	15191	23179, 31167, 39155, 47143, 55131
7049	transmembrane protein 117	536799	7204	445243	15192	23180, 31168, 39156, 47144, 55132
7050	transmembrane protein 119	392806	7205	376553	15193	23181, 31169, 39157, 47145, 55133
7051	transmembrane protein 119	433191	7206	409520	15194	23182, 31170, 39158, 47146, 55134
7052	transmembrane protein 119	547567	7207	447345	15195	23183, 31171, 39159, 47147, 55135
7053	transmembrane protein 119	549031	7208	448583	15196	23184, 31172, 39160, 47148, 55136
7054	transmembrane protein 119	549447	7209	447120	15197	23185, 31173, 39161, 47149, 55137
7055	transmembrane protein 120B	342607	7210	345152	15198	23186, 31174, 39162, 47150, 55138
7056	transmembrane protein 120B	449592	7211	404991	15199	23187, 31175, 39163, 47151, 55139
7057	transmembrane protein 121	392519	7212	376304	15200	23188, 31176, 39164, 47152, 55140
7058	transmembrane protein 121	431372	7213	407456	15201	23189, 31177, 39165, 47153, 55141
7059	transmembrane protein 125	432792	7214	429275	15202	23190, 31178, 39166, 47154, 55142
7060	transmembrane protein 125	439858	7215	429775	15203	23191, 31179, 39167, 47155, 55143

7061	transmembrane protein 125	456751	7216	428627	15204	23192, 31180, 39168, 47156, 55144
7062	transmembrane protein 126B	358867	7217	351737	15205	23193, 31181, 39169, 47157, 55145
7063	transmembrane protein 126B	393375	7218	377039	15206	23194, 31182, 39170, 47158, 55146
7064	transmembrane protein 126B	534341	7219	433471	15207	23195, 31183, 39171, 47159, 55147
7065	transmembrane protein 126B	526822	7220	433449	15208	23196, 31184, 39172, 47160, 55148
7066	transmembrane protein 128	254742	7221	254742	15209	23197, 31185, 39173, 47161, 55149
7067	transmembrane protein 128	382753	7222	372201	15210	23198, 31186, 39174, 47162, 55150
7068	transmembrane protein 128	538516	7223	442300	15211	23199, 31187, 39175, 47163, 55151
7069	transmembrane protein 128	540397	7224	439174	15212	23200, 31188, 39176, 47164, 55152
7070	transmembrane protein 129	382936	7225	372394	15213	23201, 31189, 39177, 47165, 55153
7071	transmembrane protein 129	536901	7226	441812	15214	23202, 31190, 39178, 47166, 55154
7072	transmembrane protein 129	303277	7227	305243	15215	23203, 31191, 39179, 47167, 55155
7073	transmembrane protein 130	339375	7228	341256	15216	23204, 31192, 39180, 47168, 55156
7074	transmembrane protein 130	345589	7229	330262	15217	23205, 31193, 39181, 47169, 55157
7075	transmembrane protein 130	416379	7230	413163	15218	23206, 31194, 39182, 47170, 55158
7076	transmembrane protein 130	546258	7231	445869	15219	23207, 31195, 39183, 47171, 55159
7077	transmembrane protein 131	186436	7232	186436	15220	23208, 31196, 39184, 47172, 55160
7078	transmembrane protein 131	418629	7233	391566	15221	23209, 31197, 39185, 47173, 55161

7079	transmembrane protein 131	425805	7234	401670	15222	23210, 31198, 39186, 47174, 55162
7080	transmembrane protein 132B	299308	7235	299308	15223	23211, 31199, 39187, 47175, 55163
7081	transmembrane protein 132C	435159	7236	410852	15224	23212, 31200, 39188, 47176, 55164
7082	transmembrane protein 132D	389441	7237	374092	15225	23213, 31201, 39189, 47177, 55165
7083	transmembrane protein 132D	422113	7238	408581	15226	23214, 31202, 39190, 47178, 55166
7084	transmembrane protein 132E	321639	7239	316532	15227	23215, 31203, 39191, 47179, 55167
7085	transmembrane protein 133	303130	7240	303999	15228	23216, 31204, 39192, 47180, 55168
7086	transmembrane protein 134	308022	7241	312615	15229	23217, 31205, 39193, 47181, 55169
7087	transmembrane protein 134	393877	7242	377455	15230	23218, 31206, 39194, 47182, 55170
7088	transmembrane protein 135	305494	7243	306344	15231	23219, 31207, 39195, 47183, 55171
7089	transmembrane protein 135	340353	7244	345513	15232	23220, 31208, 39196, 47184, 55172
7090	transmembrane protein 135	355734	7245	347973	15233	23221, 31209, 39197, 47185, 55173
7091	transmembrane protein 135	535167	7246	439525	15234	23222, 31210, 39198, 47186, 55174
7092	transmembrane protein 135	544294	7247	441089	15235	23223, 31211, 39199, 47187, 55175
7093	transmembrane protein 136	314475	7248	312672	15236	23224, 31212, 39200, 47188, 55176
7094	transmembrane protein 136	375095	7249	364236	15237	23225, 31213, 39201, 47189, 55177
7095	transmembrane protein 136	529187	7250	434862	15238	23226, 31214, 39202, 47190, 55178
7096	transmembrane protein 139	359333	7251	352284	15239	23227, 31215, 39203, 47191, 55179

7097	transmembrane protein 139	409102	7252	386879	15240	23228, 31216, 39204, 47192, 55180
7098	transmembrane protein 139	409244	7253	386335	15241	23229, 31217, 39205, 47193, 55181
7099	transmembrane protein 139	409541	7254	387044	15242	23230, 31218, 39206, 47194, 55182
7100	transmembrane protein 139	410004	7255	386564	15243	23231, 31219, 39207, 47195, 55183
7101	transmembrane protein 140	275767	7256	275767	15244	23232, 31220, 39208, 47196, 55184
7102	transmembrane protein 140	456488	7257	401207	15245	23233, 31221, 39209, 47197, 55185
7103	transmembrane protein 141	290079	7258	290079	15246	23234, 31222, 39210, 47198, 55186
7104	transmembrane protein 143	293261	7259	293261	15247	23235, 31223, 39211, 47199, 55187
7105	transmembrane protein 143	377431	7260	366649	15248	23236, 31224, 39212, 47200, 55188
7106	transmembrane protein 143	435956	7261	397038	15249	23237, 31225, 39213, 47201, 55189
7107	transmembrane protein 143	436660	7262	390270	15250	23238, 31226, 39214, 47202, 55190
7108	transmembrane protein 143	541566	7263	444275	15251	23239, 31227, 39215, 47203, 55191
7109	transmembrane protein 144	296529	7264	296529	15252	23240, 31228, 39216, 47204, 55192
7110	transmembrane protein 144	502698	7265	425907	15253	23241, 31229, 39217, 47205, 55193
7111	transmembrane protein 144	503200	7266	420990	15254	23242, 31230, 39218, 47206, 55194
7112	transmembrane protein 144	504569	7267	422082	15255	23243, 31231, 39219, 47207, 55195
7113	transmembrane protein 144	505049	7268	425266	15256	23244, 31232, 39220, 47208, 55196
7114	transmembrane protein 144	505189	7269	421289	15257	23245, 31233, 39221, 47209, 55197

7115	transmembrane protein 144	508243	7270	422297	15258	23246, 31234, 39222, 47210, 55198
7116	transmembrane protein 144	511038	7271	422255	15259	23247, 31235, 39223, 47211, 55199
7117	transmembrane protein 144	512481	7272	424659	15260	23248, 31236, 39224, 47212, 55200
7118	transmembrane protein 144	514558	7273	426211	15261	23249, 31237, 39225, 47213, 55201
7119	transmembrane protein 144	514971	7274	422899	15262	23250, 31238, 39226, 47214, 55202
7120	transmembrane protein 145	301204	7275	301204	15263	23251, 31239, 39227, 47215, 55203
7121	transmembrane protein 146	381613	7276	371026	15264	23252, 31240, 39228, 47216, 55204
7122	transmembrane protein 146	381614	7277	371027	15265	23253, 31241, 39229, 47217, 55205
7123	transmembrane protein 146	381624	7278	371037	15266	23254, 31242, 39230, 47218, 55206
7124	transmembrane protein 147	222284	7279	222284	15267	23255, 31243, 39231, 47219, 55207
7125	transmembrane protein 147	392204	7280	376040	15268	23256, 31244, 39232, 47220, 55208
7126	transmembrane protein 147	392205	7281	376041	15269	23257, 31245, 39233, 47221, 55209
7127	transmembrane protein 147	593027	7282	466262	15270	23258, 31246, 39234, 47222, 55210
7128	transmembrane protein 14A	211314	7283	211314	15271	23259, 31247, 39235, 47223, 55211
7129	transmembrane protein 14B	379530	7284	368845	15272	23260, 31248, 39236, 47224, 55212
7130	transmembrane protein 14B	379542	7285	368858	15273	23261, 31249, 39237, 47225, 55213
7131	transmembrane protein 14B	472062	7286	419375	15274	23262, 31250, 39238, 47226, 55214
7132	transmembrane protein 14B	475942	7287	418730	15275	23263, 31251, 39239, 47227, 55215

7133	transmembrane protein 14C	229563	7288	229563	15276	23264, 31252, 39240, 47228, 55216
7134	transmembrane protein 14C	342277	7289	343293	15277	23265, 31253, 39241, 47229, 55217
7135	transmembrane protein 14C	541412	7290	444561	15278	23266, 31254, 39242, 47230, 55218
7136	transmembrane protein 14E	408960	7291	386163	15279	23267, 31255, 39243, 47231, 55219
7137	transmembrane protein 150A	306353	7292	302715	15280	23268, 31256, 39244, 47232, 55220
7138	transmembrane protein 150A	334462	7293	334708	15281	23269, 31257, 39245, 47233, 55221
7139	transmembrane protein 150A	409668	7294	387292	15282	23270, 31258, 39246, 47234, 55222
7140	transmembrane protein 150A	425160	7295	394945	15283	23271, 31259, 39247, 47235, 55223
7141	transmembrane protein 150B	326652	7296	320757	15284	23272, 31260, 39248, 47236, 55224
7142	transmembrane protein 150B	438693	7297	412658	15285	23273, 31261, 39249, 47237, 55225
7143	transmembrane protein 150C	449862	7298	403438	15286	23274, 31262, 39250, 47238, 55226
7144	transmembrane protein 150C	454948	7299	414988	15287	23275, 31263, 39251, 47239, 55227
7145	transmembrane protein 150C	515780	7300	420919	15288	23276, 31264, 39252, 47240, 55228
7146	transmembrane protein 151A	327259	7301	326244	15289	23277, 31265, 39253, 47241, 55229
7147	transmembrane protein 151B	430110	7302	410997	15290	23278, 31266, 39254, 47242, 55230
7148	transmembrane protein 151B	451188	7303	393161	15291	23279, 31267, 39255, 47243, 55231
7149	transmembrane protein 154	304385	7304	302144	15292	23280, 31268, 39256, 47244, 55232
7150	transmembrane protein 154	504064	7305	422156	15293	23281, 31269, 39257, 47245, 55233

7151	transmembrane protein 156	381938	7306	371364	15294	23282, 31270, 39258, 47246, 55234
7152	transmembrane protein 160	253047	7307	253047	15295	23283, 31271, 39259, 47247, 55235
7153	transmembrane protein 161A	162044	7308	162044	15296	23284, 31272, 39260, 47248, 55236, 56101, 56134
7154	transmembrane protein 161A	450333	7309	404208	15297	23285, 31273, 39261, 47249, 55237
7155	transmembrane protein 161B	296595	7310	296595	15298	23286, 31274, 39262, 47250, 55238
7156	transmembrane protein 161B	443393	7311	395621	15299	23287, 31275, 39263, 47251, 55239
7157	transmembrane protein 163	281924	7312	281924	15300	23288, 31276, 39264, 47252, 55240
7158	transmembrane protein 163	537539	7313	445702	15301	23289, 31277, 39265, 47253, 55241
7159	transmembrane protein 164	288381	7314	288381	15302	23290, 31278, 39266, 47254, 55242
7160	transmembrane protein 164	372068	7315	361138	15303	23291, 31279, 39267, 47255, 55243
7161	transmembrane protein 164	372072	7316	384075	15304	23292, 31280, 39268, 47256, 55244
7162	transmembrane protein 164	372073	7317	361143	15305	23293, 31281, 39269, 47257, 55245
7163	transmembrane protein 164	501872	7318	438333	15306	23294, 31282, 39270, 47258, 55246
7164	transmembrane protein 165	381334	7319	370736	15307	23295, 31283, 39271, 47259, 55247
7165	transmembrane protein 165	542052	7320	437816	15308	23296, 31284, 39272, 47260, 55248
7166	transmembrane protein 167A	502346	7321	424707	15309	23297, 31285, 39273, 47261, 55249
7167	transmembrane protein 167B	338272	7322	342148	15310	23298, 31286, 39274, 47262, 55250
7168	transmembrane protein 168	312814	7323	323068	15311	23299, 31287, 39275, 47263, 55251

7169	transmembrane protein 168	447395	7324	410307	15312	23300, 31288, 39276, 47264, 55252
7170	transmembrane protein 168	454074	7325	390696	15313	23301, 31289, 39277, 47265, 55253
7171	transmembrane protein 169	295658	7326	295658	15314	23302, 31290, 39278, 47266, 55254
7172	transmembrane protein 169	406027	7327	384100	15315	23303, 31291, 39279, 47267, 55255
7173	transmembrane protein 169	433112	7328	400798	15316	23304, 31292, 39280, 47268, 55256
7174	transmembrane protein 169	437356	7329	401305	15317	23305, 31293, 39281, 47269, 55257
7175	transmembrane protein 169	454545	7330	412524	15318	23306, 31294, 39282, 47270, 55258
7176	transmembrane protein 169	455479	7331	413257	15319	23307, 31295, 39283, 47271, 55259
7177	transmembrane protein 17	335390	7332	335094	15320	23308, 31296, 39284, 47272, 55260
7178	transmembrane protein 170A	357613	7333	350230	15321	23309, 31297, 39285, 47273, 55261
7179	transmembrane protein 170A	561878	7334	454404	15322	23310, 31298, 39286, 47274, 55262
7180	transmembrane protein 170B	379426	7335	368737	15323	23311, 31299, 39287, 47275, 55263
7181	transmembrane protein 170B	543875	7336	442131	15324	23312, 31300, 39288, 47276, 55264
7182	transmembrane protein 171	287773	7337	287773	15325	23313, 31301, 39289, 47277, 55265
7183	transmembrane protein 171	454765	7338	415030	15326	23314, 31302, 39290, 47278, 55266
7184	transmembrane protein 174	296776	7339	296776	15327	23315, 31303, 39291, 47279, 55267
7185	transmembrane protein 175	264771	7340	264771	15328	23316, 31304, 39292, 47280, 55268
7186	transmembrane protein 175	359768	7341	352814	15329	23317, 31305, 39293, 47281, 55269

7187	transmembrane protein 175	514546	7342	425763	15330	23318, 31306, 39294, 47282, 55270
7188	transmembrane protein 175	515740	7343	427039	15331	23319, 31307, 39295, 47283, 55271
7189	transmembrane protein 176A	4103	7344	4103	15332	23320, 31308, 39296, 47284, 55272, 56102, 56135
7190	transmembrane protein 176A	484928	7345	417626	15333	23321, 31309, 39297, 47285, 55273
7191	transmembrane protein 176B	326442	7346	318409	15334	23322, 31310, 39298, 47286, 55274
7192	transmembrane protein 176B	429904	7347	397810	15335	23323, 31311, 39299, 47287, 55275
7193	transmembrane protein 176B	434545	7348	413531	15336	23324, 31312, 39300, 47288, 55276
7194	transmembrane protein 176B	447204	7349	410269	15337	23325, 31313, 39301, 47289, 55277
7195	transmembrane protein 176B	450753	7350	404831	15338	23326, 31314, 39302, 47290, 55278
7196	transmembrane protein 176B	492607	7351	419258	15339	23327, 31315, 39303, 47291, 55279
7197	transmembrane protein 176B	528038	7352	434910	15340	23328, 31316, 39304, 47292, 55280
7198	transmembrane protein 177	272521	7353	272521	15341	23329, 31317, 39305, 47293, 55281
7199	transmembrane protein 177	401466	7354	385966	15342	23330, 31318, 39306, 47294, 55282
7200	transmembrane protein 177	415646	7355	413982	15343	23331, 31319, 39307, 47295, 55283
7201	transmembrane protein 177	424086	7356	402661	15344	23332, 31320, 39308, 47296, 55284
7202	transmembrane protein 177	445518	7357	405898	15345	23333, 31321, 39309, 47297, 55285
7203	transmembrane protein 178	281961	7358	281961	15346	23334, 31322, 39310, 47298, 55286
7204	transmembrane protein 178	378734	7359	368008	15347	23335, 31323, 39311, 47299, 55287

7205	transmembrane protein 179	341595	7360	340477	15348	23336, 31324, 39312, 47300, 55288
7206	transmembrane protein 179	556573	7361	450958	15349	23337, 31325, 39313, 47301, 55289
7207	transmembrane protein 179B	333449	7362	333697	15350	23338, 31326, 39314, 47302, 55290
7208	transmembrane protein 180	238936	7363	238936	15351	23339, 31327, 39315, 47303, 55291
7209	transmembrane protein 180	366277	7364	437572	15352	23340, 31328, 39316, 47304, 55292
7210	transmembrane protein 180	369930	7365	358946	15353	23341, 31329, 39317, 47305, 55293
7211	transmembrane protein 180	369931	7366	358947	15354	23342, 31330, 39318, 47306, 55294
7212	transmembrane protein 180	447593	7367	393816	15355	23343, 31331, 39319, 47307, 55295
7213	transmembrane protein 182	409528	7368	387258	15356	23344, 31332, 39320, 47308, 55296
7214	transmembrane protein 182	412401	7369	394178	15357	23345, 31333, 39321, 47309, 55297
7215	transmembrane protein 183A	367242	7370	356211	15358	23346, 31334, 39322, 47310, 55298
7216	transmembrane protein 184A	297477	7371	297477	15359	23347, 31335, 39323, 47311, 55299
7217	transmembrane protein 184A	414730	7372	398382	15360	23348, 31336, 39324, 47312, 55300
7218	transmembrane protein 184A	431208	7373	403499	15361	23349, 31337, 39325, 47313, 55301
7219	transmembrane protein 184A	441933	7374	389092	15362	23350, 31338, 39326, 47314, 55302
7220	transmembrane protein 184B	361684	7375	354441	15363	23351, 31339, 39327, 47315, 55303
7221	transmembrane protein 184B	361906	7376	355210	15364	23352, 31340, 39328, 47316, 55304
7222	transmembrane protein 184B	403210	7377	385608	15365	23353, 31341, 39329, 47317, 55305

7223	transmembrane protein 184B	436674	7378	413085	15366	23354, 31342, 39330, 47318, 55306
7224	transmembrane protein 185B	426077	7379	453399	15367	23355, 31343, 39331, 47319, 55307
7225	transmembrane protein 186	333050	7380	331640	15368	23356, 31344, 39332, 47320, 55308
7226	transmembrane protein 187	369982	7381	358999	15369	23357, 31345, 39333, 47321, 55309
7227	transmembrane protein 187	425274	7382	390108	15370	23358, 31346, 39334, 47322, 55310
7228	transmembrane protein 187	431598	7383	412872	15371	23359, 31347, 39335, 47323, 55311
7229	transmembrane protein 188	389134	7384	373786	15372	23360, 31348, 39336, 47324, 55312
7230	transmembrane protein 188	427478	7385	394224	15373	23361, 31349, 39337, 47325, 55313
7231	transmembrane protein 188	458059	7386	405635	15374	23362, 31350, 39338, 47326, 55314
7232	transmembrane protein 189	371650	7387	360713	15375	23363, 31351, 39339, 47327, 55315
7233	transmembrane protein 189	371652	7388	360715	15376	23364, 31352, 39340, 47328, 55316
7234	transmembrane protein 189	371656	7389	360719	15377	23365, 31353, 39341, 47329, 55317
7235	transmembrane protein 189	557021	7390	450635	15378	23366, 31354, 39342, 47330, 55318
7236	transmembrane protein 19	266673	7391	266673	15379	23367, 31355, 39343, 47331, 55319
7237	transmembrane protein 19	547816	7392	449176	15380	23368, 31356, 39344, 47332, 55320
7238	transmembrane protein 19	549735	7393	449955	15381	23369, 31357, 39345, 47333, 55321
7239	transmembrane protein 19	550524	7394	448587	15382	23370, 31358, 39346, 47334, 55322
7240	transmembrane protein 19	550787	7395	448069	15383	23371, 31359, 39347, 47335, 55323

7241	transmembrane protein 190	291934	7396	291934	15384	23372, 31360, 39348, 47336, 55324
7242	transmembrane protein 192	306480	7397	305069	15385	23373, 31361, 39349, 47337, 55325
7243	transmembrane protein 192	506087	7398	425335	15386	23374, 31362, 39350, 47338, 55326
7244	transmembrane protein 194A	300128	7399	300128	15387	23375, 31363, 39351, 47339, 55327
7245	transmembrane protein 194A	379391	7400	368701	15388	23376, 31364, 39352, 47340, 55328
7246	transmembrane protein 196	405764	7401	384234	15389	23377, 31365, 39353, 47341, 55329
7247	transmembrane protein 196	433641	7402	406460	15390	23378, 31366, 39354, 47342, 55330
7248	transmembrane protein 198	344458	7403	343507	15391	23379, 31367, 39355, 47343, 55331
7249	transmembrane protein 198	373883	7404	362990	15392	23380, 31368, 39356, 47344, 55332
7250	transmembrane protein 198	421791	7405	388087	15393	23381, 31369, 39357, 47345, 55333
7251	transmembrane protein 199	292114	7406	292114	15394	23382, 31370, 39358, 47346, 55334
7252	transmembrane protein 199	509083	7407	427614	15395	23383, 31371, 39359, 47347, 55335
7253	transmembrane protein 200A	296978	7408	296978	15396	23384, 31372, 39360, 47348, 55336
7254	transmembrane protein 200A	392429	7409	376224	15397	23385, 31373, 39361, 47349, 55337
7255	transmembrane protein 200A	545622	7410	438928	15398	23386, 31374, 39362, 47350, 55338
7256	transmembrane protein 200B	420504	7411	428544	15399	23387, 31375, 39363, 47351, 55339
7257	transmembrane protein 200B	521452	7412	428459	15400	23388, 31376, 39364, 47352, 55340
7258	transmembrane protein 200C	383490	7413	372982	15401	23389, 31377, 39365, 47353, 55341

7259	transmembrane protein 200C	581347	7414	463375	15402	23390, 31378, 39366, 47354, 55342
7260	transmembrane protein 201	340305	7415	344772	15403	23391, 31379, 39367, 47355, 55343
7261	transmembrane protein 201	340381	7416	344503	15404	23392, 31380, 39368, 47356, 55344
7262	transmembrane protein 201	377376	7417	366593	15405	23393, 31381, 39369, 47357, 55345
7263	transmembrane protein 203	343666	7418	375053	15406	23394, 31382, 39370, 47358, 55346
7264	transmembrane protein 203	537254	7419	446302	15407	23395, 31383, 39371, 47359, 55347
7265	transmembrane protein 204	253934	7420	253934	15408	23396, 31384, 39372, 47360, 55348
7266	transmembrane protein 204	566264	7421	454945	15409	23397, 31385, 39373, 47361, 55349
7267	transmembrane protein 206	261455	7422	261455	15410	23398, 31386, 39374, 47362, 55350
7268	transmembrane protein 206	535273	7423	438863	15411	23399, 31387, 39375, 47363, 55351
7269	transmembrane protein 207	354905	7424	346981	15412	23400, 31388, 39376, 47364, 55352
7270	transmembrane protein 208	304800	7425	305892	15413	23401, 31389, 39377, 47365, 55353
7271	transmembrane protein 209	336804	7426	338388	15414	23402, 31390, 39378, 47366, 55354
7272	transmembrane protein 209	397622	7427	380747	15415	23403, 31391, 39379, 47367, 55355
7273	transmembrane protein 209	462753	7428	419697	15416	23404, 31392, 39380, 47368, 55356
7274	transmembrane protein 209	471077	7429	418474	15417	23405, 31393, 39381, 47369, 55357
7275	transmembrane protein 209	473456	7430	417258	15418	23406, 31394, 39382, 47370, 55358
7276	transmembrane protein 209	484249	7431	441312	15419	23407, 31395, 39383, 47371, 55359

7277	transmembrane protein 211	382744	7432	372192	15420	23408, 31396, 39384, 47372, 55360
7278	transmembrane protein 211	407886	7433	385494	15421	23409, 31397, 39385, 47373, 55361
7279	transmembrane protein 211	423535	7434	387813	15422	23410, 31398, 39386, 47374, 55362
7280	transmembrane protein 213	422794	7435	402388	15423	23411, 31399, 39387, 47375, 55363
7281	transmembrane protein 213	442682	7436	390407	15424	23412, 31400, 39388, 47376, 55364
7282	transmembrane protein 214	238788	7437	238788	15425	23413, 31401, 39389, 47377, 55365
7283	transmembrane protein 214	321326	7438	319469	15426	23414, 31402, 39390, 47378, 55366
7284	transmembrane protein 214	404032	7439	384417	15427	23415, 31403, 39391, 47379, 55367
7285	transmembrane protein 214	535207	7440	441664	15428	23416, 31404, 39392, 47380, 55368
7286	transmembrane protein 214	537397	7441	445286	15429	23417, 31405, 39393, 47381, 55369
7287	transmembrane protein 215	342743	7442	345468	15430	23418, 31406, 39394, 47382, 55370
7288	transmembrane protein 217	336655	7443	338164	15431	23419, 31407, 39395, 47383, 55371
7289	transmembrane protein 217	356757	7444	349198	15432	23420, 31408, 39396, 47384, 55372
7290	transmembrane protein 218	279968	7445	279968	15433	23421, 31409, 39397, 47385, 55373
7291	transmembrane protein 218	455225	7446	399803	15434	23422, 31410, 39398, 47386, 55374
7292	transmembrane protein 218	526175	7447	436177	15435	23423, 31411, 39399, 47387, 55375
7293	transmembrane protein 218	527271	7448	436162	15436	23424, 31412, 39400, 47388, 55376
7294	transmembrane protein 218	527766	7449	435526	15437	23425, 31413, 39401, 47389, 55377

7295	transmembrane protein 218	529583	7450	433374	15438	23426, 31414, 39402, 47390, 55378
7296	transmembrane protein 218	531909	7451	436596	15439	23427, 31415, 39403, 47391, 55379
7297	transmembrane protein 218	532407	7452	434597	15440	23428, 31416, 39404, 47392, 55380
7298	transmembrane protein 219	279396	7453	279396	15441	23429, 31417, 39405, 47393, 55381
7299	transmembrane protein 219	414689	7454	388485	15442	23430, 31418, 39406, 47394, 55382
7300	transmembrane protein 22	393079	7455	376794	15443	23431, 31419, 39407, 47395, 55383
7301	transmembrane protein 22	446465	7456	400839	15444	23432, 31420, 39408, 47396, 55384
7302	transmembrane protein 220	341871	7457	339830	15445	23433, 31421, 39409, 47397, 55385
7303	transmembrane protein 220	455996	7458	396973	15446	23434, 31422, 39410, 47398, 55386
7304	transmembrane protein 222	374073	7459	363186	15447	23435, 31423, 39411, 47399, 55387
7305	transmembrane protein 222	374076	7460	363189	15448	23436, 31424, 39412, 47400, 55388
7306	transmembrane protein 223	307366	7461	303987	15449	23437, 31425, 39413, 47401, 55389
7307	transmembrane protein 225	375026	7462	364166	15450	23438, 31426, 39414, 47402, 55390
7308	transmembrane protein 229A	455783	7463	395244	15451	23439, 31427, 39415, 47403, 55391
7309	transmembrane protein 229B	357461	7464	350050	15452	23440, 31428, 39416, 47404, 55392
7310	transmembrane protein 229B	554278	7465	452402	15453	23441, 31429, 39417, 47405, 55393
7311	transmembrane protein 229B	554480	7466	450859	15454	23442, 31430, 39418, 47406, 55394
7312	transmembrane protein 229B	555638	7467	452201	15455	23443, 31431, 39419, 47407, 55395

7313	transmembrane protein 229B	555994	7468	452144	15456	23444, 31432, 39420, 47408, 55396
7314	transmembrane protein 229B	557006	7469	451774	15457	23445, 31433, 39421, 47409, 55397
7315	transmembrane protein 229B	557779	7470	452025	15458	23446, 31434, 39422, 47410, 55398
7316	transmembrane protein 231	258173	7471	258173	15459	23447, 31435, 39423, 47411, 55399
7317	transmembrane protein 231	398114	7472	381184	15460	23448, 31436, 39424, 47412, 55400
7318	transmembrane protein 232	429839	7473	394680	15461	23449, 31437, 39425, 47413, 55401
7319	transmembrane protein 232	455884	7474	401477	15462	23450, 31438, 39426, 47414, 55402
7320	transmembrane protein 233	426426	7475	403130	15463	23451, 31439, 39427, 47415, 55403
7321	transmembrane protein 234	309777	7476	309792	15464	23452, 31440, 39428, 47416, 55404
7322	transmembrane protein 234	344461	7477	344021	15465	23453, 31441, 39429, 47417, 55405
7323	transmembrane protein 234	461402	7478	433020	15466	23454, 31442, 39430, 47418, 55406
7324	transmembrane protein 234	483001	7479	434295	15467	23455, 31443, 39431, 47419, 55407
7325	transmembrane protein 234	489170	7480	436631	15468	23456, 31444, 39432, 47420, 55408
7326	transmembrane protein 234	545122	7481	442664	15469	23457, 31445, 39433, 47421, 55409
7327	transmembrane protein 235	374946	7482	364084	15470	23458, 31446, 39434, 47422, 55410
7328	transmembrane protein 235	421688	7483	402790	15471	23459, 31447, 39435, 47423, 55411
7329	transmembrane protein 235	543327	7484	445762	15472	23460, 31448, 39436, 47424, 55412
7330	transmembrane protein 235	550981	7485	447766	15473	23461, 31449, 39437, 47425, 55413

7331	transmembrane protein 235	551068	7486	446514	15474	23462, 31450, 39438, 47426, 55414
7332	transmembrane protein 235	586400	7487	466793	15475	23463, 31451, 39439, 47427, 55415
7333	transmembrane protein 236	338221	7488	348463	15476	23464, 31452, 39440, 47428, 55416
7334	transmembrane protein 236	377495	7489	366715	15477	23465, 31453, 39441, 47429, 55417
7335	transmembrane protein 236	457860	7490	414144	15478	23466, 31454, 39442, 47430, 55418
7336	transmembrane protein 236	480516	7491	417134	15479	23467, 31455, 39443, 47431, 55419
7337	transmembrane protein 240	378733	7492	368007	15480	23468, 31456, 39444, 47432, 55420
7338	transmembrane protein 240	425828	7493	400311	15481	23469, 31457, 39445, 47433, 55421
7339	transmembrane protein 241	383233	7494	372720	15482	23470, 31458, 39446, 47434, 55422
7340	transmembrane protein 241	399707	7495	382615	15483	23471, 31459, 39447, 47435, 55423
7341	transmembrane protein 241	450466	7496	414899	15484	23472, 31460, 39448, 47436, 55424
7342	transmembrane protein 241	542162	7497	440152	15485	23473, 31461, 39449, 47437, 55425
7343	transmembrane protein 242	367144	7498	356112	15486	23474, 31462, 39450, 47438, 55426
7344	transmembrane protein 242	400788	7499	383594	15487	23475, 31463, 39451, 47439, 55427
7345	transmembrane protein 249	526263	7500	435362	15488	23476, 31464, 39452, 47440, 55428
7346	transmembrane protein 26	399293	7501	382232	15489	23477, 31465, 39453, 47441, 55429
7347	transmembrane protein 26	399298	7502	382237	15490	23478, 31466, 39454, 47442, 55430
7348	transmembrane protein 26	503886	7503	425286	15491	23479, 31467, 39455, 47443, 55431

7349	transmembrane protein 31	319560	7504	316940	15492	23480, 31468, 39456, 47444, 55432
7350	transmembrane protein 33	325094	7505	441455	15493	23481, 31469, 39457, 47445, 55433
7351	transmembrane protein 33	504986	7506	422473	15494	23482, 31470, 39458, 47446, 55434
7352	transmembrane protein 33	508448	7507	422810	15495	23483, 31471, 39459, 47447, 55435
7353	transmembrane protein 33	513702	7508	427006	15496	23484, 31472, 39460, 47448, 55436
7354	transmembrane protein 35	372930	7509	362021	15497	23485, 31473, 39461, 47449, 55437
7355	transmembrane protein 35	444892	7510	412421	15498	23486, 31474, 39462, 47450, 55438
7356	transmembrane protein 37	306406	7511	303148	15499	23487, 31475, 39463, 47451, 55439
7357	transmembrane protein 38A	187762	7512	187762	15500	23488, 31476, 39464, 47452, 55440
7358	transmembrane protein 38B	374688	7513	363820	15501	23489, 31477, 39465, 47453, 55441
7359	transmembrane protein 38B	374692	7514	363824	15502	23490, 31478, 39466, 47454, 55442
7360	transmembrane protein 38B	434214	7515	403026	15503	23491, 31479, 39467, 47455, 55443
7361	transmembrane protein 38B	435034	7516	410800	15504	23492, 31480, 39468, 47456, 55444
7362	transmembrane protein 38B	451560	7517	416680	15505	23493, 31481, 39469, 47457, 55445
7363	transmembrane protein 39A	319172	7518	326063	15506	23494, 31482, 39470, 47458, 55446
7364	transmembrane protein 39A	461654	7519	419068	15507	23495, 31483, 39471, 47459, 55447
7365	transmembrane protein 39A	468676	7520	418796	15508	23496, 31484, 39472, 47460, 55448
7366	transmembrane protein 39A	497993	7521	419405	15509	23497, 31485, 39473, 47461, 55449

7367	transmembrane protein 39B	336294	7522	338165	15510	23498, 31486, 39474, 47462, 55450
7368	transmembrane protein 39B	373633	7523	362736	15511	23499, 31487, 39475, 47463, 55451
7369	transmembrane protein 39B	373634	7524	362737	15512	23500, 31488, 39476, 47464, 55452
7370	transmembrane protein 39B	427288	7525	391719	15513	23501, 31489, 39477, 47465, 55453
7371	transmembrane protein 39B	438825	7526	414616	15514	23502, 31490, 39478, 47466, 55454
7372	transmembrane protein 39B	456834	7527	390057	15515	23503, 31491, 39479, 47467, 55455
7373	transmembrane protein 40	264728	7528	264728	15516	23504, 31492, 39480, 47468, 55456
7374	transmembrane protein 40	314124	7529	322837	15517	23505, 31493, 39481, 47469, 55457
7375	transmembrane protein 40	431022	7530	407396	15518	23506, 31494, 39482, 47470, 55458
7376	transmembrane protein 40	435218	7531	405740	15519	23507, 31495, 39483, 47471, 55459
7377	transmembrane protein 40	435575	7532	396895	15520	23508, 31496, 39484, 47472, 55460
7378	transmembrane protein 41A	421852	7533	406885	15521	23509, 31497, 39485, 47473, 55461
7379	transmembrane protein 41B	299596	7534	299596	15522	23510, 31498, 39486, 47474, 55462
7380	transmembrane protein 41B	528080	7535	433126	15523	23511, 31499, 39487, 47475, 55463
7381	transmembrane protein 41B	533723	7536	436480	15524	23512, 31500, 39488, 47476, 55464
7382	transmembrane protein 42	302392	7537	306564	15525	23513, 31501, 39489, 47477, 55465
7383	transmembrane protein 45A	323523	7538	319009	15526	23514, 31502, 39490, 47478, 55466
7384	transmembrane protein 45A	403410	7539	385089	15527	23515, 31503, 39491, 47479, 55467

7385	transmembrane protein 45B	281441	7540	281441	15528	23516, 31504, 39492, 47480, 55468
7386	transmembrane protein 45B	524567	7541	436293	15529	23517, 31505, 39493, 47481, 55469
7387	transmembrane protein 50A	374358	7542	363478	15530	23518, 31506, 39494, 47482, 55470
7388	transmembrane protein 50B	420455	7543	397773	15531	23519, 31507, 39495, 47483, 55471
7389	transmembrane protein 50B	432504	7544	387622	15532	23520, 31508, 39496, 47484, 55472
7390	transmembrane protein 50B	435619	7545	411248	15533	23521, 31509, 39497, 47485, 55473
7391	transmembrane protein 50B	440644	7546	395003	15534	23522, 31510, 39498, 47486, 55474
7392	transmembrane protein 50B	542230	7547	439768	15535	23523, 31511, 39499, 47487, 55475
7393	transmembrane protein 51	303840	7548	303666	15536	23524, 31512, 39500, 47488, 55476
7394	transmembrane protein 51	376008	7549	365176	15537	23525, 31513, 39501, 47489, 55477
7395	transmembrane protein 51	376014	7550	365182	15538	23526, 31514, 39502, 47490, 55478
7396	transmembrane protein 51	400796	7551	383600	15539	23527, 31515, 39503, 47491, 55479
7397	transmembrane protein 51	428417	7552	394899	15540	23528, 31516, 39504, 47492, 55480
7398	transmembrane protein 51	434578	7553	409665	15541	23529, 31517, 39505, 47493, 55481
7399	transmembrane protein 51	451326	7554	412298	15542	23530, 31518, 39506, 47494, 55482
7400	transmembrane protein 52	310991	7555	311122	15543	23531, 31519, 39507, 47495, 55483
7401	transmembrane protein 52	378598	7556	367861	15544	23532, 31520, 39508, 47496, 55484
7402	transmembrane protein 52	378602	7557	367865	15545	23533, 31521, 39509, 47497, 55485

7403	transmembrane protein 52	416272	7558	409669	15546	23534, 31522, 39510, 47498, 55486
7404	transmembrane protein 53	372235	7559	361309	15547	23535, 31523, 39511, 47499, 55487
7405	transmembrane protein 53	372237	7560	361311	15548	23536, 31524, 39512, 47500, 55488
7406	transmembrane protein 53	372242	7561	361316	15549	23537, 31525, 39513, 47501, 55489
7407	transmembrane protein 53	372243	7562	361317	15550	23538, 31526, 39514, 47502, 55490
7408	transmembrane protein 53	372244	7563	361318	15551	23539, 31527, 39515, 47503, 55491
7409	transmembrane protein 53	420706	7564	391576	15552	23540, 31528, 39516, 47504, 55492
7410	transmembrane protein 54	329151	7565	328630	15553	23541, 31529, 39517, 47505, 55493
7411	transmembrane protein 54	373463	7566	362562	15554	23542, 31530, 39518, 47506, 55494
7412	transmembrane protein 55B	250489	7567	250489	15555	23543, 31531, 39519, 47507, 55495
7413	transmembrane protein 55B	398020	7568	381102	15556	23544, 31532, 39520, 47508, 55496
7414	transmembrane protein 56	370203	7569	359222	15557	23545, 31533, 39521, 47509, 55497
7415	transmembrane protein 56	455656	7570	417043	15558	23546, 31534, 39522, 47510, 55498
7416	transmembrane protein 56	456991	7571	395364	15559	23547, 31535, 39523, 47511, 55499
7417	transmembrane protein 57	374343	7572	363463	15560	23548, 31536, 39524, 47512, 55500
7418	transmembrane protein 57	399763	7573	382666	15561	23549, 31537, 39525, 47513, 55501
7419	transmembrane protein 57	399766	7574	382668	15562	23550, 31538, 39526, 47514, 55502
7420	transmembrane protein 59	234831	7575	234831	15563	23551, 31539, 39527, 47515, 55503

7421	transmembrane protein 59	371337	7576	360388	15564	23552, 31540, 39528, 47516, 55504
7422	transmembrane protein 59	371338	7577	360389	15565	23553, 31541, 39529, 47517, 55505
7423	transmembrane protein 59	371341	7578	360392	15566	23554, 31542, 39530, 47518, 55506
7424	transmembrane protein 59	371344	7579	360395	15567	23555, 31543, 39531, 47519, 55507
7425	transmembrane protein 59	371348	7580	360399	15568	23556, 31544, 39532, 47520, 55508
7426	transmembrane protein 59	420738	7581	413792	15569	23557, 31545, 39533, 47521, 55509
7427	transmembrane protein 59	440019	7582	399761	15570	23558, 31546, 39534, 47522, 55510
7428	transmembrane protein 59	452421	7583	397772	15571	23559, 31547, 39535, 47523, 55511
7429	transmembrane protein 59-like	262817	7584	262817	15572	23560, 31548, 39536, 47524, 55512
7430	transmembrane protein 59-like	600490	7585	470879	15573	23561, 31549, 39537, 47525, 55513
7431	transmembrane protein 60	257663	7586	257663	15574	23562, 31550, 39538, 47526, 55514
7432	transmembrane protein 61	371268	7587	360315	15575	23563, 31551, 39539, 47527, 55515
7433	transmembrane protein 62	260403	7588	260403	15576	23564, 31552, 39540, 47528, 55516
7434	transmembrane protein 63A	366835	7589	355800	15577	23565, 31553, 39541, 47529, 55517
7435	transmembrane protein 63A	436966	7590	409002	15578	23566, 31554, 39542, 47530, 55518
7436	transmembrane protein 63A	537914	7591	445237	15579	23567, 31555, 39543, 47531, 55519
7437	transmembrane protein 63B	259746	7592	259746	15580	23568, 31556, 39544, 47532, 55520
7438	transmembrane protein 63B	323267	7593	327154	15581	23569, 31557, 39545, 47533, 55521

7439	transmembrane protein 63B	532634	7594	437163	15582	23570, 31558, 39546, 47534, 55522
7440	transmembrane protein 63C	298351	7595	298351	15583	23571, 31559, 39547, 47535, 55523
7441	transmembrane protein 63C	536110	7596	439055	15584	23572, 31560, 39548, 47536, 55524
7442	transmembrane protein 63C	554346	7597	451237	15585	23573, 31561, 39549, 47537, 55525
7443	transmembrane protein 63C	554766	7598	451842	15586	23574, 31562, 39550, 47538, 55526
7444	transmembrane protein 63C	555338	7599	451398	15587	23575, 31563, 39551, 47539, 55527
7445	transmembrane protein 63C	556514	7600	451404	15588	23576, 31564, 39552, 47540, 55528
7446	transmembrane protein 63C	557408	7601	450879	15589	23577, 31565, 39553, 47541, 55529
7447	transmembrane protein 64	418210	7602	411951	15590	23578, 31566, 39554, 47542, 55530
7448	transmembrane protein 64	458549	7603	414786	15591	23579, 31567, 39555, 47543, 55531
7449	transmembrane protein 64	519519	7604	429832	15592	23580, 31568, 39556, 47544, 55532
7450	transmembrane protein 64	521852	7605	430689	15593	23581, 31569, 39557, 47545, 55533
7451	transmembrane protein 65	297632	7606	297632	15594	23582, 31570, 39558, 47546, 55534
7452	transmembrane protein 66	256255	7607	256255	15595	23583, 31571, 39559, 47547, 55535
7453	transmembrane protein 66	536273	7608	441723	15596	23584, 31572, 39560, 47548, 55536
7454	transmembrane protein 66	541035	7609	445146	15597	23585, 31573, 39561, 47549, 55537
7455	transmembrane protein 66	545648	7610	441351	15598	23586, 31574, 39562, 47550, 55538
7456	transmembrane protein 68	334667	7611	335416	15599	23587, 31575, 39563, 47551, 55539

7457	transmembrane protein 68	434581	7612	395204	15600	23588, 31576, 39564, 47552, 55540
7458	transmembrane protein 68	520414	7613	429758	15601	23589, 31577, 39565, 47553, 55541
7459	transmembrane protein 68	521229	7614	429210	15602	23590, 31578, 39566, 47554, 55542
7460	transmembrane protein 68	522090	7615	430542	15603	23591, 31579, 39567, 47555, 55543
7461	transmembrane protein 68	522576	7616	431047	15604	23592, 31580, 39568, 47556, 55544
7462	transmembrane protein 68	523180	7617	427939	15605	23593, 31581, 39569, 47557, 55545
7463	transmembrane protein 68	523423	7618	429175	15606	23594, 31582, 39570, 47558, 55546
7464	transmembrane protein 68	540934	7619	443586	15607	23595, 31583, 39571, 47559, 55547
7465	transmembrane protein 69	372025	7620	361095	15608	23596, 31584, 39572, 47560, 55548
7466	transmembrane protein 72	389583	7621	374234	15609	23597, 31585, 39573, 47561, 55549
7467	transmembrane protein 72	544540	7622	439911	15610	23598, 31586, 39574, 47562, 55550
7468	transmembrane protein 74B	381894	7623	371318	15611	23599, 31587, 39575, 47563, 55551
7469	transmembrane protein 74B	429036	7624	400552	15612	23600, 31588, 39576, 47564, 55552
7470	transmembrane protein 75	539634	7625	446264	15613	23601, 31589, 39577, 47565, 55553
7471	transmembrane protein 78	323223	7626	324799	15614	23602, 31590, 39578, 47566, 55554
7472	transmembrane protein 79	295694	7627	295694	15615	23603, 31591, 39579, 47567, 55555
7473	transmembrane protein 79	357501	7628	350100	15616	23604, 31592, 39580, 47568, 55556
7474	transmembrane protein 79	405535	7629	384748	15617	23605, 31593, 39581, 47569, 55557

7475	transmembrane protein 79	456810	7630	394736	15618	23606, 31594, 39582, 47570, 55558
7476	transmembrane protein 80	397510	7631	380646	15619	23607, 31595, 39583, 47571, 55559
7477	transmembrane protein 80	397512	7632	380648	15620	23608, 31596, 39584, 47572, 55560
7478	transmembrane protein 81	367167	7633	356135	15621	23609, 31597, 39585, 47573, 55561
7479	transmembrane protein 82	375782	7634	364938	15622	23610, 31598, 39586, 47574, 55562
7480	transmembrane protein 85	249209	7635	249209	15623	23611, 31599, 39587, 47575, 55563
7481	transmembrane protein 85	267750	7636	267750	15624	23612, 31600, 39588, 47576, 55564
7482	transmembrane protein 86A	280734	7637	280734	15625	23613, 31601, 39589, 47577, 55565
7483	transmembrane protein 86A	535380	7638	441843	15626	23614, 31602, 39590, 47578, 55566
7484	transmembrane protein 86B	327042	7639	321038	15627	23615, 31603, 39591, 47579, 55567
7485	transmembrane protein 87A	307216	7640	305894	15628	23616, 31604, 39592, 47580, 55568
7486	transmembrane protein 87A	389834	7641	374484	15629	23617, 31605, 39593, 47581, 55569
7487	transmembrane protein 87A	448392	7642	405379	15630	23618, 31606, 39594, 47582, 55570
7488	transmembrane protein 87A	535305	7643	438181	15631	23619, 31607, 39595, 47583, 55571
7489	transmembrane protein 87B	283206	7644	283206	15632	23620, 31608, 39596, 47584, 55572
7490	transmembrane protein 88	301599	7645	301599	15633	23621, 31609, 39597, 47585, 55573
7491	transmembrane protein 89	330862	7646	329557	15634	23622, 31610, 39598, 47586, 55574
7492	transmembrane protein 8A	382942	7647	372400	15635	23623, 31611, 39599, 47587, 55575

7493	transmembrane protein 8A	431232	7648	401338	15636	23624, 31612, 39600, 47588, 55576
7494	transmembrane protein 8B	377988	7649	367227	15637	23625, 31613, 39601, 47589, 55577
7495	transmembrane protein 8B	377991	7650	367230	15638	23626, 31614, 39602, 47590, 55578
7496	transmembrane protein 8B	377996	7651	367235	15639	23627, 31615, 39603, 47591, 55579
7497	transmembrane protein 8B	439587	7652	395810	15640	23628, 31616, 39604, 47592, 55580
7498	transmembrane protein 9	367329	7653	356298	15641	23629, 31617, 39605, 47593, 55581
7499	transmembrane protein 9	367330	7654	356299	15642	23630, 31618, 39606, 47594, 55582
7500	transmembrane protein 9	367332	7655	356301	15643	23631, 31619, 39607, 47595, 55583
7501	transmembrane protein 9	367333	7656	356302	15644	23632, 31620, 39608, 47596, 55584
7502	transmembrane protein 9	367334	7657	356303	15645	23633, 31621, 39609, 47597, 55585
7503	transmembrane protein 9	414605	7658	398557	15646	23634, 31622, 39610, 47598, 55586
7504	transmembrane protein 9	435310	7659	390184	15647	23635, 31623, 39611, 47599, 55587
7505	transmembrane protein 9	455367	7660	405329	15648	23636, 31624, 39612, 47600, 55588
7506	transmembrane protein 91	342187	7661	345589	15649	23637, 31625, 39613, 47601, 55589
7507	transmembrane protein 91	356385	7662	348750	15650	23638, 31626, 39614, 47602, 55590
7508	transmembrane protein 91	392002	7663	375859	15651	23639, 31627, 39615, 47603, 55591
7509	transmembrane protein 91	413014	7664	413192	15652	23640, 31628, 39616, 47604, 55592
7510	transmembrane protein 91	436170	7665	407003	15653	23641, 31629, 39617, 47605, 55593

7511	transmembrane protein 91	447302	7666	405647	15654	23642, 31630, 39618, 47606, 55594
7512	transmembrane protein 91	535712	7667	443375	15655	23643, 31631, 39619, 47607, 55595
7513	transmembrane protein 91	537354	7668	437868	15656	23644, 31632, 39620, 47608, 55596
7514	transmembrane protein 91	544232	7669	437779	15657	23645, 31633, 39621, 47609, 55597
7515	transmembrane protein 91	546362	7670	441729	15658	23646, 31634, 39622, 47610, 55598
7516	transmembrane protein 92	300433	7671	300433	15659	23647, 31635, 39623, 47611, 55599
7517	transmembrane protein 92	507382	7672	425144	15660	23648, 31636, 39624, 47612, 55600
7518	transmembrane protein 93	248378	7673	248378	15661	23649, 31637, 39625, 47613, 55601
7519	transmembrane protein 93	397133	7674	380322	15662	23650, 31638, 39626, 47614, 55602
7520	transmembrane protein 98	261713	7675	261713	15663	23651, 31639, 39627, 47615, 55603
7521	transmembrane protein 98	394642	7676	378138	15664	23652, 31640, 39628, 47616, 55604
7522	transmembrane protein 98	395149	7677	398446	15665	23653, 31641, 39629, 47617, 55605
7523	transmembrane protein 98	439138	7678	406394	15666	23654, 31642, 39630, 47618, 55606
7524	transmembrane protein 98	579849	7679	463245	15667	23655, 31643, 39631, 47619, 55607
7525	transmembrane protein 99	301665	7680	301665	15668	23656, 31644, 39632, 47620, 55608
7526	transmembrane protein 99	436612	7681	390036	15669	23657, 31645, 39633, 47621, 55609
7527	Transmembrane protein FLJ78588	358533	7682	351335	15670	23658, 31646, 39634, 47622, 55610
7528	transmembrane protein with metallophosphoesterase domain	342462	7683	343398	15671	23659, 31647, 39635, 47623, 55611

7529	transmembrane protein with metallophosphoesterase domain	416695	7684	400715	15672	23660, 31648, 39636, 47624, 55612
7530	transmembrane protein, adipocyte asscociated 1	296210	7685	296210	15673	23661, 31649, 39637, 47625, 55613
7531	transmembrane protein, adipocyte asscociated 1	355552	7686	347748	15674	23662, 31650, 39638, 47626, 55614
7532	transmembrane protein, adipocyte asscociated 1	450633	7687	413428	15675	23663, 31651, 39639, 47627, 55615
7533	transmembrane protein, adipocyte asscociated 1	462228	7688	419299	15676	23664, 31652, 39640, 47628, 55616
7534	transmembrane protein, adipocyte asscociated 1	469111	7689	419533	15677	23665, 31653, 39641, 47629, 55617
7535	transmembrane protein, adipocyte asscociated 1	489960	7690	418298	15678	23666, 31654, 39642, 47630, 55618
7536	transmembrane protein, adipocyte asscociated 1	490290	7691	417113	15679	23667, 31655, 39643, 47631, 55619
7537	transmembrane protein, adipocyte asscociated 1	490643	7692	419822	15680	23668, 31656, 39644, 47632, 55620
7538	tribbles homolog 3 (Drosophila)	217233	7693	217233	15681	23669, 31657, 39645, 47633, 55621
7539	tribbles homolog 3 (Drosophila)	422053	7694	415416	15682	23670, 31658, 39646, 47634, 55622
7540	tribbles homolog 3 (Drosophila)	449710	7695	391873	15683	23671, 31659, 39647, 47635, 55623
7541	tripartite motif containing 10	259941	7696	259941	15684	23672, 31660, 39648, 47636, 55624
7542	tripartite motif containing 10	354038	7697	343695	15685	23673, 31661, 39649, 47637, 55625
7543	tripartite motif containing 10	548533	7698	448988	15686	23674, 31662, 39650, 47638, 55626
7544	tripartite motif containing 16	336708	7699	338989	15687	23675, 31663, 39651, 47639, 55627
7545	tripartite motif containing 16	578237	7700	463188	15688	23676, 31664, 39652, 47640, 55628
7546	tripartite motif containing 4	349062	7701	275736	15689	23677, 31665, 39653, 47641, 55629

7547	tripartite motif containing 4	354241	7702	346186	15690	23678, 31666, 39654, 47642, 55630
7548	tripartite motif containing 4	355947	7703	348216	15691	23679, 31667, 39655, 47643, 55631
7549	tripartite motif containing 4	542799	7704	439655	15692	23680, 31668, 39656, 47644, 55632
7550	tripartite motif containing 59	309784	7705	311219	15693	23681, 31669, 39657, 47645, 55633
7551	tripartite motif containing 59	471155	7706	418699	15694	23682, 31670, 39658, 47646, 55634
7552	tripartite motif containing 59	471396	7707	420520	15695	23683, 31671, 39659, 47647, 55635
7553	tripartite motif containing 59	479460	7708	417081	15696	23684, 31672, 39660, 47648, 55636
7554	tripartite motif containing 59	494486	7709	417605	15697	23685, 31673, 39661, 47649, 55637
7555	tripartite motif containing 59	543469	7710	444313	15698	23686, 31674, 39662, 47650, 55638
7556	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	338687	7711	340970	15699	23687, 31675, 39663, 47651, 55639
7557	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	372931	7712	362022	15700	23688, 31676, 39664, 47652, 55640
7558	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	372935	7713	362026	15701	23689, 31677, 39665, 47653, 55641
7559	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	372936	7714	362027	15702	23690, 31678, 39666, 47654, 55642
7560	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	372939	7715	362030	15703	23691, 31679, 39667, 47655, 55643
7561	TRM2 tRNA methyltransferase 2 homolog B (S. cerevisiae)	545398	7716	438134	15704	23692, 31680, 39668, 47656, 55644
7562	t-SNARE domain containing 1	307180	7717	303437	15705	23693, 31681, 39669, 47657, 55645

7563	t-SNARE domain containing 1	519651	7718	429679	15706	23694, 31682, 39670, 47658, 55646
7564	t-SNARE domain containing 1	520166	7719	427770	15707	23695, 31683, 39671, 47659, 55647
7565	t-SNARE domain containing 1	520462	7720	429626	15708	23696, 31684, 39672, 47660, 55648
7566	t-SNARE domain containing 1	524325	7721	428763	15709	23697, 31685, 39673, 47661, 55649
7567	tudor and KH domain containing	368822	7722	357812	15710	23698, 31686, 39674, 47662, 55650
7568	tudor and KH domain containing	368823	7723	357813	15711	23699, 31687, 39675, 47663, 55651
7569	tudor and KH domain containing	368824	7724	357815	15712	23700, 31688, 39676, 47664, 55652
7570	tudor and KH domain containing	368825	7725	357817	15713	23701, 31689, 39677, 47665, 55653
7571	tudor and KH domain containing	368827	7726	357819	15714	23702, 31690, 39678, 47666, 55654
7572	tudor and KH domain containing	440583	7727	416645	15715	23703, 31691, 39679, 47667, 55655
7573	tudor and KH domain containing	458431	7728	395718	15716	23704, 31692, 39680, 47668, 55656
7574	tudor and KH domain containing	526378	7729	431557	15717	23705, 31693, 39681, 47669, 55657
7575	tumor necrosis factor receptor superfamily, member 19	248484	7730	248484	15718	23706, 31694, 39682, 47670, 55658
7576	tumor necrosis factor receptor superfamily, member 19	382258	7731	371693	15719	23707, 31695, 39683, 47671, 55659
7577	tumor necrosis factor receptor superfamily, member 19	382263	7732	371698	15720	23708, 31696, 39684, 47672, 55660
7578	tumor necrosis factor receptor superfamily, member 19	403372	7733	385408	15721	23709, 31697, 39685, 47673, 55661
7579	tumor protein p53 inducible protein 11	308212	7734	309532	15722	23710, 31698, 39686, 47674, 55662

7580	tumor protein p53 inducible protein 11	308220	7735	309551	15723	23711, 31699, 39687, 47675, 55663
7581	tumor protein p53 inducible protein 11	395648	7736	379009	15724	23712, 31700, 39688, 47676, 55664
7582	tumor protein p53 inducible protein 11	525680	7737	433474	15725	23713, 31701, 39689, 47677, 55665
7583	tumor protein p53 inducible protein 11	525683	7738	434461	15726	23714, 31702, 39690, 47678, 55666
7584	tumor protein p53 inducible protein 11	527685	7739	431556	15727	23715, 31703, 39691, 47679, 55667
7585	tumor protein p53 inducible protein 11	528473	7740	433454	15728	23716, 31704, 39692, 47680, 55668
7586	tumor protein p53 inducible protein 11	530035	7741	432089	15729	23717, 31705, 39693, 47681, 55669
7587	tumor protein p53 inducible protein 11	533443	7742	437284	15730	23718, 31706, 39694, 47682, 55670
7588	tumor protein p53 inducible protein 11	533937	7743	432926	15731	23719, 31707, 39695, 47683, 55671
7589	tumor protein p53 inducible protein 11	533940	7744	436152	15732	23720, 31708, 39696, 47684, 55672
7590	tumor protein p53 inducible protein 13	301057	7745	301057	15733	23721, 31709, 39697, 47685, 55673
7591	tumor protein p53 inducible protein 13	378818	7746	368095	15734	23722, 31710, 39698, 47686, 55674
7592	tweety homolog 2 (Drosophila)	269346	7747	269346	15735	23723, 31711, 39699, 47687, 55675
7593	tweety homolog 2 (Drosophila)	441391	7748	394576	15736	23724, 31712, 39700, 47688, 55676
7594	tweety homolog 3 (Drosophila)	258796	7749	258796	15737	23725, 31713, 39701, 47689, 55677
7595	tweety homolog 3 (Drosophila)	403167	7750	385015	15738	23726, 31714, 39702, 47690, 55678
7596	tweety homolog 3 (Drosophila)	407643	7751	385316	15739	23727, 31715, 39703, 47691, 55679
7597	U2 small nuclear RNA auxiliary factor 1-like 4	292879	7752	292879	15740	23728, 31716, 39704, 47692, 55680

7598	U2 small nuclear RNA auxiliary factor 1-like 4	378975	7753	368258	15741	23729, 31717, 39705, 47693, 55681
7599	U2 small nuclear RNA auxiliary factor 1-like 4	392196	7754	376034	15742	23730, 31718, 39706, 47694, 55682
7600	U2 small nuclear RNA auxiliary factor 1-like 4	412391	7755	397645	15743	23731, 31719, 39707, 47695, 55683
7601	UBA domain containing 2	376440	7756	365623	15744	23732, 31720, 39708, 47696, 55684
7602	UBA domain containing 2	403766	7757	383911	15745	23733, 31721, 39709, 47697, 55685
7603	ubiquinol-cytochrome c reductase, complex III subunit X	330029	7758	332887	15746	23734, 31722, 39710, 47698, 55686
7604	ubiquinol-cytochrome c reductase, complex III subunit X	332801	7759	333278	15747	23735, 31723, 39711, 47699, 55687
7605	ubiquinol-cytochrome c reductase, complex III subunit X	401406	7760	384962	15748	23736, 31724, 39712, 47700, 55688
7606	ubiquinol-cytochrome c reductase, complex III subunit X	406782	7761	385696	15749	23737, 31725, 39713, 47701, 55689
7607	ubiquinol-cytochrome c reductase, complex III subunit XI	262946	7762	262946	15750	23738, 31726, 39714, 47702, 55690
7608	ubiquitin protein ligase E3 component n-recognin 4	375217	7763	364365	15751	23739, 31727, 39715, 47703, 55691
7609	ubiquitin protein ligase E3 component n-recognin 4	375218	7764	364366	15752	23740, 31728, 39716, 47704, 55692
7610	ubiquitin protein ligase E3 component n-recognin 4	375224	7765	364372	15753	23741, 31729, 39717, 47705, 55693
7611	ubiquitin protein ligase E3 component n-recognin 4	375225	7766	364373	15754	23742, 31730, 39718, 47706, 55694
7612	ubiquitin protein ligase E3 component n-recognin 4	375226	7767	364374	15755	23743, 31731, 39719, 47707, 55695
7613	ubiquitin protein ligase E3 component n-recognin 4	375254	7768	364403	15756	23744, 31732, 39720, 47708, 55696

7614	ubiquitin protein ligase E3 component n-recognin 4	375267	7769	364416	15757	23745, 31733, 39721, 47709, 55697
7615	ubiquitin protein ligase E3 component n-recognin 4	417040	7770	404897	15758	23746, 31734, 39722, 47710, 55698
7616	ubiquitin protein ligase E3 component n-recognin 4	419533	7771	391875	15759	23747, 31735, 39723, 47711, 55699
7617	ubiquitin protein ligase E3 component n-recognin 4	425413	7772	395313	15760	23748, 31736, 39724, 47712, 55700
7618	ubiquitin protein ligase E3 component n-recognin 4	429347	7773	394173	15761	23749, 31737, 39725, 47713, 55701
7619	ubiquitin protein ligase E3 component n-recognin 4	543981	7774	444070	15762	23750, 31738, 39726, 47714, 55702
7620	ubiquitin specific peptidase 19	398888	7775	381863	15763	23751, 31739, 39727, 47715, 55703
7621	ubiquitin specific peptidase 19	425298	7776	412679	15764	23752, 31740, 39728, 47716, 55704
7622	ubiquitin specific peptidase 19	417901	7777	395260	15765	23753, 31741, 39729, 47717, 55705
7623	ubiquitin specific peptidase 19	434032	7778	401197	15766	23754, 31742, 39730, 47718, 55706
7624	ubiquitin specific peptidase 19	453664	7779	400090	15767	23755, 31743, 39731, 47719, 55707
7625	ubiquitin specific peptidase 8	307179	7780	302239	15768	23756, 31744, 39732, 47720, 55708
7626	ubiquitin specific peptidase 8	396440	7781	379717	15769	23757, 31745, 39733, 47721, 55709
7627	ubiquitin specific peptidase 8	396444	7782	379721	15770	23758, 31746, 39734, 47722, 55710
7628	ubiquitin specific peptidase 8	433963	7783	405537	15771	23759, 31747, 39735, 47723, 55711
7629	ubiquitin specific peptidase 8	558091	7784	454059	15772	23760, 31748, 39736, 47724, 55712
7630	ubiquitin specific peptidase 8	560297	7785	453206	15773	23761, 31749, 39737, 47725, 55713
7631	ubiquitin specific peptidase 8	560982	7786	453427	15774	23762, 31750, 39738, 47726, 55714

7632	ubiquitin-conjugating enzyme E2 J2	450390	7787	407565	15775	23763, 31751, 39739, 47727, 55715
7633	ubiquitin-conjugating enzyme E2, J1, U	435041	7788	451261	15776	23764, 31752, 39740, 47728, 55716
7634	ubiquitin-conjugating enzyme E2, J1, U	536477	7789	441898	15777	23765, 31753, 39741, 47729, 55717
7635	ubiquitin-conjugating enzyme E2, J2	339385	7790	340197	15778	23766, 31754, 39742, 47730, 55718
7636	ubiquitin-conjugating enzyme E2, J2	347370	7791	344857	15779	23767, 31755, 39743, 47731, 55719
7637	ubiquitin-conjugating enzyme E2, J2	348298	7792	342541	15780	23768, 31756, 39744, 47732, 55720
7638	ubiquitin-conjugating enzyme E2, J2	349431	7793	305826	15781	23769, 31757, 39745, 47733, 55721
7639	ubiquitin-conjugating enzyme E2, J2	360466	7794	353653	15782	23770, 31758, 39746, 47734, 55722
7640	ubiquitin-conjugating enzyme E2, J2	400929	7795	383718	15783	23771, 31759, 39747, 47735, 55723
7641	ubiquitin-conjugating enzyme E2, J2	400930	7796	383719	15784	23772, 31760, 39748, 47736, 55724
7642	ubiquitin-conjugating enzyme E2, J2	422076	7797	401898	15785	23773, 31761, 39749, 47737, 55725
7643	ubiquitin-conjugating enzyme E2, J2	435198	7798	393301	15786	23774, 31762, 39750, 47738, 55726
7644	ubiquitin-conjugating enzyme E2, J2	488418	7799	427244	15787	23775, 31763, 39751, 47739, 55727
7645	ubiquitin-conjugating enzyme E2, J2	502382	7800	424342	15788	23776, 31764, 39752, 47740, 55728
7646	ubiquitin-conjugating enzyme E2D 3	321805	7801	318494	15789	23777, 31765, 39753, 47741, 55729
7647	ubiquitin-conjugating enzyme E2D 3	338145	7802	337208	15790	23778, 31766, 39754, 47742, 55730
7648	ubiquitin-conjugating enzyme E2D 3	343106	7803	345285	15791	23779, 31767, 39755, 47743, 55731
7649	ubiquitin-conjugating enzyme E2D 3	349311	7804	344069	15792	23780, 31768, 39756, 47744, 55732

7650	ubiquitin-conjugating enzyme E2D 3	357194	7805	349722	15793	23781, 31769, 39757, 47745, 55733
7651	ubiquitin-conjugating enzyme E2D 3	394801	7806	378280	15794	23782, 31770, 39758, 47746, 55734
7652	ubiquitin-conjugating enzyme E2D 3	394803	7807	378282	15795	23783, 31771, 39759, 47747, 55735
7653	ubiquitin-conjugating enzyme E2D 3	394804	7808	378283	15796	23784, 31772, 39760, 47748, 55736
7654	ubiquitin-conjugating enzyme E2D 3	453744	7809	396901	15797	23785, 31773, 39761, 47749, 55737
7655	ubiquitin-conjugating enzyme E2D 3	502690	7810	425762	15798	23786, 31774, 39762, 47750, 55738
7656	ubiquitin-conjugating enzyme E2D 3	508238	7811	423487	15799	23787, 31775, 39763, 47751, 55739
7657	ubiquitin-conjugating enzyme E2D 3	508249	7812	421310	15800	23788, 31776, 39764, 47752, 55740
7658	UBX domain protein 4	272638	7813	272638	15801	23789, 31777, 39765, 47753, 55741
7659	UBX domain protein 4	430594	7814	400407	15802	23790, 31778, 39766, 47754, 55742
7660	UBX domain protein 7	296328	7815	296328	15803	23791, 31779, 39767, 47755, 55743
7661	UBX domain protein 7	535858	7816	440716	15804	23792, 31780, 39768, 47756, 55744
7662	UDP glucuronosyltransferase 2 family, polypeptide A3	251566	7817	251566	15805	23793, 31781, 39769, 47757, 55745
7663	UDP glucuronosyltransferase 2 family, polypeptide A3	420231	7818	440115	15806	23794, 31782, 39770, 47758, 55746
7664	UDP glucuronosyltransferase 2 family, polypeptide B10	265403	7819	265403	15807	23795, 31783, 39771, 47759, 55747
7665	UDP glycosyltransferase 3 family, polypeptide A1	274278	7820	274278	15808	23796, 31784, 39772, 47760, 55748
7666	UDP glycosyltransferase 3 family,	333811	7821	328033	15809	23797, 31785, 39773, 47761, 55749

	polypeptide A1					
7667	UDP glycosyltransferase 8	310836	7822	311648	15810	23798, 31786, 39774, 47762, 55750
7668	UDP glycosyltransferase 8	394511	7823	378019	15811	23799, 31787, 39775, 47763, 55751
7669	UDP glycosyltransferase 8	507710	7824	421446	15812	23800, 31788, 39776, 47764, 55752
7670	UDP-Gal:betaGal beta 1,3-galactosyltransferase polypeptide 6	379198	7825	368496	15813	23801, 31789, 39777, 47765, 55753
7671	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	305861	7826	303740	15814	23802, 31790, 39778, 47766, 55754
7672	UDP-Gal:betaGlcNAc beta 1,3-galactosyltransferase, polypeptide 1	392690	7827	376456	15815	23803, 31791, 39779, 47767, 55755
7673	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	311181	7828	309096	15816	23804, 31792, 39780, 47768, 55756
7674	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 1	538757	7829	440059	15817	23805, 31793, 39781, 47769, 55757
7675	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	301998	7830	305595	15818	23806, 31794, 39782, 47770, 55758
7676	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2	405767	7831	384692	15819	23807, 31795, 39783, 47771, 55759
7677	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	326505	7832	316173	15820	23808, 31796, 39784, 47772, 55760
7678	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	460419	7833	420778	15821	23809, 31797, 39785, 47773, 55761

7679	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	464191	7834	418785	15822	23810, 31798, 39786, 47774, 55762
7680	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	464923	7835	418477	15823	23811, 31799, 39787, 47775, 55763
7681	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	465010	7836	417868	15824	23812, 31800, 39788, 47776, 55764
7682	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 5	481531	7837	417301	15825	23813, 31801, 39789, 47777, 55765
7683	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 7	287590	7838	287590	15826	23814, 31802, 39790, 47778, 55766
7684	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 8	321702	7839	312700	15827	23815, 31803, 39791, 47779, 55767
7685	UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 9	449549	7840	400157	15828	23816, 31804, 39792, 47780, 55768
7686	UDP-glucuronosyltransferase 2A3 precursor	547910	7841	447309	15829	23817, 31805, 39793, 47781, 55769
7687	UDP-glucuronosyltransferase 2A3 precursor	549931	7842	447700	15830	23818, 31806, 39794, 47782, 55770
7688	UDP-glucuronosyltransferase 2B10 isoform 1 precursor	549514	7843	449012	15831	23819, 31807, 39795, 47783, 55771
7689	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	320311	7844	315835	15832	23820, 31808, 39796, 47784, 55772

7690	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	415421	7845	410093	15833	23821, 31809, 39797, 47785, 55773
7691	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	419245	7846	397581	15834	23822, 31810, 39798, 47786, 55774
7692	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	422997	7847	389449	15835	23823, 31811, 39799, 47787, 55775
7693	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	430044	7848	395122	15836	23824, 31812, 39800, 47788, 55776
7694	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	431668	7849	395020	15837	23825, 31813, 39801, 47789, 55777
7695	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	434507	7850	416787	15838	23826, 31814, 39802, 47790, 55778
7696	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	443352	7851	408155	15839	23827, 31815, 39803, 47791, 55779
7697	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11	447796	7852	412142	15840	23828, 31816, 39804, 47792, 55780

	(GalNAc-T11)					
7698	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 11 (GalNAc-T11)	452146	7853	393399	15841	23829, 31817, 39805, 47793, 55781
7699	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 5 (GalNAc-T5)	259056	7854	259056	15842	23830, 31818, 39806, 47794, 55782
7700	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 1	337827	7855	336729	15843	23831, 31819, 39807, 47795, 55783
7701	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 1	448469	7856	402970	15844	23832, 31820, 39808, 47796, 55784
7702	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 1	536652	7857	445877	15845	23833, 31821, 39809, 47797, 55785
7703	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 1	553669	7858	451200	15846	23834, 31822, 39810, 47798, 55786
7704	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 2	339732	7859	344260	15847	23835, 31823, 39811, 47799, 55787
7705	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 2	543679	7860	445852	15848	23836, 31824, 39812, 47800, 55788

7706	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 4	227756	7861	227756	15849	23837, 31825, 39813, 47801, 55789
7707	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 5	392800	7862	376548	15850	23838, 31826, 39814, 47802, 55790
7708	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 5	431418	7863	392582	15851	23839, 31827, 39815, 47803, 55791
7709	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 6	404275	7864	385382	15852	23840, 31828, 39816, 47804, 55792
7710	UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase-like 6	506823	7865	423313	15853	23841, 31829, 39817, 47805, 55793
7711	UDP-N-acteylglucosamine pyrophosphorylase 1	271469	7866	271469	15854	23842, 31830, 39818, 47806, 55794
7712	UDP-N-acteylglucosamine pyrophosphorylase 1	367924	7867	356901	15855	23843, 31831, 39819, 47807, 55795
7713	UDP-N-acteylglucosamine pyrophosphorylase 1	367925	7868	356902	15856	23844, 31832, 39820, 47808, 55796
7714	UDP-N-acteylglucosamine pyrophosphorylase 1	367926	7869	356903	15857	23845, 31833, 39821, 47809, 55797
7715	UDP-N-acteylglucosamine pyrophosphorylase 1	412525	7870	395648	15858	23846, 31834, 39822, 47810, 55798
7716	unc-13 homolog B (C. elegans)	378495	7871	367756	15859	23847, 31835, 39823, 47811, 55799
7717	unc-13 homolog B (C. elegans)	378496	7872	367757	15860	23848, 31836, 39824, 47812, 55800
7718	unc-13 homolog B (C. elegans)	396787	7873	380006	15861	23849, 31837, 39825, 47813, 55801

7719	unc-13 homolog B (C. elegans)	535471	7874	441503	15862	23850, 31838, 39826, 47814, 55802
7720	unc-13 homolog C (C. elegans)	260323	7875	260323	15863	23851, 31839, 39827, 47815, 55803
7721	unc-13 homolog C (C. elegans)	537900	7876	442569	15864	23852, 31840, 39828, 47816, 55804
7722	unc-13 homolog C (C. elegans)	545554	7877	438156	15865	23853, 31841, 39829, 47817, 55805
7723	unc-5 homolog C (C. elegans)-like	244565	7878	244565	15866	23854, 31842, 39830, 47818, 55806
7724	unc-5 homolog C (C. elegans)-like	373164	7879	362258	15867	23855, 31843, 39831, 47819, 55807
7725	unc-5 homolog D (C. elegans)	404895	7880	385143	15868	23856, 31844, 39832, 47820, 55808
7726	unc-5 homolog D (C. elegans)	453357	7881	394303	15869	23857, 31845, 39833, 47821, 55809
7727	unc-50 homolog (C. elegans)	357765	7882	350409	15870	23858, 31846, 39834, 47822, 55810
7728	unc-50 homolog (C. elegans)	409347	7883	386466	15871	23859, 31847, 39835, 47823, 55811
7729	unc-50 homolog (C. elegans)	409975	7884	387146	15872	23860, 31848, 39836, 47824, 55812
7730	unc-51-like kinase 2 (C. elegans)	361658	7885	354877	15873	23861, 31849, 39837, 47825, 55813
7731	unc-51-like kinase 2 (C. elegans)	395544	7886	378914	15874	23862, 31850, 39838, 47826, 55814
7732	Uncharacterized protein	452392	7887	391806	15875	23863, 31851, 39839, 47827, 55815
7733	Uncharacterized protein	540229	7888	441269	15876	23864, 31852, 39840, 47828, 55816
7734	Uncharacterized protein	546887	7889	447974	15877	23865, 31853, 39841, 47829, 55817
7735	Uncharacterized protein	548145	7890	449195	15878	23866, 31854, 39842, 47830, 55818
7736	Uncharacterized protein	550239	7891	448807	15879	23867, 31855, 39843, 47831, 55819

7737	Uncharacterized protein	552745	7892	447257	15880	23868, 31856, 39844, 47832, 55820
7738	Uncharacterized protein C20orf141	380589	7893	369963	15881	23869, 31857, 39845, 47833, 55821
7739	Uncharacterized proteincDNA FLJ52651	517889	7894	431116	15882	23870, 31858, 39846, 47834, 55822
7740	unconventional SNARE in the ER 1 homolog (S. cerevisiae)	263897	7895	263897	15883	23871, 31859, 39847, 47835, 55823
7741	up-regulated during skeletal muscle growth 5 homolog (mouse)	309579	7896	311245	15884	23872, 31860, 39848, 47836, 55824
7742	up-regulated during skeletal muscle growth 5 homolog (mouse)	337003	7897	337705	15885	23873, 31861, 39849, 47837, 55825
7743	up-regulated during skeletal muscle growth 5 homolog (mouse)	369811	7898	358826	15886	23874, 31862, 39850, 47838, 55826
7744	up-regulated during skeletal muscle growth 5 homolog (mouse)	369815	7899	358830	15887	23875, 31863, 39851, 47839, 55827
7745	up-regulated during skeletal muscle growth 5 homolog (mouse)	369825	7900	358840	15888	23876, 31864, 39852, 47840, 55828
7746	uroplakin 3B-like	340457	7901	342938	15889	23877, 31865, 39853, 47841, 55829
7747	urotensin 2 receptor	313135	7902	323516	15890	23878, 31866, 39854, 47842, 55830
7748	vacuolar protein sorting 16 homolog (S. cerevisiae)	380443	7903	369808	15891	23879, 31867, 39855, 47843, 55831
7749	vacuolar protein sorting 16 homolog (S. cerevisiae)	380445	7904	369810	15892	23880, 31868, 39856, 47844, 55832
7750	vacuolar protein sorting 16 homolog (S. cerevisiae)	380469	7905	369836	15893	23881, 31869, 39857, 47845, 55833
7751	vacuolar protein sorting 16 homolog (S. cerevisiae)	417508	7906	409840	15894	23882, 31870, 39858, 47846, 55834
7752	vacuolar protein sorting 16 homolog (S. cerevisiae)	453689	7907	417031	15895	23883, 31871, 39859, 47847, 55835

7753	vacuolar protein sorting 18 homolog (S. cerevisiae)	220509	7908	220509	15896	23884, 31872, 39860, 47848, 55836
7754	vacuolar protein sorting 29 homolog (S. cerevisiae)	397678	7909	380795	15897	23885, 31873, 39861, 47849, 55837
7755	vacuolar protein sorting 29 homolog (S. cerevisiae)	447578	7910	400048	15898	23886, 31874, 39862, 47850, 55838
7756	vacuolar protein sorting 29 homolog (S. cerevisiae)	549578	7911	447058	15899	23887, 31875, 39863, 47851, 55839
7757	vacuolar protein sorting 52 homolog (S. cerevisiae)	383210	7912	372697	15900	23888, 31876, 39864, 47852, 55840
7758	vacuolar protein sorting 52 homolog (S. cerevisiae)	418054	7913	414785	15901	23889, 31877, 39865, 47853, 55841
7759	vacuolar protein sorting 52 homolog (S. cerevisiae)	428608	7914	406988	15902	23890, 31878, 39866, 47854, 55842
7760	vacuolar protein sorting 52 homolog (S. cerevisiae)	436044	7915	395282	15903	23891, 31879, 39867, 47855, 55843
7761	vacuolar protein sorting 52 homolog (S. cerevisiae)	441058	7916	390831	15904	23892, 31880, 39868, 47856, 55844
7762	vacuolar protein sorting 52 homolog (S. cerevisiae)	443860	7917	404016	15905	23893, 31881, 39869, 47857, 55845
7763	vacuolar protein sorting 52 homolog (S. cerevisiae)	445902	7918	409952	15906	23894, 31882, 39870, 47858, 55846
7764	vacuolar protein sorting 52 homolog (S. cerevisiae)	448042	7919	391197	15907	23895, 31883, 39871, 47859, 55847
7765	vacuolar protein sorting 52 homolog (S. cerevisiae)	548751	7920	446504	15908	23896, 31884, 39872, 47860, 55848
7766	vacuolar protein sorting 52 homolog (S. cerevisiae)	549522	7921	449313	15909	23897, 31885, 39873, 47861, 55849
7767	vacuolar protein sorting 52 homolog (S. cerevisiae)	551233	7922	447409	15910	23898, 31886, 39874, 47862, 55850
7768	vacuolar protein sorting 52 homolog (S. cerevisiae)	552552	7923	448022	15911	23899, 31887, 39875, 47863, 55851
7769	v-akt murine thymoma viral oncogene homolog 1	349310	7924	270202	15912	23900, 31888, 39876, 47864, 55852
7770	Valyl-tRNA synthetase, mitochondrial	383369	7925	372860	15913	23901, 31889, 39877, 47865, 55853

7771	Valyl-tRNA synthetase, mitochondrial	416187	7926	414807	15914	23902, 31890, 39878, 47866, 55854
7772	Valyl-tRNA synthetase, mitochondrial	431578	7927	415560	15915	23903, 31891, 39879, 47867, 55855
7773	Valyl-tRNA synthetase, mitochondrial	548227	7928	448060	15916	23904, 31892, 39880, 47868, 55856
7774	Valyl-tRNA synthetase, mitochondrial	549900	7929	447763	15917	23905, 31893, 39881, 47869, 55857
7775	Valyl-tRNA synthetase, mitochondrial	553245	7930	447141	15918	23906, 31894, 39882, 47870, 55858
7776	vesicle transport through interaction with t-SNAREs homolog 1B (yeast)	554659	7931	450731	15919	23907, 31895, 39883, 47871, 55859
7777	vesicle-associated membrane protein 4	236192	7932	236192	15920	23908, 31896, 39884, 47872, 55860
7778	vesicle-associated membrane protein 4	367740	7933	356714	15921	23909, 31897, 39885, 47873, 55861
7779	vesicle-associated membrane protein 4	415773	7934	415627	15922	23910, 31898, 39886, 47874, 55862
7780	vesicle-associated membrane protein 4	474047	7935	435933	15923	23911, 31899, 39887, 47875, 55863
7781	vesicular, overexpressed in cancer, prosurvival protein 1	285279	7936	285279	15924	23912, 31900, 39888, 47876, 55864
7782	vesicular, overexpressed in cancer, prosurvival protein 1	545390	7937	446442	15925	23913, 31901, 39889, 47877, 55865
7783	vezatin, adherens junctions transmembrane protein	261219	7938	261219	15926	23914, 31902, 39890, 47878, 55866
7784	vezatin, adherens junctions transmembrane protein	397796	7939	380898	15927	23915, 31903, 39891, 47879, 55867
7785	vezatin, adherens junctions transmembrane protein	436874	7940	410083	15928	23916, 31904, 39892, 47880, 55868
7786	vitamin K epoxide reductase complex, subunit 1-like 1	360768	7941	353998	15929	23917, 31905, 39893, 47881, 55869

7787	VMA21 vacuolar H+-ATPase homolog (S. cerevisiae)	330374	7942	333255	15930	23918, 31906, 39894, 47882, 55870
7788	VMA21 vacuolar H+-ATPase homolog (S. cerevisiae)	370361	7943	359386	15931	23919, 31907, 39895, 47883, 55871
7789	vomeronasal 1 receptor 2	341702	7944	351244	15932	23920, 31908, 39896, 47884, 55872
7790	V-set and immunoglobulin domain containing 1	217957	7945	217957	15933	23921, 31909, 39897, 47885, 55873, 56103, 56136
7791	V-set and immunoglobulin domain containing 1	415430	7946	402219	15934	23922, 31910, 39898, 47886, 55874
7792	V-set and immunoglobulin domain containing 10	359236	7947	352172	15935	23923, 31911, 39899, 47887, 55875
7793	V-set and immunoglobulin domain containing 10 like	335624	7948	335623	15936	23924, 31912, 39900, 47888, 55876
7794	V-set and immunoglobulin domain containing 10 like	542561	7949	443102	15937	23925, 31913, 39901, 47889, 55877
7795	V-set and immunoglobulin domain containing 4	374737	7950	363869	15938	23926, 31914, 39902, 47890, 55878
7796	V-set and immunoglobulin domain containing 4	412866	7951	394143	15939	23927, 31915, 39903, 47891, 55879
7797	V-set and immunoglobulin domain containing 4	423830	7952	414594	15940	23928, 31916, 39904, 47892, 55880
7798	V-set and immunoglobulin domain containing 4	427538	7953	393108	15941	23929, 31917, 39905, 47893, 55881
7799	V-set and immunoglobulin domain containing 4	455586	7954	411581	15942	23930, 31918, 39906, 47894, 55882
7800	V-set and immunoglobulin domain containing 8	368100	7955	357080	15943	23931, 31919, 39907, 47895, 55883
7801	V-set and transmembrane domain containing 4	298454	7956	298454	15944	23932, 31920, 39908, 47896, 55884
7802	V-set and transmembrane domain containing 4	332853	7957	331062	15945	23933, 31921, 39909, 47897, 55885

7803	V-set and transmembrane domain containing 5	409977	7958	386607	15946	23934, 31922, 39910, 47898, 55886
7804	V-set domain containing T cell activation inhibitor 1	328189	7959	328168	15947	23935, 31923, 39911, 47899, 55887
7805	V-set domain containing T cell activation inhibitor 1	359008	7960	351899	15948	23936, 31924, 39912, 47900, 55888
7806	V-set domain containing T cell activation inhibitor 1	369456	7961	358468	15949	23937, 31925, 39913, 47901, 55889
7807	V-set domain containing T cell activation inhibitor 1	369458	7962	358470	15950	23938, 31926, 39914, 47902, 55890
7808	V-set domain containing T cell activation inhibitor 1	539893	7963	444724	15951	23939, 31927, 39915, 47903, 55891
7809	WAS protein family homolog 4 pseudogene	326592	7964	317542	15952	23940, 31928, 39916, 47904, 55892
7810	WAS protein family homolog 4 pseudogene	538848	7965	441402	15953	23941, 31929, 39917, 47905, 55893
7811	WAS protein family homolog 6 pseudogene	285718	7966	285718	15954	23942, 31930, 39918, 47906, 55894
7812	WAS protein family homolog 6 pseudogene	359512	7967	352498	15955	23943, 31931, 39919, 47907, 55895
7813	WD repeat and FYVE domain containing 3	295888	7968	295888	15956	23944, 31932, 39920, 47908, 55896
7814	WD repeat and FYVE domain containing 3	322366	7969	318466	15957	23945, 31933, 39921, 47909, 55897
7815	WD repeat and FYVE domain containing 3	502713	7970	422741	15958	23946, 31934, 39922, 47910, 55898
7816	WD repeat and FYVE domain containing 3	509172	7971	425699	15959	23947, 31935, 39923, 47911, 55899
7817	WD repeat containing planar cell polarity effector	272321	7972	272321	15960	23948, 31936, 39924, 47912, 55900
7818	WD repeat domain 44	254029	7973	254029	15961	23949, 31937, 39925, 47913, 55901
7819	WD repeat domain 44	318919	7974	317678	15962	23950, 31938, 39926, 47914, 55902
7820	WD repeat domain 44	371822	7975	360887	15963	23951, 31939, 39927, 47915, 55903

7821	WD repeat domain 44	371825	7976	360890	15964	23952, 31940, 39928, 47916, 55904
7822	WD repeat domain 44	371848	7977	360914	15965	23953, 31941, 39929, 47917, 55905
7823	WD repeat domain 45	322995	7978	365543	15966	23954, 31942, 39930, 47918, 55906
7824	WD repeat domain 45	356463	7979	348848	15967	23955, 31943, 39931, 47919, 55907
7825	WD repeat domain 45	376368	7980	365546	15968	23956, 31944, 39932, 47920, 55908
7826	WD repeat domain 45	376372	7981	365551	15969	23957, 31945, 39933, 47921, 55909
7827	WD repeat domain 45	423215	7982	397657	15970	23958, 31946, 39934, 47922, 55910
7828	WD repeat domain 45	465382	7983	420534	15971	23959, 31947, 39935, 47923, 55911
7829	WD repeat domain 45	553851	7984	451962	15972	23960, 31948, 39936, 47924, 55912
7830	WD repeat domain 83 opposite strand	222190	7985	222190	15973	23961, 31949, 39937, 47925, 55913
7831	WD repeat domain 83 opposite strand	596731	7986	468969	15974	23962, 31950, 39938, 47926, 55914
7832	WD repeat domain 93	268130	7987	268130	15975	23963, 31951, 39939, 47927, 55915
7833	WD repeat domain 93	560294	7988	453971	15976	23964, 31952, 39940, 47928, 55916
7834	WD repeat domain, phosphoinositide interacting 1	262139	7989	262139	15977	23965, 31953, 39941, 47929, 55917
7835	WD repeat domain, phosphoinositide interacting 1	546360	7990	437345	15978	23966, 31954, 39942, 47930, 55918
7836	WD repeat domain, phosphoinositide interacting 2	288828	7991	288828	15979	23967, 31955, 39943, 47931, 55919
7837	WD repeat domain, phosphoinositide interacting 2	315176	7992	313532	15980	23968, 31956, 39944, 47932, 55920
7838	WD repeat domain, phosphoinositide interacting 2	382384	7993	371821	15981	23969, 31957, 39945, 47933, 55921

7839	WD repeat domain, phosphoinositide interacting 2	401525	7994	384945	15982	23970, 31958, 39946, 47934, 55922
7840	WD repeat domain, phosphoinositide interacting 2	404704	7995	385297	15983	23971, 31959, 39947, 47935, 55923
7841	WD repeat domain, phosphoinositide interacting 2	484262	7996	429654	15984	23972, 31960, 39948, 47936, 55924
7842	WDR45-like	392325	7997	376139	15985	23973, 31961, 39949, 47937, 55925
7843	WDR45-like	539012	7998	438383	15986	23974, 31962, 39950, 47938, 55926
7844	Williams-Beuren syndrome chromosome region 16	329959	7999	333799	15987	23975, 31963, 39951, 47939, 55927
7845	Williams-Beuren syndrome chromosome region 16	503250	8000	437702	15988	23976, 31964, 39952, 47940, 55928
7846	Williams-Beuren syndrome chromosome region 16	543840	8001	441127	15989	23977, 31965, 39953, 47941, 55929
7847	Williams-Beuren syndrome chromosome region 17	333538	8002	329654	15990	23978, 31966, 39954, 47942, 55930
7848	WSC domain containing 1	317744	8003	323087	15991	23979, 31967, 39955, 47943, 55931
7849	WSC domain containing 1	539421	8004	446032	15992	23980, 31968, 39956, 47944, 55932
7850	WSC domain containing 2	261400	8005	261400	15993	23981, 31969, 39957, 47945, 55933
7851	WSC domain containing 2	332082	8006	331933	15994	23982, 31970, 39958, 47946, 55934
7852	WSC domain containing 2	547525	8007	448047	15995	23983, 31971, 39959, 47947, 55935
7853	WSC domain containing 2	549903	8008	447272	15996	23984, 31972, 39960, 47948, 55936
7854	xin actin-binding repeat containing 1	340369	8009	343140	15997	23985, 31973, 39961, 47949, 55937
7855	xin actin-binding repeat containing 1	396251	8010	379550	15998	23986, 31974, 39962, 47950, 55938

7856	xin actin-binding repeat containing 1	421646	8011	391645	15999	23987, 31975, 39963, 47951, 55939
7857	XK, Kell blood group complex subunit-related family, member 4	327381	8012	328326	16000	23988, 31976, 39964, 47952, 55940
7858	XK, Kell blood group complex subunit-related family, member 4	543752	8013	444213	16001	23989, 31977, 39965, 47953, 55941
7859	XK, Kell blood group complex subunit-related family, member 6	304437	8014	307120	16002	23990, 31978, 39966, 47954, 55942
7860	XK, Kell blood group complex subunit-related family, member 6	416569	8015	416707	16003	23991, 31979, 39967, 47955, 55943
7861	XK, Kell blood group complex subunit-related family, member 7	217299	8016	217299	16004	23992, 31980, 39968, 47956, 55944
7862	XK, Kell blood group complex subunit-related family, member 8	373884	8017	362991	16005	23993, 31981, 39969, 47957, 55945
7863	XK, Kell blood group complex subunit-related family, member 9	408926	8018	386141	16006	23994, 31982, 39970, 47958, 55946
7864	XK, Kell blood group complex subunit-related family, member 9	520030	8019	431088	16007	23995, 31983, 39971, 47959, 55947
7865	xyloside xylosyltransferase 1	310380	8020	309640	16008	23996, 31984, 39972, 47960, 55948
7866	xyloside xylosyltransferase 1	355729	8021	347967	16009	23997, 31985, 39973, 47961, 55949
7867	xyloside xylosyltransferase 1	356740	8022	349179	16010	23998, 31986, 39974, 47962, 55950
7868	xyloside xylosyltransferase 1	437101	8023	409865	16011	23999, 31987, 39975, 47963, 55951
7869	xyloside xylosyltransferase 1	458652	8024	408351	16012	24000, 31988, 39976, 47964, 55952
7870	ybeY metallopeptidase (putative)	329319	8025	329614	16013	24001, 31989, 39977, 47965, 55953

7871	ybeY metallopeptidase (putative)	339195	8026	340675	16014	24002, 31990, 39978, 47966, 55954
7872	ybeY metallopeptidase (putative)	397691	8027	380805	16015	24003, 31991, 39979, 47967, 55955
7873	ybeY metallopeptidase (putative)	397692	8028	380806	16016	24004, 31992, 39980, 47968, 55956
7874	ybeY metallopeptidase (putative)	397694	8029	380808	16017	24005, 31993, 39981, 47969, 55957
7875	ybeY metallopeptidase (putative)	397701	8030	380813	16018	24006, 31994, 39982, 47970, 55958
7876	Yip1 domain family, member 1	72644	8031	72644	16019	24007, 31995, 39983, 47971, 55959, 56104, 56137
7877	Yip1 domain family, member 1	371399	8032	360452	16020	24008, 31996, 39984, 47972, 55960
7878	Yip1 domain family, member 1	412288	8033	416507	16021	24009, 31997, 39985, 47973, 55961
7879	Yip1 domain family, member 1	464950	8034	432266	16022	24010, 31998, 39986, 47974, 55962
7880	Yip1 domain family, member 1	539954	8035	439926	16023	24011, 31999, 39987, 47975, 55963
7881	Yip1 domain family, member 2	253031	8036	253031	16024	24012, 32000, 39988, 47976, 55964
7882	Yip1 domain family, member 4	238831	8037	238831	16025	24013, 32001, 39989, 47977, 55965
7883	Yip1 domain family, member 6	374622	8038	363751	16026	24014, 32002, 39990, 47978, 55966
7884	Yip1 domain family, member 6	451537	8039	401799	16027	24015, 32003, 39991, 47979, 55967
7885	Yip1 domain family, member 6	462683	8040	417573	16028	24016, 32004, 39992, 47980, 55968
7886	Yip1 domain family, member 7	332990	8041	332772	16029	24017, 32005, 39993, 47981, 55969
7887	Yip1 domain family, member 7	415895	8042	412696	16030	24018, 32006, 39994, 47982, 55970
7888	Yip1 interacting factor homolog B (S. cerevisiae)	329420	8043	329559	16031	24019, 32007, 39995, 47983, 55971

7889	Yip1 interacting factor homolog B (S. cerevisiae)	337679	8044	337411	16032	24020, 32008, 39996, 47984, 55972
7890	Yip1 interacting factor homolog B (S. cerevisiae)	339413	8045	343435	16033	24021, 32009, 39997, 47985, 55973
7891	Yip1 interacting factor homolog B (S. cerevisiae)	392124	8046	375971	16034	24022, 32010, 39998, 47986, 55974
7892	YKT6 v-SNARE homolog (S. cerevisiae)	223369	8047	223369	16035	24023, 32011, 39999, 47987, 55975
7893	YKT6 v-SNARE homolog (S. cerevisiae)	496112	8048	420805	16036	24024, 32012, 40000, 47988, 55976
7894	YY2 transcription factor	429584	8049	389381	16037	24025, 32013, 40001, 47989, 55977
7895	zer-1 homolog (C. elegans)	291900	8050	291900	16038	24026, 32014, 40002, 47990, 55978
7896	zer-1 homolog (C. elegans)	414921	8051	393051	16039	24027, 32015, 40003, 47991, 55979
7897	zer-1 homolog (C. elegans)	427848	8052	389271	16040	24028, 32016, 40004, 47992, 55980
7898	zinc activated ligand-gated ion channel	334586	8053	334854	16041	24029, 32017, 40005, 47993, 55981
7899	zinc activated ligand-gated ion channel	392503	8054	376291	16042	24030, 32018, 40006, 47994, 55982
7900	zinc finger and AT hook domain containing	318135	8055	326997	16043	24031, 32019, 40007, 47995, 55983
7901	zinc finger and SCAN domain containing 20	326544	8056	324450	16044	24032, 32020, 40008, 47996, 55984
7902	zinc finger and SCAN domain containing 20	361328	8057	355053	16045	24033, 32021, 40009, 47997, 55985
7903	zinc finger and SCAN domain containing 20	373411	8058	362510	16046	24034, 32022, 40010, 47998, 55986
7904	zinc finger and SCAN domain containing 20	373413	8059	362512	16047	24035, 32023, 40011, 47999, 55987
7905	zinc finger and SCAN domain containing 20	401072	8060	383850	16048	24036, 32024, 40012, 48000, 55988
7906	zinc finger CCCH-type containing 12A	373082	8061	362174	16049	24037, 32025, 40013, 48001, 55989

7907	zinc finger CCCH-type containing 12A	373087	8062	362179	16050	24038, 32026, 40014, 48002, 55990
7908	zinc finger CCCH-type containing 15	337859	8063	338788	16051	24039, 32027, 40015, 48003, 55991
7909	zinc finger CCCH-type containing 15	536434	8064	439885	16052	24040, 32028, 40016, 48004, 55992
7910	zinc finger CCCH-type containing 15	544130	8065	440525	16053	24041, 32029, 40017, 48005, 55993
7911	zinc finger protein 620	314529	8066	322265	16054	24042, 32030, 40018, 48006, 55994
7912	zinc finger protein 620	420891	8067	406156	16055	24043, 32031, 40019, 48007, 55995
7913	zinc finger protein-like 1	294258	8068	294258	16056	24044, 32032, 40020, 48008, 55996
7914	zinc finger protein-like 1	526334	8069	434454	16057	24045, 32033, 40021, 48009, 55997
7915	zinc finger protein-like 1	532200	8070	437090	16058	24046, 32034, 40022, 48010, 55998
7916	zinc finger, DHHC-type containing 1	348579	8071	340299	16059	24047, 32035, 40023, 48011, 55999
7917	zinc finger, DHHC-type containing 11	283441	8072	283441	16060	24048, 32036, 40024, 48012, 56000
7918	zinc finger, DHHC-type containing 11	424784	8073	397719	16061	24049, 32037, 40025, 48013, 56001
7919	zinc finger, DHHC-type containing 12	372663	8074	361748	16062	24050, 32038, 40026, 48014, 56002
7920	zinc finger, DHHC-type containing 12	372664	8075	361749	16063	24051, 32039, 40027, 48015, 56003
7921	zinc finger, DHHC-type containing 12	372667	8076	361752	16064	24052, 32040, 40028, 48016, 56004
7922	zinc finger, DHHC-type containing 12	372672	8077	361757	16065	24053, 32041, 40029, 48017, 56005
7923	zinc finger, DHHC-type containing 12	406904	8078	384205	16066	24054, 32042, 40030, 48018, 56006
7924	zinc finger, DHHC-type containing 12	452105	8079	387587	16067	24055, 32043, 40031, 48019, 56007

7925	zinc finger, DHHC-type containing 14	359775	8080	352821	16068	24056, 32044, 40032, 48020, 56008
7926	zinc finger, DHHC-type containing 14	414563	8081	410713	16069	24057, 32045, 40033, 48021, 56009
7927	zinc finger, DHHC-type containing 14	538483	8082	444176	16070	24058, 32046, 40034, 48022, 56010
7928	zinc finger, DHHC-type containing 16	345745	8083	304487	16071	24059, 32047, 40035, 48023, 56011
7929	zinc finger, DHHC-type containing 16	352634	8084	345383	16072	24060, 32048, 40036, 48024, 56012
7930	zinc finger, DHHC-type containing 16	353979	8085	323360	16073	24061, 32049, 40037, 48025, 56013
7931	zinc finger, DHHC-type containing 16	370842	8086	359879	16074	24062, 32050, 40038, 48026, 56014
7932	zinc finger, DHHC-type containing 16	370846	8087	359883	16075	24063, 32051, 40039, 48027, 56015
7933	zinc finger, DHHC-type containing 16	370854	8088	359891	16076	24064, 32052, 40040, 48028, 56016
7934	zinc finger, DHHC-type containing 16	393760	8089	377357	16077	24065, 32053, 40041, 48029, 56017
7935	zinc finger, DHHC-type containing 16	414567	8090	400719	16078	24066, 32054, 40042, 48030, 56018
7936	zinc finger, DHHC-type containing 16	417044	8091	396286	16079	24067, 32055, 40043, 48031, 56019
7937	zinc finger, DHHC-type containing 16	420089	8092	405240	16080	24068, 32056, 40044, 48032, 56020
7938	zinc finger, DHHC-type containing 16	433086	8093	398532	16081	24069, 32057, 40045, 48033, 56021
7939	zinc finger, DHHC-type containing 18	374142	8094	363257	16082	24070, 32058, 40046, 48034, 56022
7940	zinc finger, DHHC-type containing 19	296326	8095	296326	16083	24071, 32059, 40047, 48035, 56023
7941	zinc finger, DHHC-type containing 2	262096	8096	262096	16084	24072, 32060, 40048, 48036, 56024
7942	zinc finger, DHHC-type containing 20	320220	8097	313583	16085	24073, 32061, 40049, 48037, 56025

7943	zinc finger, DHHC-type containing 20	382466	8098	371905	16086	24074, 32062, 40050, 48038, 56026
7944	zinc finger, DHHC-type containing 20	400590	8099	383433	16087	24075, 32063, 40051, 48039, 56027
7945	zinc finger, DHHC-type containing 20	415724	8100	401232	16088	24076, 32064, 40052, 48040, 56028
7946	zinc finger, DHHC-type containing 20	422251	8101	396819	16089	24077, 32065, 40053, 48041, 56029
7947	zinc finger, DHHC-type containing 20	542645	8102	443236	16090	24078, 32066, 40054, 48042, 56030
7948	zinc finger, DHHC-type containing 21	380916	8103	370303	16091	24079, 32067, 40055, 48043, 56031
7949	zinc finger, DHHC-type containing 22	319374	8104	318222	16092	24080, 32068, 40056, 48044, 56032
7950	zinc finger, DHHC-type containing 22	555327	8105	450478	16093	24081, 32069, 40057, 48045, 56033
7951	zinc finger, DHHC-type containing 22	555389	8106	451337	16094	24082, 32070, 40058, 48046, 56034
7952	zinc finger, DHHC-type containing 23	330212	8107	330485	16095	24083, 32071, 40059, 48047, 56035
7953	zinc finger, DHHC-type containing 23	491556	8108	420292	16096	24084, 32072, 40060, 48048, 56036
7954	zinc finger, DHHC-type containing 24	310442	8109	309429	16097	24085, 32073, 40061, 48049, 56037
7955	zinc finger, DHHC-type containing 3	296127	8110	296127	16098	24086, 32074, 40062, 48050, 56038
7956	zinc finger, DHHC-type containing 3	339420	8111	404108	16099	24087, 32075, 40063, 48051, 56039
7957	zinc finger, DHHC-type containing 3	424952	8112	395502	16100	24088, 32076, 40064, 48052, 56040
7958	zinc finger, DHHC-type containing 4	335965	8113	337475	16101	24089, 32077, 40065, 48053, 56041
7959	zinc finger, DHHC-type containing 4	396706	8114	379934	16102	24090, 32078, 40066, 48054, 56042
7960	zinc finger, DHHC-type containing 4	396707	8115	379935	16103	24091, 32079, 40067, 48055, 56043

7961	zinc finger, DHHC-type containing 4	396709	8116	379937	16104	24092, 32080, 40068, 48056, 56044
7962	zinc finger, DHHC-type containing 4	396713	8117	379941	16105	24093, 32081, 40069, 48057, 56045
7963	zinc finger, DHHC-type containing 4	405731	8118	385027	16106	24094, 32082, 40070, 48058, 56046
7964	zinc finger, DHHC-type containing 4	483589	8119	418496	16107	24095, 32083, 40071, 48059, 56047
7965	zinc finger, DHHC-type containing 5	287169	8120	287169	16108	24096, 32084, 40072, 48060, 56048
7966	zinc finger, DHHC-type containing 5	527985	8121	432202	16109	24097, 32085, 40073, 48061, 56049
7967	zinc finger, DHHC-type containing 6	369404	8122	358412	16110	24098, 32086, 40074, 48062, 56050
7968	zinc finger, DHHC-type containing 6	369405	8123	358413	16111	24099, 32087, 40075, 48063, 56051
7969	zinc finger, DHHC-type containing 7	313732	8124	315604	16112	24100, 32088, 40076, 48064, 56052
7970	zinc finger, DHHC-type containing 7	344861	8125	341681	16113	24101, 32089, 40077, 48065, 56053
7971	zinc finger, FYVE domain containing 16	338008	8126	337159	16114	24102, 32090, 40078, 48066, 56054
7972	zinc finger, FYVE domain containing 16	505560	8127	426848	16115	24103, 32091, 40079, 48067, 56055
7973	zinc finger, FYVE domain containing 16	510158	8128	423663	16116	24104, 32092, 40080, 48068, 56056
7974	zinc finger, FYVE domain containing 20	253699	8129	253699	16117	24105, 32093, 40081, 48069, 56057
7975	zinc finger, FYVE domain containing 20	418832	8130	389567	16118	24106, 32094, 40082, 48070, 56058
7976	zinc finger, FYVE domain containing 20	435849	8131	391039	16119	24107, 32095, 40083, 48071, 56059
7977	zinc finger, FYVE domain containing 20	476527	8132	422551	16120	24108, 32096, 40084, 48072, 56060
7978	zinc finger, FYVE domain containing 20	507357	8133	427038	16121	24109, 32097, 40085, 48073, 56061

7979	zinc finger, FYVE domain containing 9	287727	8134	287727	16122	24110, 32098, 40086, 48074, 56062
7980	zinc finger, FYVE domain containing 9	357206	8135	349737	16123	24111, 32099, 40087, 48075, 56063
7981	zinc finger, FYVE domain containing 9	361625	8136	355358	16124	24112, 32100, 40088, 48076, 56064
7982	zinc finger, FYVE domain containing 9	371591	8137	360647	16125	24113, 32101, 40089, 48077, 56065
7983	zinc fingers and homeoboxes 2	314393	8138	314709	16126	24114, 32102, 40090, 48078, 56066
7984	zinc fingers and homeoboxes 2	534247	8139	452720	16127	24115, 32103, 40091, 48079, 56067
7985	ZMYM6 neighbor	373337	8140	362435	16128	24116, 32104, 40092, 48080, 56068
7986	zona pellucida-like domain containing 1	306176	8141	307801	16129	24117, 32105, 40093, 48081, 56069
7987	zona pellucida-like domain containing 1	466937	8142	418253	16130	24118, 32106, 40094, 48082, 56070
7988	zona pellucida-like domain containing 1	491959	8143	420265	16131	24119, 32107, 40095, 48083, 56071

[000230] In one embodiment, the polypeptide of interest is a plasma membrane protein. As a non-limiting example, the polynucleotides, primary constructs and/or mmRNA may encode a plasma membrane protein such as, but not limited to any of SEQ ID NOs: 8144, 8145, 8146, 8147, 8148, 8155, 8156, 8163, 8178, 8179, 8180, 8181, 8182, 8183, 8185, 8186, 8189, 8190, 8191, 8192, 8195, 8196, 8197, 8200, 8202, 8204, 8211, 8212, 8216, 8218, 8223, 8231, 8232, 8233, 8236, 8237, 8239, 8240, 8241, 8242, 8248, 8249, 8250, 8251, 8252, 8253, 8254, 8255, 8256, 8257, 8258, 8259, 8260, 8262, 8264, 8265, 8266, 8267, 8268, 8275, 8280, 8281, 8282, 8283, 8284, 8285, 8286, 8287, 8288, 8290, 8292, 8293, 8308, 8309, 8310, 8311, 8312, 8314, 8315, 8316, 8319, 8320, 8322, 8323, 8327, 8328, 8329, 8333, 8338, 8339, 8340, 8341, 8343, 8349, 8350, 8351, 8355, 8357, 8358, 8359, 8360, 8361, 8362, 8363, 8364, 8365, 8366, 8369, 8371, 8372, 8379, 8381, 8387, 8391, 8392, 8395, 8396, 8402, 8407, 8408, 8409, 8410, 8411, 8412, 8414, 8419, 8422, 8423, 8425, 8426, 8427, 8430, 8431, 8433, 8435, 8440, 8441, 8445, 8446, 8447, 8448,

8449, 8450, 8452, 8453, 8454, 8455, 8458, 8459, 8462, 8463, 8464, 8467, 8468, 8469, 8470, 8472, 8474, 8475, 8476, 8479, 8480, 8481, 8488, 8489, 8490, 8497, 8504, 8506, 8510, 8511, 8512, 8514, 8518, 8520, 8521, 8522, 8523, 8525, 8527, 8529, 8530, 8531, 8532, 8540, 8543, 8545, 8546, 8547, 8548, 8549, 8551, 8554, 8557, 8558, 8561, 8563, 8564, 8565, 8566, 8568, 8569, 8570, 8571, 8572, 8573, 8575, 8576, 8577, 8578, 8580, 8581, 8583, 8588, 8589, 8594, 8596, 8597, 8599, 8601, 8602, 8604, 8606, 8609, 8612, 8615, 8618, 8620, 8622, 8625, 8632, 8635, 8636, 8637, 8638, 8639, 8643, 8645, 8651, 8652, 8655, 8656, 8657, 8658, 8659, 8661, 8663, 8669, 8670, 8672, 8683, 8695, 8701, 8703, 8704, 8705, 8706, 8711, 8712, 8713, 8714, 8717, 8722, 8723, 8724, 8725, 8727, 8729, 8731, 8733, 8734, 8736, 8739, 8749, 8750, 8751, 8752, 8753, 8754, 8755, 8757, 8758, 8760, 8761, 8762, 8764, 8765, 8766, 8767, 8768, 8770, 8772, 8773, 8774, 8775, 8779, 8780, 8782, 8784, 8786, 8787, 8788, 8789, 8790, 8791, 8793, 8794, 8795, 8796, 8799, 8801, 8803, 8804, 8814, 8815, 8817, 8818, 8819, 8820, 8822, 8824, 8825, 8826, 8827, 8833, 8834, 8836, 8839, 8841, 8842, 8844, 8846, 8847, 8852, 8855, 8856, 8867, 8868, 8869, 8870, 8872, 8875, 8876, 8877, 8879, 8881, 8882, 8884, 8888, 8891, 8892, 8893, 8895, 8896, 8897, 8898, 8905, 8907, 8908, 8909, 8910, 8911, 8912, 8913, 8917, 8919, 8921, 8922, 8923, 8924, 8927, 8931, 8932, 8934, 8936, 8937, 8938, 8939, 8940, 8941, 8942, 8943, 8944, 8946, 8947, 8948, 8949, 8953, 8956, 8959, 8961, 8963, 8964, 8965, 8966, 8974, 8977, 8978, 8981, 8985, 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, 9018, 9020, 9024, 9026, 9027, 9028, 9029, 9030, 9033, 9036, 9038, 9040, 9042, 9052, 9053, 9054, 9059, 9062, 9065, 9069, 9071, 9073, 9074, 9075, 9076, 9077, 9090, 9091, 9092, 9096, 9101, 9102, 9103, 9104, 9106, 9108, 9110, 9115, 9118, 9123, 9127, 9129, 9130, 9131, 9132, 9135, 9136, 9137, 9138, 9139, 9140, 9141, 9142, 9143, 9146, 9148, 9149, 9151, 9152, 9153, 9154, 9155, 9156, 9157, 9158, 9162, 9163, 9164, 9166, 9167, 9168, 9169, 9194, 9195, 9196, 9197, 9198, 9203, 9204, 9208, 9210, 9216, 9217, 9218, 9220, 9221, 9224, 9225, 9229, 9231, 9235, 9240, 9241, 9242, 9243, 9244, 9245, 9246, 9248, 9250, 9251, 9252, 9253, 9254, 9260, 9265, 9266, 9267, 9269, 9271, 9275, 9278, 9279, 9281, 9282, 9283, 9284, 9285, 9289, 9292, 9293, 9305, 9306, 9310, 9311, 9313, 9314, 9321, 9323, 9324, 9329, 9330, 9332, 9333, 9337, 9338, 9339, 9340, 9342, 9343, 9344, 9345, 9346, 9348, 9350, 9351,

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[000231] In one embodiment, the polypeptide of interest is an intracellular membrane protein. As a non-limiting example, the polynucleotides, primary constructs and/or mmRNA may encode an intracellular membrane bound protein such as, but not limited to, any of SEQ ID NOs: 8166, 8167, 8168, 8169, 8171, 8173, 8174, 8176, 8199, 8205, 8206, 8207, 8210, 8220, 8221, 8222, 8271, 8277, 8278, 8279, 8297, 8303, 8306, 8324, 8326, 8334, 8336, 8337, 8429, 8443, 8483, 8484, 8485, 8486, 8487, 8491, 8492, 8493,

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[000232] In one embodiment, the polypeptide of interest is a plasma membrane protein or an intracellular membrane protein. As a non-limiting example, the polynucleotides, primary constructs and/or mmRNA may encode a plasma membrane protein or an intracellular membrane protein such as, but not limited to, any of SEQ ID NOs: 8144-16131.

Protein Cleavage Signals and Sites

[000233] 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.

[000234] 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: 56140 refers to when n=4 and SEQ ID NO: 56141 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*	56138
	R-X-K/R-R*	56139
	K/R-Xn-K/R*	56140 or 56141

Thrombin	L-V-P-R*-G-S	56142
	L-V-P-R*	56143
	A/F/G/I/L/T/V/M-A/F/G/I/L/T/V/W-P-R*	56144
Factor Xa	I-E-G-R*	56145
	I-D-G-R*	56146
	A-E-G-R*	56147
	A/F/G/I/L/T/V/M-D/E-G-R*	56148

[000235] 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.

[000236] 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.

[000237] In one embodiment, the polypeptides of the present invention include at least one protein cleavage signal and/or site.

[000238] 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.

[000239] In one embodiment, the primary constructs or mmRNA of the present invention includes at least one encoded protein cleavage signal and/or site.

[000240] 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.

[000241] 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.

[000242] 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.

[000243] 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

[000244] 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.

[000245] 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.

[000246] 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

[000247] 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).

[000248] 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.

[000249] 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

[000250] 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)

[000251] 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.

[000252] 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.

[000253] 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.

[000254] 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).

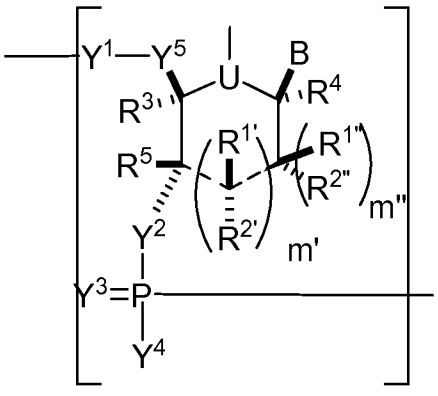
[000255] The polynucleotides, primary constructs, and mmRNA can optionally include other agents (e.g., RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc.). In some embodiments, the 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.

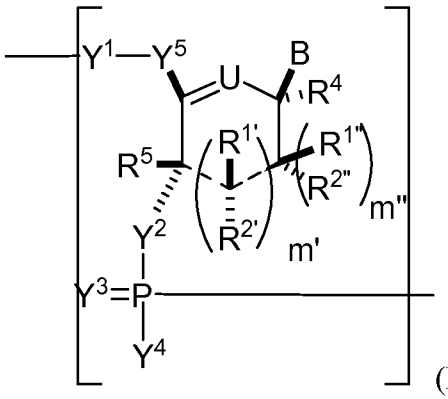
Polynucleotides and Primary Constructs

[000256] 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.

[000257] 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,

[000258] wherein

[000259] 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;

[000260] --- is a single bond or absent;

[000261] 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);

[000262] 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;

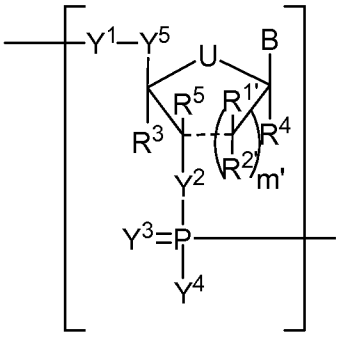
[000263] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000264] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

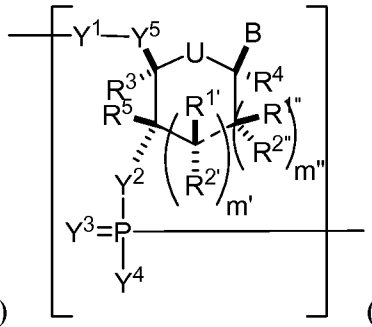
[000265] n is an integer from 1 to 100,000; and

[000266] 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

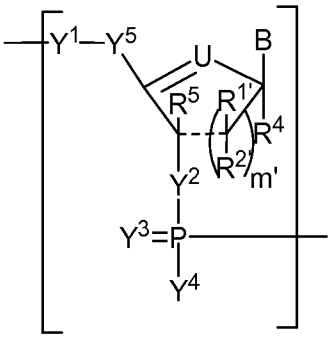
the combination of B, $R^{1"}$, and R^3 or the combination of B, $R^{2"}$, and R^3 can optionally form a tricyclic or tetracyclic group (e.g., a tricyclic or tetracyclic heterocyclyl, such as in Formula (IIo)-(IIp) herein).In some embodiments, the polynucleotide, primary construct, or mmRNA includes 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.



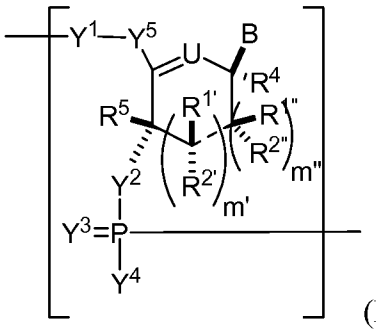
(Ia-2)



(Ia-3)

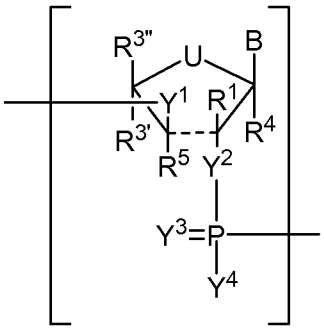


(Ia-4),

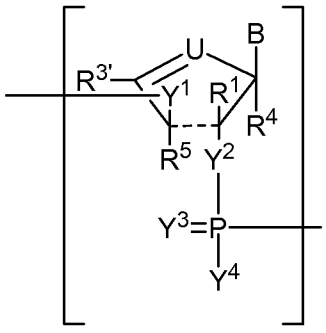


(Ia-5).

[000267] 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,

[000268] wherein

[000269] 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;

[000270] --- is a single bond or absent;

[000271] 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);

[000272] 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;

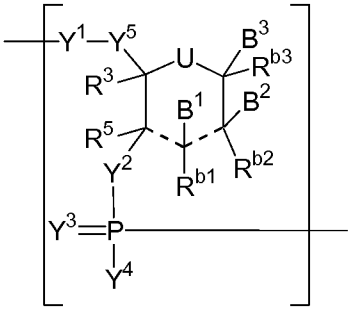
[000273] each of Y^1, Y^2, and Y^3 is, independently, O, S, Se, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted aryl;

[000274] 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;

[000275] n is an integer from 1 to 100,000; and

[000276] B is a nucleobase.

[000277] 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,

[000278] wherein

[000279] 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;

[000280] --- is a single bond or absent;

[000281] 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;

[000282] 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;

[000283] 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;

[000284] 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;

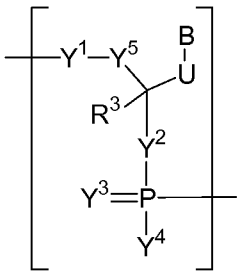
[000285] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000286] n is an integer from 1 to 100,000; and

[000287] wherein the ring including U can include one or more double bonds.

[000288] In particular embodiments, the ring including U does not have a double bond between U-CB^3R^{b3} or between CB^3R^{b3}-$C^{B2}R^{b2}$.

[000289] 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,

[000290] wherein

[000291] 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;

[000292] 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;

[000293] 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;

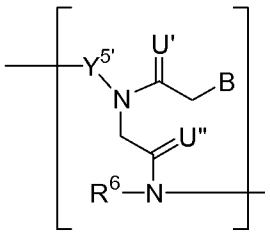
[000294] each Y^4 is, independently, H, hydroxy, thiol, boranyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted thioalkoxy, optionally substituted alkoxyalkoxy, or optionally substituted amino;

[000295] each Y^5 is, independently, O, S, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000296] n is an integer from 1 to 100,000; and

[000297] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000298] 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,

[000299] wherein

[000300] 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;

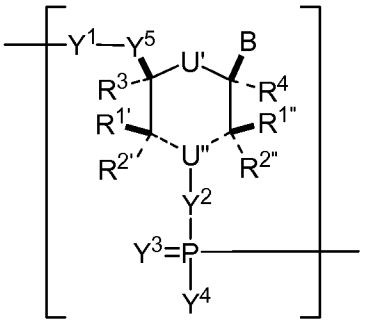
[000301] each R^6 is, independently, H, halo, hydroxy, thiol, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy, optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted hydroxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, or optionally substituted aminoalkynyl;

[000302] each $Y^{5'}$ is, independently, O, S, optionally substituted alkylene (e.g., methylene or ethylene), or optionally substituted heteroalkylene;

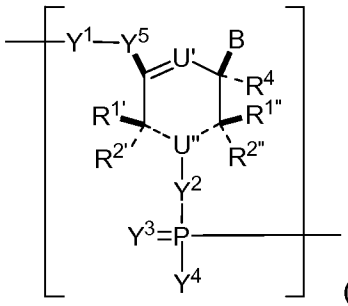
[000303] n is an integer from 1 to 100,000; and

[000304] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000305] 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,

[000306] wherein

[000307] 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);

[000308] --- is a single bond or absent;

[000309] 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);

[000310] 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;

[000311] 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;

[000312] each Y^5 is, independently, O, S, Se, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene;

[000313] n is an integer from 1 to 100,000; and

[000314] B is a nucleobase (e.g., a purine, a pyrimidine, or derivatives thereof).

[000315] 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.

[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)), 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.

[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)), 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.

[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)), 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.

[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)), 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).

[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)), 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).

[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^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).

[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 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).

[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)), each Y^3 is, independently, O or S.

[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)), 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.

[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)), 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.

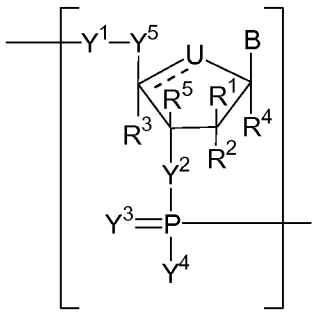
[000326] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), the ring including U is in the β-D (e.g., β-D-ribo) configuration.

[000327] 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.

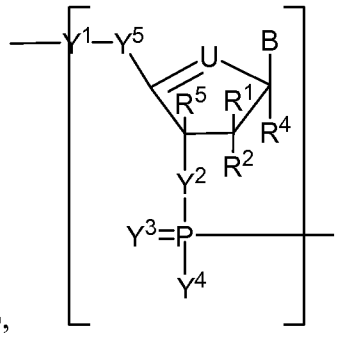
[000328] In some embodiments of the polynucleotides, primary constructs, or mmRNA (e.g., Formulas (Ia)-(Ia-5), (Ib)-(If-1), (IIa)-(IIp), (IIb-1), (IIb-2), (IIc-1)-(IIc-2), (IIn-1), (IIn-2), (IVa)-(IVl), and (IXa)-(IXr)), one or more B is not pseudouridine (ψ) or 5-methyl-cytidine (m^5C). In some embodiments, 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.

[000329] 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.

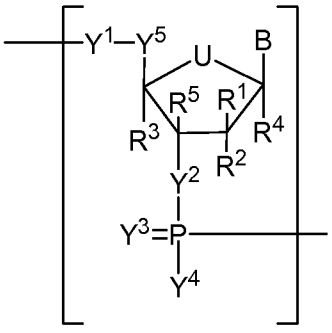
[000330] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IIa)-(IIc):



(IIa),

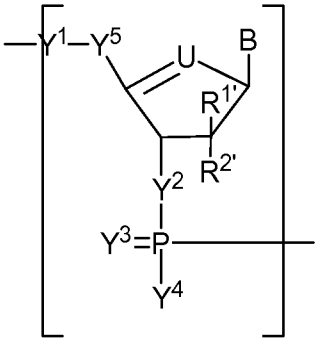


(IIb), or

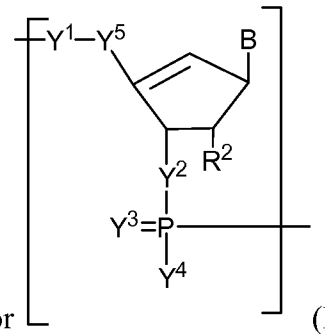


(IIc), or a pharmaceutically acceptable salt or stereoisomer thereof. In particular embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In other embodiments, each of R^1, R^2, 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.

[000331] In particular embodiments, the polynucleotidesor mmRNA includes n number of linked nucleosides having Formula (IIb-1)-(IIb-2):

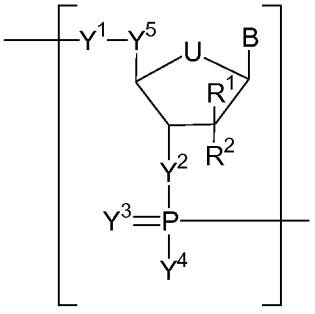


(IIb-1) or

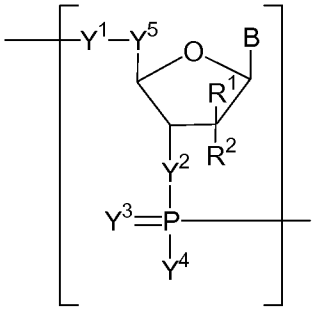


(IIb-2) or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In other embodiments, each of R^1 and R^2 is, 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).

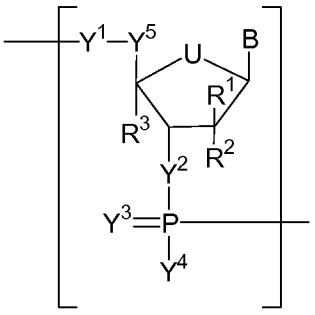
[000332] In particular embodiments, the polynucleotide, primary construct, or mmRNA includes n number of linked nucleosides having Formula (IIc-1)-(IIc-4):



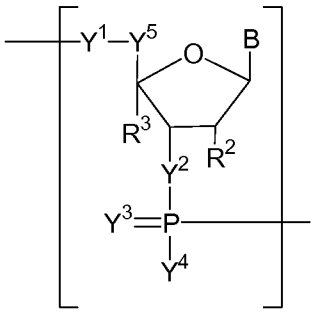
(IIc-1),



(IIc-2),

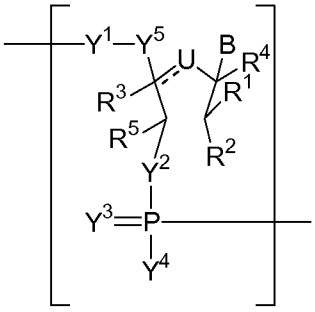
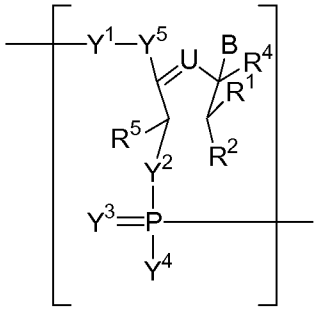
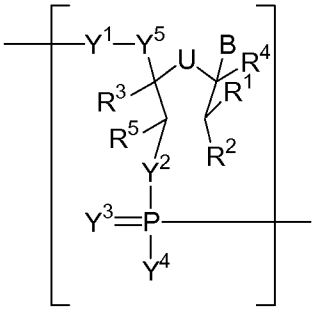


(IIc-3), or



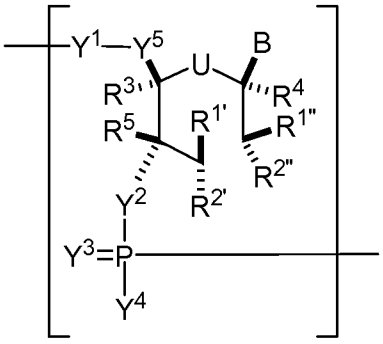
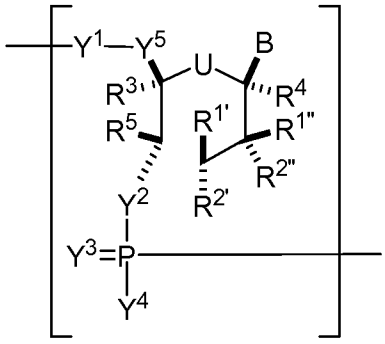
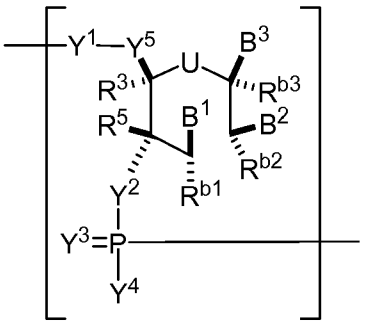
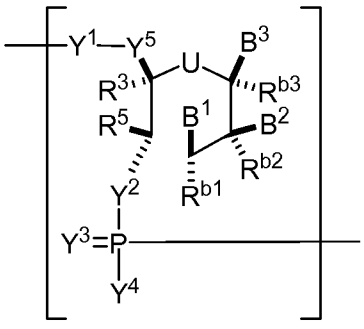
(IIc-4), or a pharmaceutically acceptable salt or stereoisomer thereof. In some embodiments, U is O or $C(R^U)_{nu}$, wherein nu is an integer from 0 to 2 and each R^U is, independently, H, halo, or optionally substituted alkyl (e.g., U is $–CH_2–$ or –CH–). In some embodiments, each of R^1, R^2, and 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.

[000333] 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


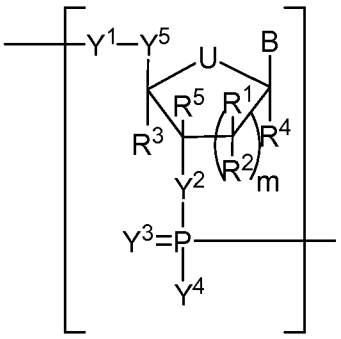
(IIf), or a pharmaceutically acceptable salt or stereoisomer thereof.

[000334] 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):

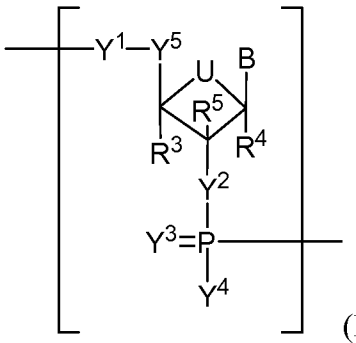

(IIg),

(IIh),

(IIi), or

(IIj), or a pharmaceutically acceptable salt or stereoisomer thereof.

[000335] 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

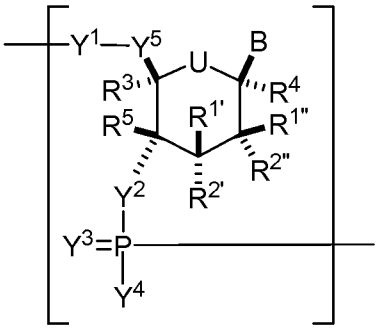
(IIk)-(IIm):



(IIk),

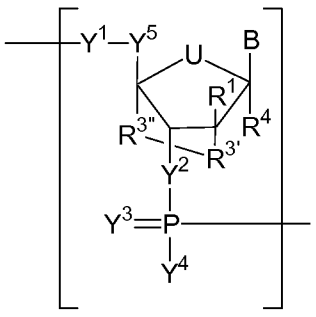


(III), or



(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.

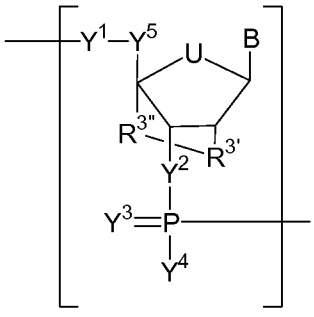
[000336] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a locked modified ribose. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) includes n number of linked nucleosides having Formula (IIn):



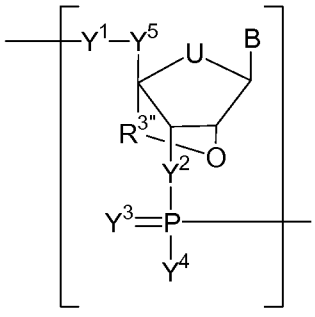
(IIn), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein $R^{3'}$ is O, S, or $-NR^{N1}-$, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted

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 $-CH_2CH_2CH_2-$)).

[000337] In some embodiments, the polynucleotide, primary construct, or mmRNA includes n number of linked nucleosides having Formula (IIn-1)-(II-n2):

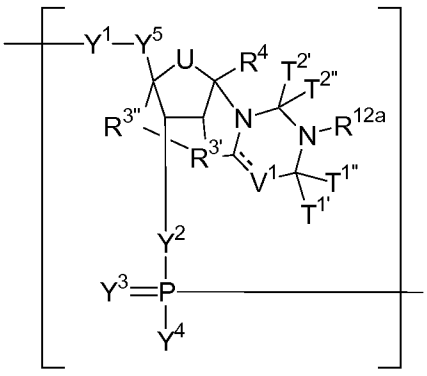
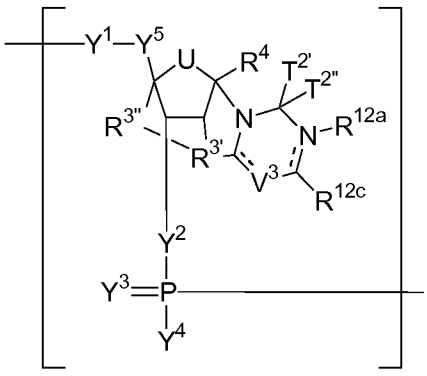


(IIn-1) or



(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 $-CH_2CH_2CH_2-$)).

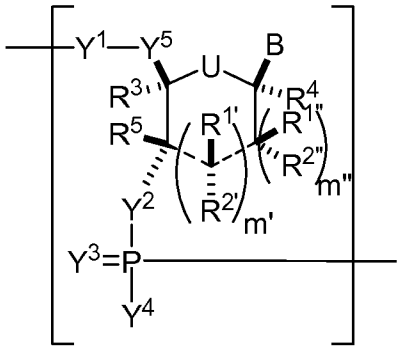
[000338] In some embodiments, the polynucleotide, primary construct, or mmRNA includes a locked modified ribose that forms a tetracyclic heterocyclyl. In some embodiments, the polynucleotide, primary construct, or mmRNA (e.g., the first region, the first flanking region, or the second flanking region) 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.

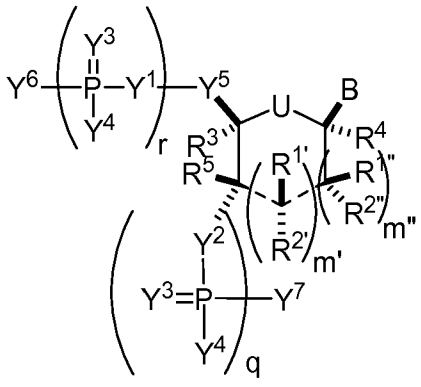
[000339] Any of the formulas for the polynucleotides, primary constructs, or mmRNA can include one or more nucleobases described herein (e.g., Formulas (b1)-(b43)).

[000340] 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:

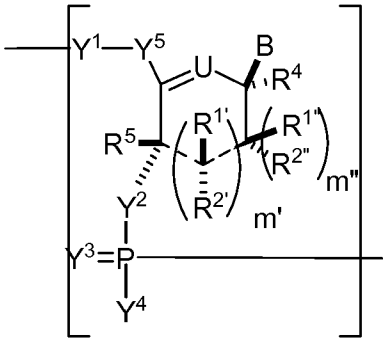


(IIIa),

with an RNA polymerase, and a cDNA template.

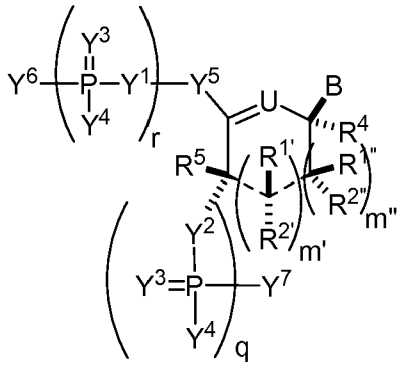
[000341] In a further embodiment, the present invention provides methods of amplifying a polynucleotide, primary construct, or mmRNA comprising at least one nucleotide (e.g., mmRNA molecule), the method comprising: reacting a compound of Formula (IIIa), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

[000342] 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:



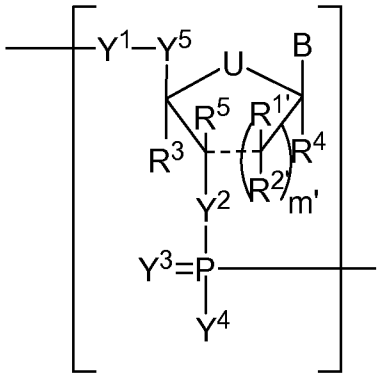
(IIIa-1),

with an RNA polymerase, and a cDNA template.

[000343] 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:

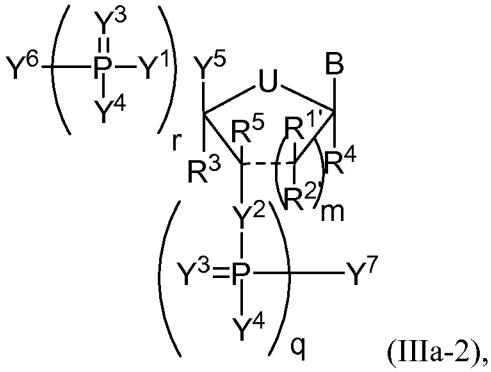
[000344] reacting a compound of Formula (IIIa-1), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

[000345] 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.

[000346] 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:

[000347] reacting a compound of Formula (IIIa-2), as defined herein, with a primer, a cDNA template, and an RNA polymerase.

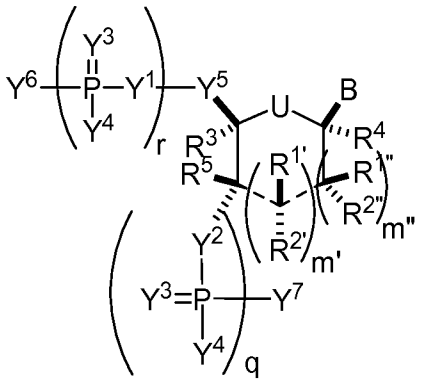
[000348] In some embodiments, the reaction may be repeated from 1 to about 7,000 times. In any of the embodiments herein, B may be a nucleobase of Formula (b1)-(b43).

[000349] The polynucleotides, primary constructs, and mmRNA can optionally include 5′ and/or 3′ flanking regions, which are described herein.

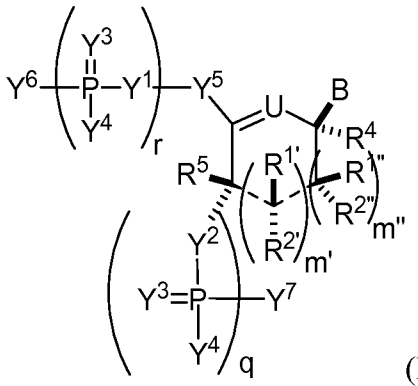
Modified RNA (mmRNA) Molecules

[000350] 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):

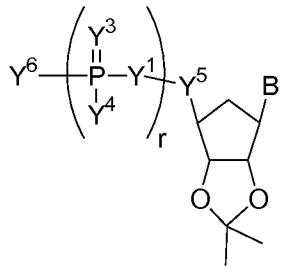


(IIIa),

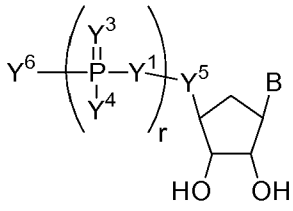


(IIIa-1) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the substituents are as described herein (e.g., for Formula (Ia) and (Ia-1)), and wherein when B is an unmodified nucleobase selected from cytosine, guanine, uracil and adenine, then at least one of Y^1, Y^2, or Y^3 is not O.

[000351] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IVa)-(IVb):



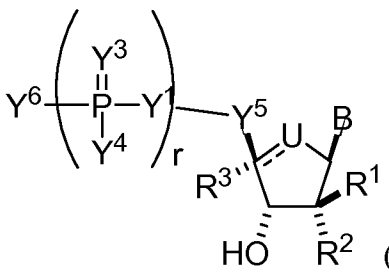
(IVa) or

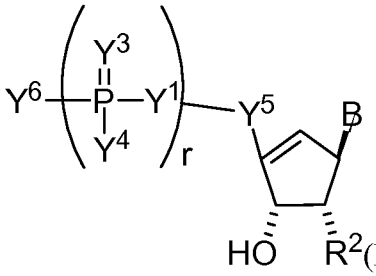


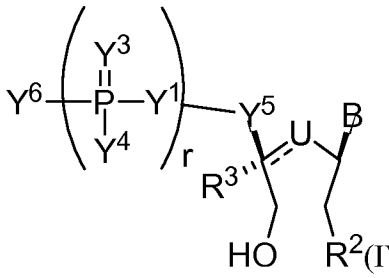
(IVb), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (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),

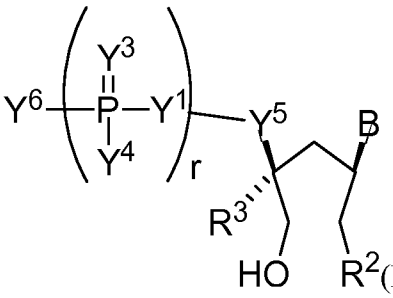
(b24), (b25), and (b32)-(b36), such as formula (b10) or (b32)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified guanine (e.g., any one of formulas (b15)-(b17) and (b37)-(b40)). In particular embodiments, Formula (IVa) or (IVb) is combined with a modified adenine (e.g., any one of formulas (b18)-(b20) and (b41)-(b43)).

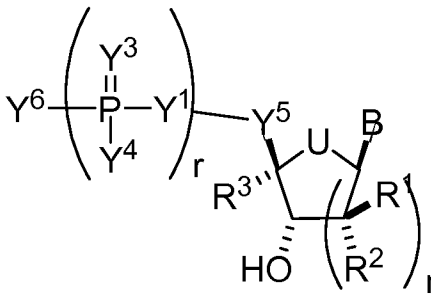
[000352] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IVc)-(IVk):

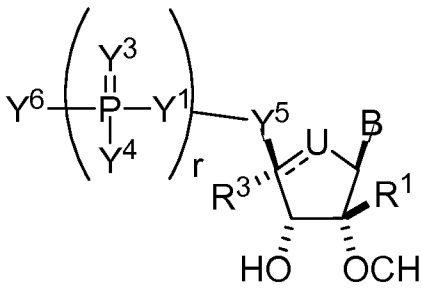

(IVc),

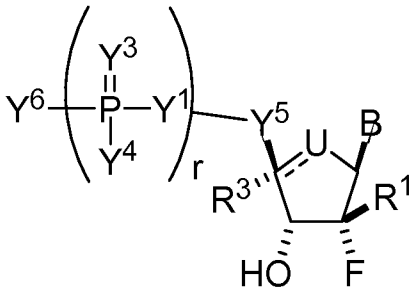

(IVd),

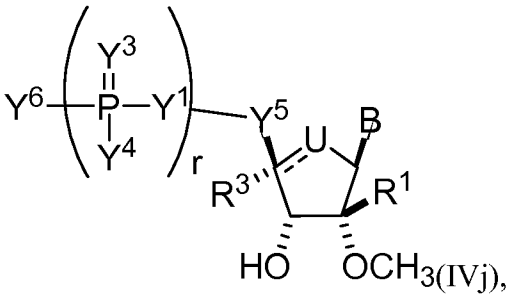

(IVe),

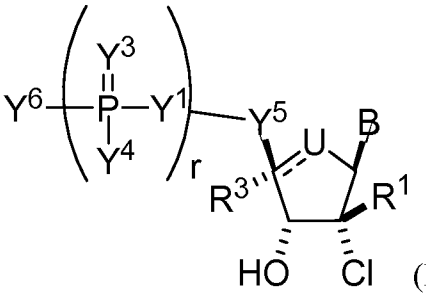

(IVf),


(IVg),

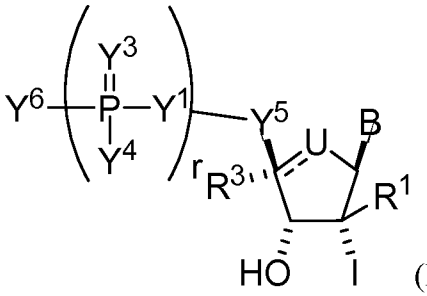

(IVh),


(IVi),


(IVj),

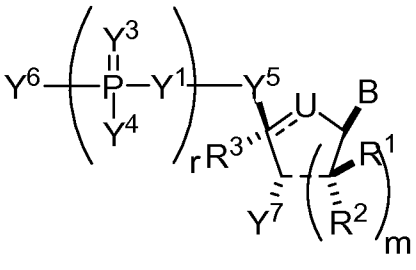


(IVk), or

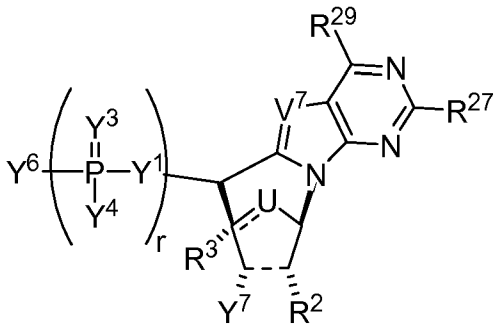


(IVl), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IVc)-(IVk) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (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)).

[000353] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (Va) or (Vb):

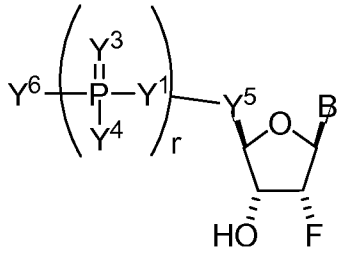


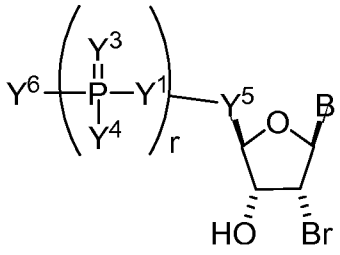
(Va) or

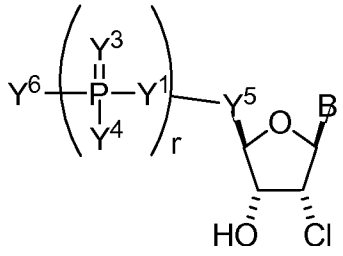


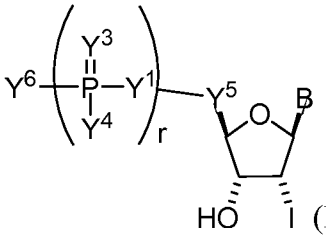
(Vb), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)).

[000354] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXa)-(IXd):

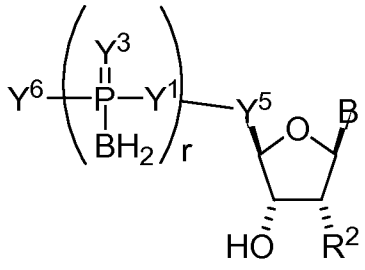

(IXa),

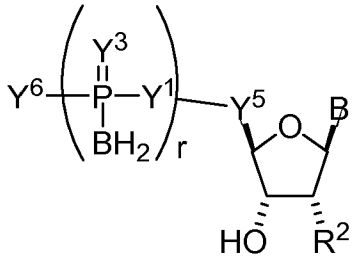

(IXb),

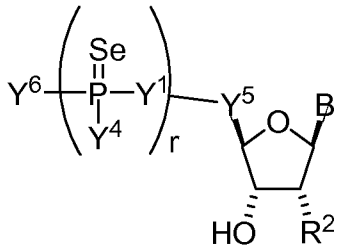

(IXc), or


(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)).

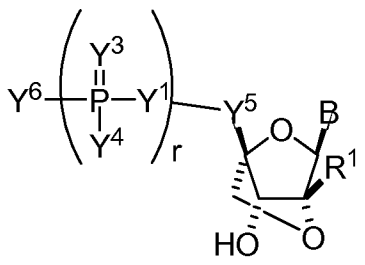
[000355] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXe)-(IXg):

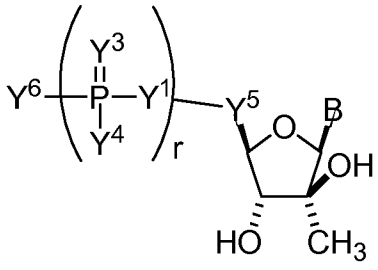

(IXe),

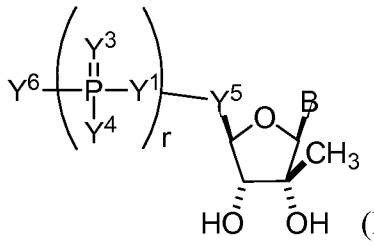

(IXf), or

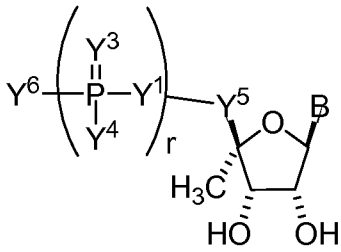

(IXg), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXe)-(IXg) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (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)).

[000356] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXh)-(IXk):


(IXh),

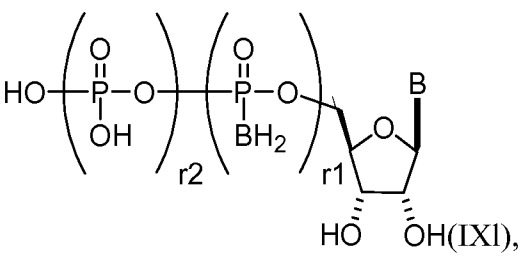

(IXi),

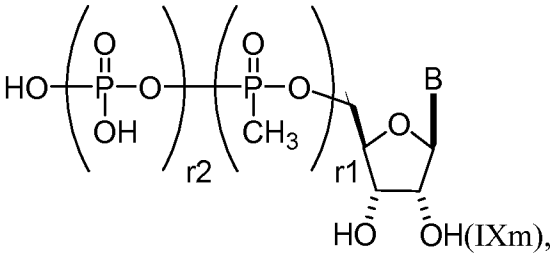

(IXj), or

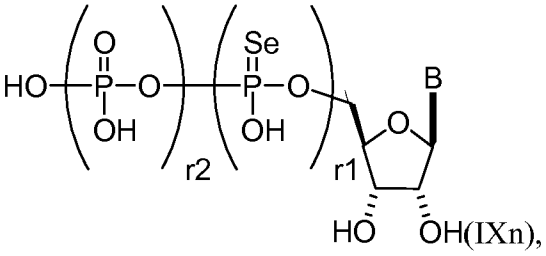

(IXk), or a

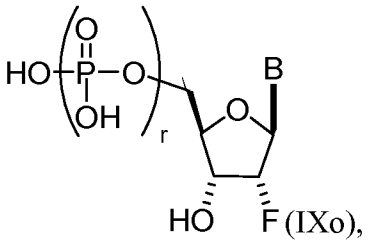
pharmaceutically acceptable salt or stereoisomer thereof, wherein B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXh)-(IXk) is combined with a modified uracil (e.g., any one of formulas (b1)-(b9), (b21)-(b23), and (b28)-(b31), such as formula (b1), (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)).

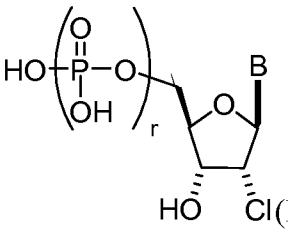
[000357] In other embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, has Formula (IXl)-(IXr):

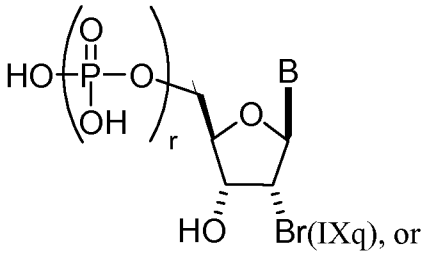


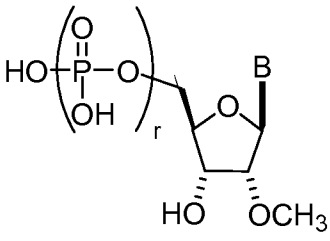






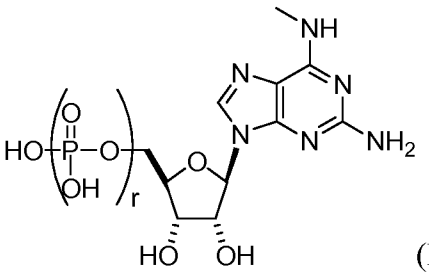




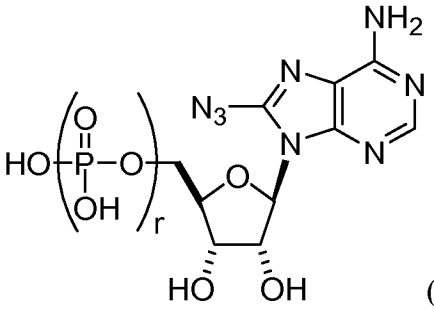


(IXr) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r1 and r2 is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5) and B is as described herein (e.g., any one of (b1)-(b43)). In particular embodiments, one of Formulas (IXl)-(IXr) is 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)).

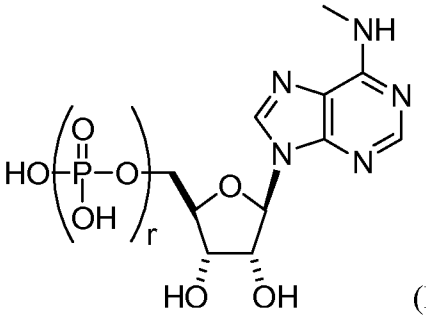
[000358] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be selected from the group consisting of:



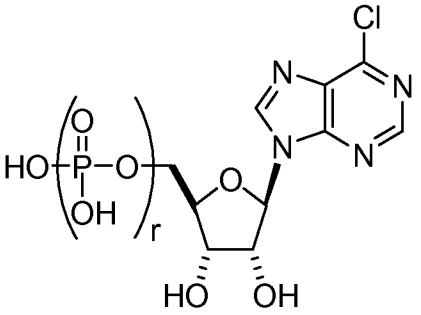
(BB- 1),



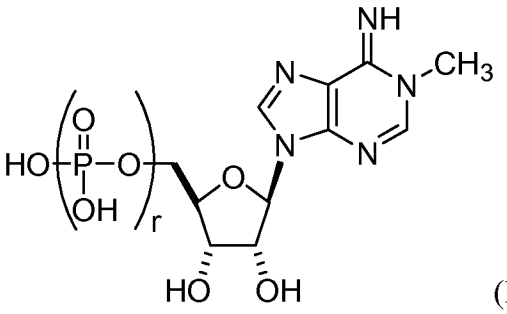
(BB- 2),



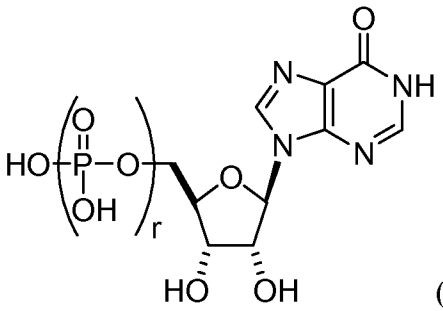
(BB- 3),



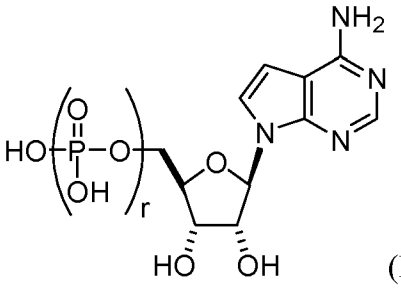
(BB- 4),



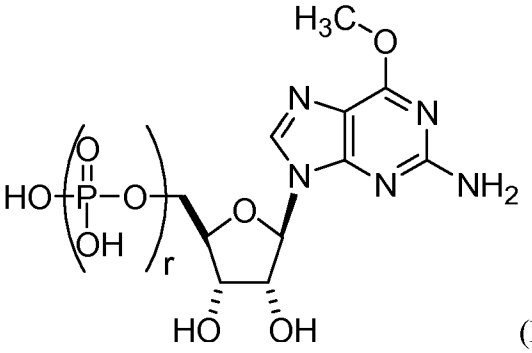
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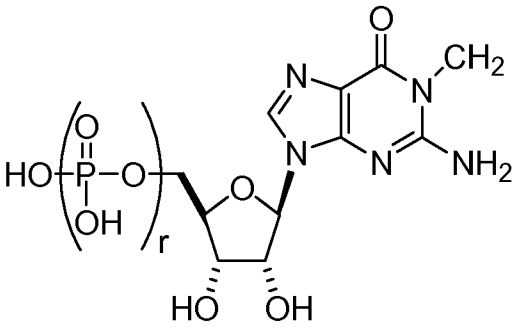
(BB- 6),



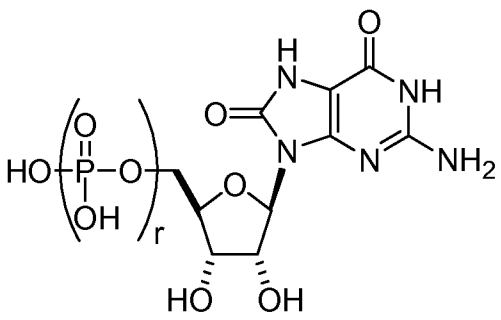
(BB- 7),

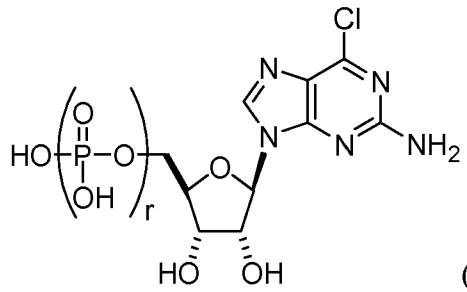


(BB- 8),

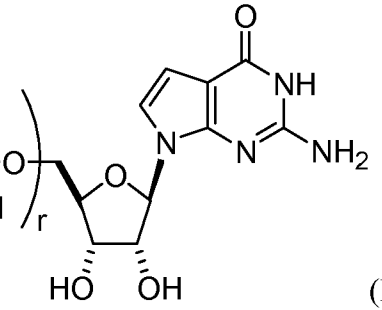


(BB- 9),





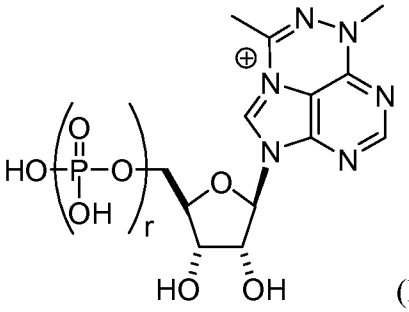
(BB- 10),



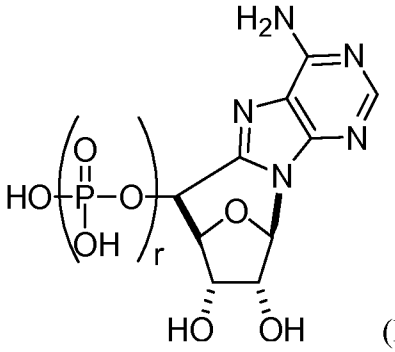
(BB- 11), and

(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).

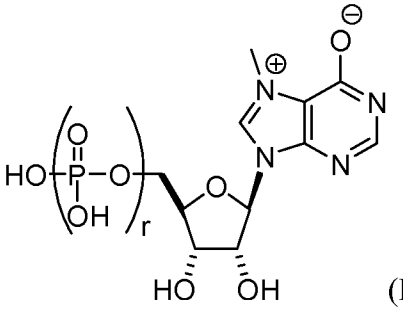
[000359] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be selected from the group consisting of:



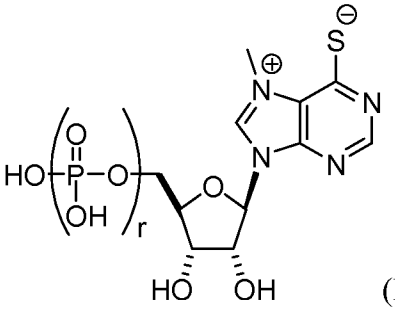
(BB- 13),



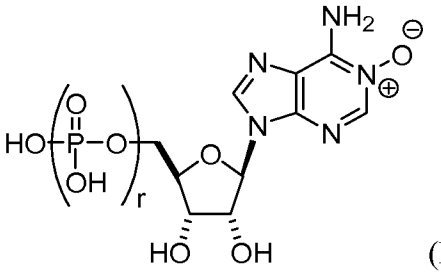
(BB- 14),



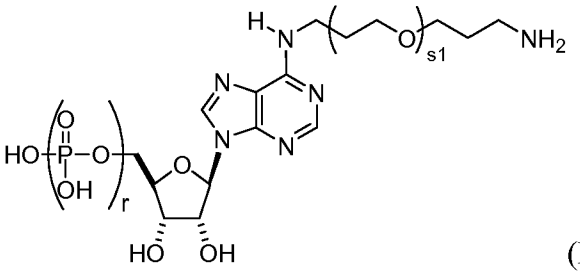
(BB- 15),



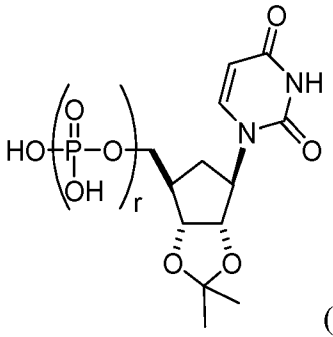
(BB- 16),



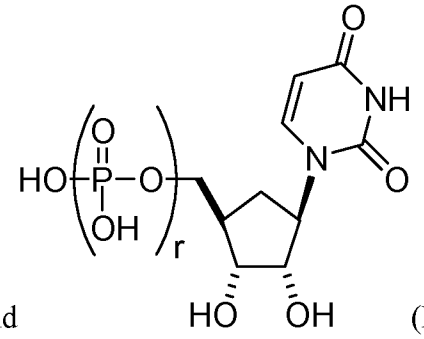
(BB- 17),



(BB- 18),



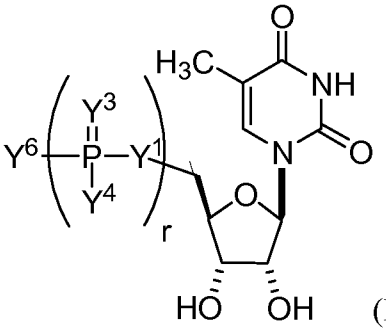
(BB- 19),



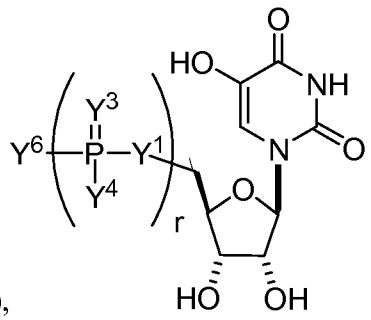
and (BB- 20), or a pharmaceutically acceptable salt or

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.

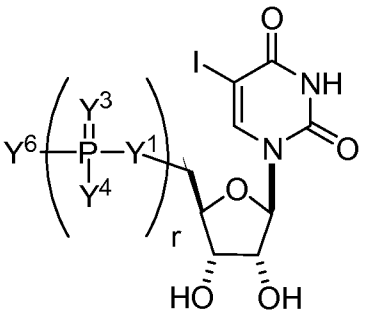
[000360] In some embodiments, the building block molecule, which may be incorporated into a nucleic acid (e.g., RNA, mRNA, polynucleotide, primary construct, or mmRNA), is a modified uridine (e.g., selected from the group consisting of:



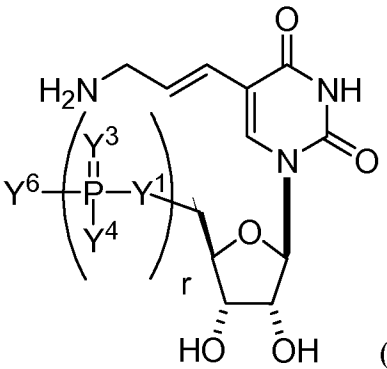
(BB- 21),



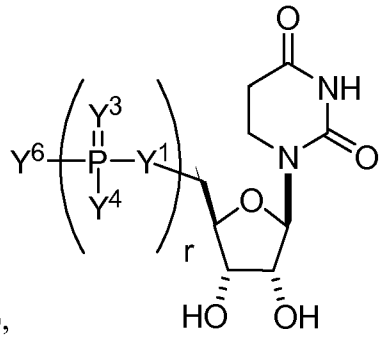
(BB- 22),



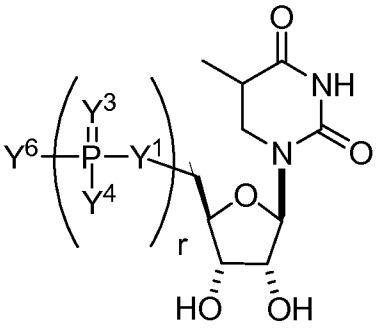
(BB- 23),



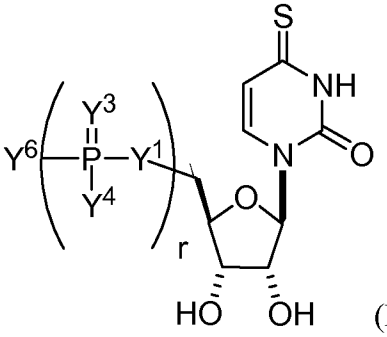
(BB- 24),



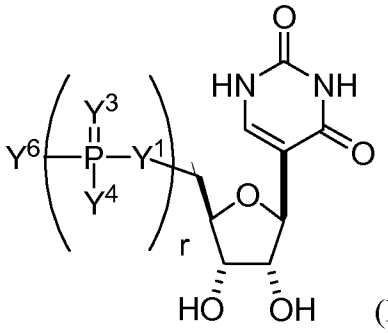
(BB- 25),



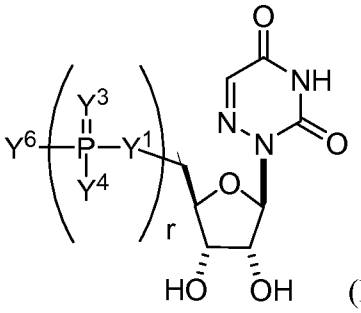
(BB- 26),



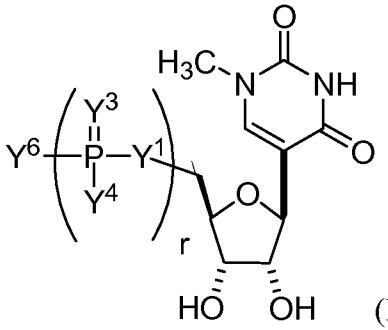
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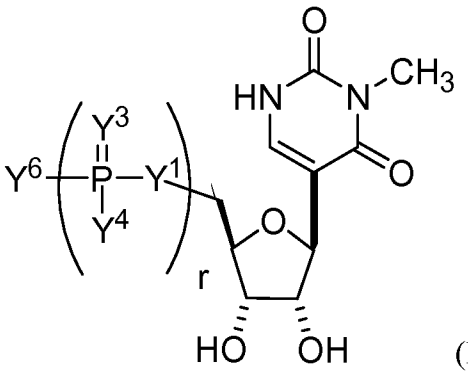
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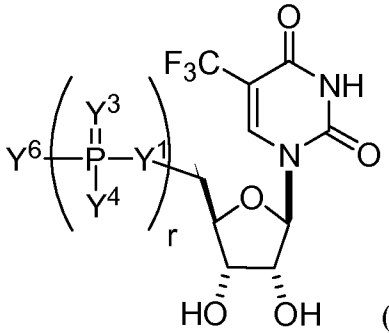
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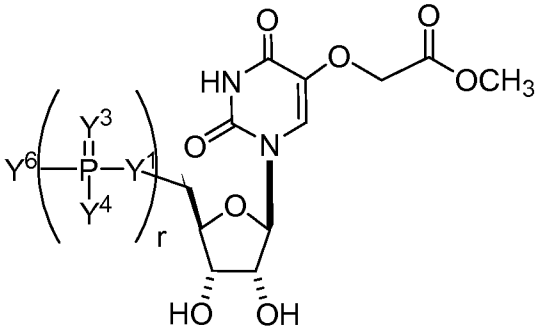
(BB- 30),



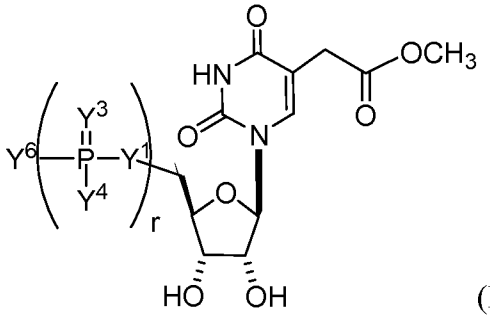
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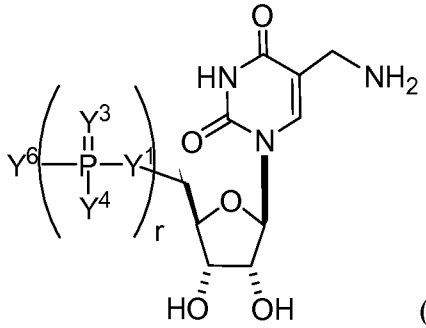
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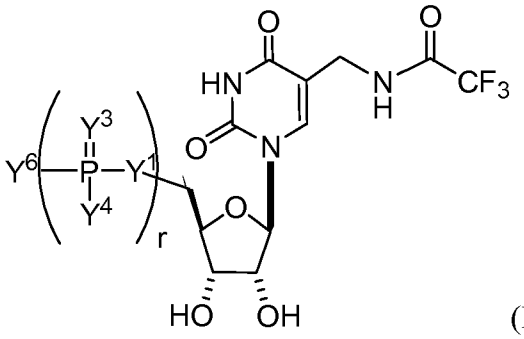
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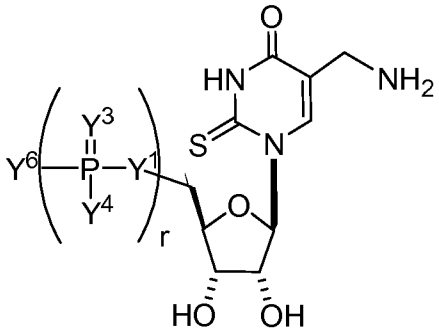
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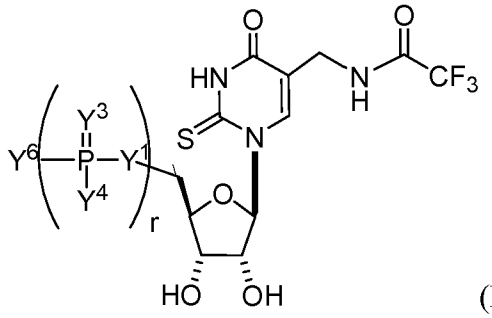
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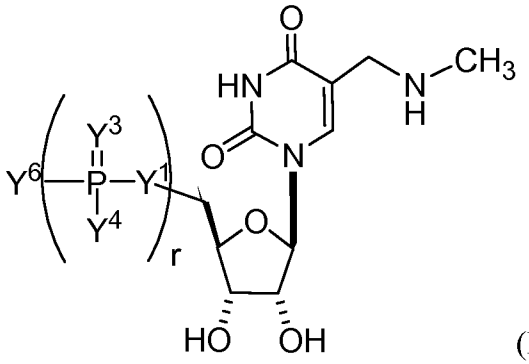
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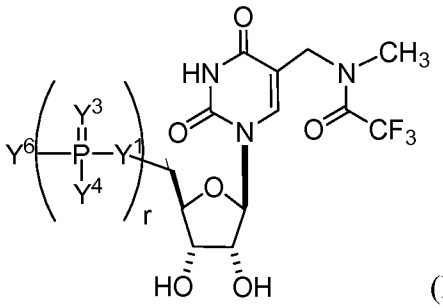
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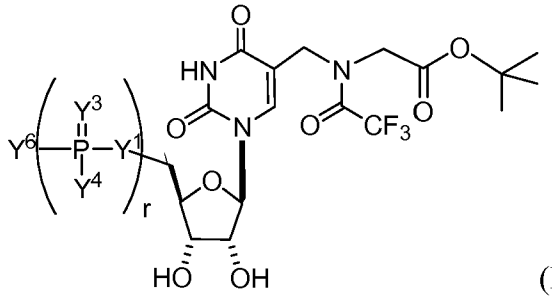
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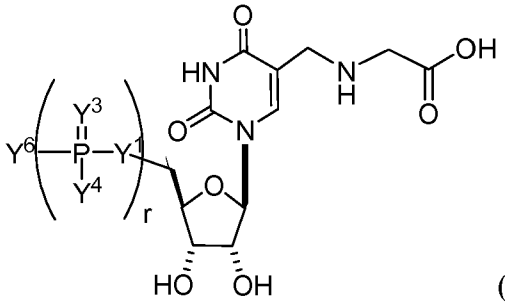
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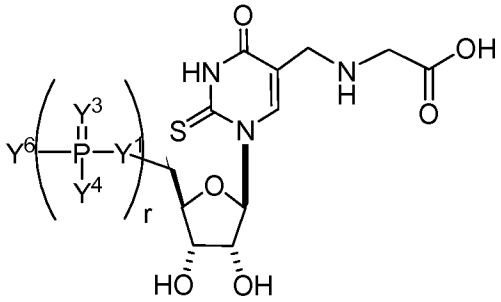
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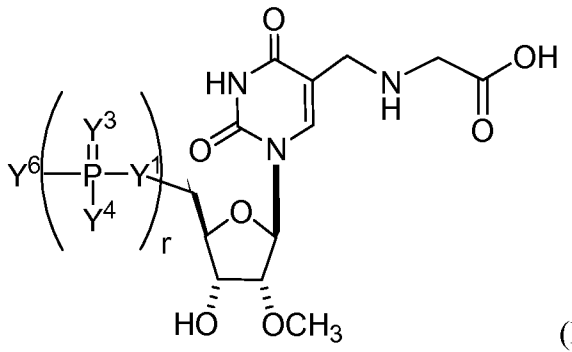
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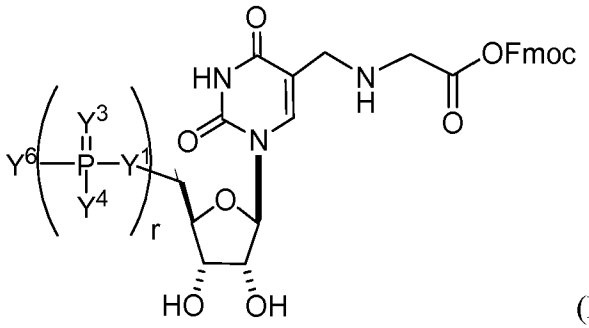
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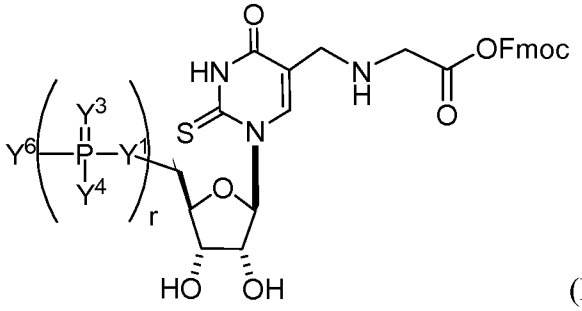
(BB- 42),



(BB- 43),

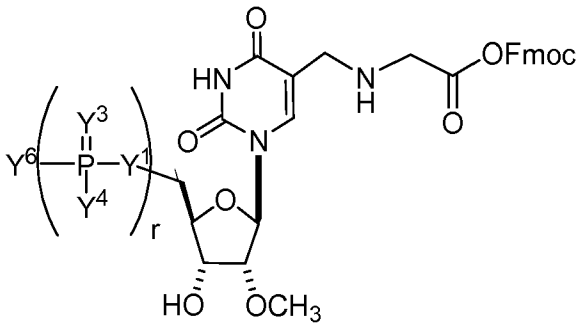


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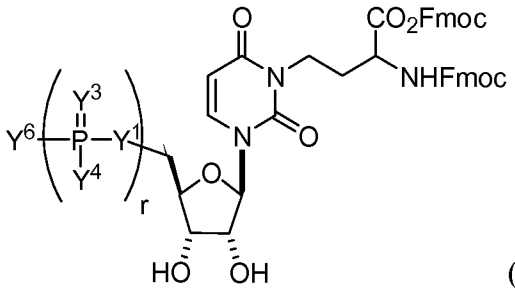


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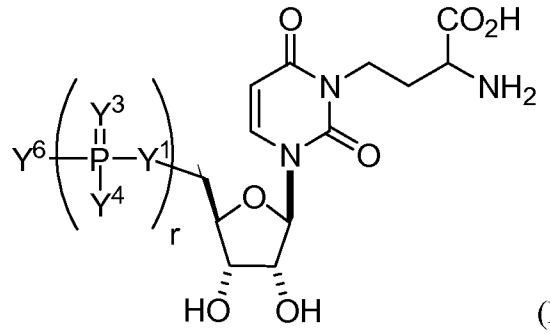
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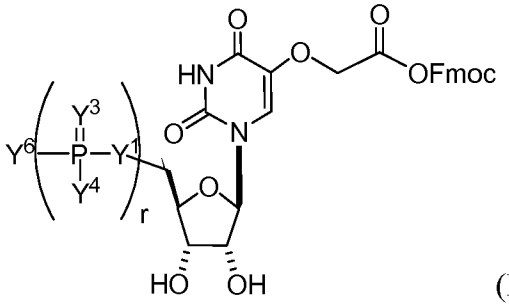
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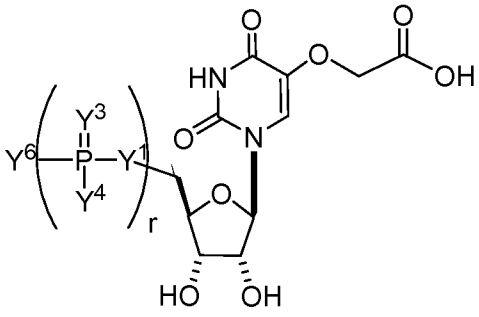
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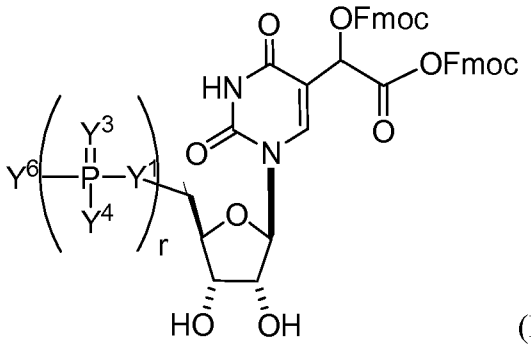


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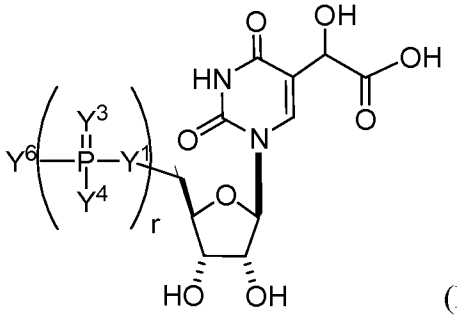
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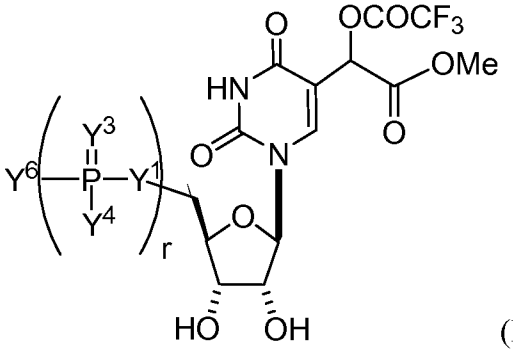


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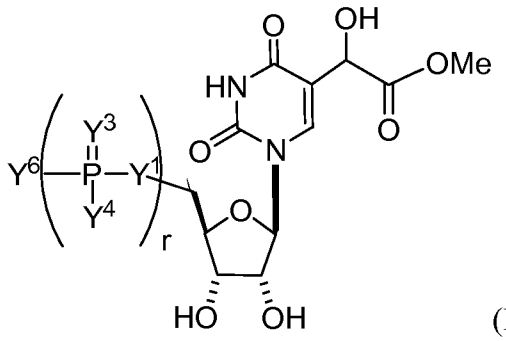
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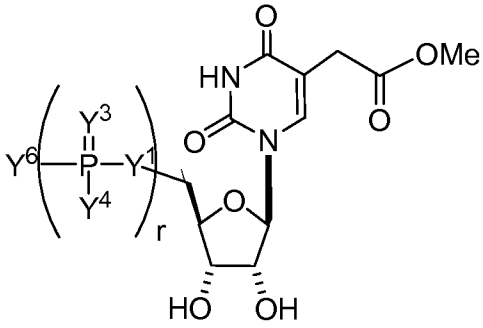
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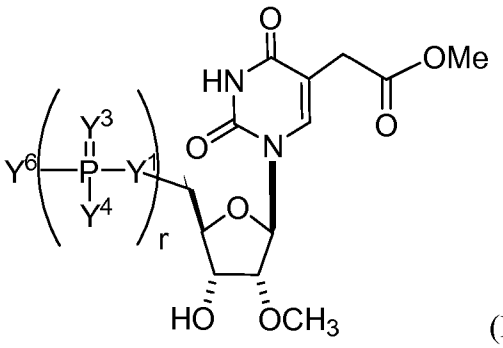
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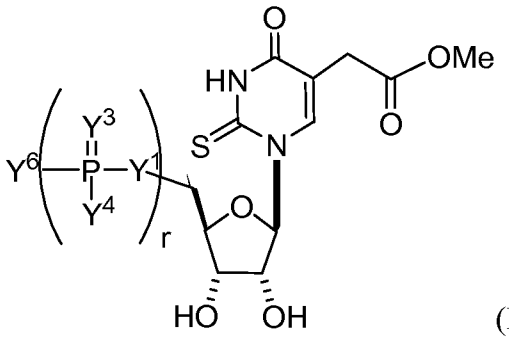


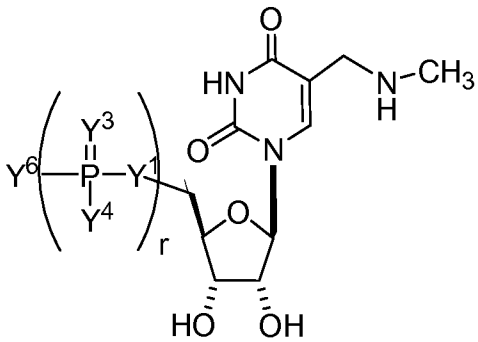
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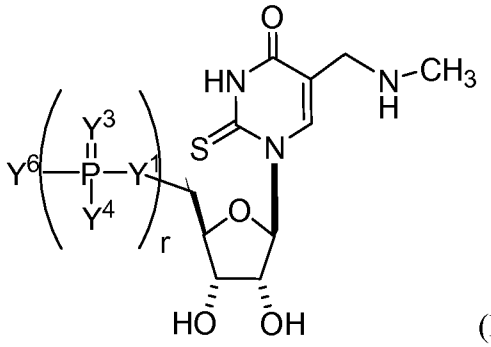
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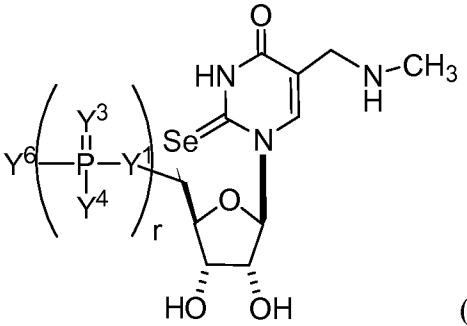




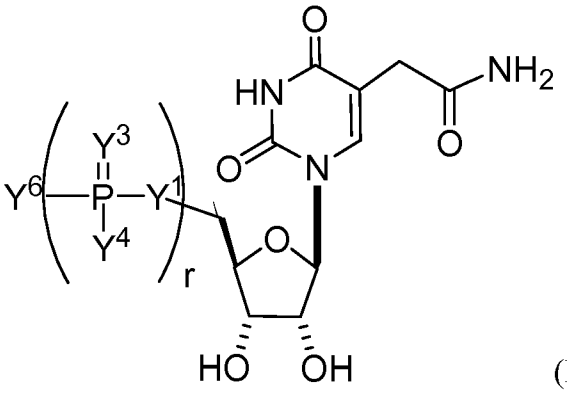
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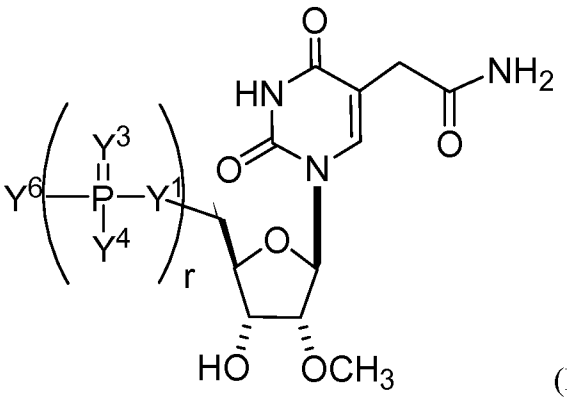


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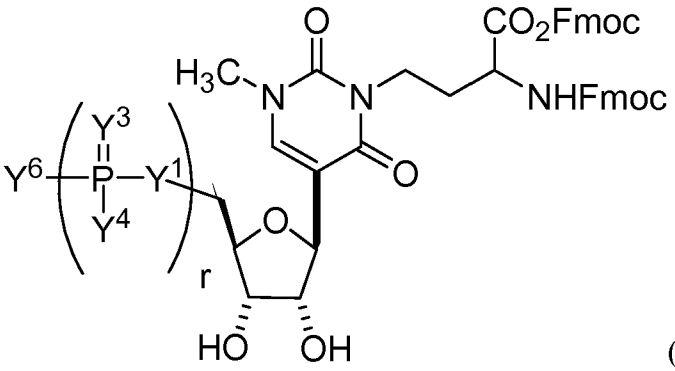


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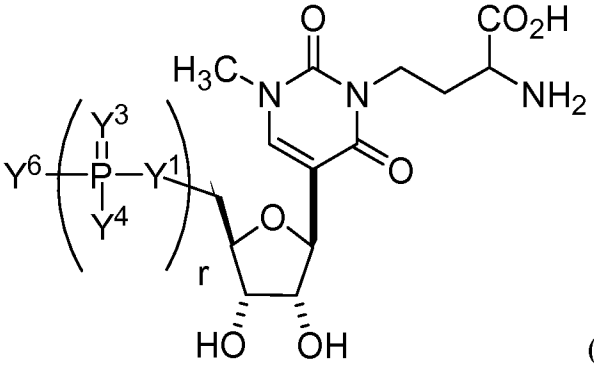
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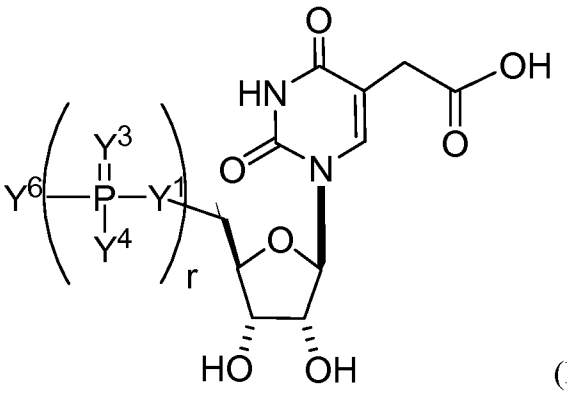
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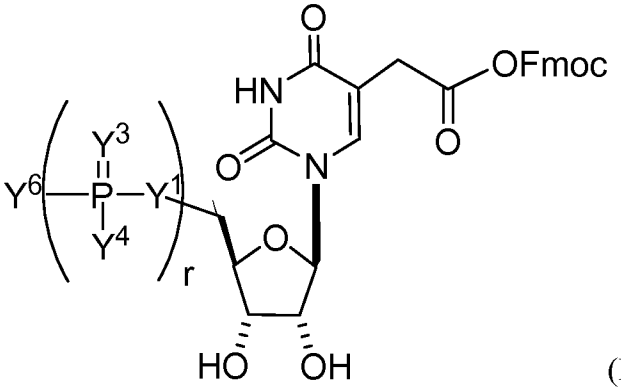
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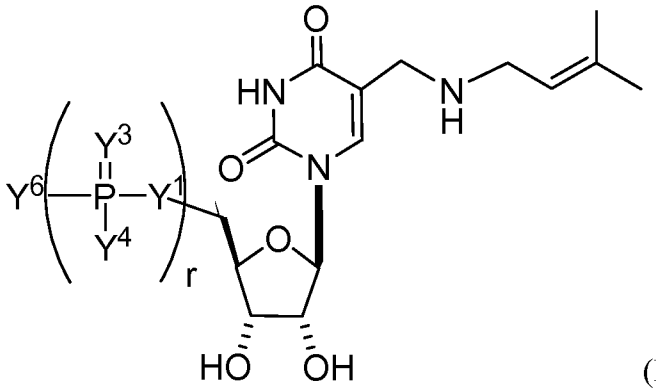
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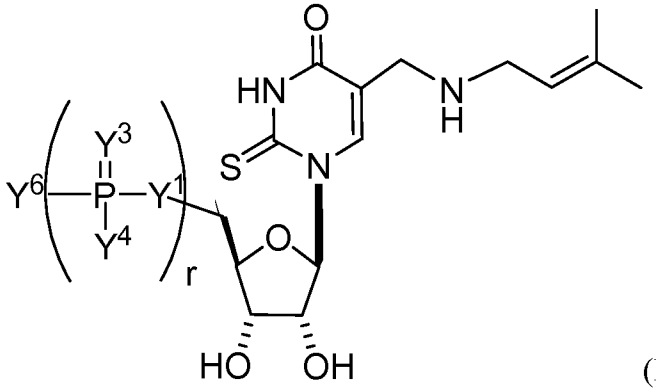
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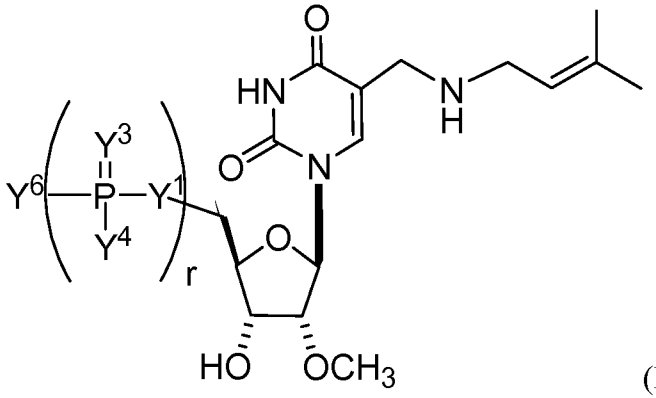
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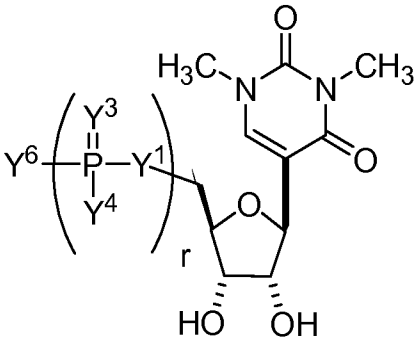
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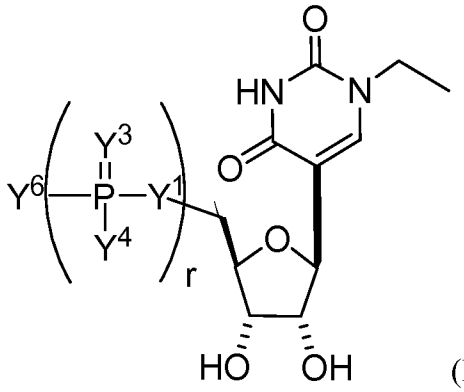
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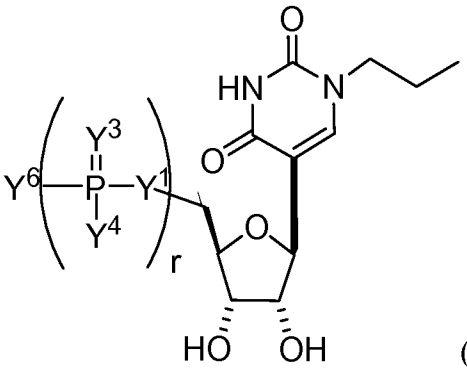
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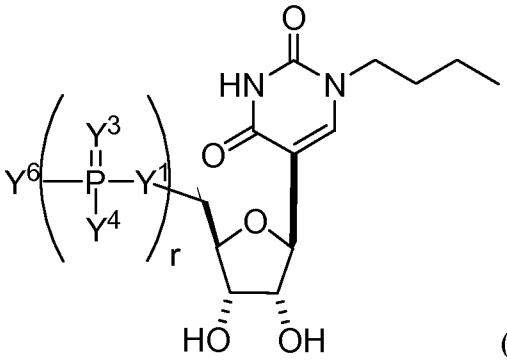
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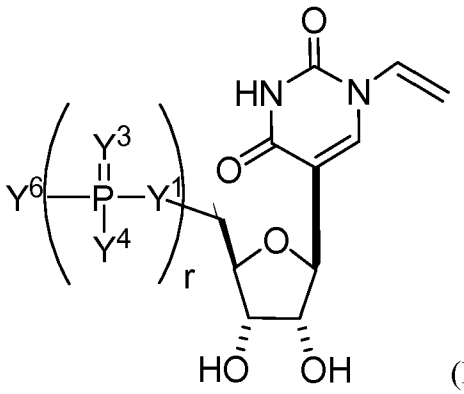
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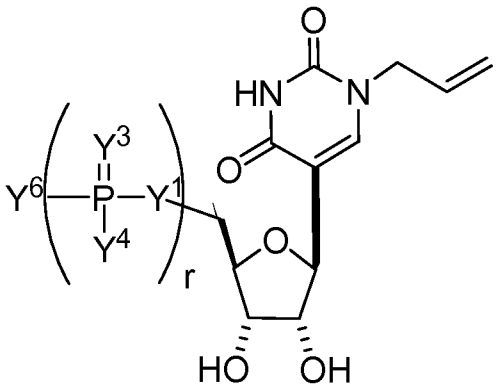
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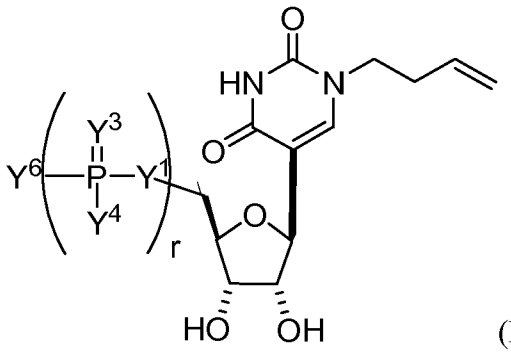
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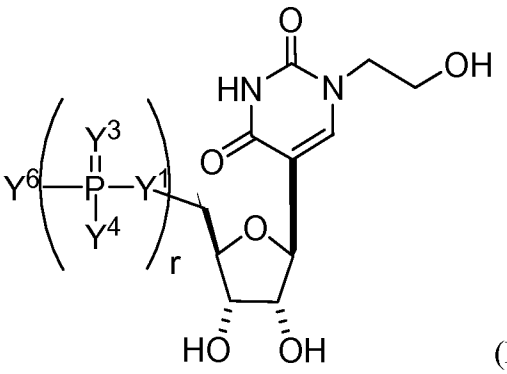
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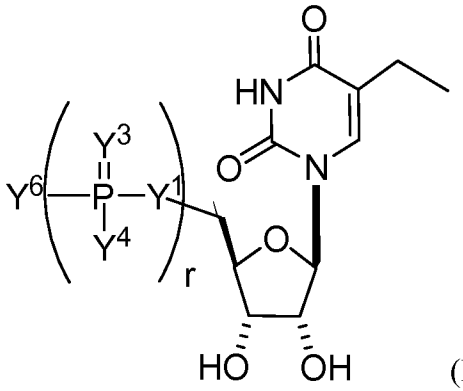
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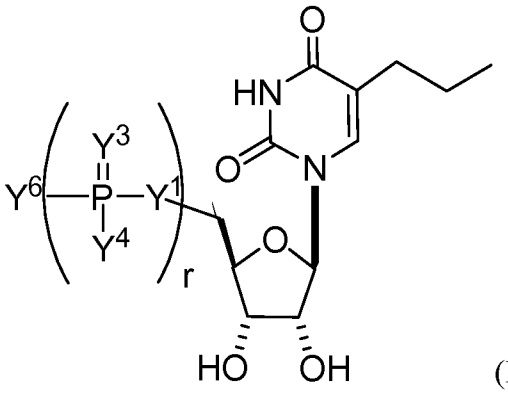
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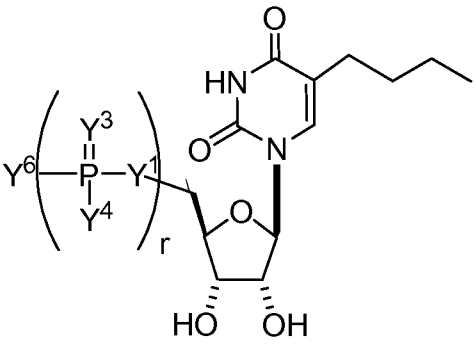
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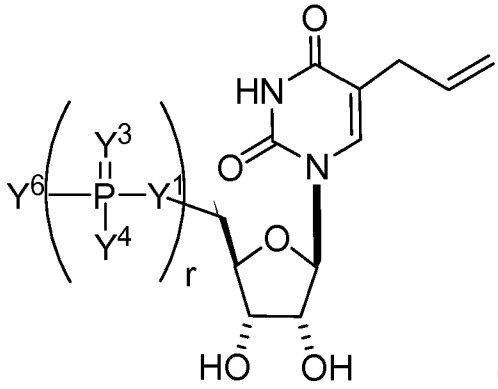
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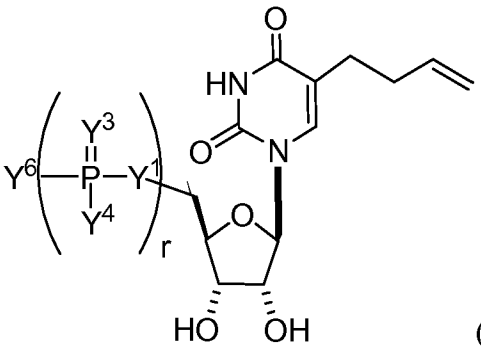
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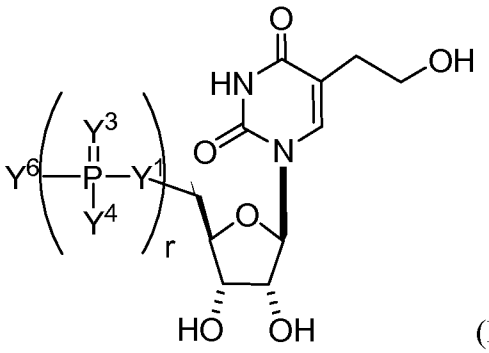
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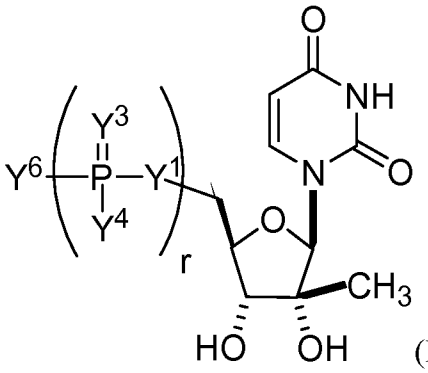
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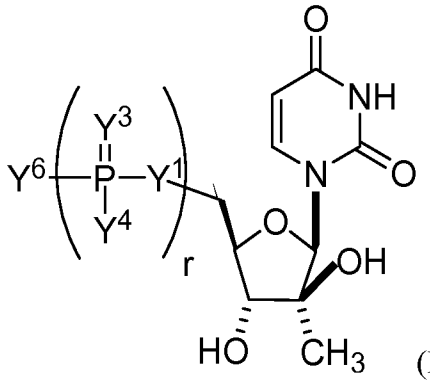


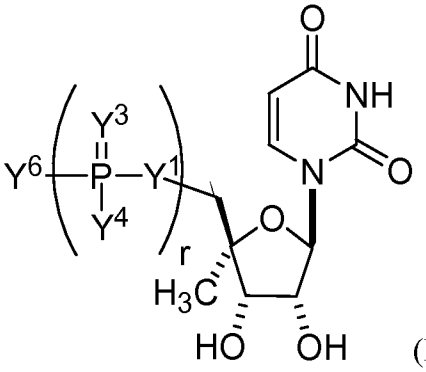
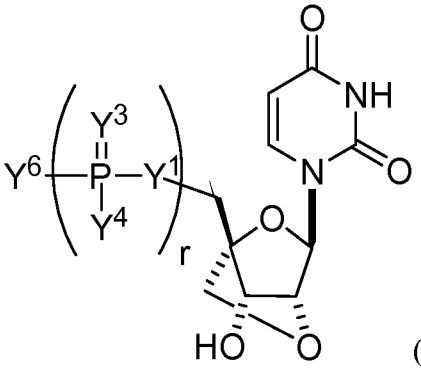
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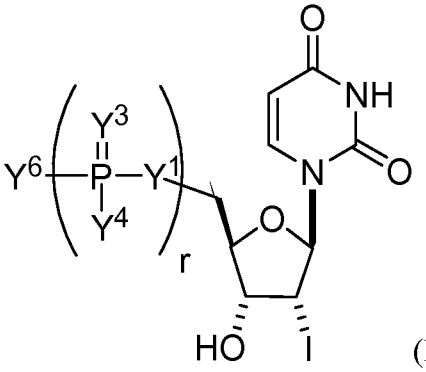
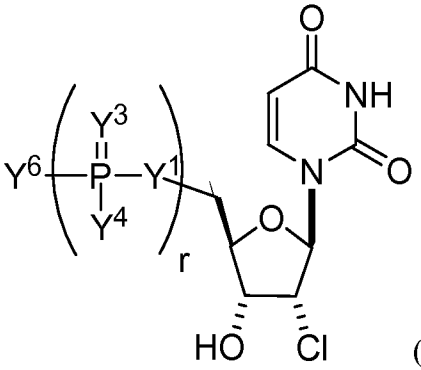


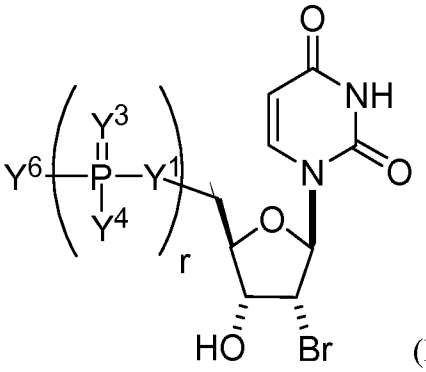
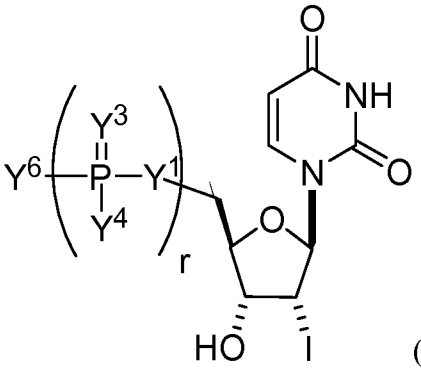
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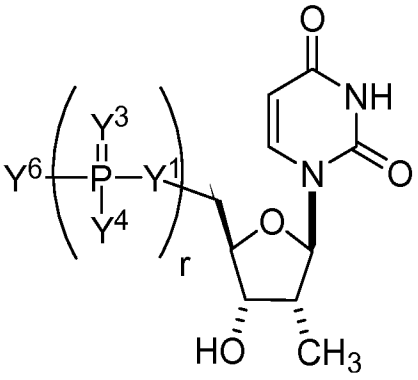


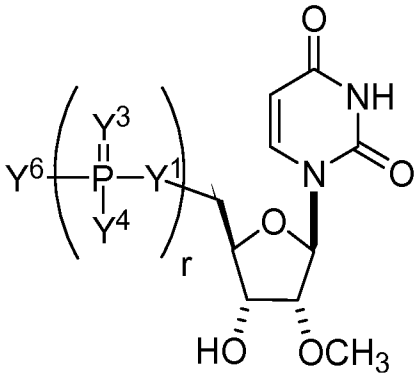
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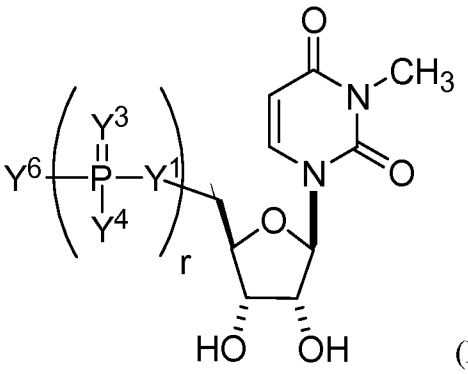
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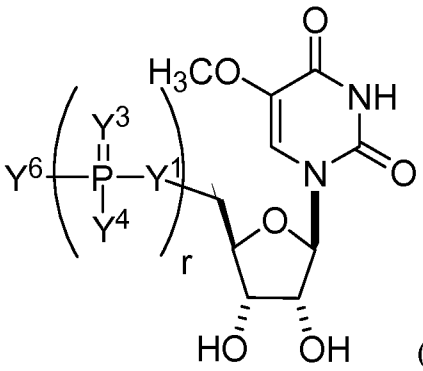
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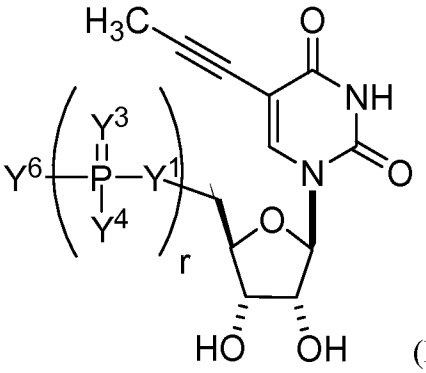
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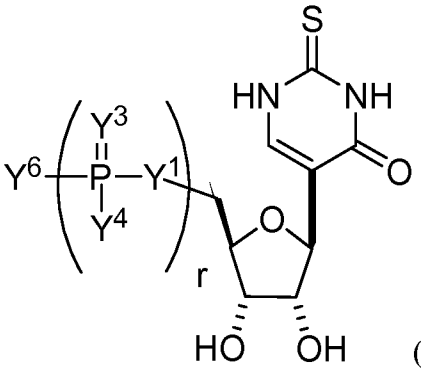

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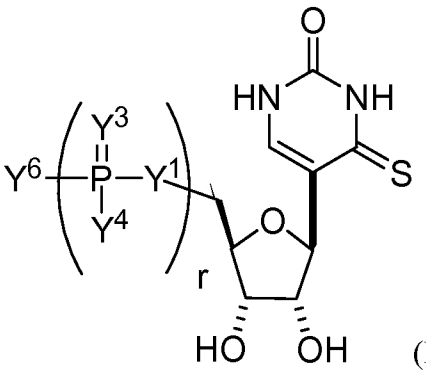

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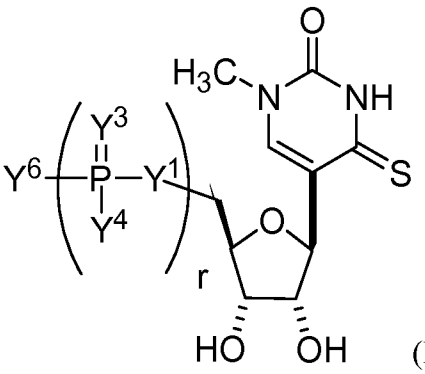

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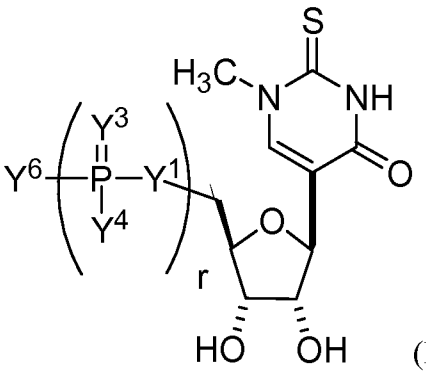

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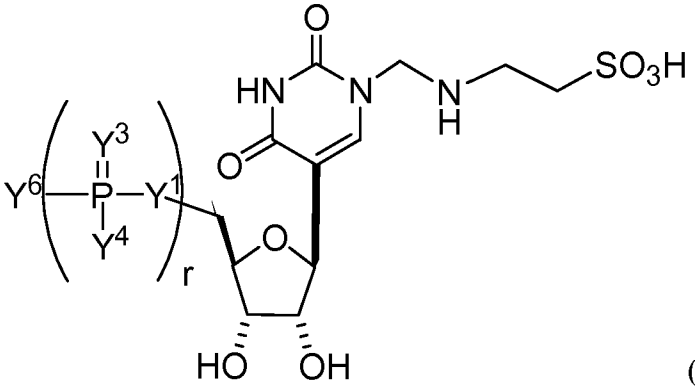

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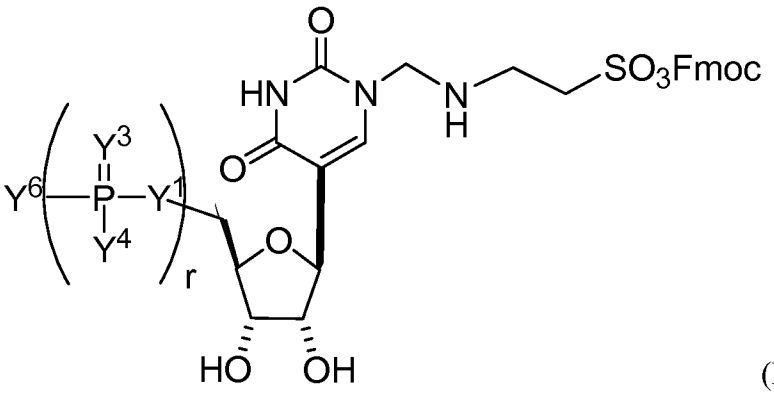

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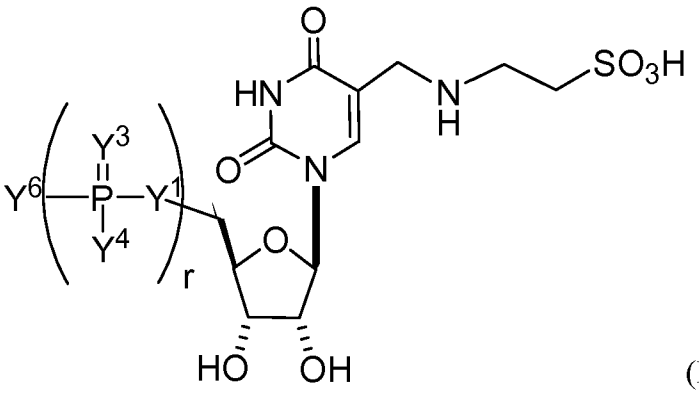
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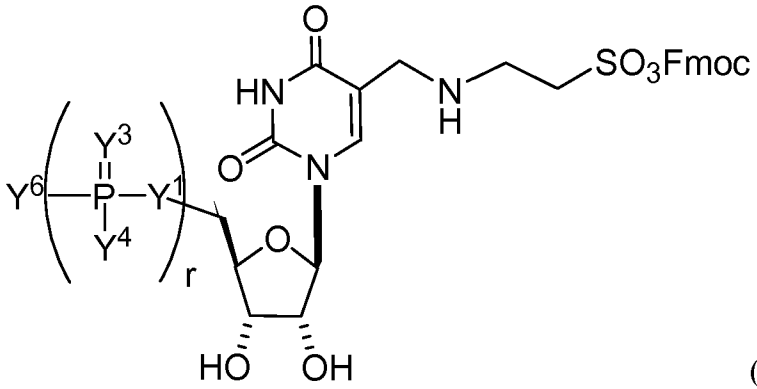
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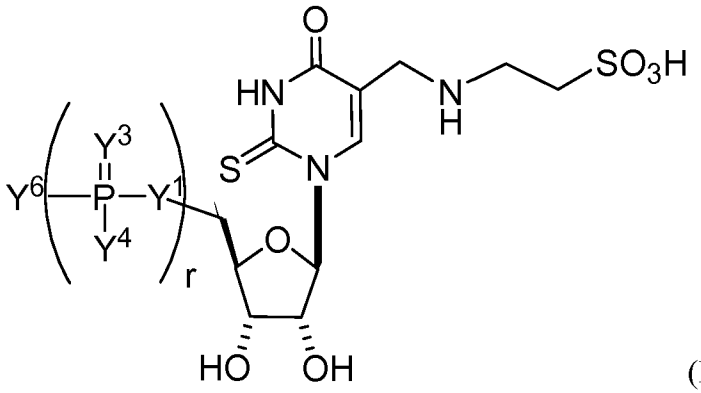
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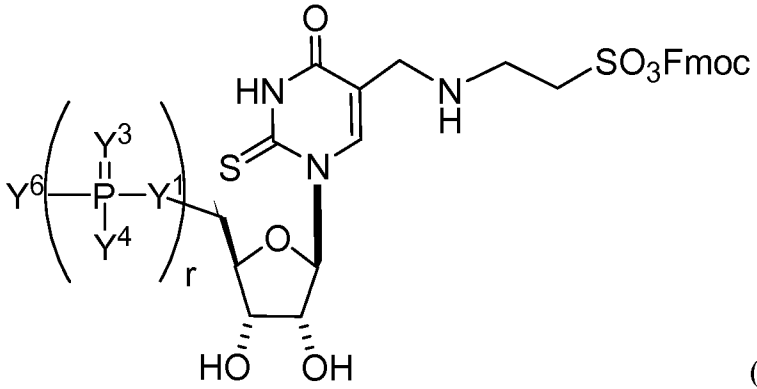
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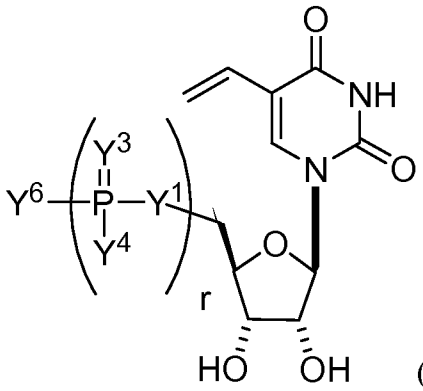
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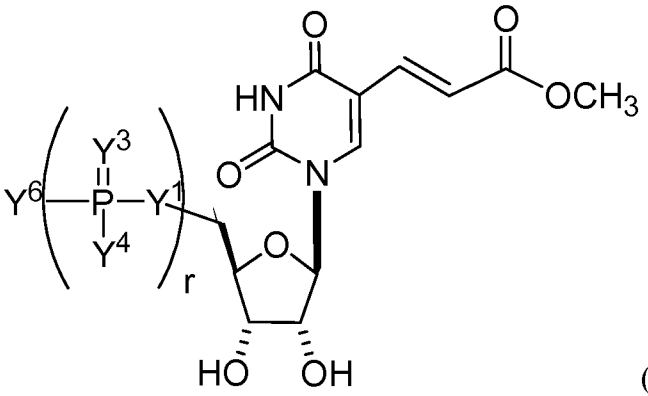
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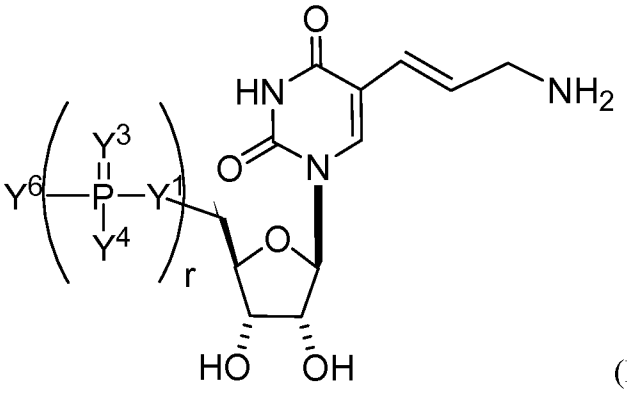
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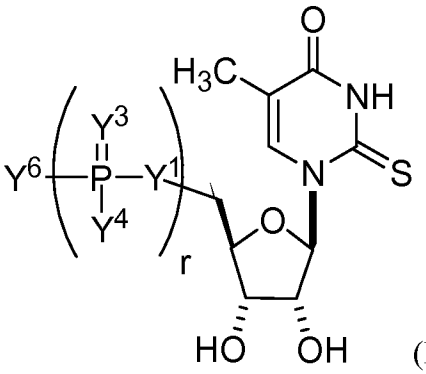
(BB- 108),



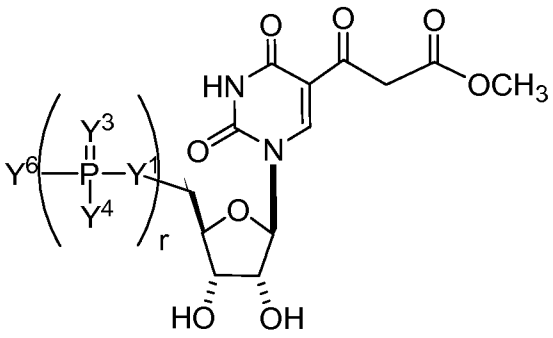
(BB- 109),



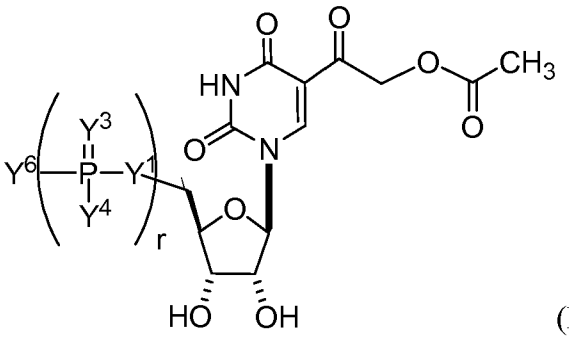
(BB- 110),



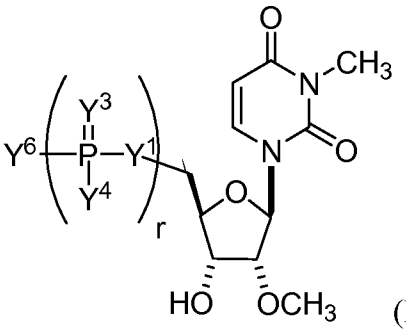
(BB- 111),

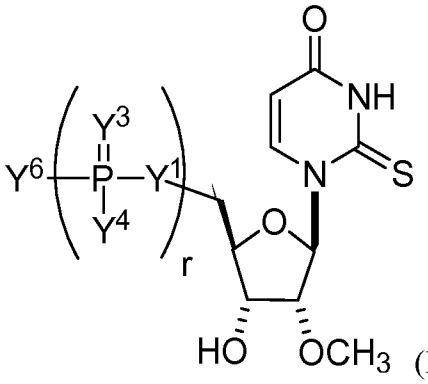


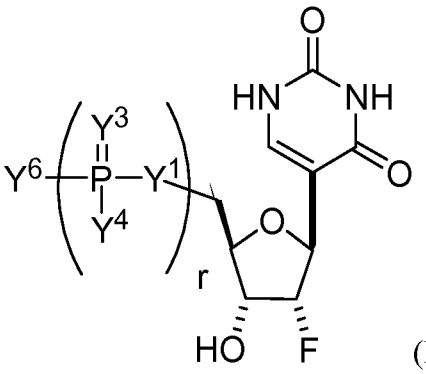
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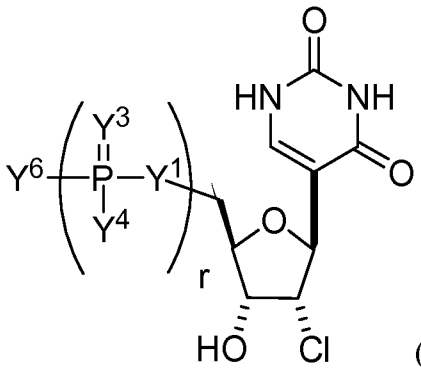


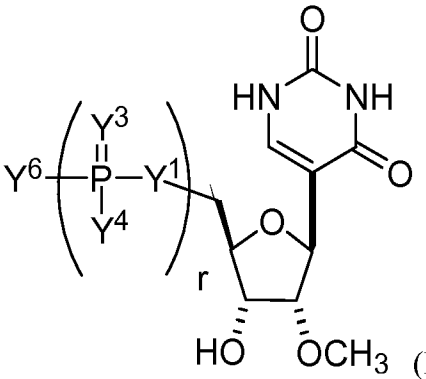
(BB- 113),

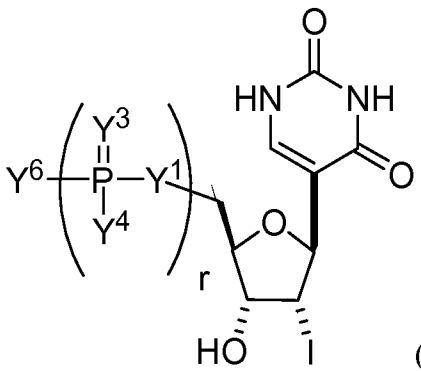

(BB- 114),

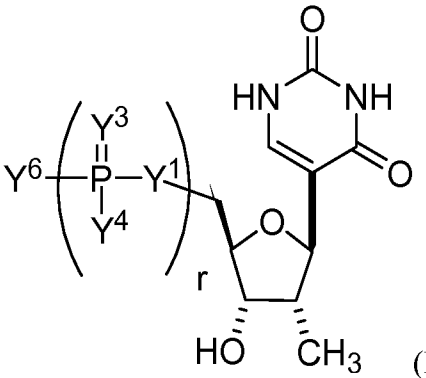

(BB- 115),

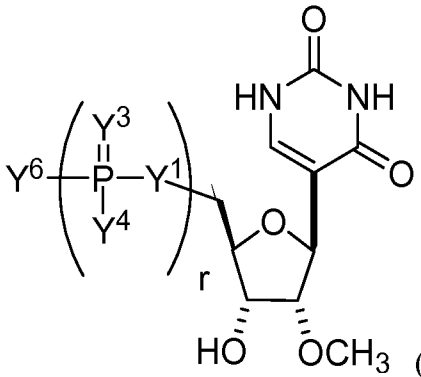

(BB- 116),

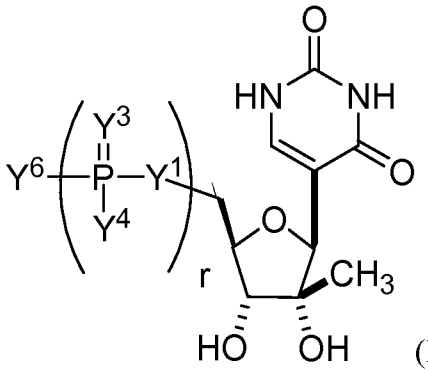

(BB- 117),


(BB- 118),

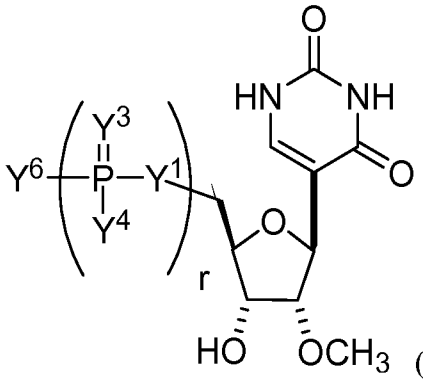

(BB- 119),


(BB- 120),

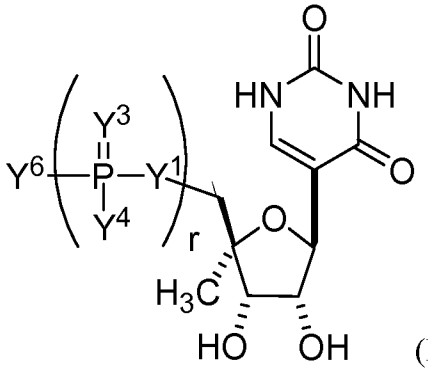

(BB- 121),



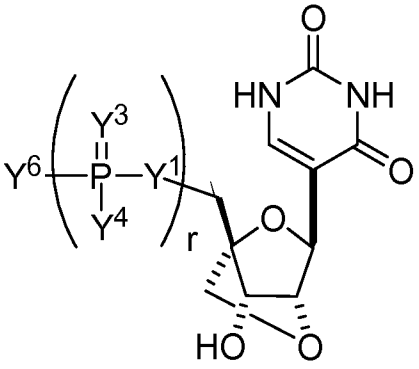
(BB- 122),



(BB- 123),

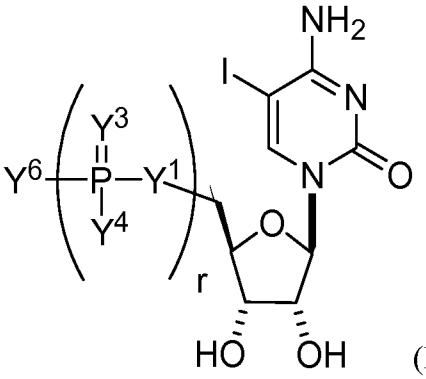


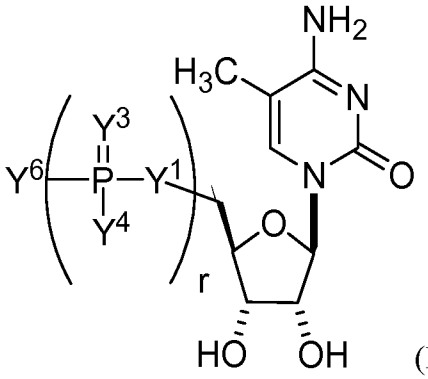
(BB- 124), and

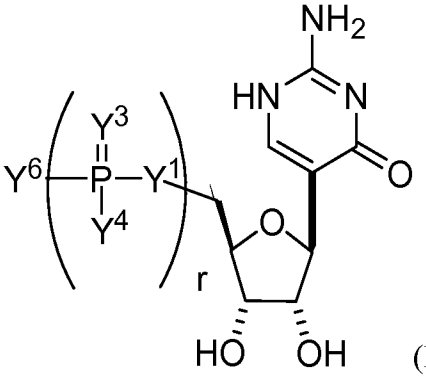


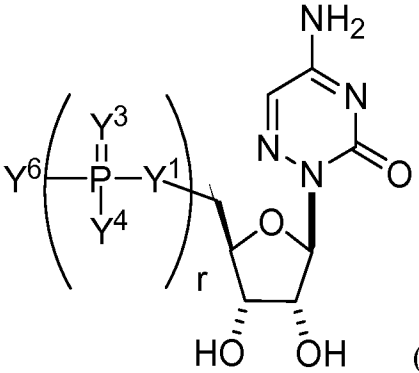
(BB-125), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3, Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)).

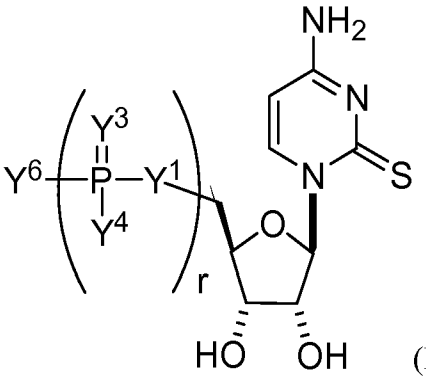
[000361] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, is a modified cytidine (e.g., selected from the group consisting of:

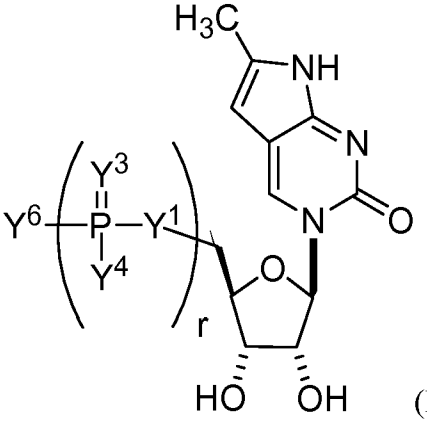

(BB- 126),

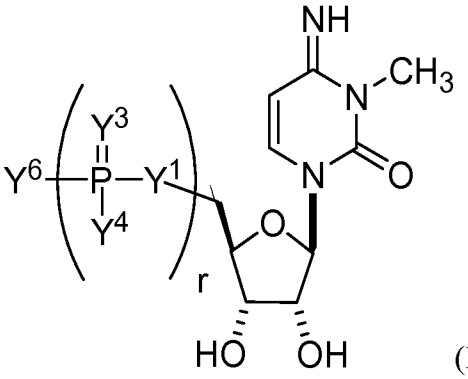

(BB- 127),

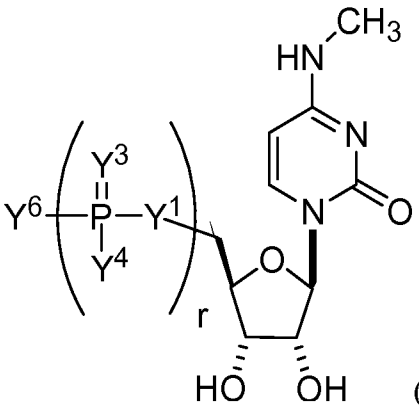

(BB- 128),

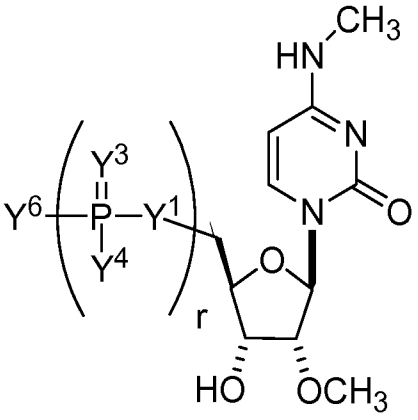

(BB- 129),

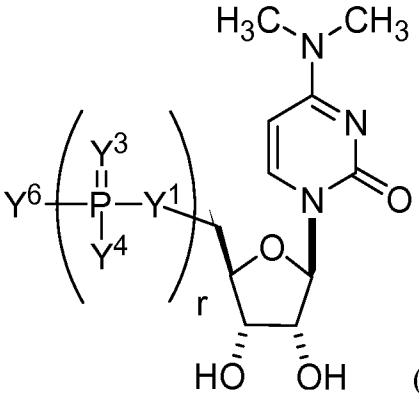

(BB- 130),

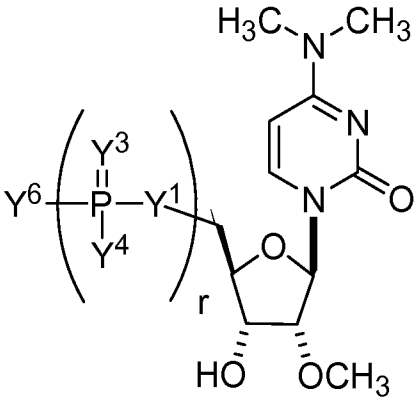

(BB- 131),

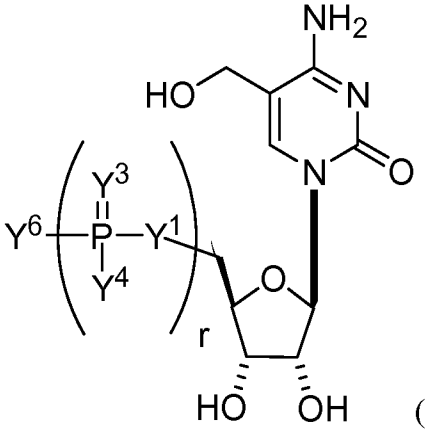

(BB- 132),

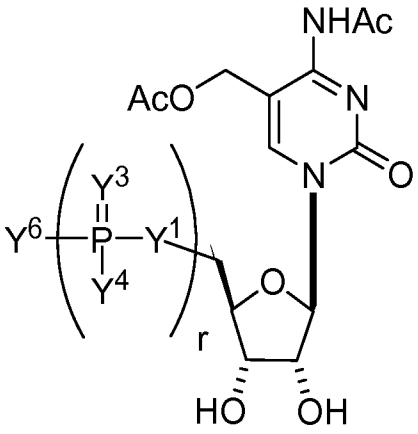

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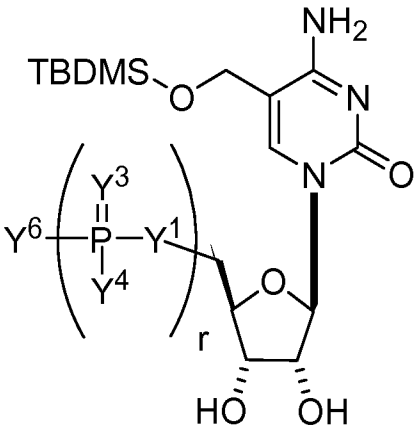

(BB- 134),

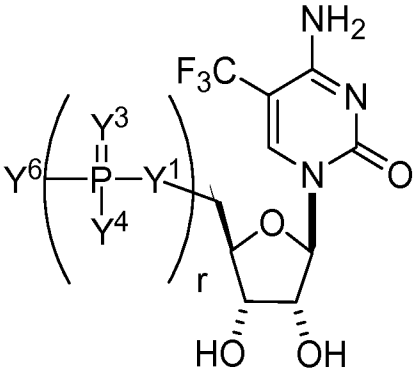

(BB- 135),

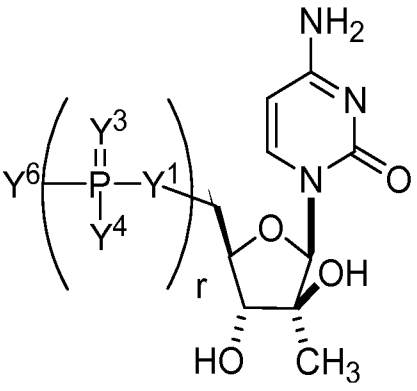

(BB- 136),

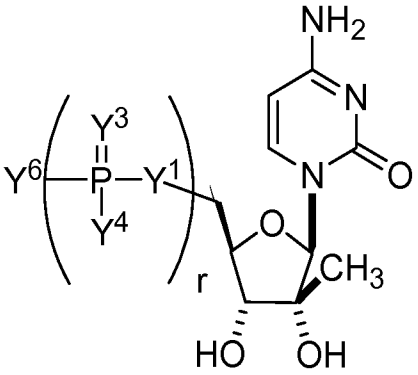

(BB- 137),

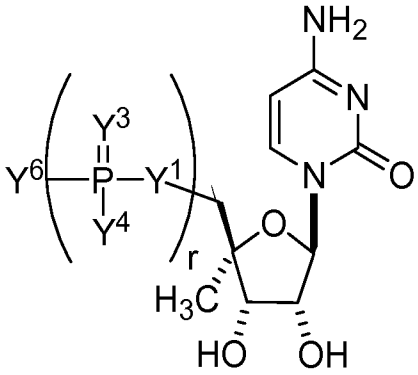

(BB- 138),

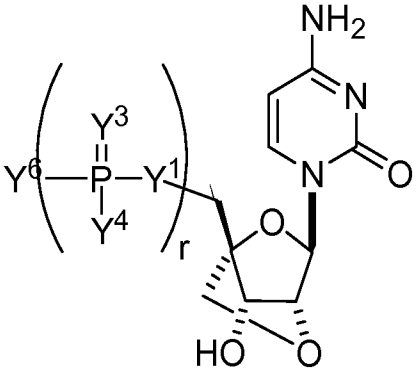

(BB- 139),

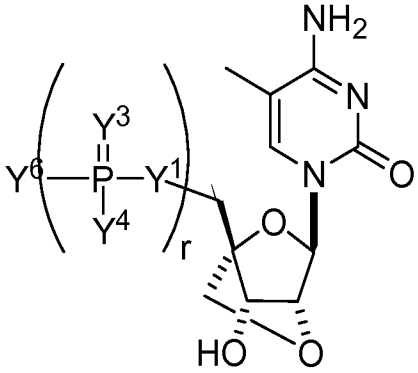

(BB- 140),

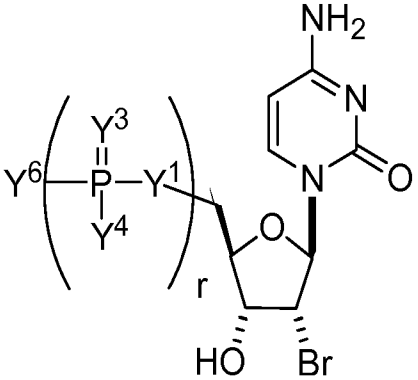

(BB- 141),

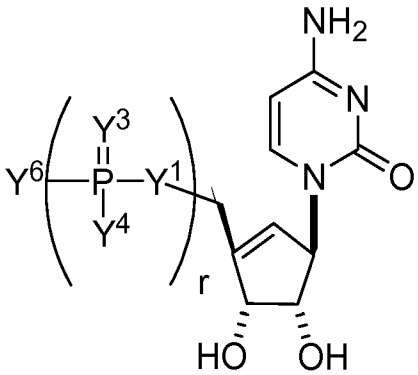

(BB- 142),

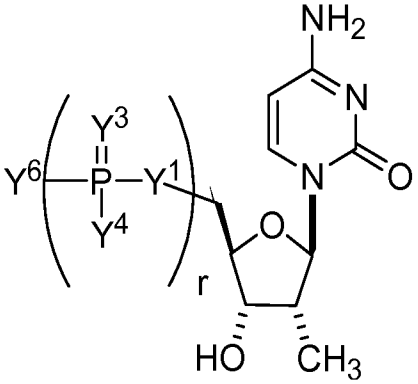

(BB- 143),

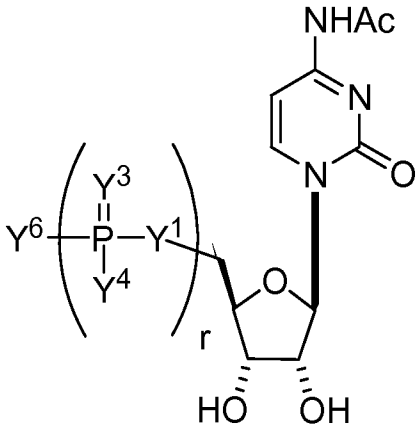

(BB- 144),

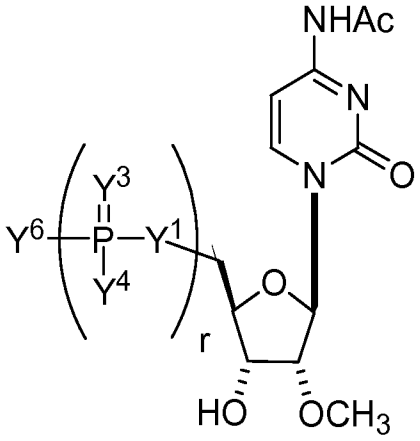

(BB- 145),


(BB- 146),

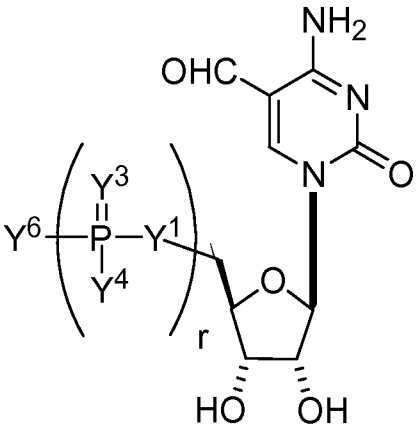

(BB- 147),


(BB- 148),

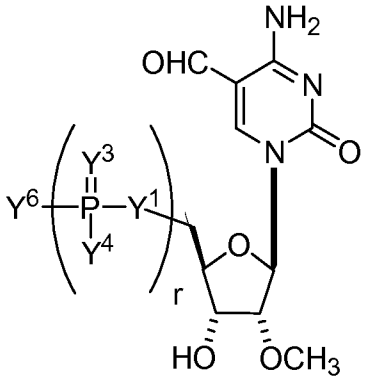

(BB- 149),



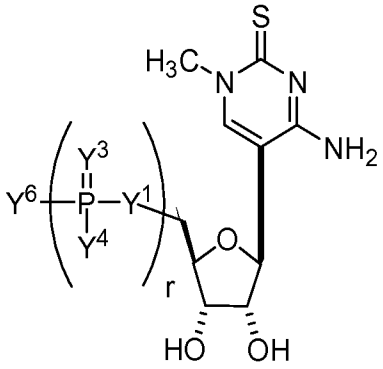
(BB- 150),



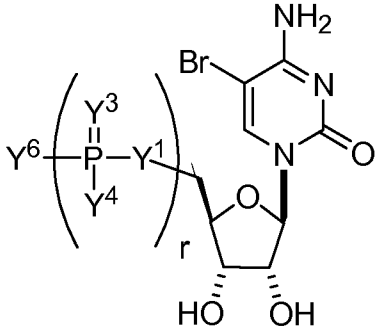
(BB- 151),



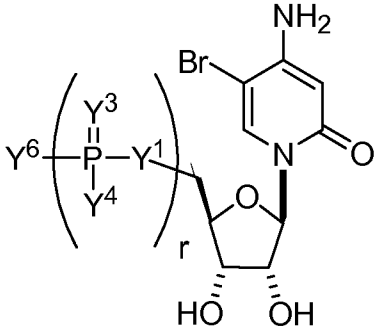
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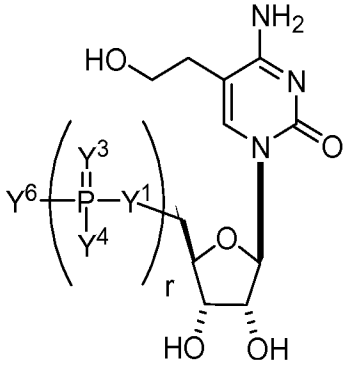
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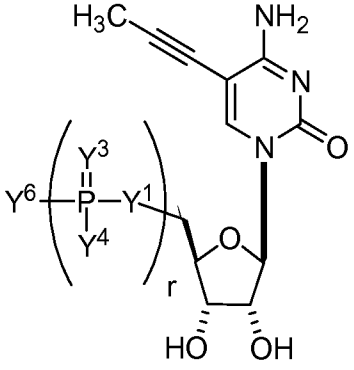
(BB- 154),



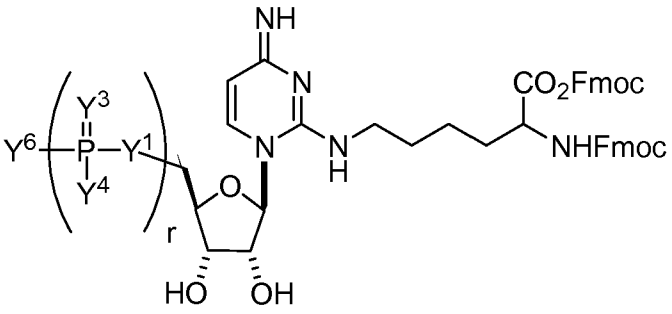
(BB- 155),



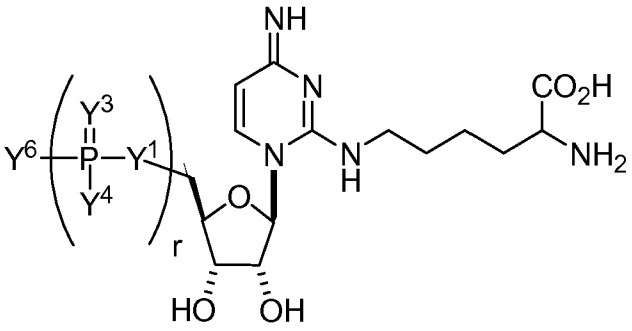
(BB- 156),



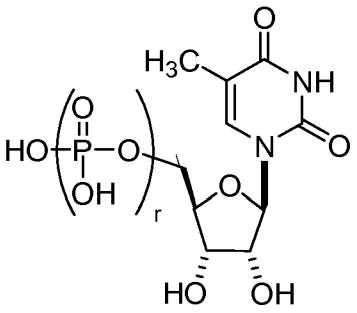
(BB- 157),



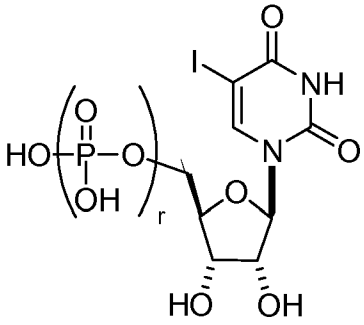
(BB- 158), and



(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:

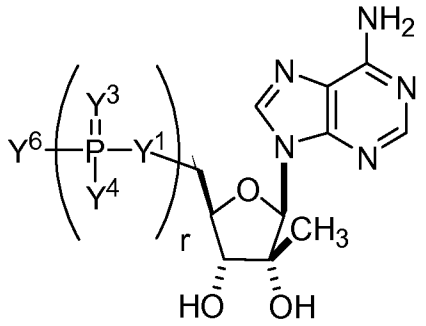


(BB- 160) or

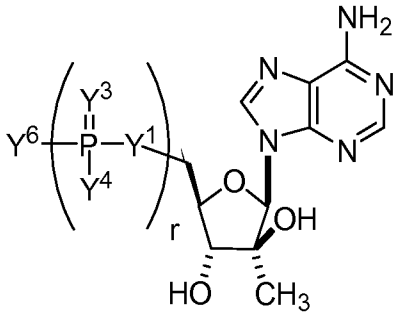


(BB- 161), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein each r is, independently, an integer from 0 to 5 (e.g., from 0 to 3, from 1 to 3, or from 1 to 5).

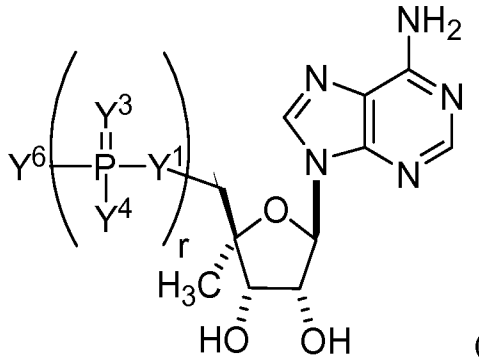
[000362] In some embodiments, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, is a modified adenosine (e.g., selected from the group consisting of:



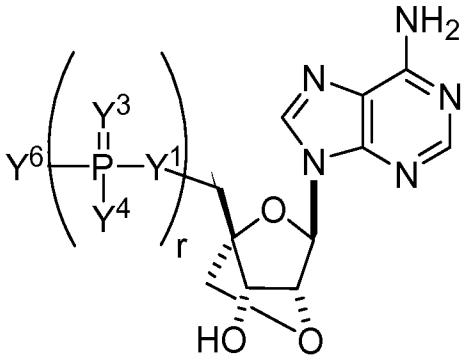
(BB- 162),



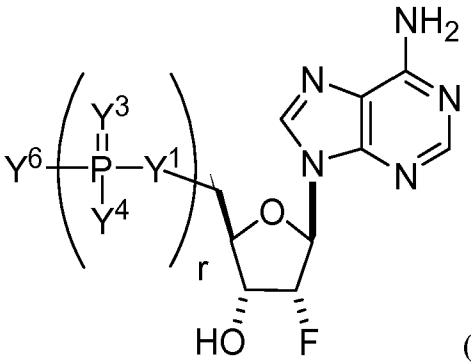
(BB- 163),



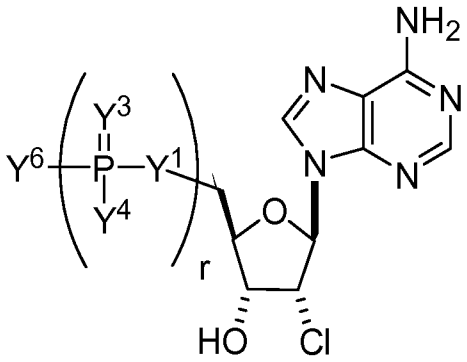
(BB- 164),



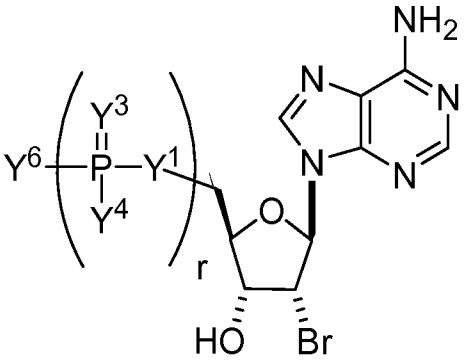
(BB-165),



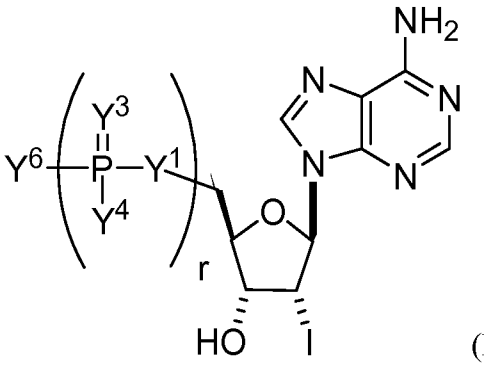
(BB- 166),



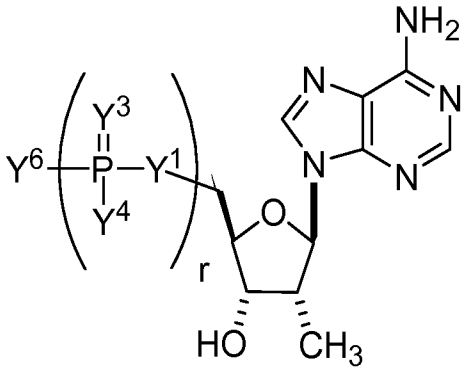
(BB- 167),



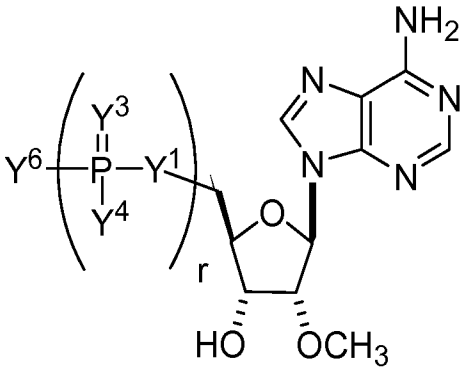
(BB- 168),



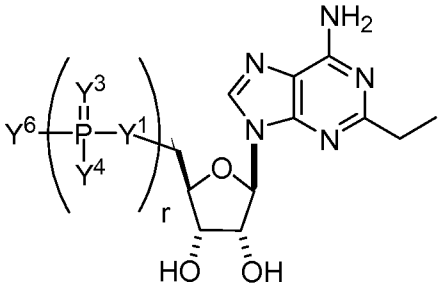
(BB- 169),



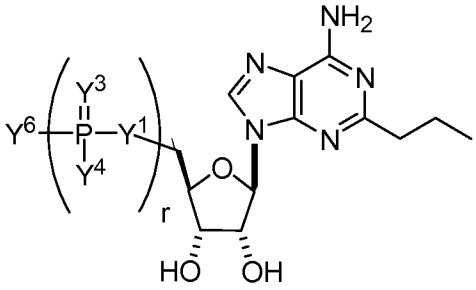
(BB- 170),



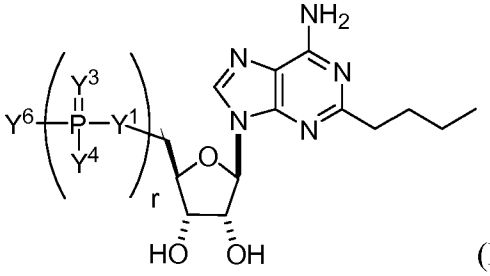
(BB- 171),



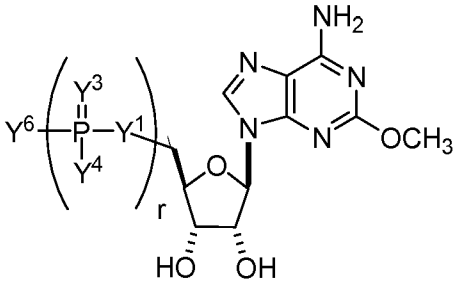
(BB- 172),



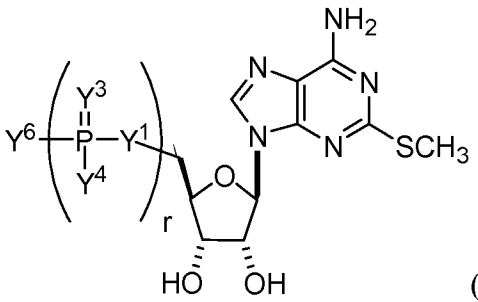
(BB- 173),



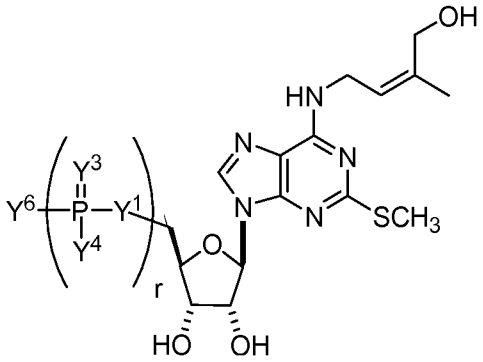
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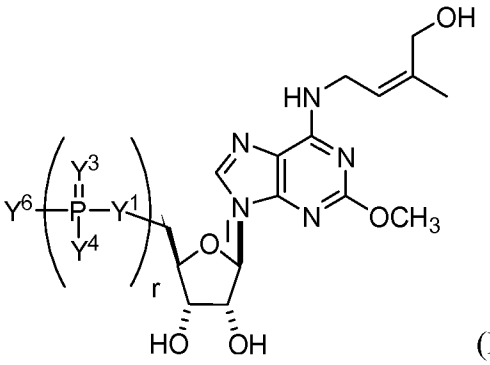


(BB- 175),



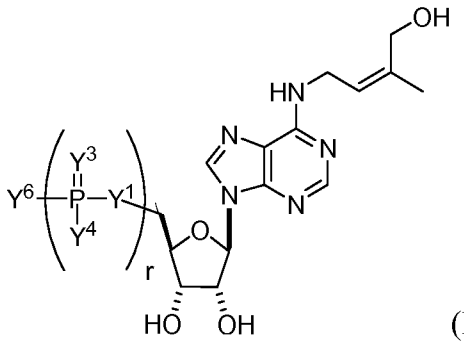
(BB- 176),



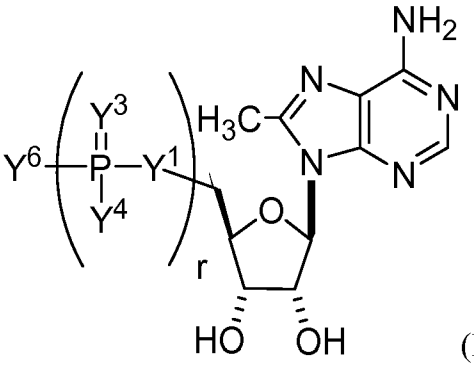


(BB- 177),

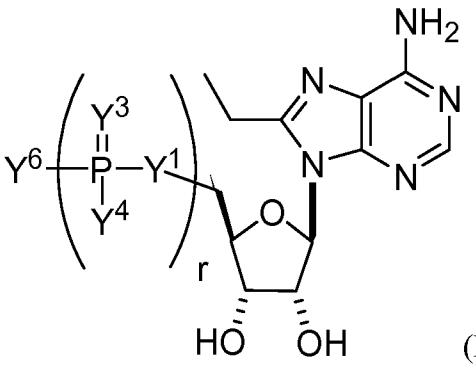
(BB- 178),



(BB- 179),

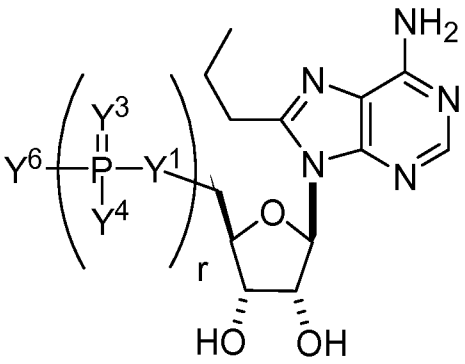


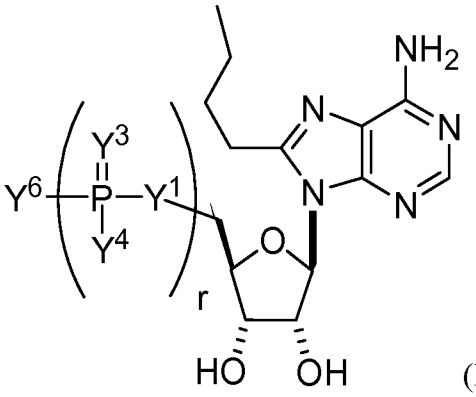
(BB-



180),

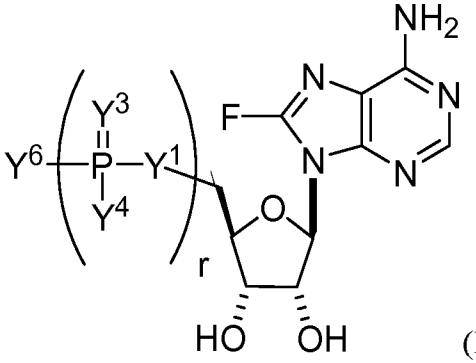
(BB- 181),



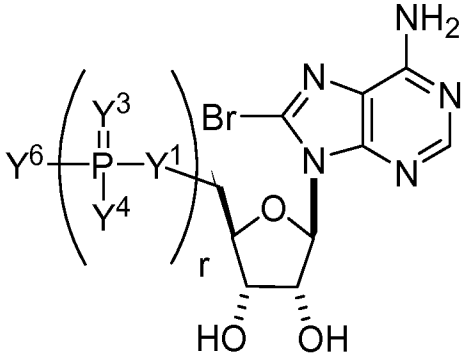


(BB- 182),

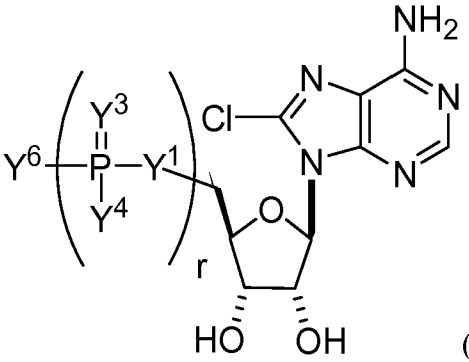
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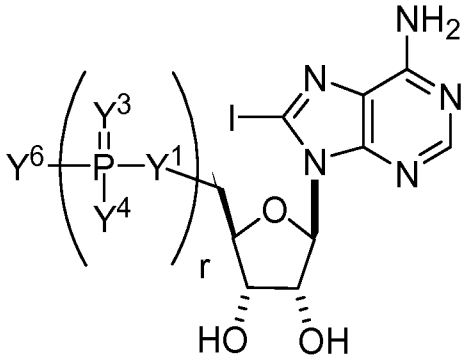
(BB- 184),



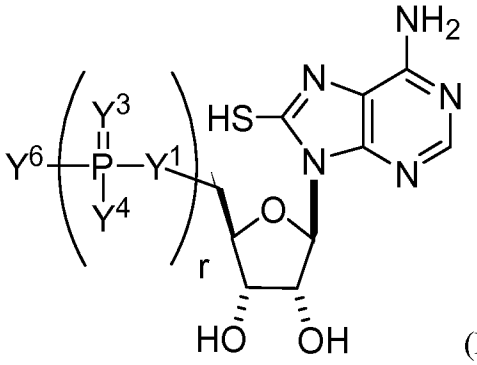
(BB- 185),



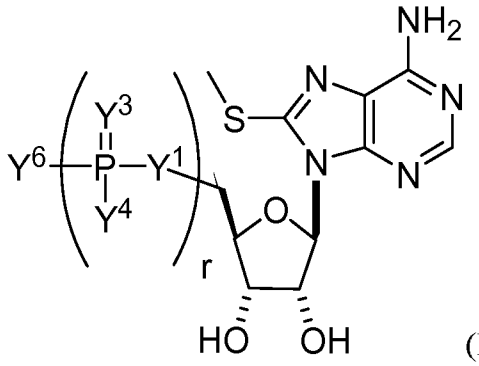
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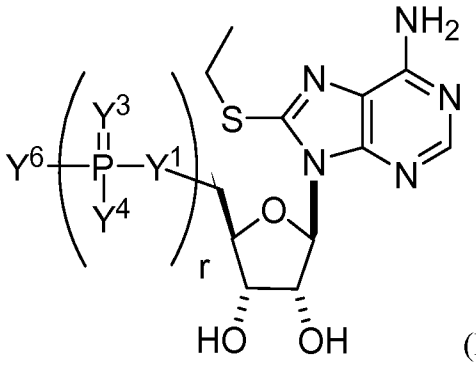
(BB- 187),



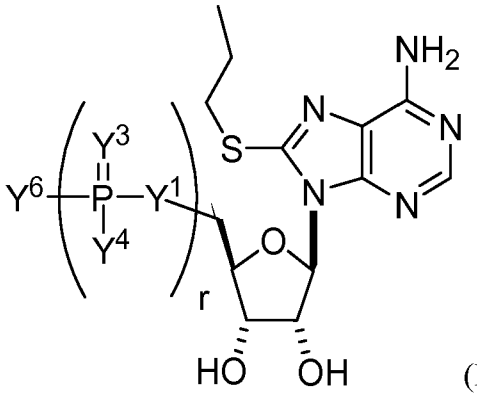
(BB- 188),



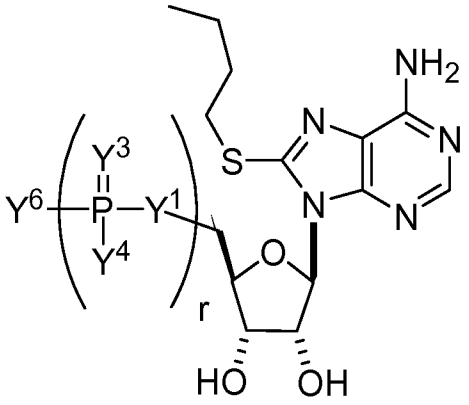
(BB- 189),



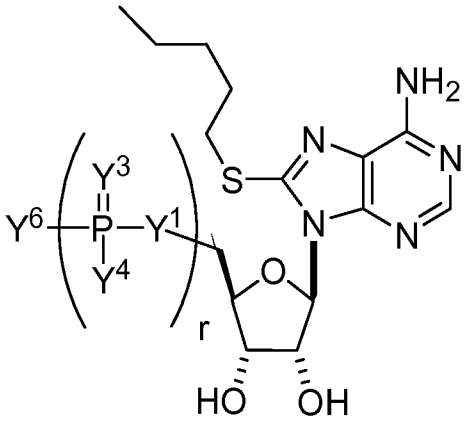
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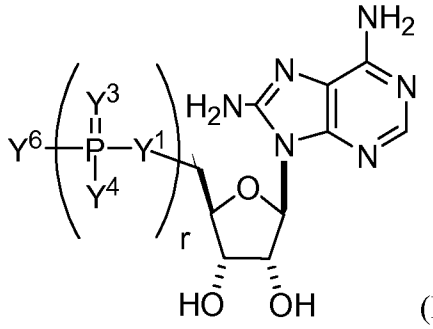
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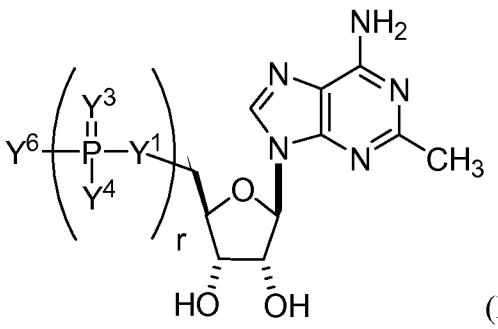
(BB- 192),



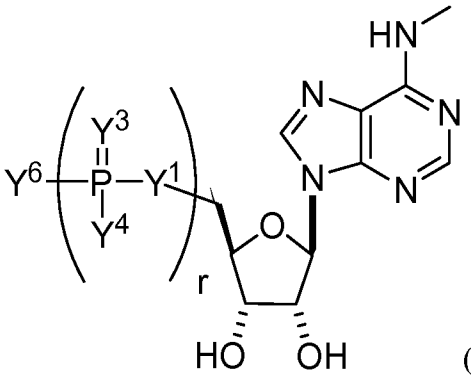
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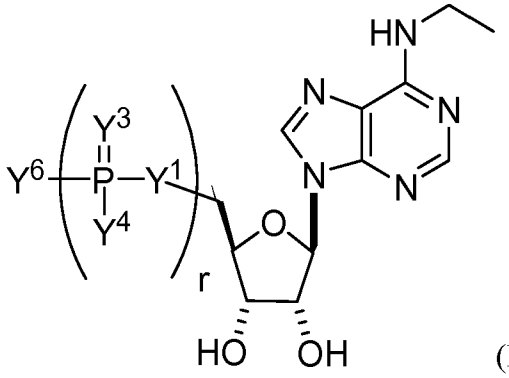
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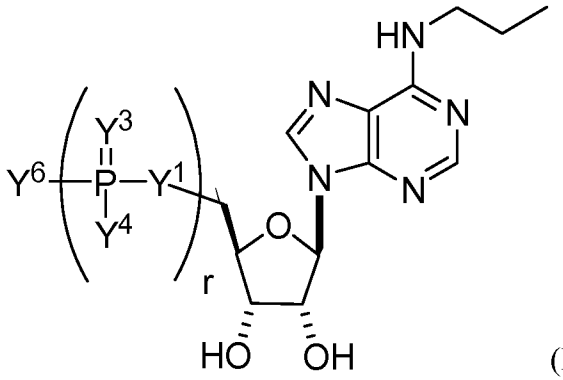
(BB-



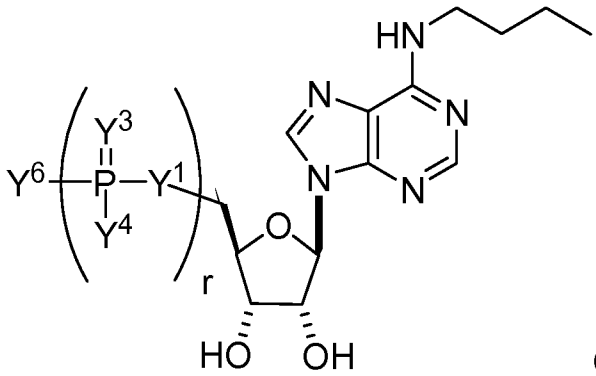
195), (BB- 196),



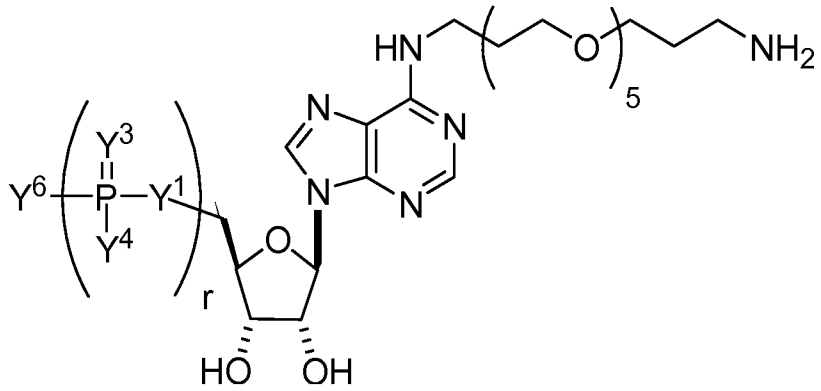
(BB- 197),



(BB- 198),

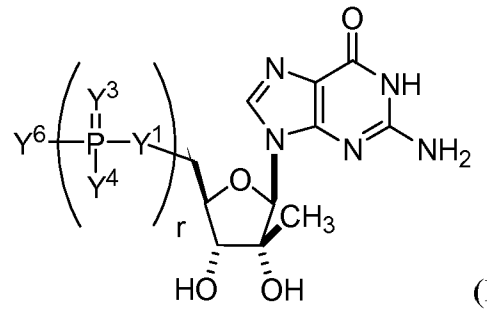


(BB- 199), and

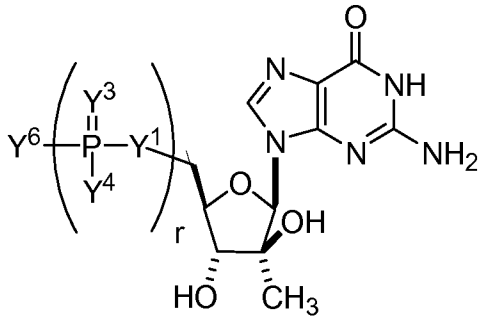


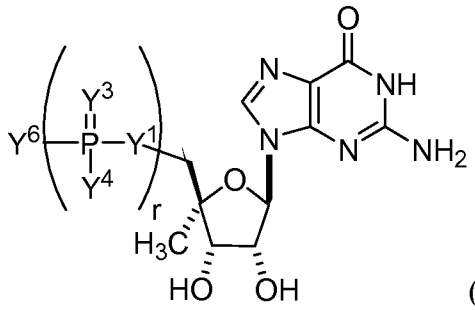
(BB- 200) or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3, Y^4, Y^6, and r are as described herein (e.g., each r is, independently, an integer from 0 to 5, such as from 0 to 3, from 1 to 3, or from 1 to 5)).

[000363] 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:



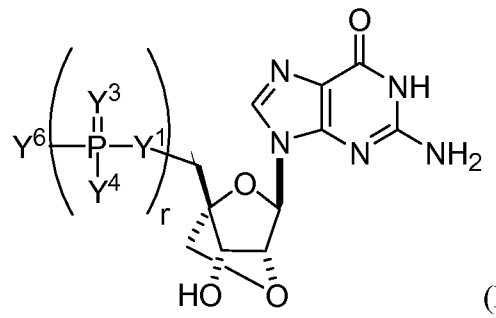
(BB- 201),



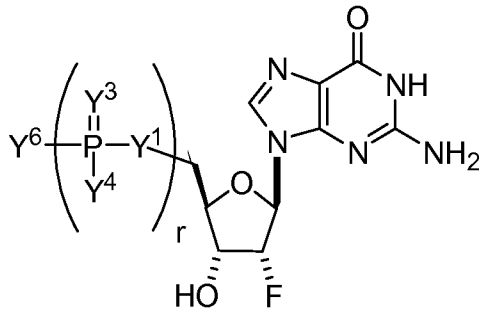


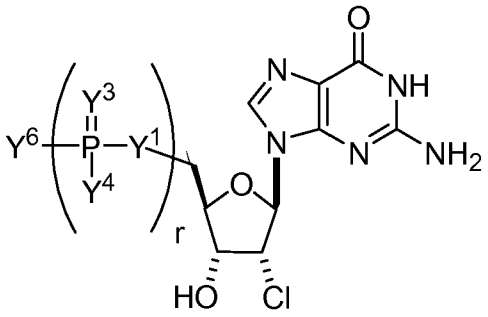
(BB- 202),

(BB- 203),



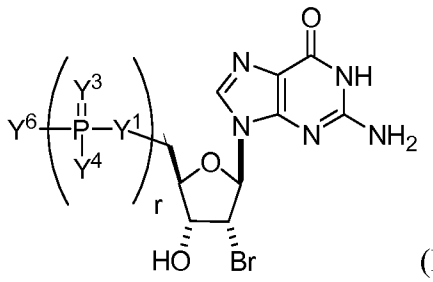
(BB- 204),



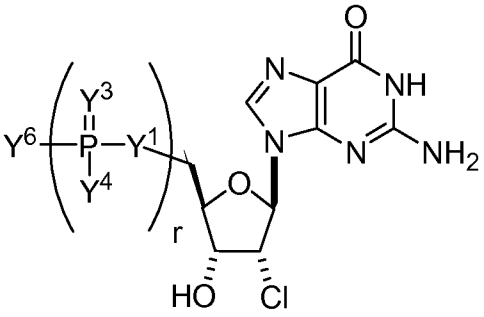


(BB- 205),

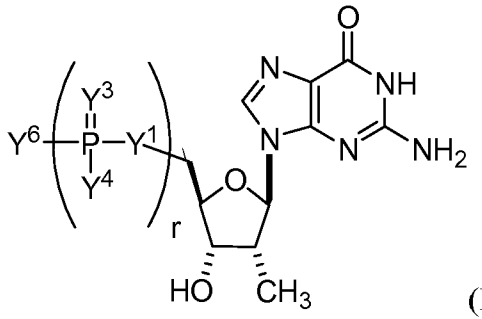
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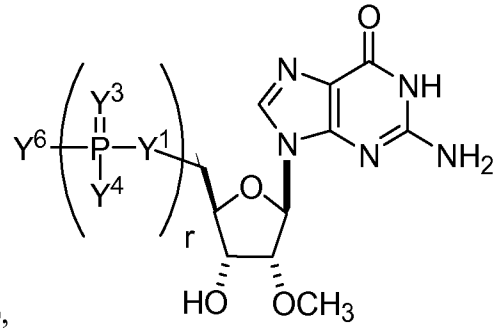
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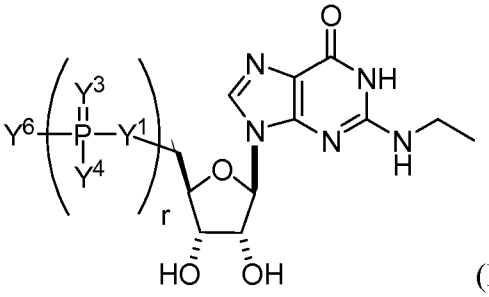


(BB- 208),



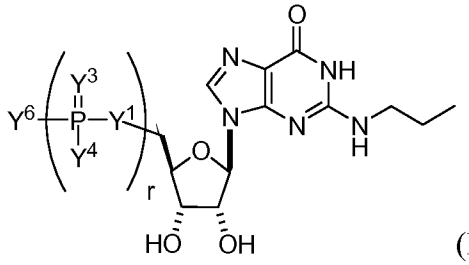
(BB- 209),



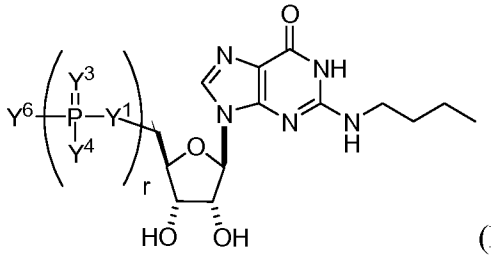


(BB- 210),

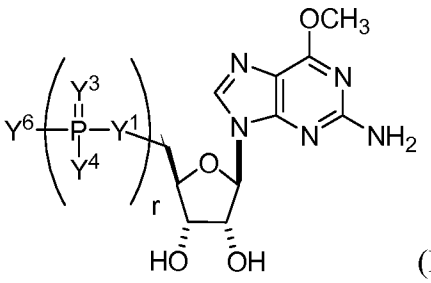
(BB- 211),



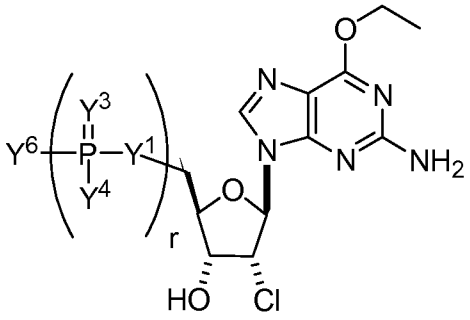
(BB- 212),



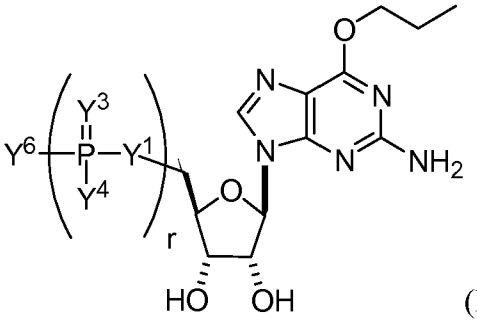
(BB-



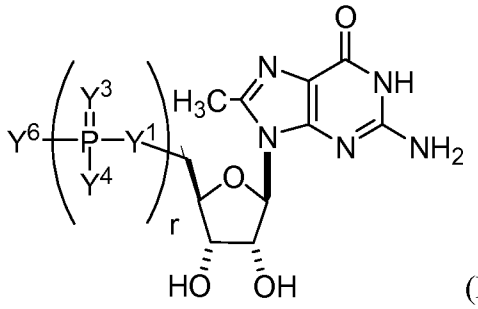
213),



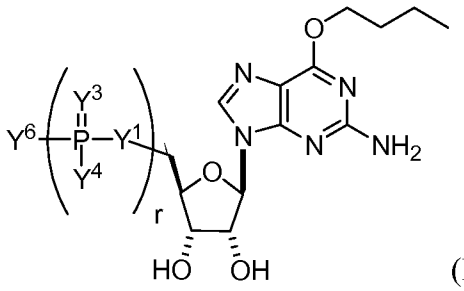
(BB- 214),



(BB- 215),

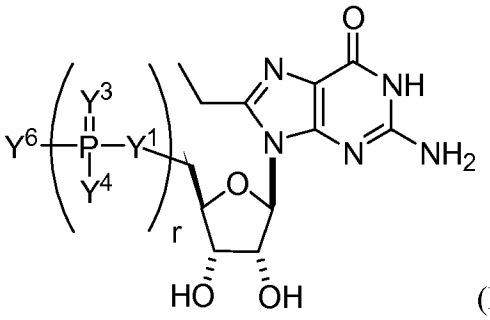


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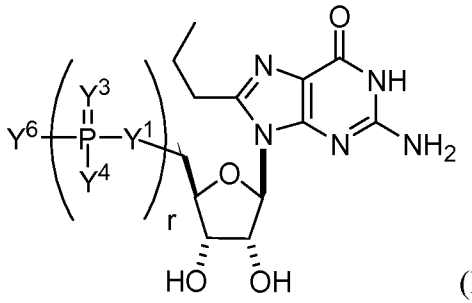
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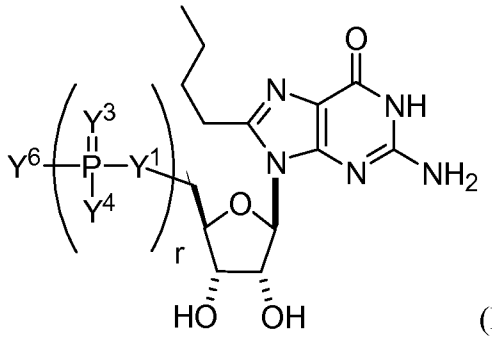


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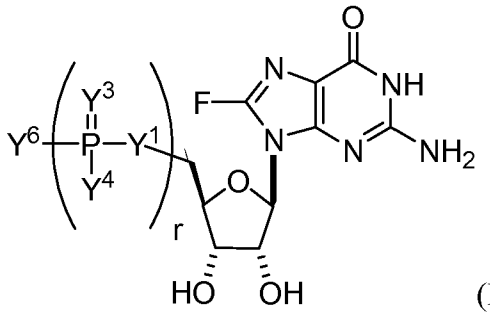
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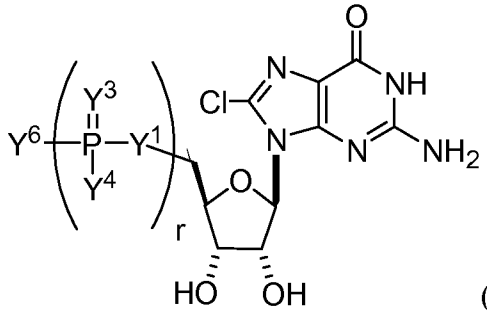
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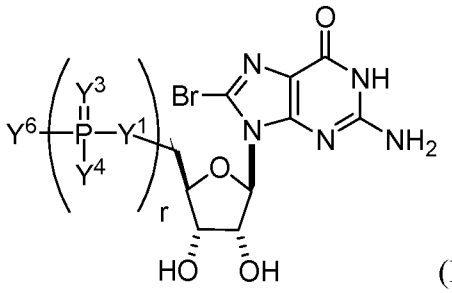
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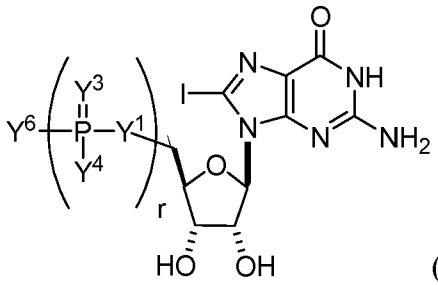
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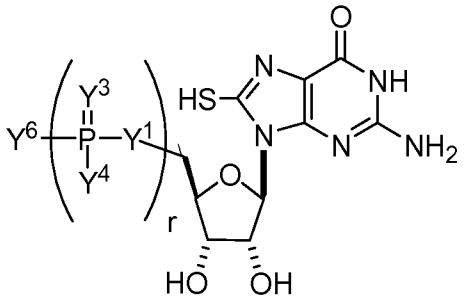
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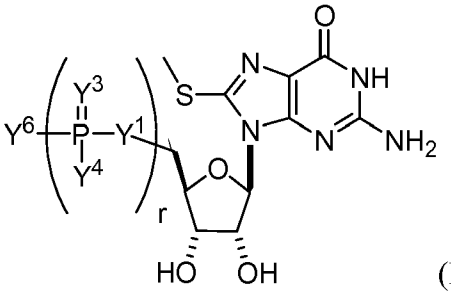
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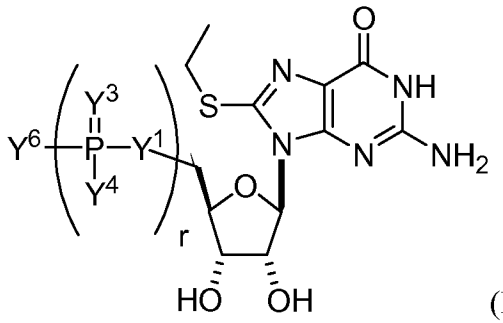


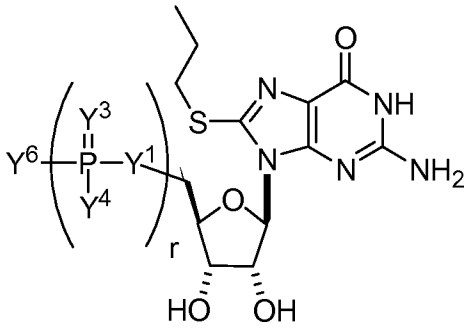
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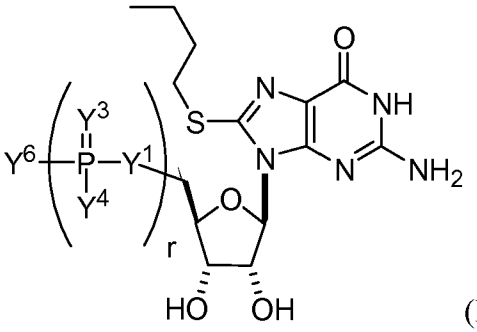
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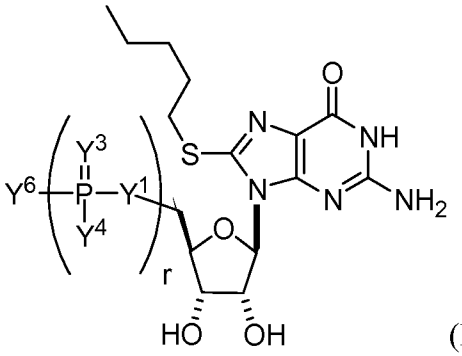


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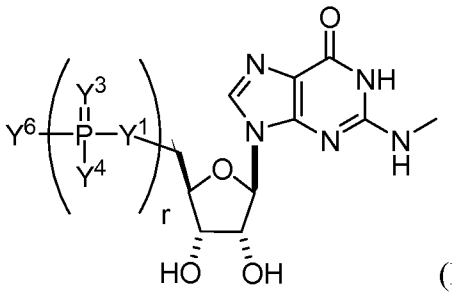


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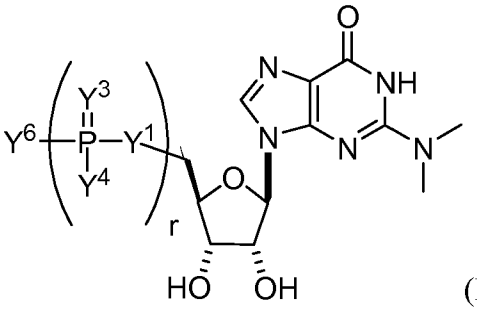
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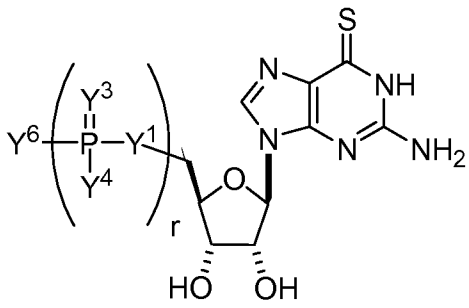
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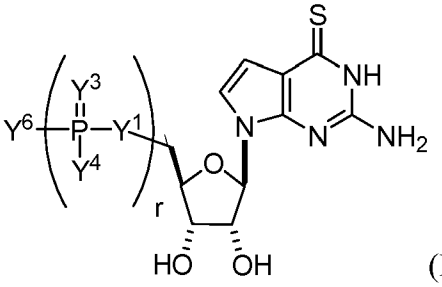
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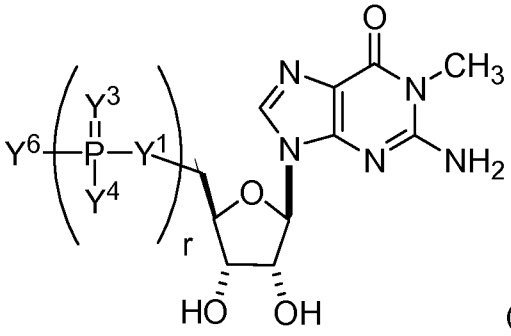
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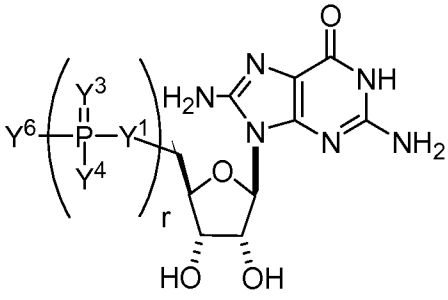
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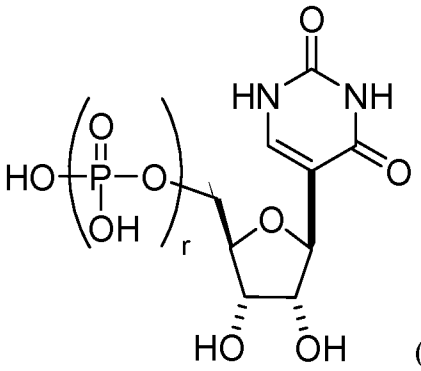
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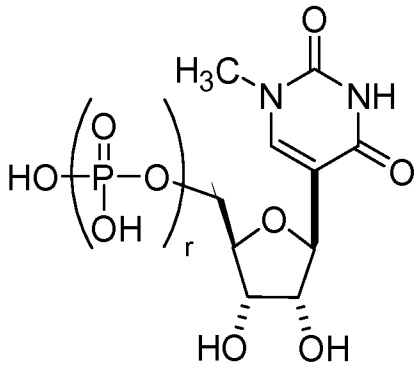
(BB- 237), or a pharmaceutically acceptable salt or stereoisomer thereof, wherein Y^1, Y^3,

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)).

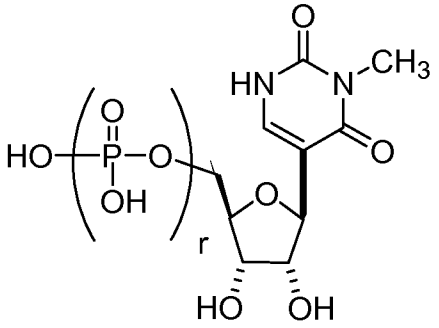
[000364] In some embodiments, the chemical modification can include replacement of C group at C-5 of the ring (e.g., for a pyrimidine nucleoside, such as cytosine or uracil) with N (e.g., replacement of the >CH group at C-5 with $>NR^{N1}$ group, wherein R^N1 is H or optionally substituted alkyl). For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:



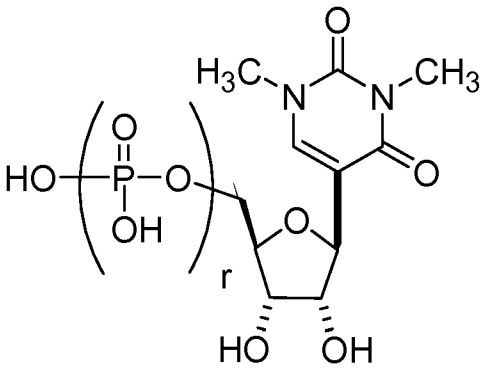
(BB- 238) or



(BB- 239)



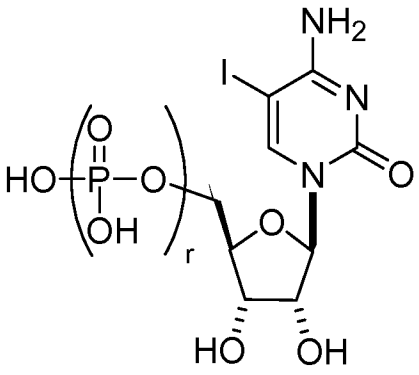
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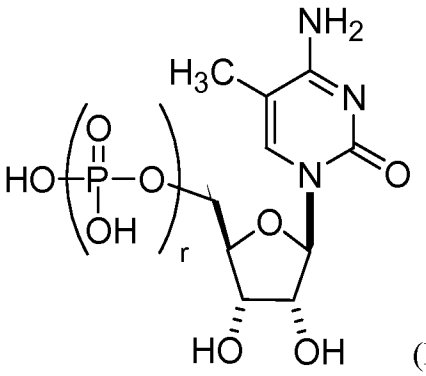
(BB- 240) or

(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).

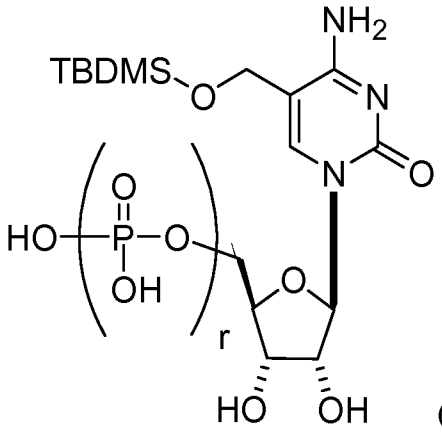
[000365] In another embodiment, the chemical modification can include replacement of the hydrogen at C-5 of cytosine with halo (e.g., Br, Cl, F, or I) or optionally substituted alkyl (e.g., methyl). For example, the building block molecule, which may be incorporated into a polynucleotide, primary construct, or mmRNA, can be:



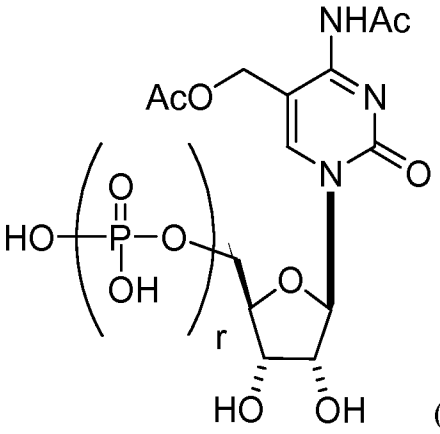
(BB- 242) or



(BB- 243)

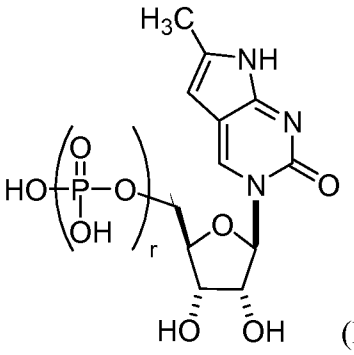


or



(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).

[000366] 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

[000367] 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.

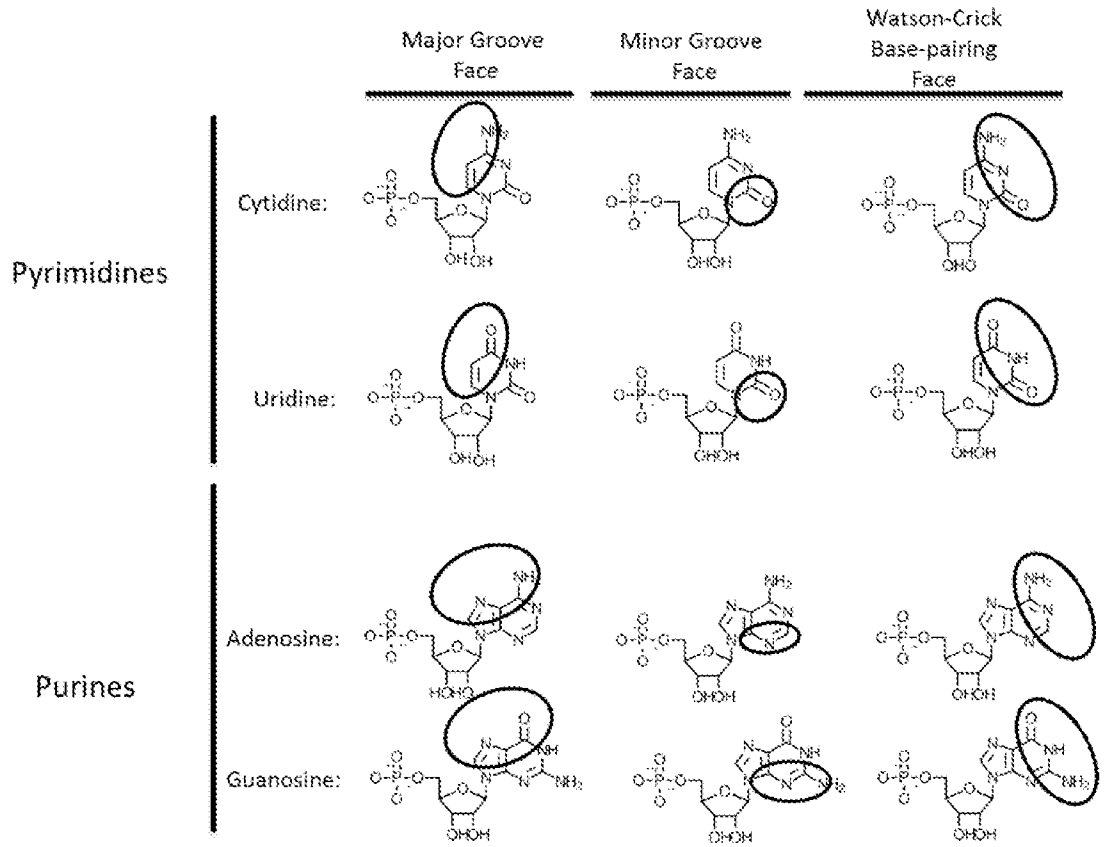
Modifications on the Nucleobase

[000368] 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).

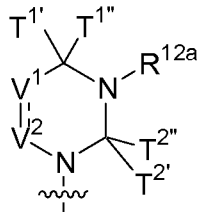
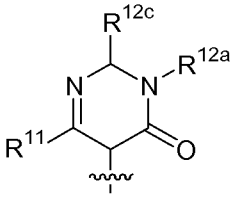
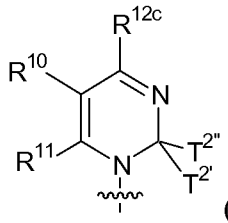
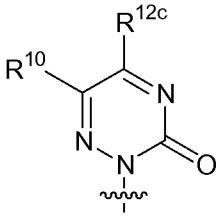
[000369] The modified nucleotide base pairing encompasses not only the standard adenosine-thymine, adenosine-uracil, or guanosine-cytosine base pairs, but also base pairs formed between nucleotides and/or modified nucleotides comprising non-standard or modified bases, wherein the arrangement of hydrogen 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.

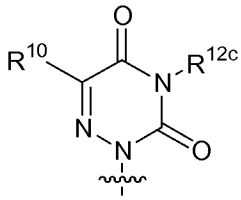
[000370] The modified nucleosides and nucleotides can include a modified nucleobase. Examples of nucleobases found in RNA include, but are not limited to, adenine, guanine, cytosine, and uracil. Examples of nucleobase found in DNA include, but are not limited to, adenine, guanine, cytosine, and thymine. 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



[000371] 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,

[000372] wherein

[000373] ⁓ is a single or double bond;

[000374] 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);

[000375] 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);

[000376] 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;

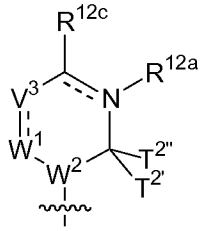
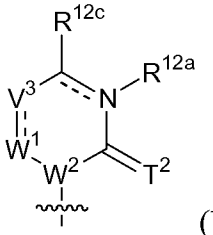
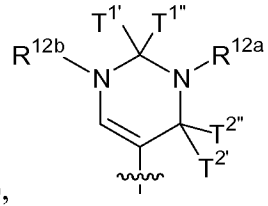
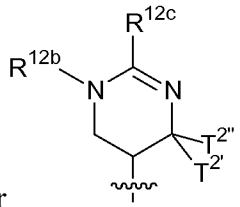
[000377] R^{11} is H or optionally substituted alkyl;

[000378] 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

[000379] 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.

[000380] Other exemplary modified uracils include those having Formula (b6)-(b9):


(b6),

(b7),

(b8), or


(b9), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000381] wherein

[000382] ⩬ is a single or double bond;

[000383] 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);

[000384] 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;

[000385] 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);

[000386] 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;

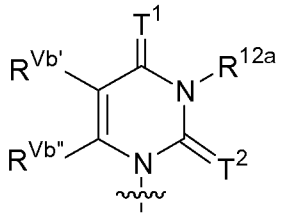
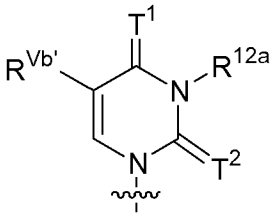
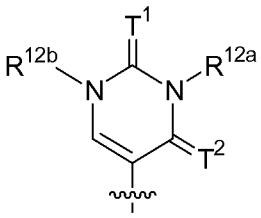
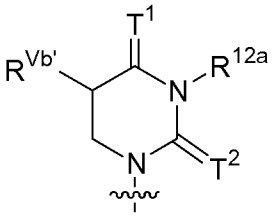
[000387] R^{12b} is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted aminoalkyl, optionally substituted aminoalkenyl, 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,

[000388] 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

[000389] 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.

[000390] Further exemplary modified uracils include those having Formula (b28)-(b31):


(b28),

(b29),

(b30), or

(b31), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000391] wherein

[000392] each of T^1 and T^2 is, independently, O (oxo), S (thio), or Se (seleno);

[000393] 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);

[000394] 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

[000395] 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),

[000396] 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.

[000397] 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.

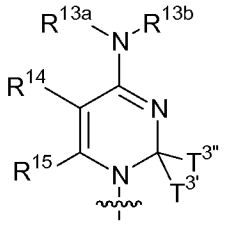
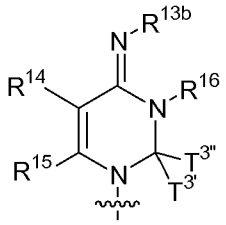
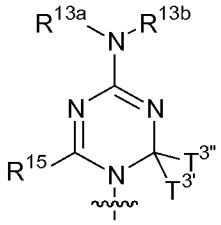
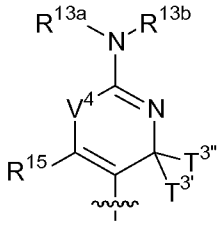
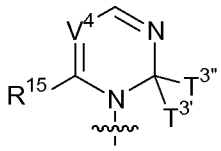
[000398] In other embodiments, each R^{12a} and R^{12b} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, or optionally substituted hydroxyalkyl. In particular embodiments, R^{12a} is H. In other embodiments, both R^{12a} and R^{12b} are H.

[000399] 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).

[000400] In some embodiments, $R^{Vb'}$ is optionally substituted alkoxycarbonylalkyl or optionally substituted carbamoylalkyl.

[000401] 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).

[000402] 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

[000403] 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);

[000404] 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;

[000405] 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);

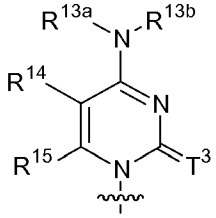
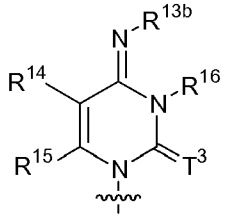
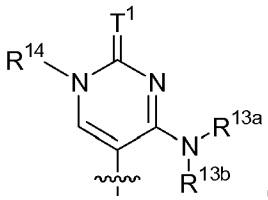
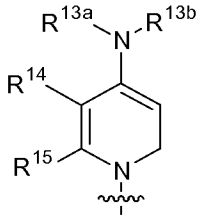
[000406] each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted

alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

[000407] 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

[000408] each of R^{15} and R^{16} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[000409] Further exemplary modified cytosines include those having Formula (b32)-(b35):


(b32),

(b33),

(b34), or

(b35), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000410] wherein

[000411] each of T^1 and T^3 is, independently, O (oxo), S (thio), or Se (seleno);

[000412] each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted

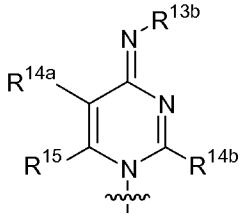
alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

[000413] 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

[000414] 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).

[000415] 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.

[000416] Further non-limiting examples of modified cytosines include compounds of Formula (b36):



(b36) or a pharmaceutically acceptable salt or stereoisomer thereof,

[000417] wherein

[000418] each R^{13b} is, independently, H, optionally substituted acyl, optionally substituted acyloxyalkyl, optionally substituted alkyl, or optionally substituted alkoxy,

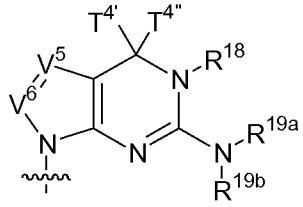
wherein the combination of R^{13b} and R^{14b} can be taken together to form optionally substituted heterocyclyl;

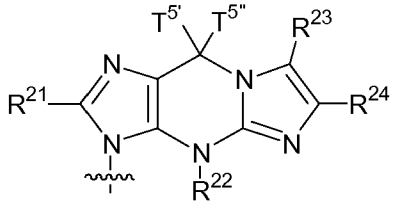
[000419] each R^{14a} and R^{14b} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl (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

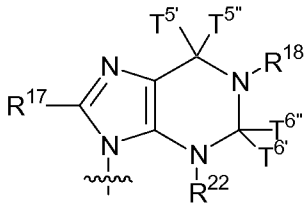
[000420] each of R^{15} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[000421] In particular embodiments, R^{14b} is an optionally substituted amino acid (e.g., optionally substituted lysine). In some embodiments, R^{14a} is H.

[000422] 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,

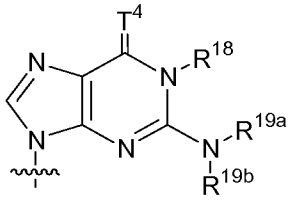
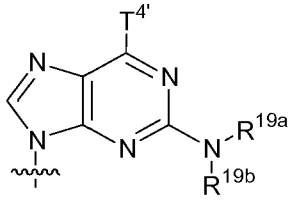
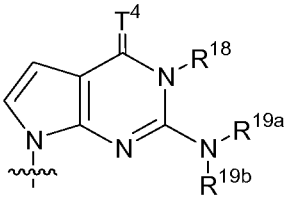
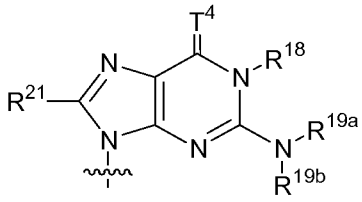
[000423] wherein

[000424] 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);

[000425] 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

[000426] 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.

[000427] Exemplary modified guanosines include compounds of Formula (b37)-(b40):


(b37),

(b38),

(b39),

or (b40), or a pharmaceutically acceptable salt or stereoisomer thereof,

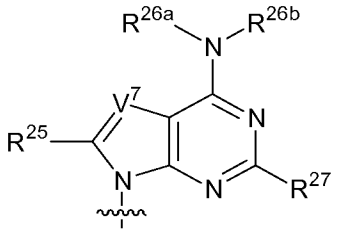
[000428] wherein

[000429] 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);

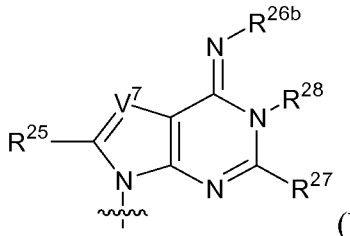
[000430] each of R^{18}, R^{19a}, R^{19b}, and R^{21} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, optionally substituted amino, or optionally substituted amino acid.

[000431] 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.

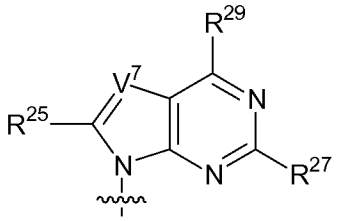
[000432] In some embodiments, B is a modified adenine. Exemplary modified adenines include compounds of Formula (b18)-(b20):



(b18),



(b19), or



(b20), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000433] wherein

[000434] 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);

[000435] each R^{25} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, or optionally substituted amino;

[000436] 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

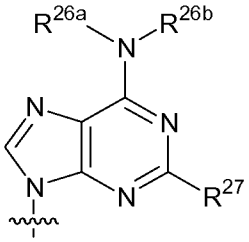
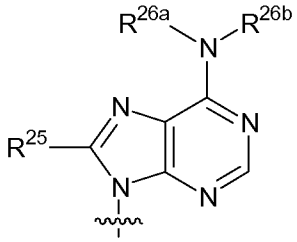
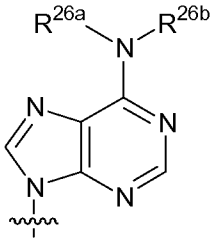
substituted hydroxyalkyl, optionally substituted hydroxyalkenyl, optionally substituted hydroxyalkynyl, optionally substituted alkoxy, or polyethylene glycol group (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR$', wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 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);

[000437] 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;

[000438] each R^{28} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

[000439] 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.

[000440] Exemplary modified adenines include compounds of Formula (b41)-(b43):

[000441]  (b41),  (b42), or  (b43), or a pharmaceutically acceptable salt or stereoisomer thereof,

[000442] wherein

[000443] each R^{25} is, independently, H, halo, thiol, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted thioalkoxy, or optionally substituted amino;

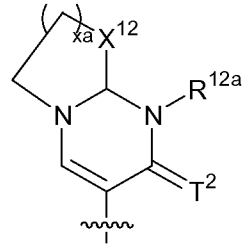
[000444] each of R^{26a} and R^{26b} is, independently, H, optionally substituted acyl, optionally substituted amino acid, optionally substituted carbamoylalkyl, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally 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

[000445] 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.

[000446] 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.

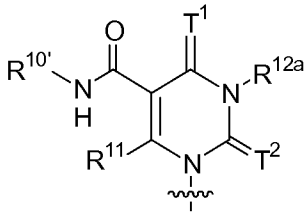
[000447] In particular embodiments, the optional substituent for R^{26a}, R^{26b}, or R^{29} is a polyethylene glycol group (e.g., -$(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10 (e.g., from 1 to 6 or from 1 to 4), each of s2 and s3, independently, is an integer from 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).

[000448] In some embodiments, B may have Formula (b21):



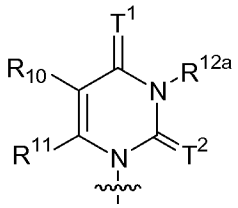
(b21), wherein X^{12} is, independently, O, S, optionally substituted alkylene (e.g., methylene), or optionally substituted heteroalkylene, xa is an integer from 0 to 3, and R^{12a} and T^2 are as described herein.

[000449] 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.

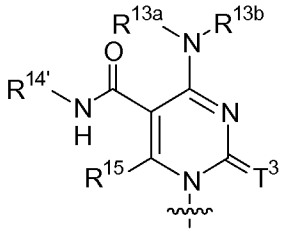
[000450] In some embodiments, B may have Formula (b23):



(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

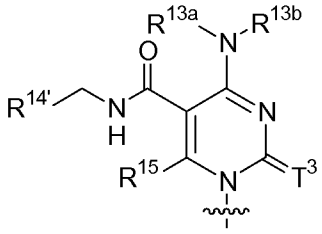
herein), T^1 (e.g., oxo or any substituent described herein), and T^2 (e.g., oxo or any substituent described herein) are as described herein.

In some embodiments, B may have Formula (b24):



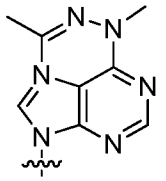
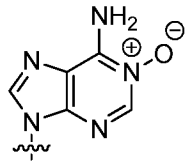
(b24), wherein $R^{14'}$ is, independently, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkaryl, optionally substituted alkheterocyclyl, optionally substituted aminoalkyl, 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.

[000451] 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.

[000452] 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).

[000453] 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.

[000454] 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.

[000455] 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.

[000456] 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)).

[000457] 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

[000458] 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).

[000459] 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.

[000460] 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).

[000461] 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

[000462] 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

[000463] 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.

[000464] 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.

[000465] 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.

[000466] 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.

[000467] 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.

[000468] 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.

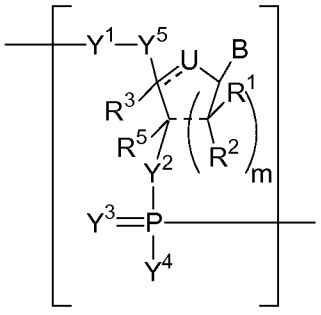
[000469] Different sugar modifications, nucleotide modifications, and/or internucleoside linkages (e.g., backbone structures) may exist at various positions in the polynucleotide, primary construct, or mmRNA. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) 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%).

[000470] 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

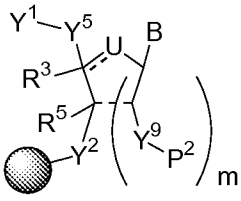
20% to 80%, from 20% to 90%, from 20% to 95%, from 20% to 100%, from 50% to 60%, from 50% to 70%, from 50% to 80%, from 50% to 90%, from 50% to 95%, from 50% to 100%, from 70% to 80%, from 70% to 90%, from 70% to 95%, from 70% to 100%, from 80% to 90%, from 80% to 95%, from 80% to 100%, from 90% to 95%, 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):



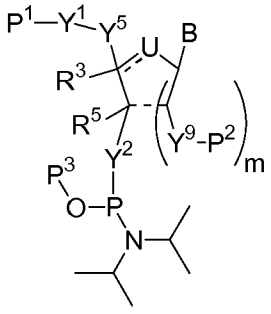
(Ia-1), comprising:

a) reacting a nucleotide of Formula (IV-1):



(IV-1),

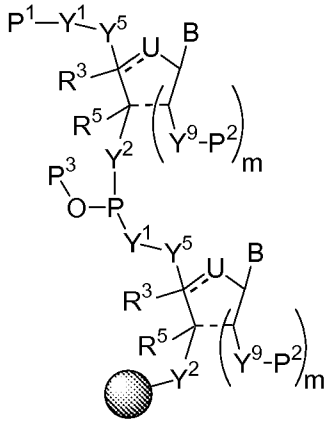
with a phosphoramidite compound of Formula (V-1):



(V-1),

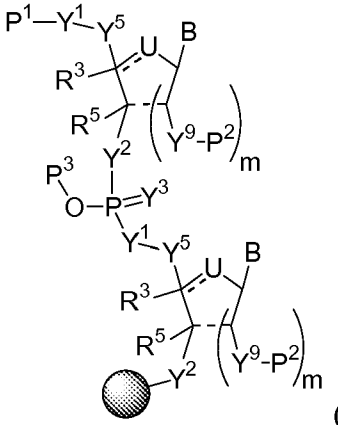
wherein Y^9 is H, hydroxy, phosphoryl, pyrophosphate, sulfate, amino, thiol, optionally substituted amino acid, or a peptide (e.g., including from 2 to 12 amino acids); and each P^1, P^2, and P^3 is, independently, a suitable protecting group; and  denotes a solid support;

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

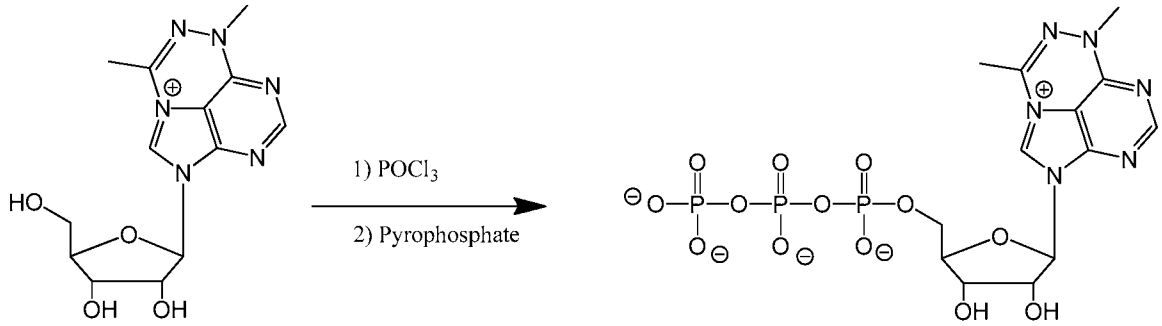
c) removing the protecting groups to yield the polynucleotide, primary construct, or mmRNA of Formula (Ia).

[000471] 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.

[000472] 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.

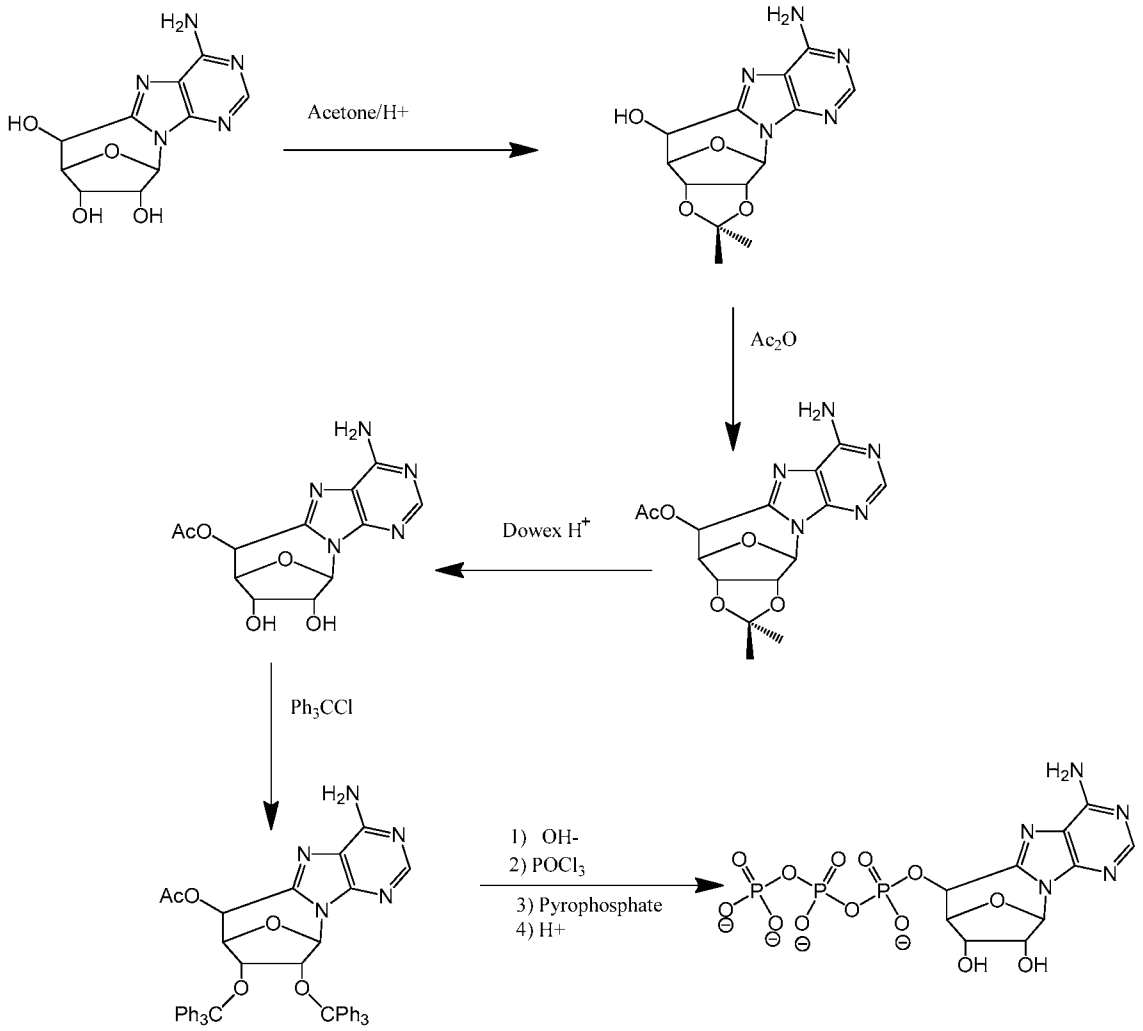
[000473] Exemplary syntheses of modified nucleotides, which are incorporated into a modified nucleic acid or mmRNA, e.g., RNA or mRNA, are provided below in Scheme 1 through Scheme 11. Scheme 1 provides a general method for phosphorylation of nucleosides, including modified nucleosides.

Scheme 1



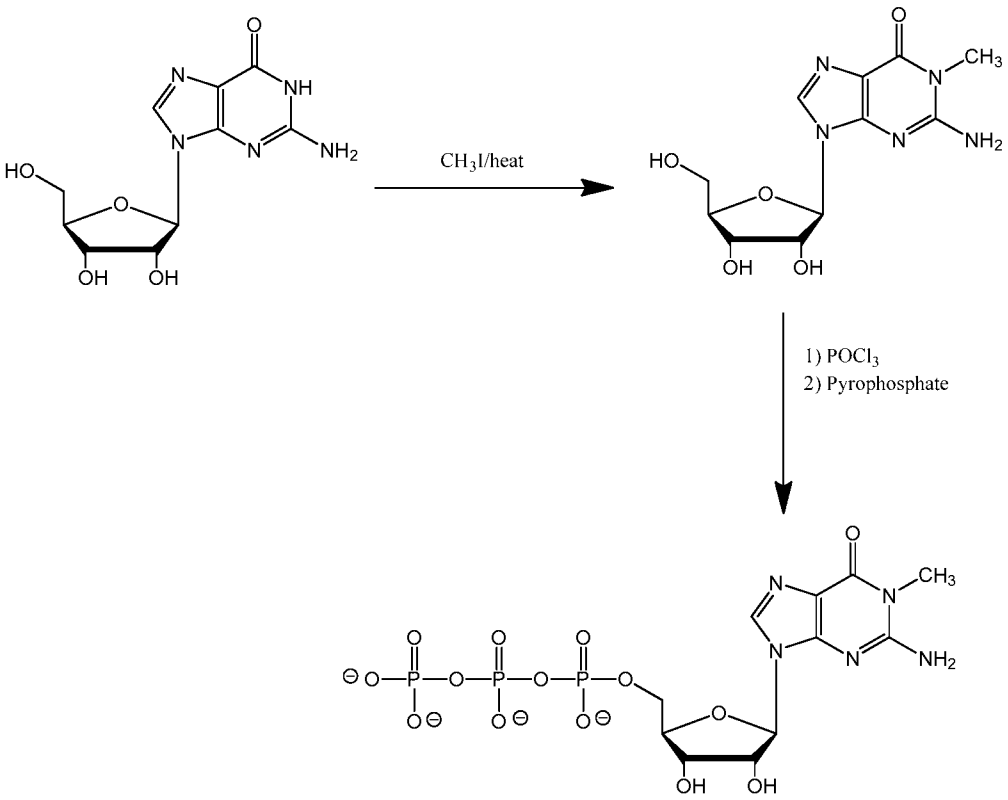
[000474] Various protecting groups may be used to control the reaction. For example, Scheme 2 provides the use of multiple protecting and deprotecting steps to promote phosphorylation at the 5′ position of the sugar, rather than the 2′ and 3′ hydroxyl groups.

Scheme 2

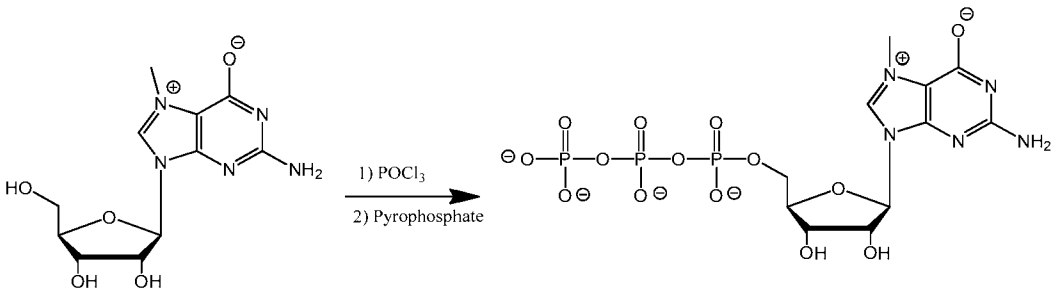


[000475] Modified nucleotides can be synthesized in any useful manner. Schemes 3, 4, and 7 provide exemplary methods for synthesizing modified nucleotides having a modified purine nucleobase; and Schemes 5 and 6 provide exemplary methods for synthesizing modified nucleotides having a modified pseudouridine or pseudoisocytidine, respectively.

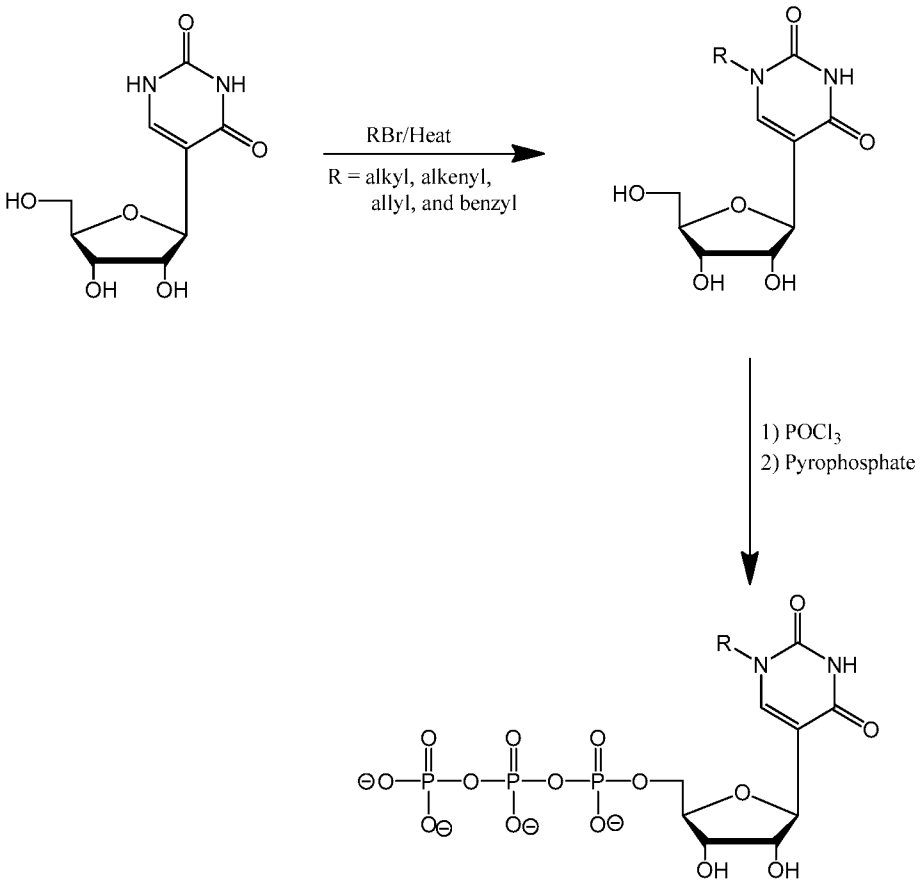
Scheme 3



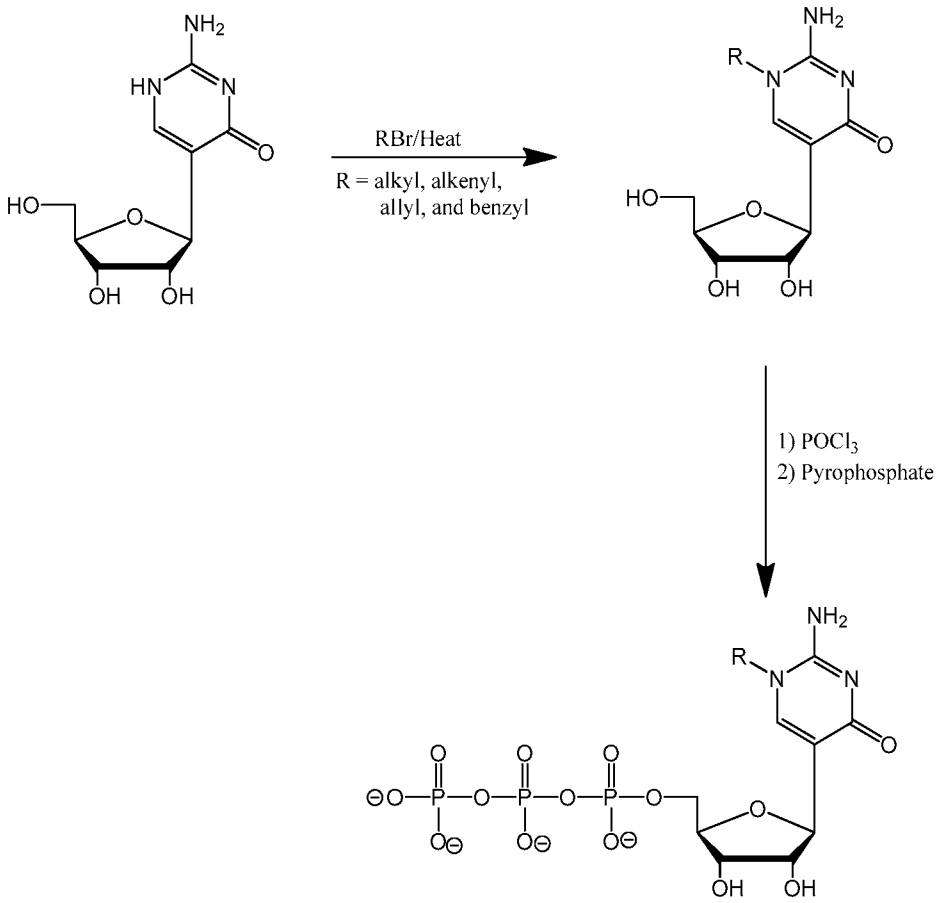
Scheme 4



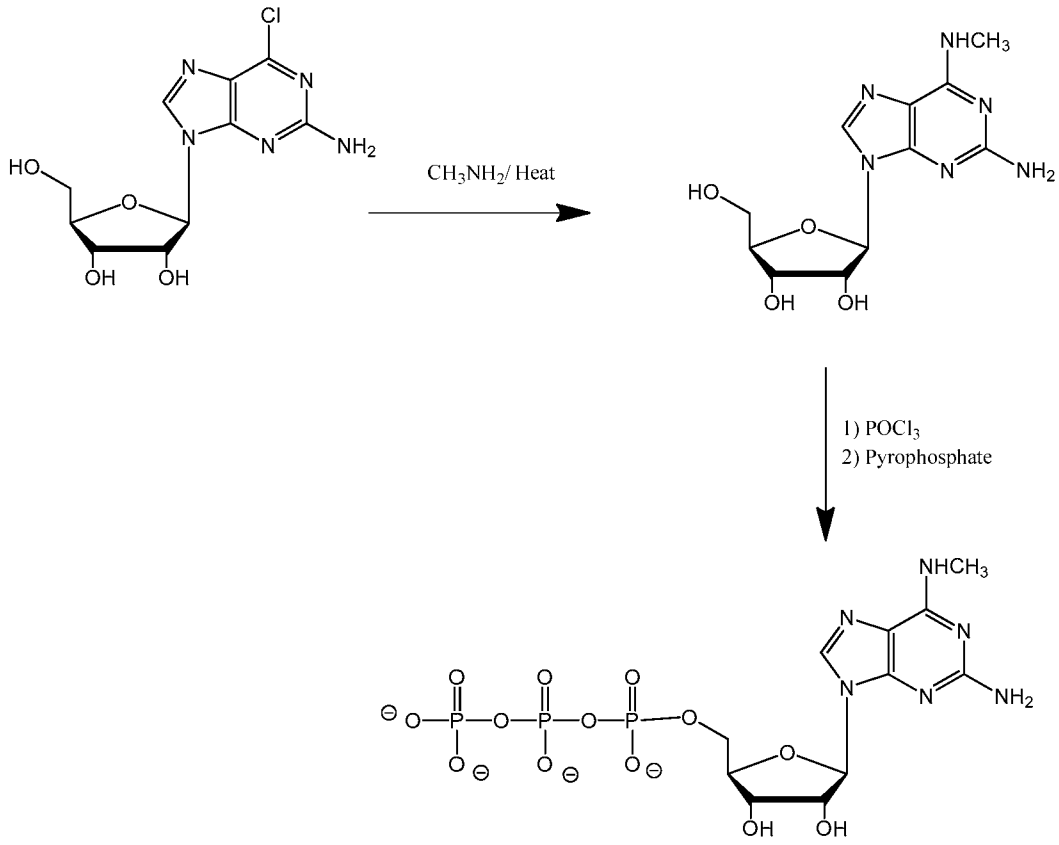
Scheme 5


RBr/Heat
R = alkyl, alkenyl,
allyl, and benzyl
1) POCl3
2) Pyrophosphate

Scheme 6

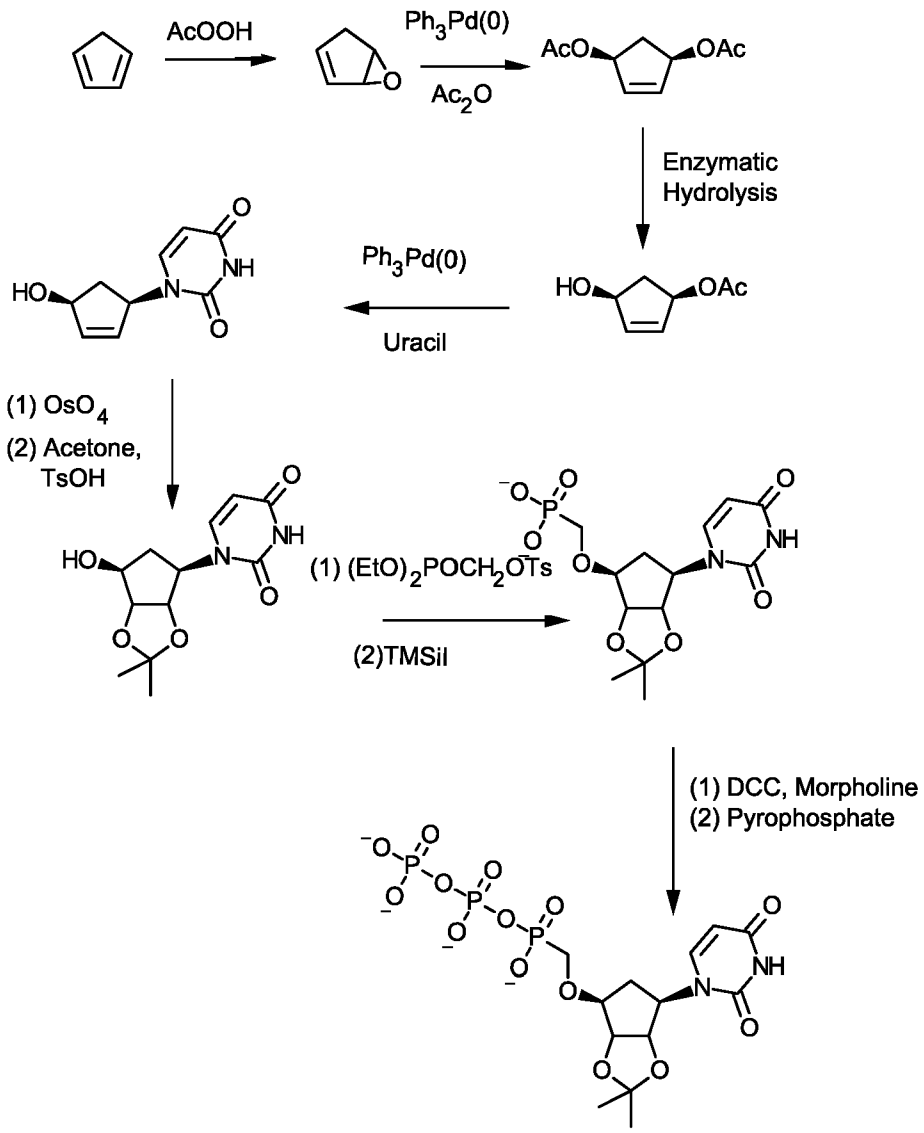

NH2
HN
N
O
HO
O
OH
OH
RBr/Heat
R = alkyl, alkenyl,
allyl, and benzyl
R
1) POCl3
2) Pyrophosphate
ΘO
P
Oϴ

Scheme 7

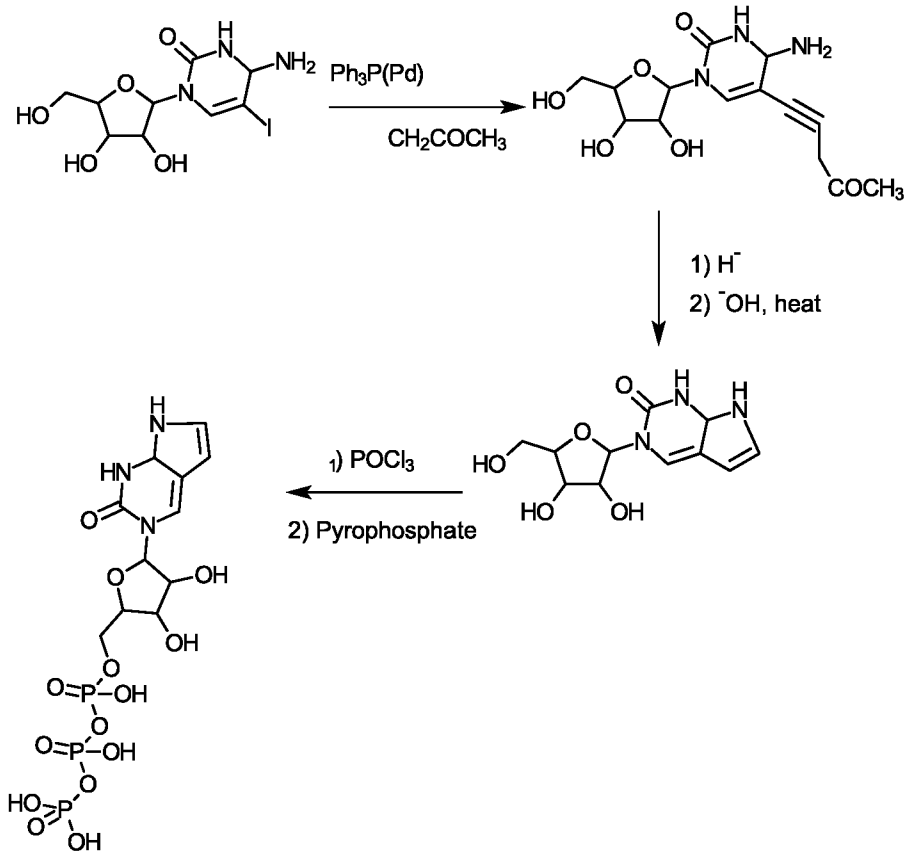


[000476] Schemes 8 and 9 provide exemplary syntheses of modified nucleotides. Scheme 10 provides a non-limiting biocatalytic method for producing nucleotides.

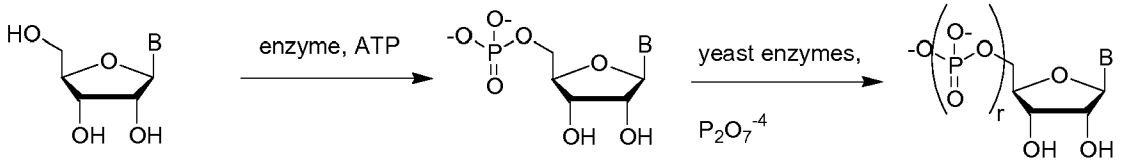
Scheme 8


AcOOH
Ph3Pd(0)
Ac2O
AcO
OAc
Enzymatic
Hydrolysis
HO
OAc
Ph3Pd(0)
Uracil
HO
NH
(1) OsO4
(2) Acetone,
TsOH
(1) (EtO)2POCH2OTs
(2)TMSil
(1) DCC, Morpholine
(2) Pyrophosphate

Scheme 9



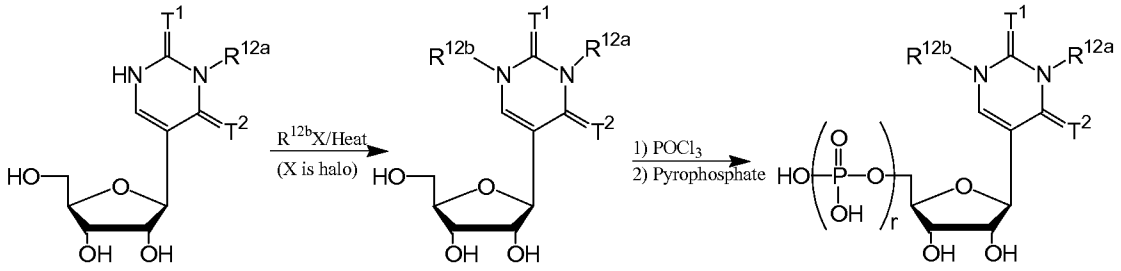
Scheme 10



[000477] 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

[000478] 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

[000479] 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	modified cytidine with (b10)/pseudouridine
	modified cytidine with (b10)/N1-methyl-pseudouridine
	modified cytidine with (b10)/5-methoxy-uridine

Formula (b10)	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

[000480] 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%).

[000481] 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%).

[000482] 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

[000483] 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).

[000484] 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.

[000485] 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.

[000486] 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.

[000487] 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.

[000488] 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

[000489] 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.

[000490] 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.

[000491] 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.

[000492] 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.

[000493] 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.

[000494] 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.

[000495] 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.

[000496] 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

[000497] 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).

[000498] 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.

[000499] *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.

[000500] 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)

[000501] 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.

[000502] 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.

[000503] 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

[000504] 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.

[000505] 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.

[000506] 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).

[000507] 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.

[000508] 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).

[000509] 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.

[000510] 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.

[000511] 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).

[000512] 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).

[000513] 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.

[000514] 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.

[000515] 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-l1,20,2-trien-10-amine or a pharmaceutically acceptable salt or stereoisomer thereof.

[000516] 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.

[000517] 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.

[000518] 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.

[000519] 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.

[000520] 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*.

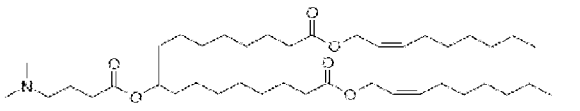
[000521] In one embodiment, the LNP formulations described herein may additionally comprise a permeability enhancer molecule. Non-limiting permeability enhancer molecules are described in US Patent Publication No. US20050222064; herein incorporated by reference in its entirety.

[000522] 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).

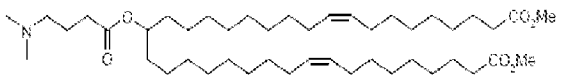
[000523] The nanoparticle formulations may be a carbohydrate nanoparticle comprising a carbohydrate carrier and a modified nucleic acid molecule (e.g., mmRNA). As a non-limiting example, the carbohydrate carrier may include, but is not limited to, an anhydride-modified phytoglycogen or glycogen-type 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).

[000524] 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.

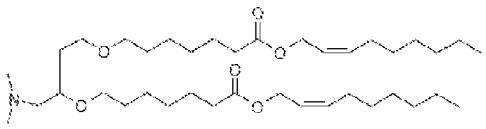
[000525] In one embodiment, the internal ester linkage may be located on either side of the saturated carbon. Non-limiting examples of reLNPs include,



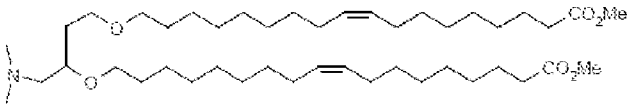
,



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and



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[000526] 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.

[000527] 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.

[000528] 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).

[000529] 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).

[000530] 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).

[000531] 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.

[000532] 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).

[000533] 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)..

[000534] 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).

[000535] 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.

[000536] 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.

[000537] 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).

[000538] 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).

[000539] 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.

[000540] 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®).

[000541] 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.

[000542] 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.

[000543] 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).

[000544] 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.

[000545] 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.

[000546] 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.

[000547] 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).

[000548] 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).

[000549] 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).

[000550] 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.

[000551] In one embodiment, the therapeutic nanoparticles may comprise at least one cationic polymer described herein and/or known in the art.

[000552] 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.

[000553] 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.

[000554] 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).

[000555] 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).

[000556] 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.

[000557] 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).

[000558] 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).

[000559] 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).

[000560] 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.

[000561] 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).

[000562] 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.

[000563] 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.

[000564] 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).

[000565] 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

[000566] 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).

[000567] 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.

[000568] 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.

[000569] 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).

[000570] 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.

[000571] 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).

[000572] 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).

[000573] 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.

[000574] 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).

[000575] 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 .

[000576] 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.

[000577] 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).

[000578] 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).

[000579] 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.

[000580] 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.

[000581] 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.

[000582] 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.

[000583] 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.

[000584] 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.

[000585] 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.

[000586] 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).

[000587] 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.

[000588] 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.

[000589] 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.

[000590] 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).

[000591] 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.

[000592] 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).

[000593] 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.

[000594] 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.

[000595] 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).

[000596] 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.

[000597] 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.

[000598] 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).

[000599] 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

[000600] 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).

[000601] 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.

[000602] 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

[000603] 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).

[000604] 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.

[000605] 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.

[000606] 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.

[000607] 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.

[000608] 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

[000609] 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

[000610] 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

[000611] 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.

[000612] 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.

[000613] 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.

[000614] 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.

[000615] 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

[000616] 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).

[000617] 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.

[000618] 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.

[000619] 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.

[000620] 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.

[000621] 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.

[000622] 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.

[000623] 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.

[000624] 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.

[000625] 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.

[000626] 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.

[000627] 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.

[000628] 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).

[000629] 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.

[000630] 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

[000631] 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).

[000632] 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).

[000633] 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

[000634] 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.

[000635] 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.

[000636] 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.

[000637] 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

[000638] 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).

[000639] 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

[000640] 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.

[000641] 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

[000642] 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.

[000643] 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).

[000644] 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.

[000645] 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).

[000646] In one embodiment, the modified mRNA may be encapsulated in a lipid nanoparticle and then the lipid nanoparticle may be encapsulated into a hyrdogel.

[000647] 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).

[000648] 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

[000649] 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

[000650] 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).

[000651] 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

[000652] 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.

[000653] 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

[000654] 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.

[000655] 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.

[000656] 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.

[000657] 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.

[000658] 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.

[000659] 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.

[000660] 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.

[000661] 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®.

[000662] 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.

[000663] 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.

[000664] 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.

[000665] 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

[000666] 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

[000667] 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

[000668] 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.

[000669] 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

[000670] 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

[000671] 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.

[000672] 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.

[000673] 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.

[000674] 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

[000675] 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

[000676] 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.

[000677] 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

[000678] 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.

[000679] 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.

[000680] 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).

[000681] In one embodiment, the invention provides for the polynucleotides, primary constructs or mmRNA compositions to be delivered in more than one injection.

[000682] 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.

[000683] 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.

[000684] 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.

[000685] 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.

[000686] 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.

[000687] 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.

[000688] 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.

[000689] 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.

[000690] 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

[000691] 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.

[000692] 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.

[000693] 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.

[000694] 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.

[000695] 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.

[000696] 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.

[000697] 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

[000698] 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.

[000699] 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).

[000700] 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.

[000701] 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

[000702] 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.

[000703] 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

[000704] 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

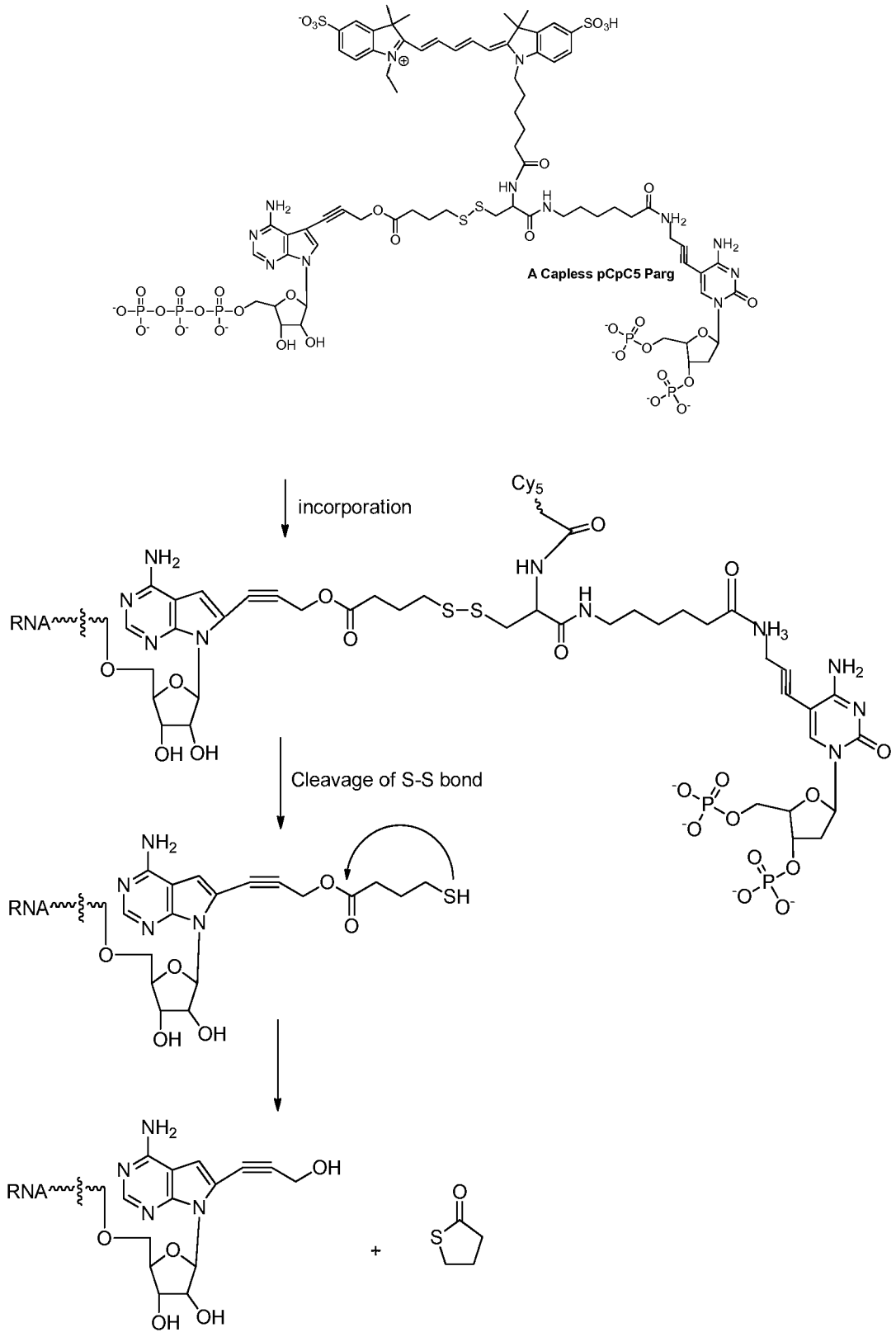
[000705] The polynucleotides, primary constructs or mmRNA described herein can be used in a number of different scenarios in which delivery of a substance (the "payload") to a biological target is desired, for example delivery of detectable substances for detection of the target, or delivery of a therapeutic 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.

[000706] 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.

[000707] 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



[000708] 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.

[000709] 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.

[000710] 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.

[000711] 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.

[000712] 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.

[000713] 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).

[000714] 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™ 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.

[000715] 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

[000716] 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.

[000717] 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

[000718] 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.

[000719] 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.

[000720] 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

[000721] 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

[000722] 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

[000723] 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

[000724] 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.

[000725] 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.

[000726] 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

[000727] 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

[000728] The pharmaceutical compositions described herein can be characterized by one or more of bioavailability, therapeutic window and/or volume of distribution.

Bioavailability

[000729] 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.

[000730] 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

[000731] 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

[000732] 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

[000733] 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

[000734] 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.

[000735] 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.

[000736] 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).

[000737] 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.

[000738] 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.

[000739] 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.

[000740] 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.

[000741] 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.

[000742] 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.

[000743] 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.

[000744] 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.

[000745] 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.

[000746] 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

[000747] 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

[000748] 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.

[000749] 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)).

[000750] 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.

[000751] 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.

[000752] 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.

[000753] 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.

[000754] 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.

[000755] 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.

[000756] 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.

[000757] 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.*

[000758] 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.

[000759] 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.

[000760] 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.

[000761] 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).

[000762] 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).

[000763] 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.

[000764] 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.

[000765] 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.

[000766] 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.

[000767] 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

[000768] 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.

[000769] 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®).

[000770] 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.

[000771] 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

[000772] 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.

[000773] 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.

[000774] 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

[000775] 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.

[000776] 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

[000777] 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

[000778] 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

[000779] 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

[000780] 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

[000781] 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.

[000782] 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

[000783] 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

[000784] 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

[000785] 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

[000786] 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

[000787] 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

[000788] 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

[000789] 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

[000790] 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

[000791] 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

[000792] 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*

[000793] 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

[000794] 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

[000795] 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

[000796] 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.

[000797] 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.

[000798] 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.

[000799] 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.

[000800] 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.

[000801] 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.

[000802] 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.

[000803] 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.

[000804] 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.

[000805] 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.

[000806] 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.

[000807] 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.

[000808] 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.

[000809] 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.

[000810] 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).

[000811] 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.

[000812] 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.

[000813] 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.

[000814] 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.

[000815] 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

[000816] 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.

[000817] 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).

[000818] 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).

[000819] 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.

[000820] 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).

[000821] 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).

[000822] In one embodiment, the polynucleotides, primary constructs or mmRNA of the present invention may encode amphipathic and/or immunogenic amphipathic peptides.

[000823] 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.

[000824] 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).

[000825] 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

[000826] 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

[000827] 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.

[000828] 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

[000829] 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

[000830] 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.

[000831] 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.

[000832] 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.

[000833] 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.

[000834] 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.

[000835] 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.

[000836] 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.

[000837] 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.

[000838] 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.

[000839] 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.

[000840] 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.

[000841] 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

[000842] 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.

[000843] 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.

[000844] 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

[000845] 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.

[000846] 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

[000847] 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.

[000848] 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

[000849] 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.

[000850] Co-administration of polynucleotides, primary constructs and mmRNA and RNAi agents are also provided herein.

Modulation of Biological Pathways

[000851] 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).

[000852] 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).

[000853] 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

[000854] 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.

[000855] 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.

[000856] 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.

[000857] 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

[000858] 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.

[000859] 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.

[000860] 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.

[000861] 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

[000862] 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.

[000863] 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.

[000864] 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).

[000865] 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

[000866] 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

[000867] 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.

[000868] 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.

[000869] 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.

[000870] 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.

[000871] 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.

[000872] 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.

[000873] 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

[000874] 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.

[000875] 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.

[000876] 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.

[000877] 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.

[000878] 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.

[000879] 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).

[000880] 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.

[000881] 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.

[000882] 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.

[000883] 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.

[000884] 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.

[000885] According to the present invention, these multi-administration devices may be utilized to deliver the single, multi- or split doses contemplated herein.

[000886] 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.

[000887] 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.

[000888] 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.

[000889] 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.

[000890] 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.

[000891] 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.

[000892] 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.

[000893] 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.

[000894] 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.

[000895] 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.

[000896] 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.

[000897] 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.

[000898] 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.

[000899] 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.

[000900] 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.

[000901] 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.

[000902] 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.

[000903] 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.

[000904] 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.

[000905] 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.

[000906] 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.

[000907] 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.

[000908] 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.

[000909] 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.

[000910] 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.

[000911] 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.

[000912] 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.

[000913] 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.

[000914] 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.

[000915] 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.

[000916] 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.

[000917] 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.

[000918] 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.

[000919] 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.

[000920] 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.

[000921] 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.

[000922] 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.

[000923] 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.

[000924] 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

[000925] 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.

[000926] 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.

[000927] 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.

[000928] 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.

[000929] 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.

[000930] 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.

[000931] 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.

[000932] 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.

[000933] 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.

[000934] 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.

[000935] 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.

[000936] 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.

[000937] 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.

[000938] 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.

[000939] 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.

[000940] 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

[000941] 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.

[000942] 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.

[000943] 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.

[000944] 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.

[000945] 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.

[000946] 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.

[000947] 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.

[000948] 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

[000949] 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.

[000950] *About:* As used herein, the term "about" means +/- 10% of the recited value.

[000951] *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.

[000952] *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.

[000953] *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.

[000954] *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).

[000955] *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.

[000956] *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.

[000957] *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.

[000958] *Biodegradable*: As used herein, the term "biodegradable" means capable of being broken down into innocuous products by the action of living things.

[000959] *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.

[000960] *Chemical terms*: The following provides the definition of various chemical terms from "acyl" to "thiol."

[000961] 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.

[000962] 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.

[000963] 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.

[000964] 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.

[000965] 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.

[000966] 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.

[000967] 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).

[000968] 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.

[000969] 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.

[000970] 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).

[000971] 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.

[000972] 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.

[000973] 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.

[000974] 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).

[000975] 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).

[000976] 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.

[000977] 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.

[000978] 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.

[000979] 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.

[000980] 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.

[000981] 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).

[000982] The term "amidine," as used herein, represents a $-C(=NH)NH_2$ group.

[000983] 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.

[000984] 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.

[000985] 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).

[000986] 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).

[000987] 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.

[000988] 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

[000989] 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.

[000990] 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.

[000991] The term "azido" represents an $–N_3$ group, which can also be represented as –N=N=N.

[000992] 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.

[000993] 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.

[000994] 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.

[000995] 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.

[000996] 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.

[000997] The term "carbonyl," as used herein, represents a C(O) group, which can also be represented as C=O.

[000998] The term "carboxyaldehyde" represents an acyl group having the structure –CHO.

[000999] The term "carboxy," as used herein, means $-CO_2H$.

[0001000] 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.

[0001001] 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.

[0001002] The term "cyano," as used herein, represents an –CN group.

[0001003] 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.

[0001004] 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.

[0001005] The term "diastereomer," as used herein means stereoisomers that are not mirror images of one another and are non-superimposable on one another.

[0001006] 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.

[0001007] 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%.

[0001008] The term "halo," as used herein, represents a halogen selected from bromine, chlorine, iodine, or fluorine.

[0001009] 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.

[0001010] 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.

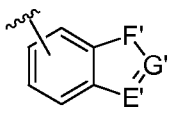
[0001011] The term "heteroalkylene," as used herein, refers to an alkylene group, as defined herein, in which one or two of the constituent carbon atoms have each been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkylene group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkylene groups.

[0001012] 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.

[0001013] 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-hexahydropyrrolo[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

[0001014] 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.

[0001015] 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.

[0001016] 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.

[0001017] 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.

[0001018] The term "hydrocarbon," as used herein, represents a group consisting only of carbon and hydrogen atoms.

[0001019] The term "hydroxy," as used herein, represents an –OH group.

[0001020] 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.

[0001021] 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.

[0001022] 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.

[0001023] 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.

[0001024] 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).

[0001025] The term "nitro," as used herein, represents an $-NO_2$ group.

[0001026] The term "oxo" as used herein, represents =O.

[0001027] 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.

[0001028] 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.

[0001029] 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.

[0001030] 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.

[0001031] 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.

[0001032] The term "sulfonyl," as used herein, represents an $-S(O)_2-$ group.

[0001033] 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.

[0001034] 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.

[0001035] 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.

[0001036] The term "thiol" represents an –SH group.

~~**[0001037]**~~ *Compound:* As used herein, the term "compound," is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted.

[0001038] 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.

[0001039] 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.

[0001040] 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.

[0001041] 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.

[0001042] *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.

[0001043] 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.

[0001044] *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.

[0001045] *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.

[0001046] *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.

[0001047] *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.

[0001048] *Delivery:* As used herein, "delivery" refers to the act or manner of delivering a compound, substance, entity, moiety, cargo or payload.

[0001049] *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.

[0001050] *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.

[0001051] *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.

[0001052] *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.

[0001053] *Distal:* As used herein, the term "distal" means situated away from the center or away from a point or region of interest.

[0001054] *Dosing regimen*: As used herein, a "dosing regimen" is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[0001055] *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.

[0001056] *Encapsulate:* As used herein, the term "encapsulate" means to enclose, surround or encase.

[0001057] *Encoded protein cleavage signal*: As used herein, "encoded protein cleavage signal" refers to the nucleotide sequence which encodes a protein cleavage signal.

[0001058] *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.

[0001059] *Exosome:* As used herein, "exosome" is a vesicle secreted by mammalian cells or a complex involved in RNA degradation.

[0001060] *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.

[0001061] *Feature:* As used herein, a "feature" refers to a characteristic, a property, or a distinctive element.

[0001062] *Formulation*: As used herein, a "formulation" includes at least a polynucleotide, primary construct or mmRNA and a delivery agent.

[0001063] *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.

[0001064] *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.

[0001065] *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.

[0001066] *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)).

[0001067] *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.

[0001068] *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).

[0001069] *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).

[0001070] *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.

[0001071] *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.

[0001072] *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.

[0001073] *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.

[0001074] *Mucus*: As used herein, "mucus" refers to the natural substance that is viscous and comprises mucin glycoproteins.

[0001075] *Naturally occurring:* As used herein, "naturally occurring" means existing in nature without artificial aid.

[0001076] *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.

[0001077] *Off-target:* As used herein, "off target" refers to any unintended effect on any one or more target, gene, or cellular transcript.

[0001078] *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.

[0001079] *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.

[0001080] *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.

[0001081] *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.

[0001082] *Paratope:* As used herein, a "paratope" refers to the antigen-binding site of an antibody.

[0001083] *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.

[0001084] *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.

[0001085] *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.

[0001086] *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.

[0001087] *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."

[0001088] *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.

[0001089] *Physicochemical:* As used herein, "physicochemical" means of or relating to a physical and/or chemical property.

[0001090] *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.

[0001091] *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.

[0001092] *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.

[0001093] *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.

[0001094] *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.

[0001095] *Protein cleavage signal:* As used herein "protein cleavage signal" refers to at least one amino acid that flags or marks a polypeptide for cleavage.

[0001096] *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.

[0001097] *Proximal:* As used herein, the term "proximal" means situated nearer to the center or to a point or region of interest.

[0001098] *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).

[0001099] *Purified:* As used herein, "purify," "purified," "purification" means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection.

[0001100] *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.

[0001101] *Signal Sequences:* As used herein, the phrase "signal sequences" refers to a sequence which can direct the transport or localization of a protein.

[0001102] *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.

[0001103] *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.

[0001104] *Split dose*: As used herein, a "split dose" is the division of single unit dose or total daily dose into two or more doses.

[0001105] *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.

[0001106] *Stabilized:* As used herein, the term "stabilize", "stabilized," "stabilized region" means to make or become stable.

[0001107] *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.

[0001108] *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.

[0001109] *Substantially equal*: As used herein as it relates to time differences between doses, the term means plus/minus 2%.

[0001110] *Substantially simultaneously*: As used herein and as it relates to plurality of doses, the term means within 2 seconds.

[0001111] *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.

[0001112] *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.

[0001113] *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.

[0001114] *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.

[0001115] *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.

[0001116] *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.

[0001117] *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.

[0001118] *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.

[0001119] *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.

[0001120] *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.

[0001121] *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.

[0001122] *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

[0001123] 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.

[0001124] 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.

[0001125] 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.

[0001126] 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.

[0001127] 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.

[0001128] 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.

[0001129] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Modified mRNA Production

[0001130] 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).

[0001131] 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*.

[0001132] 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.

[0001133] 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.

[0001134] 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.

[0001135] 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.

[0001136] 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.

[0001137] 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).

[0001138] 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
56149	cDNA sequence: ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAG CTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCC CTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTA GAGCAAGTGAGGAAGATCCAGGGCGATGGCGCAGCGCTCCAGGAGAA GCTGTGTGCCACCTACAAGCTGTGCCACCCCGAGGAGCTGGTGCTGCT CGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAG CCAGGCCCTGCAGCTGGCAGGCTGCTTGAGCCAACTCCATAGCGGCCT TTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCCGA GTTGGGTCCCACCTTGGACACACTGCAGCTGGACGTCGCCGACTTTGC CACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCC TGCAGCCCACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCCAGC GCCGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGG AGGTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGA
56150	cDNA having T7 polymerase site, AfeI and Xba restriction site: TAATACGACTCACTATA GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCAC C ATGGCTGGACCTGCCACCCAGAGCCCCATGAAGCTGATGGCCCTGCAG CTGCTGCTGTGGCACAGTGCACTCTGGACAGTGCAGGAAGCCACCCCC CTGGGCCCTGCCAGCTCCCTGCCCCAGAGCTTCCTGCTCAAGTGCTTA GAGCAAGTGAGGAAGATCCAGGGCGATGGCGCAGCGCTCCAGGAGAA GCTGTGTGCCACCTACAAGCTGTGCCACCCCGAGGAGCTGGTGCTGCT CGGACACTCTCTGGGCATCCCCTGGGCTCCCCTGAGCAGCTGCCCCAG

	CCAGGCCCTGCAGCTGGCAGGCTGCTTGAGCCAACTCCATAGCGGCCT TTTCCTCTACCAGGGGCTCCTGCAGGCCCTGGAAGGGATCTCCCCCGA GTTGGGTCCCACCTTGGACACACTGCAGCTGGACGTCGCCGACTTTGC CACCACCATCTGGCAGCAGATGGAAGAACTGGGAATGGCCCCTGCCC TGCAGCCCACCCAGGGTGCCATGCCGGCCTTCGCCTCTGCTTTCCAGC GCCGGGCAGGAGGGGTCCTGGTTGCCTCCCATCTGCAGAGCTTCCTGG AGGTGTCGTACCGCGTTCTACGCCACCTTGCCCAGCCCTGA AGCGCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTCTCTC CCTTGCACCTGTACCTCTTGGTCTTTGAATAAAGCCTGAGTAGGAAGG CGGCCGCTCGAGCATGCATCTAGA
56151	Optimized sequence; containing T7 polymerase site, AfeI and Xba restriction site TAATACGACTCACTATA GGGAAATAAGAGAGAAAAGAAGAGTAAGAAGAAATATAAGAGCCAC C ATGGCCGGTCCCGCGACCCAAAGCCCCATGAAACTTATGGCCCTGCAG TTGCTGCTTTGGCACTCGGCCCTCTGGACAGTCCAAGAAGCGACTCCT CTCGGACCTGCCTCATCGTTGCCGCAGTCATTCCTTTTGAAGTGTCTGG AGCAGGTGCGAAAGATTCAGGGCGATGGAGCCGCACTCCAAGAGAAG CTCTGCGCGACATACAAACTTTGCCATCCCGAGGAGCTCGTACTGCTC GGGCACAGCTTGGGGATTCCCTGGGCTCCTCTCTCGTCCTGTCCGTCGC AGGCTTTGCAGTTGGCAGGGTGCCTTTCCCAGCTCCACTCCGGTTTGTT CTTGTATCAGGGACTGCTGCAAGCCCTTGAGGGAATCTCGCCAGAATT GGGCCCGACGCTGGACACGTTGCAGCTCGACGTGGCGGATTTCGCAAC AACCATCTGGCAGCAGATGGAGGAACTGGGGATGGCACCCGCGCTGC AGCCCACGCAGGGGGCAATGCCGGCCTTTGCGTCCGCGTTTCAGCGCA GGGCGGGTGGAGTCCTCGTAGCGAGCCACCTTCAATCATTTTTGGAAG TCTCGTACCGGGTGCTGAGACATCTTGCGCAGCCGTGA AGCGCTGCCTTCTGCGGGGCTTGCCTTCTGGCCATGCCCTTCTTCTCTC CCTTGCACCTGTACCTCTTGGTCTTTGAATAAAGCCTGAGTAGGAAGG CGGCCGCTCGAGCATGCATCTAGA
56152	mRNA sequence (transcribed) GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAGCCA CC AUGGCCGGUCCCGCGACCCAAAGCCCCAUGAAACUUAUGGCCCUGCA GUUGCUGCUUUGGCACUCGGCCCUCUGGACAGUCCAAGAAGCGACU CCUCUCGGACCUGCCUCAUCGUUGCCGCAGUCAUUCCUUUUGAAGU GUCUGGAGCAGGUGCGAAAGAUUCAGGGCGAUGGAGCCGCACUCCA AGAGAAGCUCUGCGCGACAUACAAACUUUGCCAUCCCGAGGAGCUC GUACUGCUCGGGCACAGCUUGGGGAUUCCCUGGGCUCCUCUCUCGU CCUGUCCGUCGCAGGCUUUGCAGUUGGCAGGGUGCCUUUCCCAGCU CCACUCCGGUUUGUUCUUGUAUCAGGGACUGCUGCAAGCCCUUGAG GGAAUCUCGCCAGAAUUGGGCCCGACGCUGGACACGUUGCAGCUCG ACGUGGCGGAUUUCGCAACAACCAUCUGGCAGCAGAUGGAGGAACU GGGGAUGGCACCCGCGCUGCAGCCCACGCAGGGGGCAAUGCCGGCC UUUGCGUCCGCGUUUCAGCGCAGGGCGGGUGGAGUCCUCGUAGCGA

	GCCACCUUCAAUCAUUUUUGGAAGUCUCGUACCGGGUGCUGAGACA UCUUGCGCAGCCGUGA AGCGCUGCCUUCUGCGGGGCUUGCCUUCUGGCCAUGCCCUUCUUCUC UCCCUUGCACCUGUACCUCUUGGUCUUUGAAUAAAGCCUGAGUAGG AAG

Example 2: PCR for cDNA Production

[0001139] 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.

[0001140] 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.

[0001141] 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)

[0001142] 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.

[0001143] 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.

[0001144] 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

[0001145] 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.

[0001146] 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.

[0001147] 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

[0001148] 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.

[0001149] 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

[0001150] 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.

[0001151] 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

[0001152] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 56149; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 56152 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

[0001153] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 56149; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 56152 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

[0001154] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 56149; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 56152 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

[0001155] Synthetic mRNAs encoding human G-CSF (cDNA shown in SEQ ID NO: 56149; mRNA sequence fully modified with 5-methylcytosine at each cytosine and pseudouridine replacement at each uridine site shown in SEQ ID NO: 56152 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

[0001156] 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

[0001157] 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

[0001158] 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

[0001159] 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.

[0001160] 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.

[0001161] 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

[0001162] 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).

[0001163] 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

[0001164] 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.

[0001165] 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.

[0001166] 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

[0001167] 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: 56153; 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: 56154. The mCherry mRNA was modified with a 5meC at each cytosine and pseudouridine replacement at each uridine site.

[0001168] 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

[0001169] 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

[0001170] 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: 56153; 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.

[0001171] 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

[0001172] 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: 56153; 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

[0001173] 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: 56153; 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

[0001174] 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: 56152; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), erythropoietin (EPO) (mRNA sequence shown in SEQ ID NO: 56155; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Factor IX (mRNA sequence shown in SEQ ID NO: 56156; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or mCherry (mRNA sequence shown in SEQ ID NO: 56153; 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: 56157 and SEQ ID NO: 56158.

[0001175] 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.

[0001176] 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

[0001177] 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

[0001178] 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

[0001179] 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

[0001180] 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

[0001181] 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

[0001182] 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

[0001183] 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

[0001184] Modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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

[0001185] Modified Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 56156; 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 Vol. (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

[0001186] 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: 56156; 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

[0001187] PLGA microspheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001188] PLGA microspheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 56156; 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.

[0001189] 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

[0001190] PLGA micropsheres formulated with Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001191] Three batches of Factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001192] 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

[0001193] Factor IX mRNA RNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001194] 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: 56151. mRNA sequence shown in SEQ ID NO: 56152; 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: 56159. mRNA sequence shown in SEQ ID NO: 56156; 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%

[0001195] 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.

[0001196] 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

[0001197] 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

[0001198] G-CSF (mRNA sequence shown in SEQ ID NO: 56152; 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: 56155; 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

[0001199] 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.

[0001200] 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

[0001201] 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.

[0001202] 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

[0001203] 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.

[0001204] 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

[0001205] 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

[0001206] 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

[0001207] 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.

[0001208] 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

[0001209] 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.

[0001210] 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.

[0001211] 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

[0001212] 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

[0001213] 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

[0001214] 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

[0001215] 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

[0001216] 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

[0001217] 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

[0001218] Formulations containing modified EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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: 56152; 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

[0001219] In order to determine localization and/or trafficking of the modified mRNA, studies may be performed as follows.

[0001220] 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.

[0001221] 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

[0001222] 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

[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 G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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

[0001224] 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

[0001225] 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

[0001226] 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

[0001227] 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: 56155 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: 56152; 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

[0001228] 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

[0001229] 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

[0001230] 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

[0001231] 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).

[0001232] 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

[0001233] 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.

[0001234] 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

[0001235] mCherry mRNA (mRNA sequence shown in SEQ ID NO: 56160; 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%

[0001236] 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).

[0001237] 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.

[0001238] 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

[0001239] mCherry modified mRNA (mRNA sequence shown in SEQ ID NO: 56153; 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.

[0001240] 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

[0001241] 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.

[0001242] The ability of lipidoid-formulated Luciferase (IVT cDNA sequence as shown in SEQ ID NO: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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: 56163; mRNA sequence shown in SEQ ID NO: 56164, 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: 56153; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), and EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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

[0001243] Systemic intravenous administration of the formulations are created using various different lipidoids including, but not limited to, 98N12-5, C12-200, and MD1.

[0001244] 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.

[0001245] 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.

[0001246] 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

[0001247] 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.

[0001248] 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.

[0001249] 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.

[0001250] 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.

[0001251] 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

[0001252] 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.

[0001253] 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

[0001254] 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

[0001255] 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.

[0001256] 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.

[0001257] 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

[0001258] 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

[0001259] 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.

[0001260] 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.

[0001261] 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: 56155; 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.

[0001262] 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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.

[0001263] 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	Polypeptide per unit	Dose Splitting

				EPO	drug (pmol/ug)	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	--	--

[0001264] 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.

[0001265] 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.

[0001266] 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

[0001267] 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.

[0001268] 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

[0001269] 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.

[0001270] 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

[0001271] 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.

[0001272] 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

[0001273] 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

[0001274] 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.

[0001275] 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

[0001276] 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

[0001277] 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

[0001278] 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

[0001279] 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

[0001280] 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

[0001281] 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

[0001282] 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

[0001283] A formulation containing 100 µg of modified human erythropoietin mRNA(mRNA shown in SEQ ID NO: 56155; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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

[0001284] A formulation containing 100 µg of one of two versions of modified human G-CSF mRNA(mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001285] Three control groups were administered either 100 µg of modified luciferase mRNA (IVT cDNA sequence shown in SEQ ID NO: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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.

[0001286] 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

[0001287] 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.

[0001288] 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

[0001289] A formulation containing 100 μg of either modified mCherry mRNA (mRNA sequence shown in SEQ ID NO: 56153; 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

[0001290] 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

[0001291] 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

[0001292] 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: 56155; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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

[0001293] Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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.

[0001294] 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

[0001295] Modified human EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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

[0001296] 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

[0001297] 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

[0001298] 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.

[0001299] 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.

[0001300] 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

[0001301] 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: 56153; 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: 56154.

[0001302] 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

[0001303] 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: 56152; polyA tail of

approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Factor IX (mRNA shown in SEQ ID NO: 56156; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or mCherry (mRNA sequence shown in SEQ ID NO: 56153; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1).

[0001304] 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

[0001305] Human vascular endothelial growth factor-isoform A (VEGF-A) modified mRNA (mRNA sequence shown in SEQ ID NO: 56165; 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.

[0001306] The fully optimized mRNA encoding VEGF-A (mRNA sequence shown in SEQ ID NO: 56165; 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

[0001307] 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.

[0001308] 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: 56156; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1), Luciferase (IVT cDNA sequence shown in SEQ ID NO: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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

[0001309] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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 $p<0.05$.

[0001310] 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.

[0001311] 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	Neutrophil 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

[0001312] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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).

[0001313] 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.

[0001314] In Table 72, an asterisk(*) indicates statistical significance at $p<0.001$ compared to buffer.

[0001315] 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

[0001316] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and human EPO mmRNA (mRNA sequence shown in SEQ ID NO: 56155; 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.

[0001317] Controls included Luciferase (IVT cDNA sequence shown in SEQ ID NO: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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

[0001318] Human EPO modified mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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.

[0001319] Controls included Luciferase (mRNA sequence shown in SEQ ID NO: 56162, 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

[0001320] Studies utilizing multiple intramuscular injection sites at one time point were designed and performed.

[0001321] The design of a single multi-dose experiment involved using human erythropoietin (EPO) mmRNA (mRNA sequence shown in SEQ ID NO: 56155; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) or G-CSF mmRNA (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001322] 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.

[0001323] 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

[0001324] Several variants of mmRNAs encoding human Granulocyte colony stimulating factor (G-CSF) (mRNA sequence shown in SEQ ID NO: 56152; 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).

[0001325] 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

[0001326] 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.

[0001327] 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.

[0001328] 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

[0001329] mmRNA encoding human G-CSF (mRNA sequence shown in SEQ ID NO: 56152; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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.

[0001330] 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.

[0001331] 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

[0001332] 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).

[0001333] 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.

[0001334] 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

[0001335] 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

[0001336] 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: 56152; 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: 56162; 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: 56162; 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

[0001337] 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: 56152; 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: 56153; 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)

[0001338] 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.

[0001339] 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

[0001340] 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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: 56152;

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

[0001341] 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

[0001342] 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

[0001343] G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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: 56156; 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.

[0001344] 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

[0001345] 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

[0001346] 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

[0001347] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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 %

[0001348] 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

[0001349] 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

[0001350] 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

[0001351] 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.

[0001352] 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.

[0001353] 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

[0001354] Modified mRNA encoding human G-CSF (mRNA sequence shown in SEQ ID NO: 56152; 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: 56161; mRNA sequence shown in SEQ ID NO: 56162, 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.

[0001355] 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.

[0001356] 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

[0001357] 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).

[0001358] 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.

[0001359] 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.

[0001360] 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.

[0001361] 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).

[0001362] 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).

[0001363] 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

[0001364] 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: 56152; 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:

56162; 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: 56162; 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.

[0001365] 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

[0001366] 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: 56152; 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: 56153; 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.

[0001367] 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

[0001368] 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: 56152; 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: 56162; 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

[0001369] 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: 56152; 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: 56153; 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.

[0001370] 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

[0001371] 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: 56152; 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.	-	-

[0001372] 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

[0001373] Female BALB/C mice (n=5) were injected intramuscularly with G-CSF mRNA (G-CSF mRNA unmod) (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001374] 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.

[0001375] 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).

[0001376] 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.

[0001377] 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.

[0001378] 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

[0001379] 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: 56152; 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: 56156; 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.

[0001380] 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

[0001381] 500 ng of G-CSF (mRNA sequence shown in SEQ ID NO: 56152; 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: 56153; 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.

[0001382] 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).

[0001383] 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.

[0001384] 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	0	66	140	54	97	149

set)						
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 (4th set)	131	28	18	53	24	29
5-methylcytosine and N1-methyl-pseudouridine (4th 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

[0001385] 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: 56162; 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).

[0001386] 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.

[0001387] 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.

[0001388] 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

[0001389] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001390] 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.

[0001391] 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

[0001392] Balb-C mice (n=4) are intramuscularly injected in each leg with modified G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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: 56162; 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

[0001393] 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: 56162; 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.

[0001394] 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

[0001395] Balb-C mice (n=4) were subcutaneously injected with 200ul of 100 ug of modified luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001396] 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

[0001397] 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: 56152; 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.

[0001398] 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

[0001399] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001400] 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.

[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 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

[0001402] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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).

[0001403] 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.

[0001404] 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

[0001405] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001406] 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.

[0001407] 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).

[0001408] 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.

[0001409] 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: 56162; 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.

[0001410] 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.

[0001411] 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.

[0001412] 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

[0001413] 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.

[0001414] 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: 56162; 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.

[0001415] 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.

[0001416] 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

[0001417] 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: 56152; 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).

[0001418] 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: 56162; 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.

[0001419] 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.

[0001420] 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 (pg/ml) HeLa cells**	**G-CSF protein (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

[0001421] 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*.

[0001422] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; polyA tail of approximately 160 nucleotides not shown in sequence; 5'cap, Cap1) and G-CSF mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001423] 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	Pass	Pass	-	-	+/-	++++	NT	NT

(m^6A)								
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 (f^5C)	Pass	Pass	-***	-***	-	+	NT	NT
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/F	+**	+/-	-	+	+	NT

	Pass**	ail**						
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-carbomethoxyvinyl) 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

[0001424] 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%	A,G	Pass WT	Pass WT	+	NT	NT	NT	+

	uridine								
5-methylcytidine	100% 2-thiouridine	A,G	Pass WT	Pass WT	-	+	NT	NT	
5-methylcytidine	pseudouridine	A,G	Pass WT	Pass WT	+	+	++	+	+
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 triphosphate	pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	+/-	NT	NT	NT
2 Fluorocytosine triphosphate	N1-methyl-pseudouridine	A,2 Fluoro GTP	Pass	Pass	-	-	NT	NT	NT

Example 79. 2'Fluoro Chemistries in PBMC

[0001425] The ability of G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001426] 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

[0001427] 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.

[0001428] 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

[0001429] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001430] 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 5-methylcytosine and N1-methyl-pseudouridine	43-66A	45.8	0.4	0.18	33.4
	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

[0001431] 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.

[0001432] 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).

[0001433] 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

[0001434] Human Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001435] 250 ng of codon optimized Human Factor IX mRNA (mRNA sequence shown in SEQ ID NO: 56156; 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

[0001436] Human G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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: 56155; 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.

[0001437] Controls included Luciferase (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001438] 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

[0001439] mCherry modified mRNA (mRNA sequence shown in SEQ ID NO: 56153; 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: 56162; 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

[0001440] 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.

[0001441] 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

[0001442] Mice were injected intramuscularly with 200 ug of G-CSF modified mRNA (mRNA sequence shown in SEQ ID NO: 56152; 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

[0001443] HEK293 cells were transfected with modified mRNA (mmRNA) VEGF-A (mRNA sequence shown in SEQ ID NO: 56165; 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

[0001444] 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: 56164; 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.

[0001445] 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.

[0001446] 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

[0001447] 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: 56162; 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).

[0001448] 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.

[0001449] 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).

[0001450] 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

[0001451] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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).

[0001452] 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.

[0001453] 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.

[0001454] 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

[0001455] 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: 56162; 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.

[0001456] 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

[0001457] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001458] 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: 56162; 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.

[0001459] 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 (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 93. External Osmotic Pump Study

[0001460] 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: 56162; 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.

[0001461] 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	PBS	1.00	50	50	2.5

Luciferase					
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

[0001462] 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.

[0001463] 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: 56162; 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

[0001464] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001465] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001466] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001467] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001468] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001469] Prior to reconstitution, luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001470] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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%

[0001471] 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

[0001472] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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%

[0001473] 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

[0001474] 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

[0001475] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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%

[0001476] 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

[0001477] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001478] 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

[0001479] Lipoplexed luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001480] 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

[0001481] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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%

[0001482] 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

[0001483] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001484] 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

[0001485] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[0001486] 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.

[0001487] 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

[0001488] 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

[0001489] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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

[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, 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

[0001491] Luciferase mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001492] 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

[0001493] 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

[0001494] EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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: 56152; 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: 56156; 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%

[0001495] 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

[0001496] EPO mRNA (mRNA sequence shown in SEQ ID NO: 56155; 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: 56152; 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%

[0001497] 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

[0001498] 500 ng of VEGF mRNA (mRNA sequence shown in SEQ ID NO: 56165 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

[0001499] HEK293 cells were transfected EPO modified mRNA (mRNA sequence shown in SEQ ID NO:56155; 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: 56166; 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: 56167; 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

[0001500] 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: 56168; 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: 56153; 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: 56164; 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.

[0001501] 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

[0001502] Herceptin heavy chain (HC) mRNA (mRNA sequence shown in SEQ ID NO: 56169; 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) modified mRNA (mRNA sequence shown in SEQ ID NO: 56170; 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%

[0001503] 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

[0001504] 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.

[0001505] 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.

[0001506] 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

[0001507] 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)

[0001508] 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

[0001509] 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

[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 37ºC 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: 56165; 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.

[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 180.

[0001512] 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

[0001513] 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. Next day, 250 ng of vascular endothelial growth factor (VEGF) modified RNA (mRNA sequence shown in SEQ ID NO: 56165; 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.

[0001514] 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.

[0001515] 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

[0001516] Lipoplexed vascular endothelial growth factor (VEGF) mRNA (mRNA sequence shown in SEQ ID NO: 56165; 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

[0001517] 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 granulocyte colony stimulating factor (G-CSF) modified RNA (mRNA sequence shown in SEQ ID NO: 56152; 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.

[0001518] 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

[0001519] 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 37ºC in 5% CO_2 atmosphere overnight. Next day, 250 ng of factor IX modified RNA (mRNA sequence shown in SEQ ID NO: 56156; 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.

[0001520] 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

[0001521] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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%

[0001522] 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 186, "NT" means not tested.

Table 186. 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

[0001523] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001524] 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

[0001525] Luciferase modified mRNA (mRNA sequence shown in SEQ ID NO: 56162; 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.

[0001526] 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

[0001527] 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.

[0001528] 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.

[0001529] 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 8144-16131;

(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 8144-16131, 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 8144-16131, 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: 16132-56137.

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.

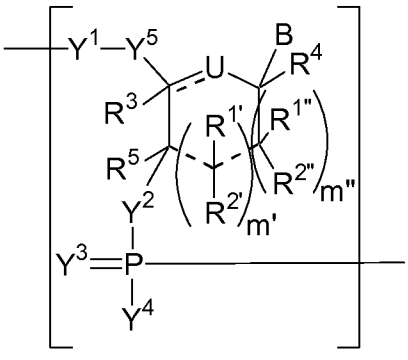
4. The isolated polynucleotide of any one of claims 1-3 which is purified.

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.

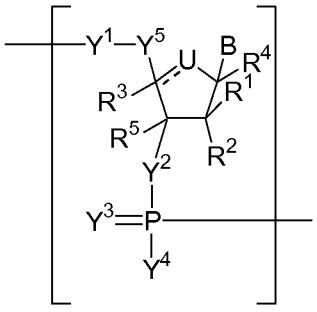
11. The isolated polynucleotide of claim 10, wherein each of R^1, $R^{1'}$, and $R^{1''}$, if present, is H.

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.

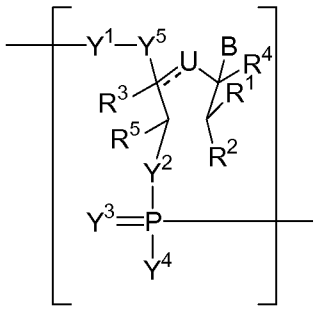
15. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleotides having Formula (IIa):



(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.

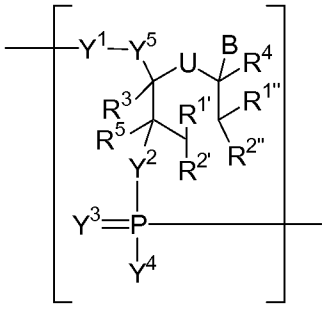
17. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleosides having Formula (IId):



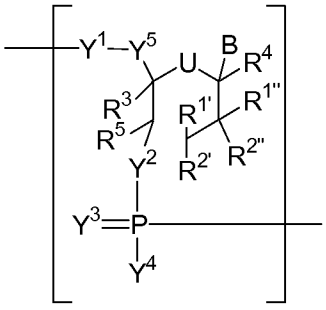
(IId), or a pharmaceutically acceptable salt or stereoisomer thereof.

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.

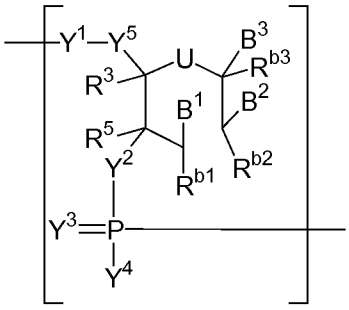
19. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleotides, each of said linked nucleotides independently having one of Formulas (IIg)-(IIj):



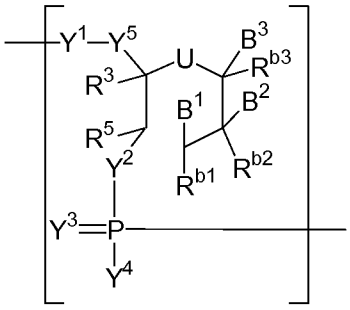
(IIg),



(IIh),

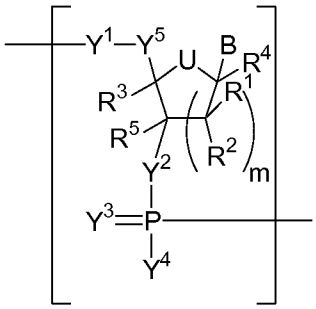


(IIi), or



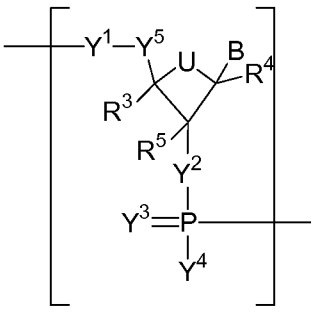
(IIj), or a pharmaceutically acceptable salt or stereoisomer thereof.

20. The isolated polynucleotide of claim 8, wherein said first region comprises n number of linked nucleosides having Formula (IIk):



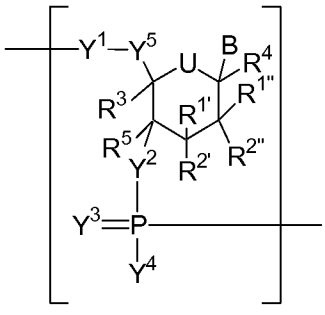
(IIk) , or a pharmaceutically acceptable salt or stereoisomer thereof.

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;

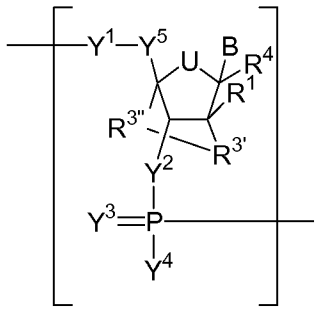
each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

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;

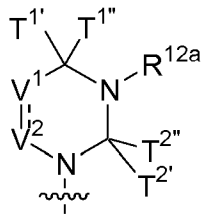
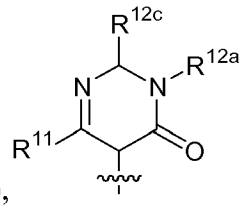
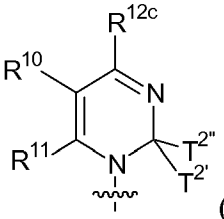
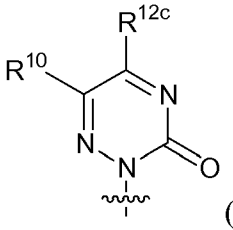
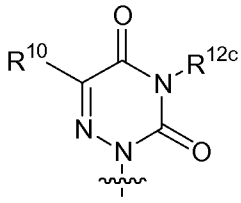
each of Y^1, Y^2, and Y^3, is, independently, O, S, $-NR^{N1}-$, optionally substituted alkylene, or optionally substituted heteroalkylene, wherein R^{N1} is H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl;

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;

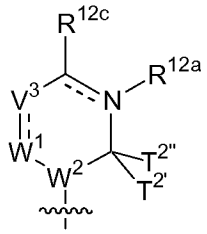
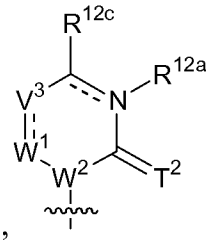
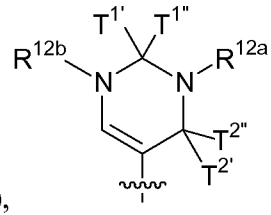
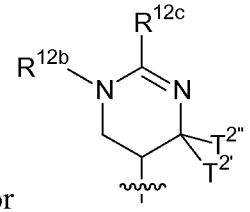
R^{10} is H, halo, optionally substituted amino acid, hydroxy, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aminoalkyl, optionally substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, 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

$\backsimeq$ 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;

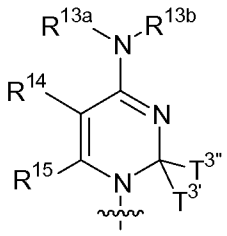
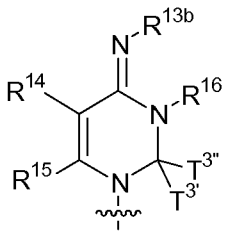
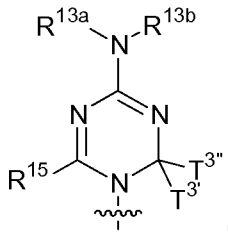
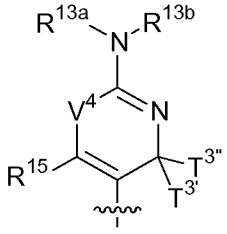
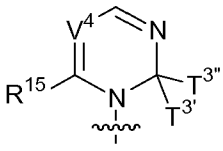
R^{12a} is H, optionally substituted alkyl, optionally substituted aminoalkyl, or absent;

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 $C_{1\text{-}20}$ 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 $C_{1\text{-}6}$ 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;

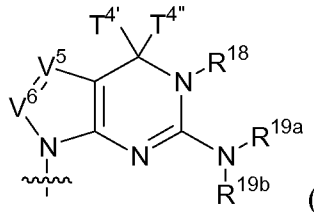
each of R^{13a} and R^{13b} is, independently, H, optionally substituted acyl, optionally substituted alkyl, or optionally substituted alkoxy, wherein the combination of R^{13b} and R^{14} can be taken together to form optionally substituted heterocyclyl;

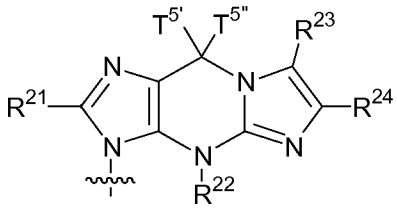
each R^{14} is, independently, H, halo, hydroxy, thiol, optionally substituted acyl, optionally substituted amino acid, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted hydroxyalkyl, optionally substituted alkoxy, optionally substituted alkenyloxy, optionally substituted alkynyloxy,

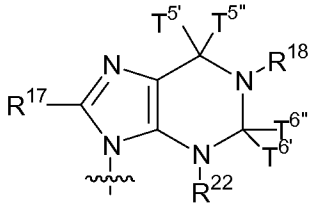
optionally substituted aminoalkoxy, optionally substituted alkoxyalkoxy, optionally substituted amino, azido, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted alkheterocyclyl, or optionally substituted aminoalkyl; and

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,

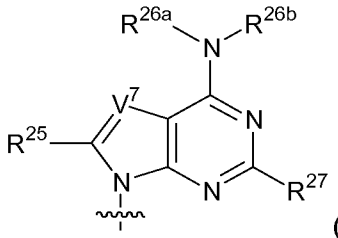
wherein

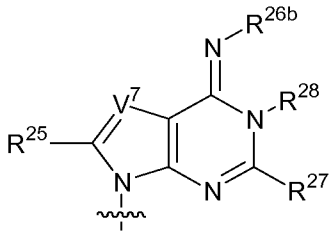
each of $T^{4'}$, $T^{4''}$, $T^{5'}$, $T^{5''}$, $T^{6'}$, and $T^{6''}$ is, independently, H, optionally substituted alkyl, or optionally substituted alkoxy, and wherein the combination of $T^{4'}$ and $T^{4''}$ or the combination of $T^{5'}$ and $T^{5''}$ or the combination of $T^{6'}$ and $T^{6''}$ together form O, S, or Se;

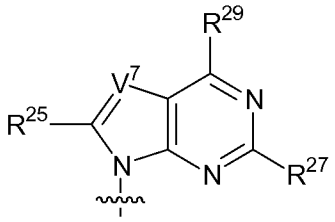
each of V^5 and V^6 is, independently, O, S, $N(R^{Vd})_{nv}$, or $C(R^{Vd})_{nv}$, wherein nv is an integer from 0 to 2 and each R^{Vd} is, independently, H, halo, optionally substituted amino acid, cyano, amidine, optionally substituted aminoalkyl, optionally substituted alkyl, optionally substituted 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;

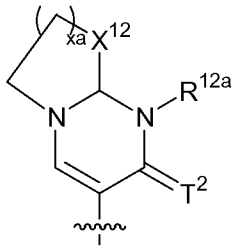
each R^{28} is, independently, H, optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl; and

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.

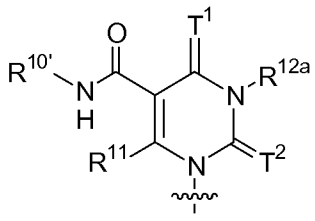
31. The isolated polynucleotide of claim 30, wherein R^{26a}, R^{26b}, or R^{29} is substituted with $-(CH_2)_{s2}(OCH_2CH_2)_{s1}(CH_2)_{s3}OR'$, wherein s1 is an integer from 1 to 10, each of s2 and s3, independently, is an integer from 0 to 10, and R' is H or C_{1-20} alkyl); or $-NR^{N1}(CH_2)_{s2}(CH_2CH_2O)_{s1}(CH_2)_{s3}NR^{N1}$, 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.

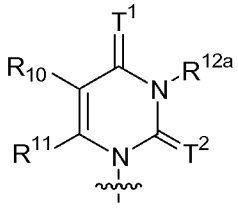
33. The isolated polynucleotide of any one of claims 8-32, wherein n number of B has Formula (b22):



(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

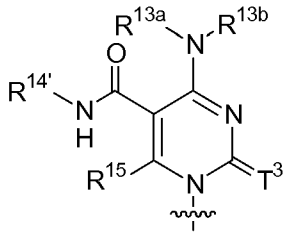
substituted alkoxy, optionally substituted alkoxycarbonylalkyl, optionally substituted alkoxycarbonylalkoxy, optionally substituted carboxyalkoxy, optionally substituted carboxyalkyl, or optionally substituted carbamoylalkyl; R^{11} is H or optionally substituted alkyl; R^{12a} is H, optionally substituted 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 8144-16131in 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

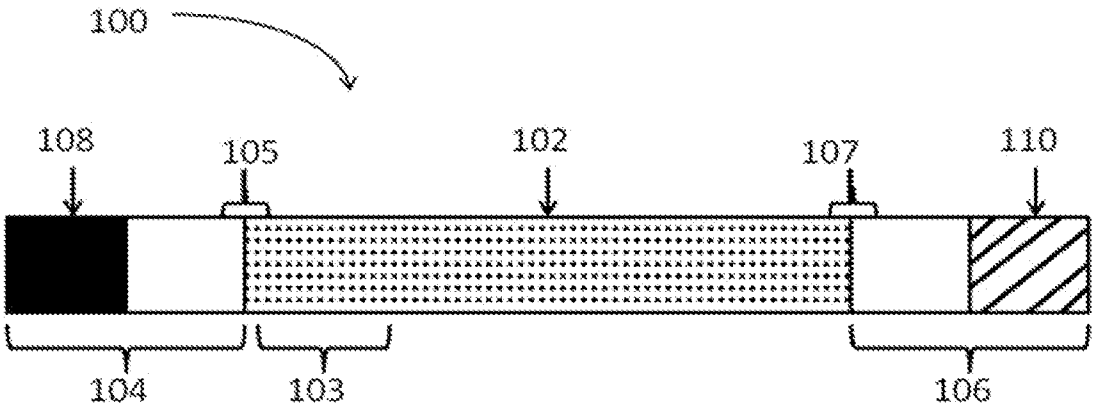
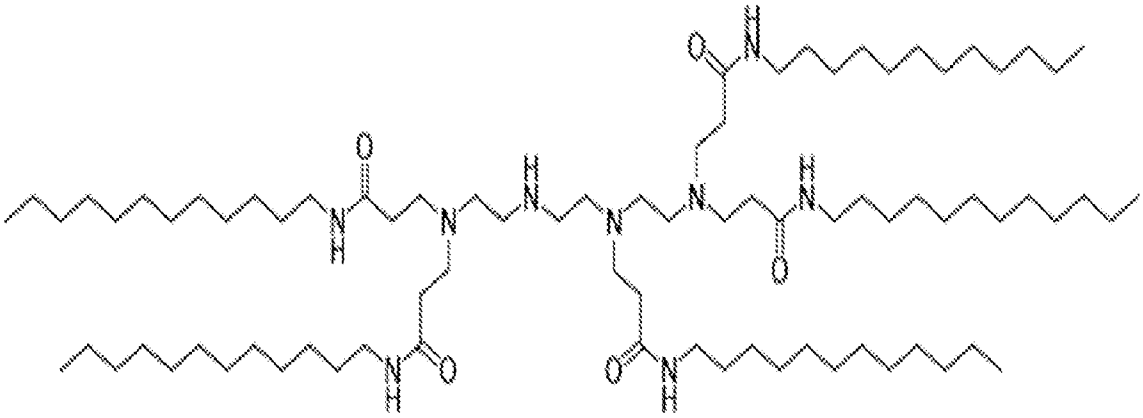
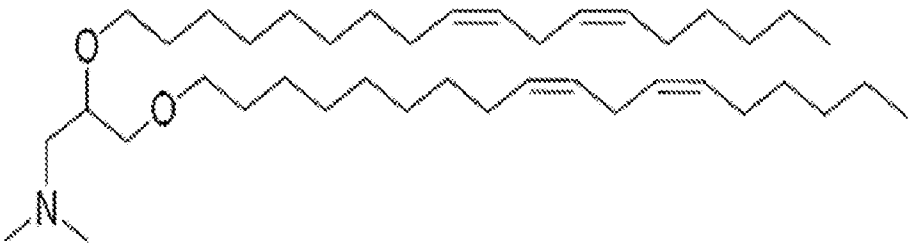


FIGURE 2

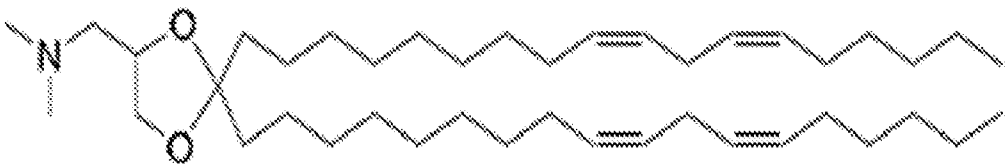
98N12-5 (TETA5-LAP)



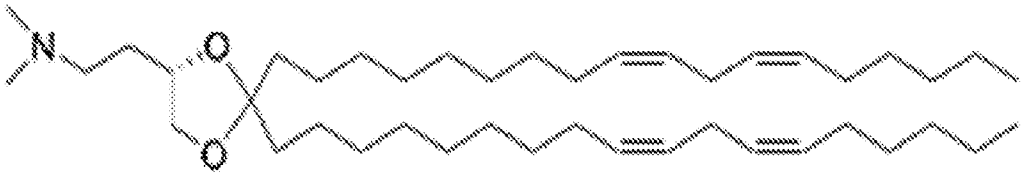
DLin-DMA



DLin-K-DMA (2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane)



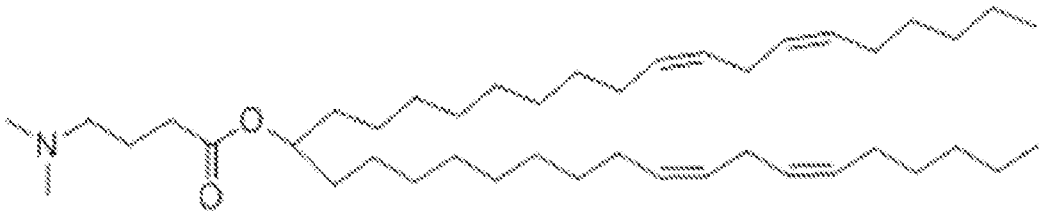
DLin-KC2-DMA



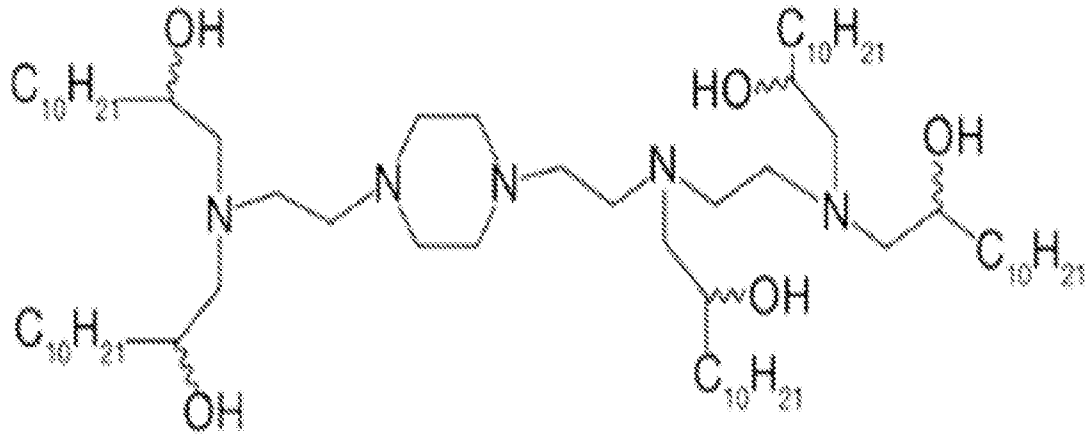
PRIOR ART

FIGURE 2 CONT.

DLin-MC3-DMA

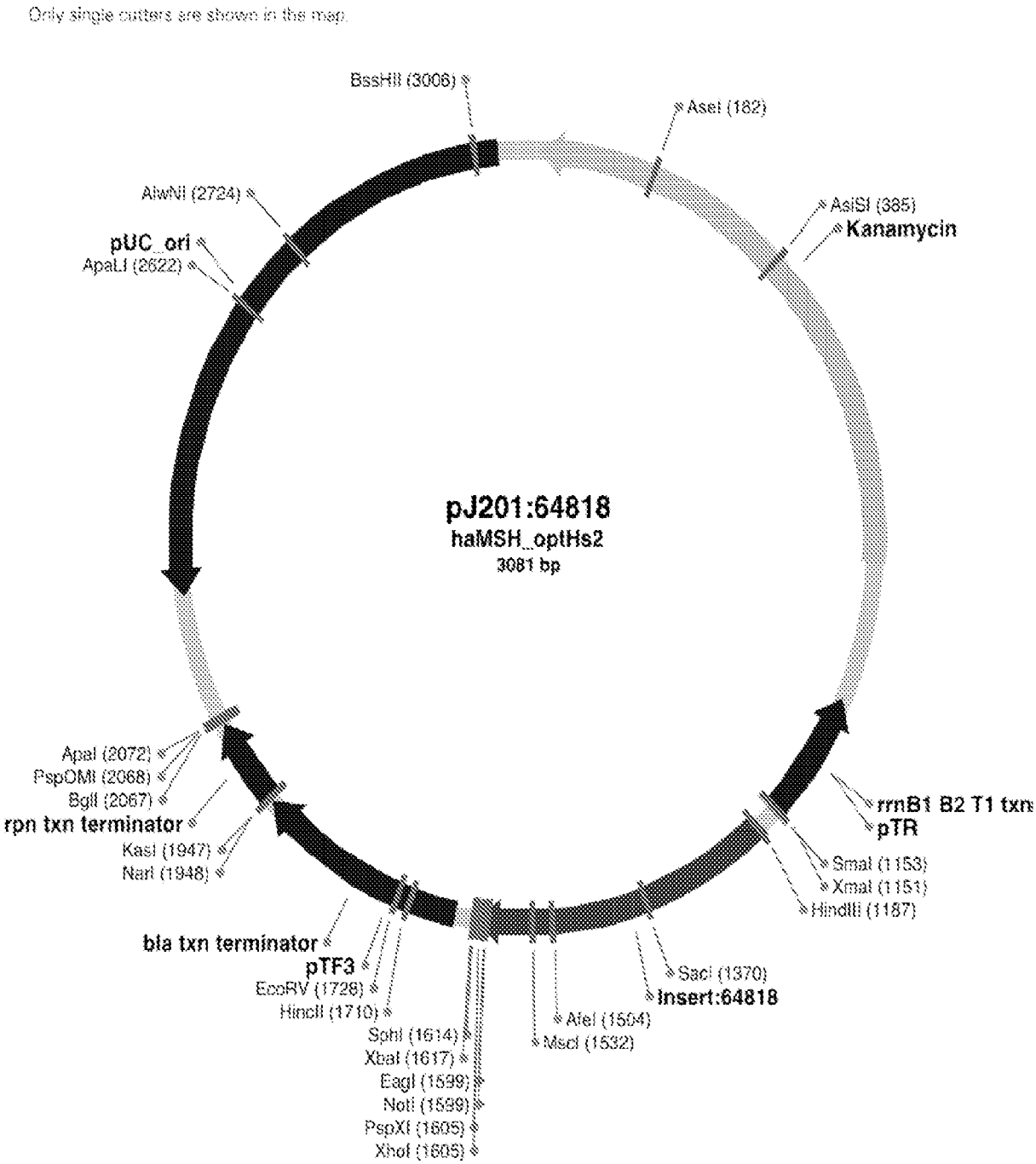


C12-200



PRIOR ART

FIGURE 3



PRIOR ART

FIGURE 4

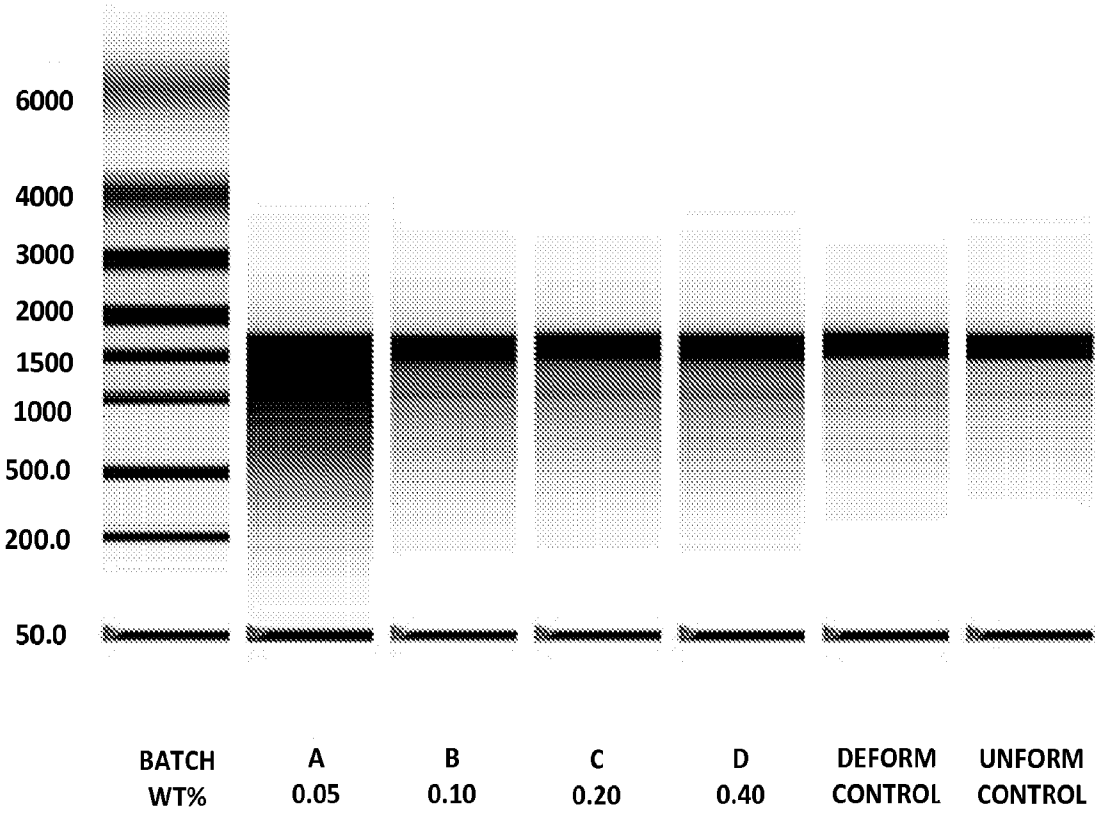

6000
4000
3000
2000
1500
1000
500.0
200.0
50.0
BATCH
WT%
A
0.05
B
0.10
C
0.20
D
0.40
DEFORM
CONTROL
UNFORM
CONTROL

FIGURE 5

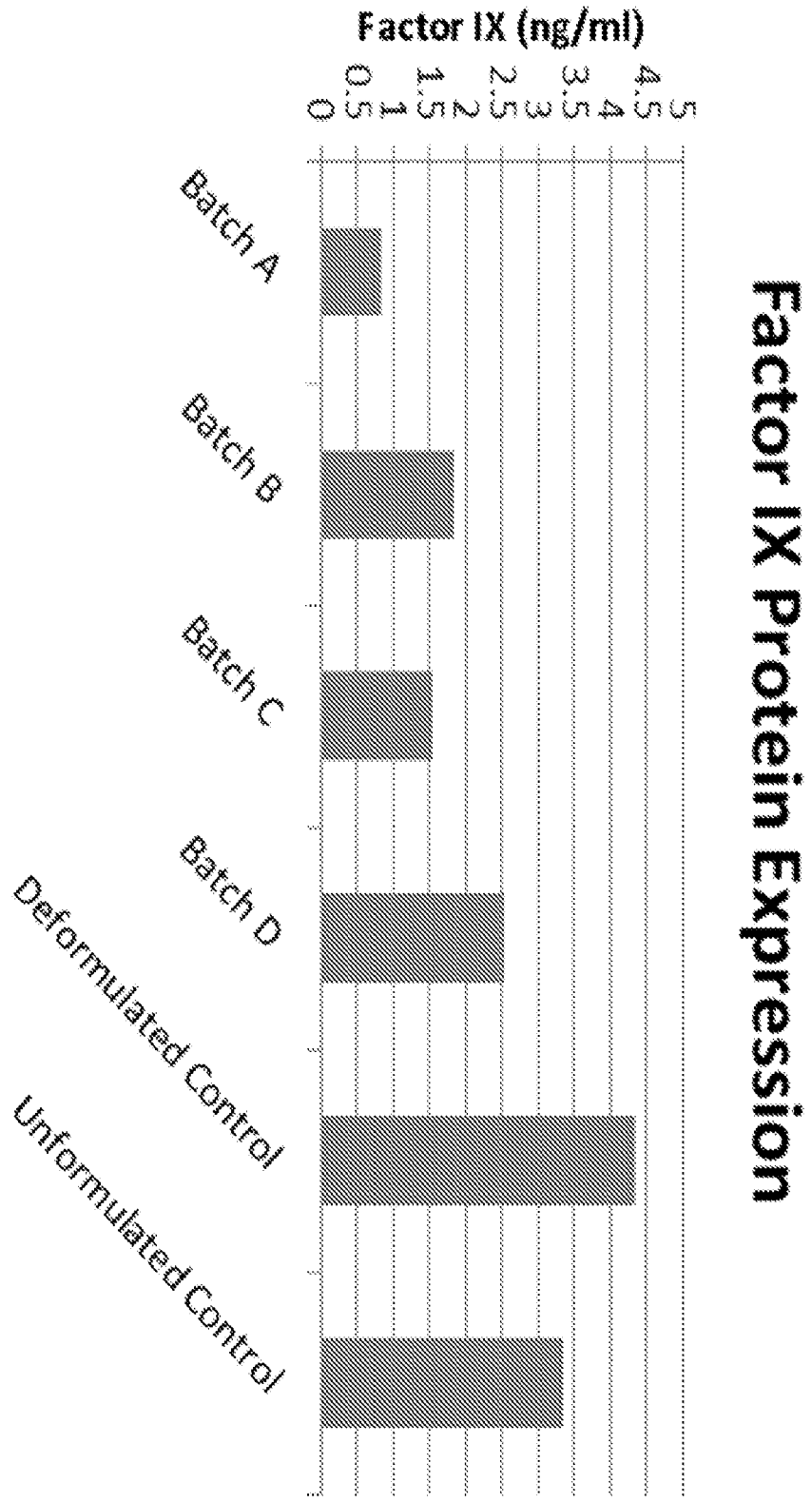

Factor IX (ng/ml)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
Batch A
Batch B
Batch C
Batch D
Deformulated Control
Unformulated Control
Factor IX Protein Expression

FIGURE 6

A.

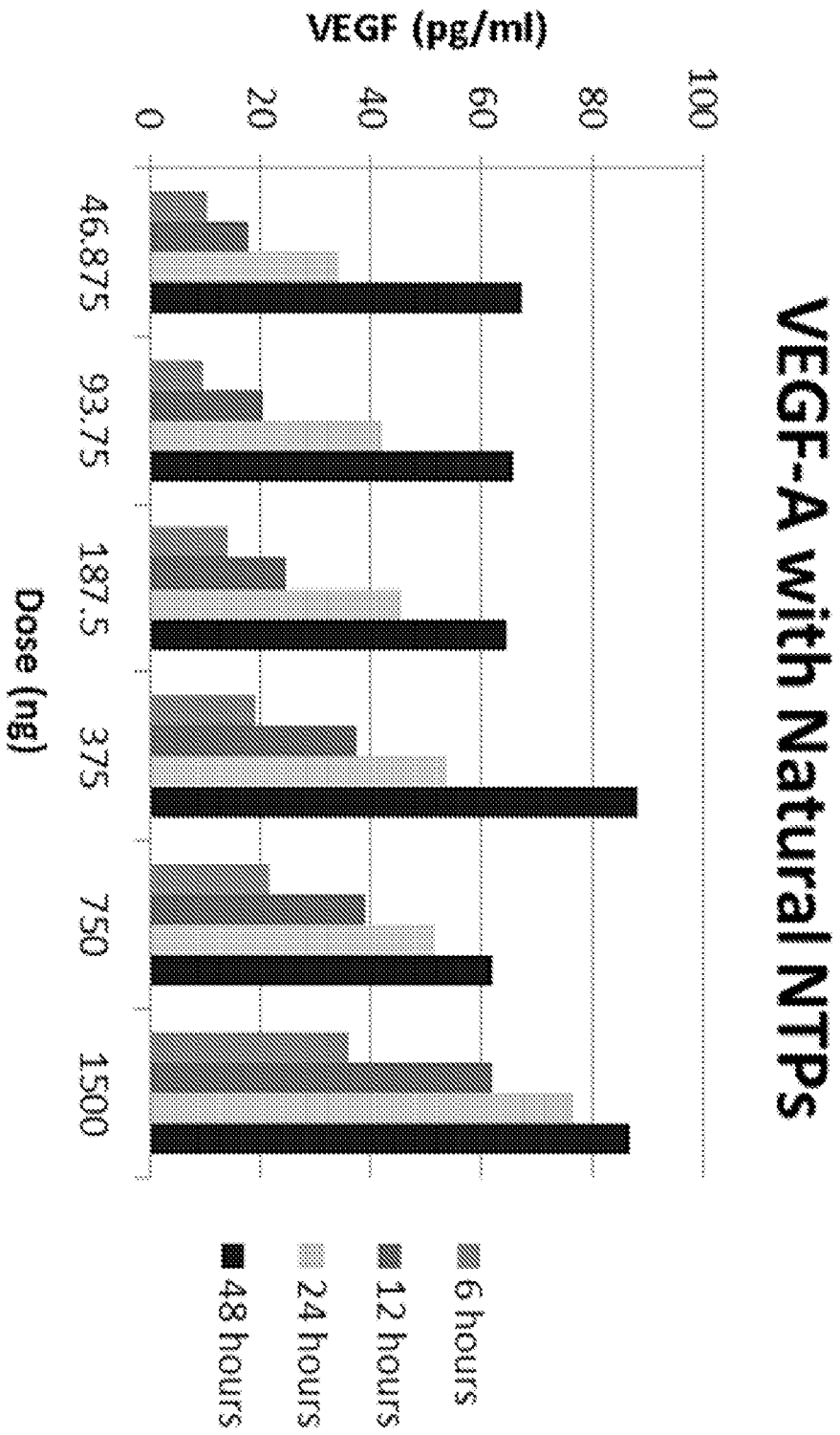

VEGF-A with Natural NTPs
VEGF (pg/ml)
0
20
40
60
80
100
Dose (ng)
46.875
93.75
187.5
375
750
1500
6 hours
12 hours
24 hours
48 hours

FIGURE 6 CONT.

B.

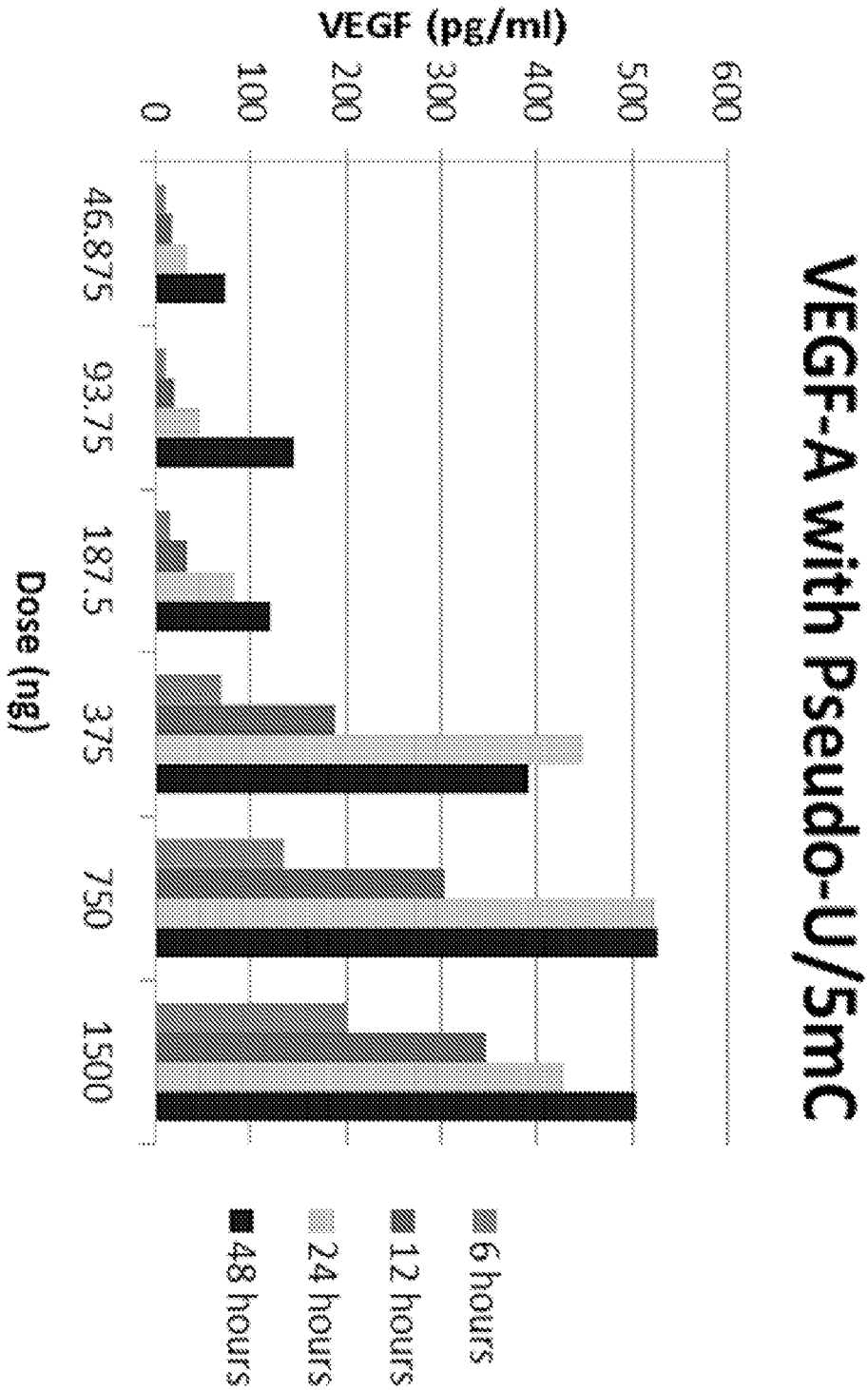


FIGURE 6 CONT.

C.

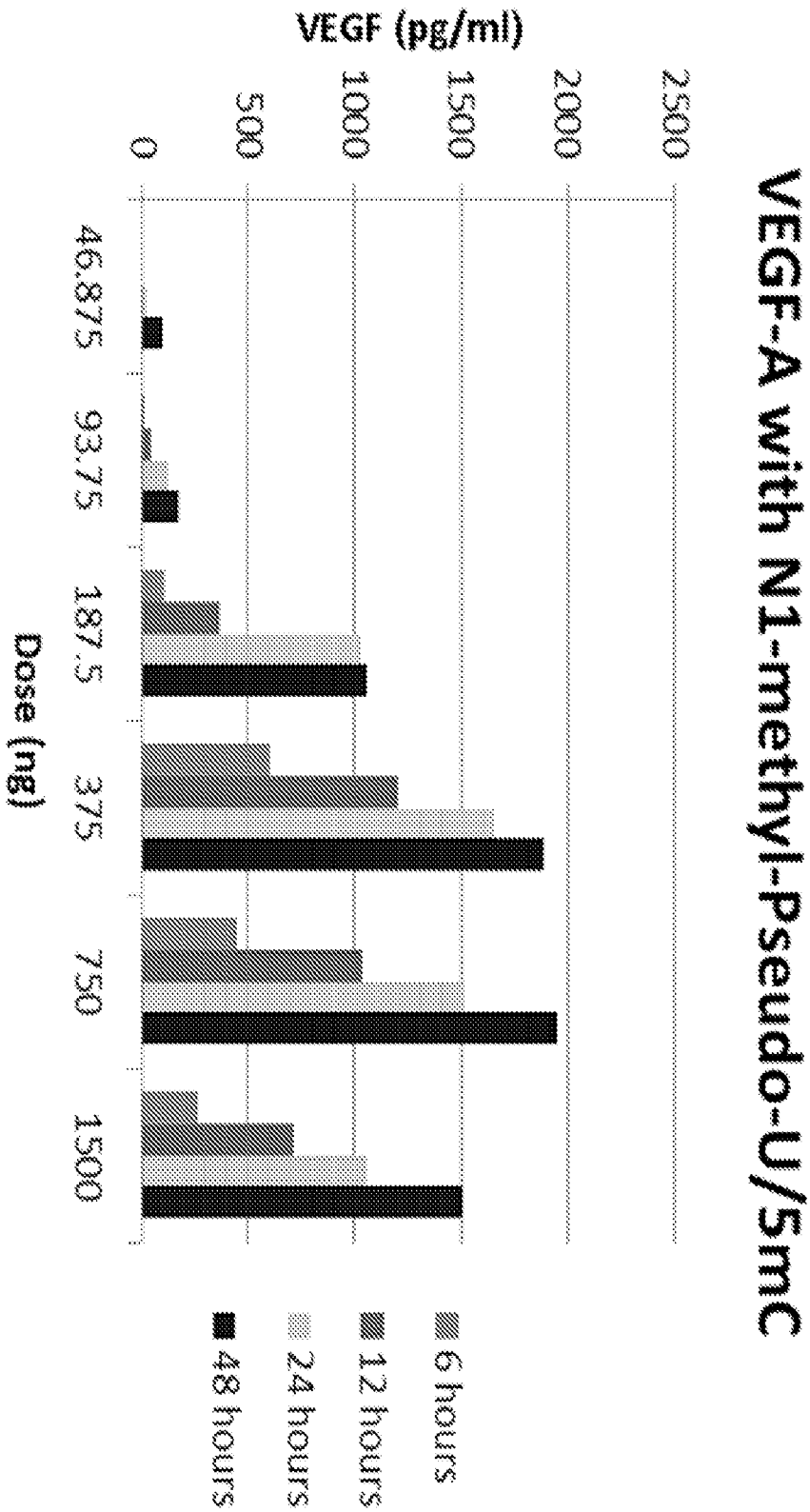


FIGURE 7

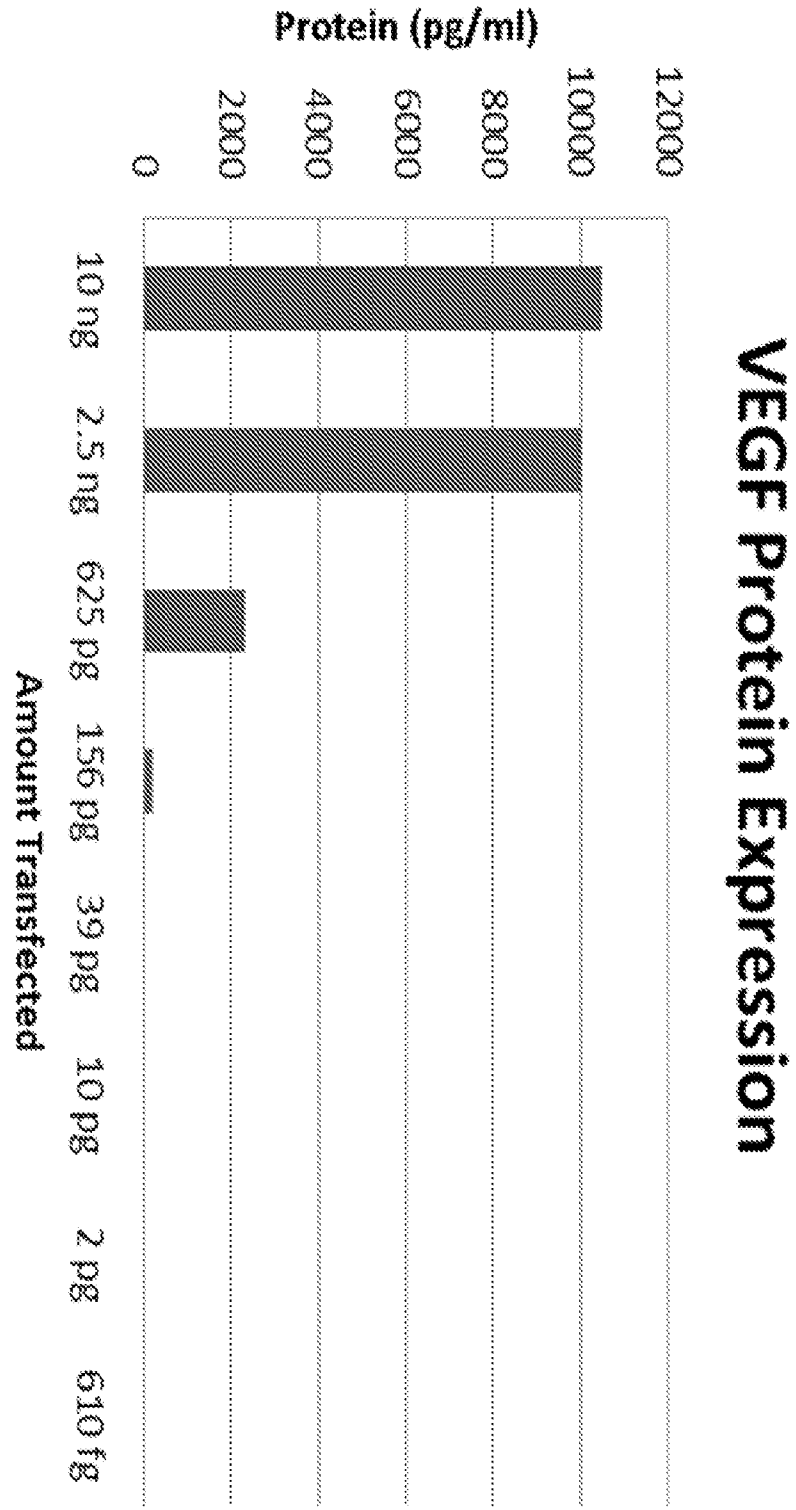

VEGF Protein Expression
Protein (pg/ml)
0
2000
4000
6000
8000
10000
12000
Amount Transfected
10 ng
2.5 ng
625 pg
156 pg
39 pg
10 pg
2 pg
610 fg

FIGURE 8

A.

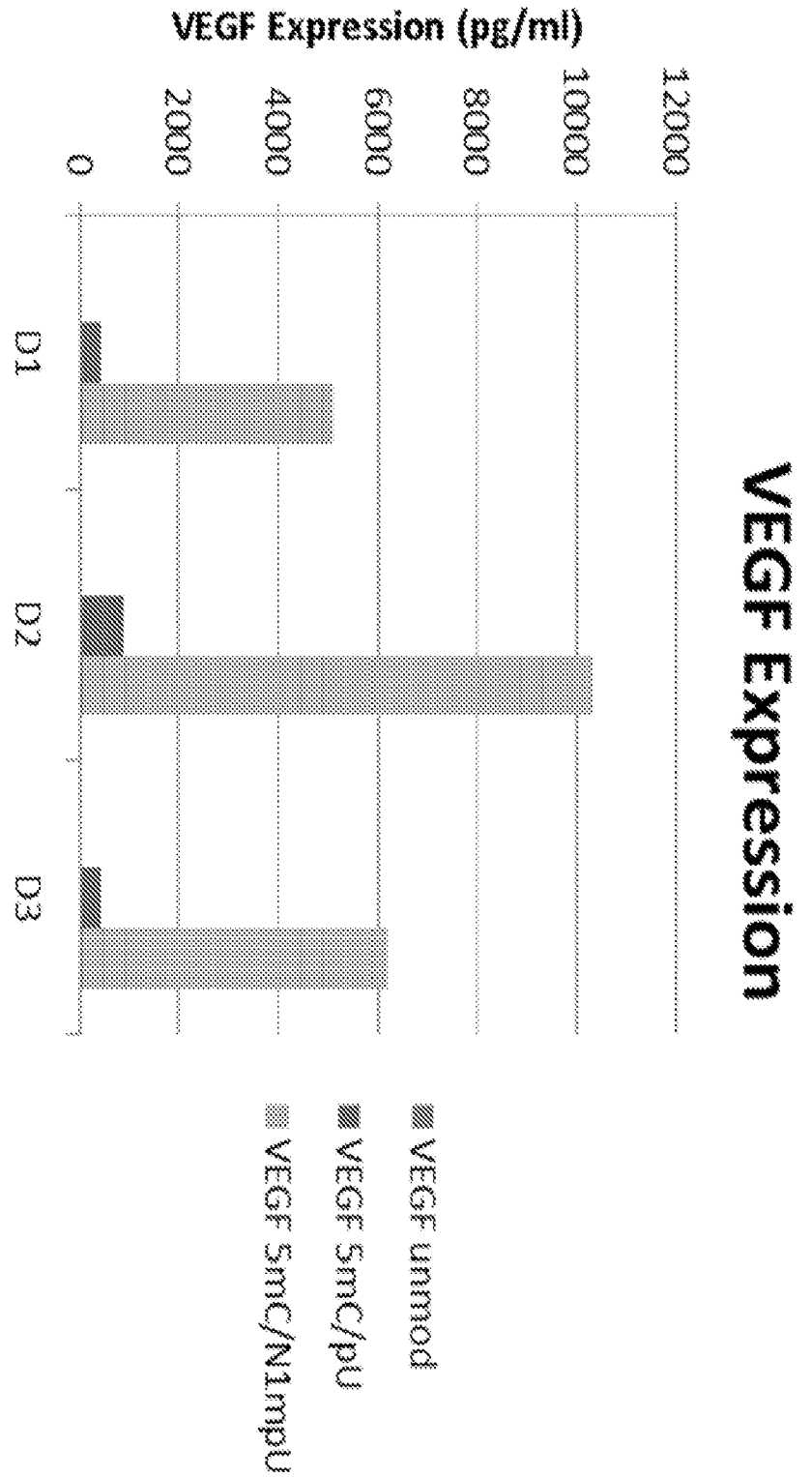

VEGF Expression (pg/ml)
0
2000
4000
6000
8000
10000
12000
D1
D2
D3
VEGF unmod
VEGF 5mC/pU
VEGF 5mC/N1mpU
VEGF Expression

FIGURE 8 CONT.

B.

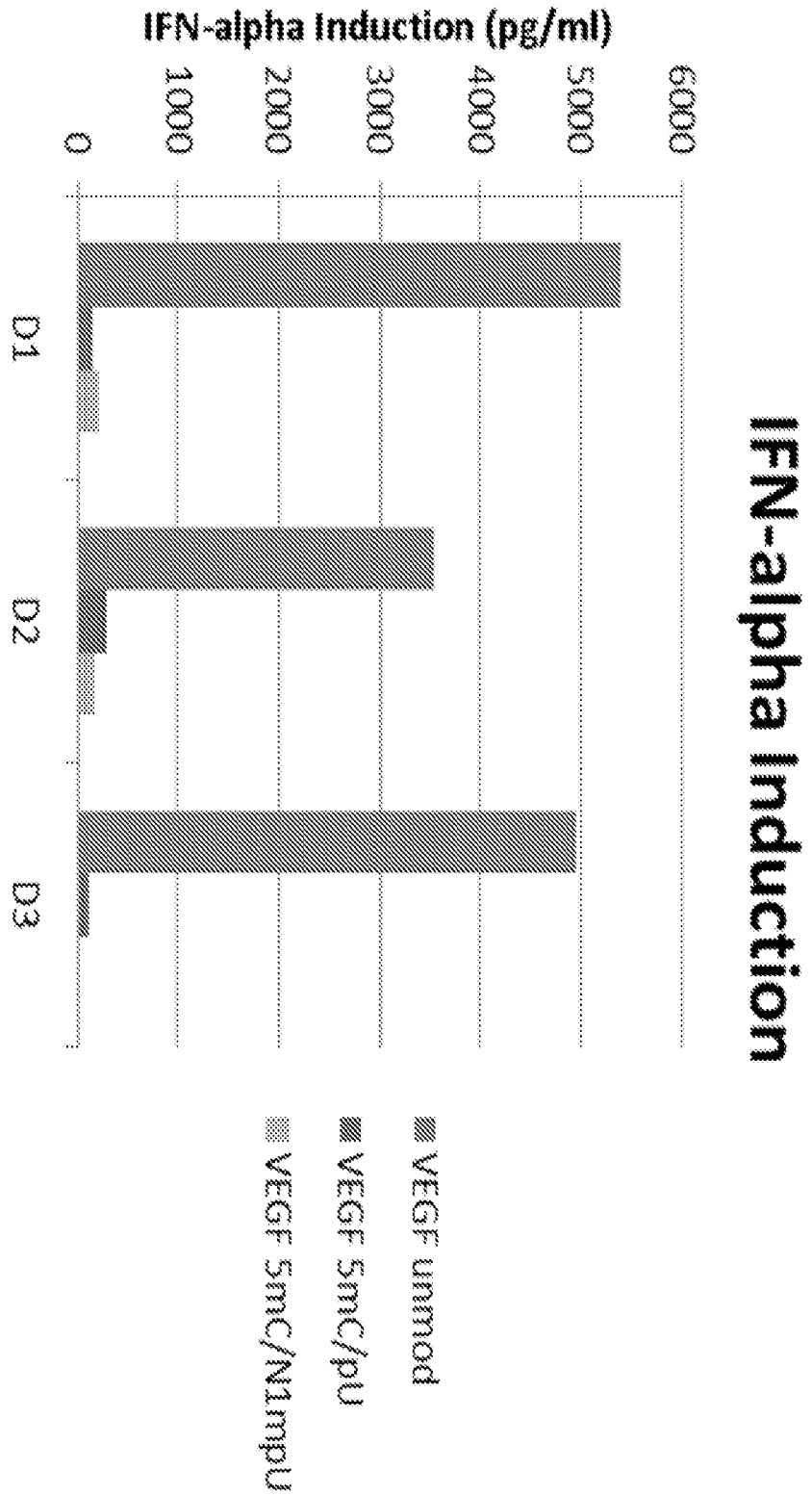


FIGURE 9

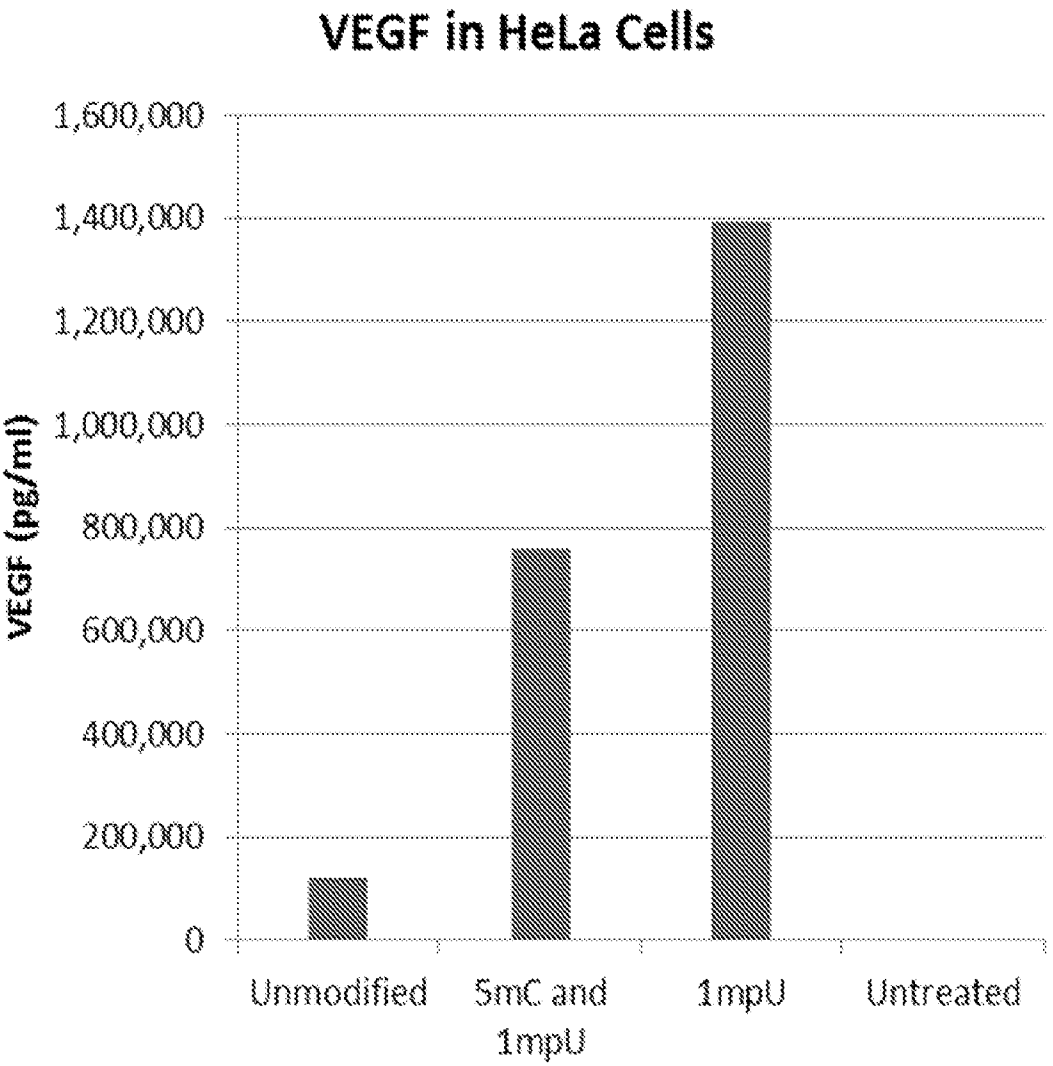

VEGF in HeLa Cells
VEGF (pg/ml)
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
Unmodified
5mC and 1mpU
1mpU
Untreated

FIGURE 10

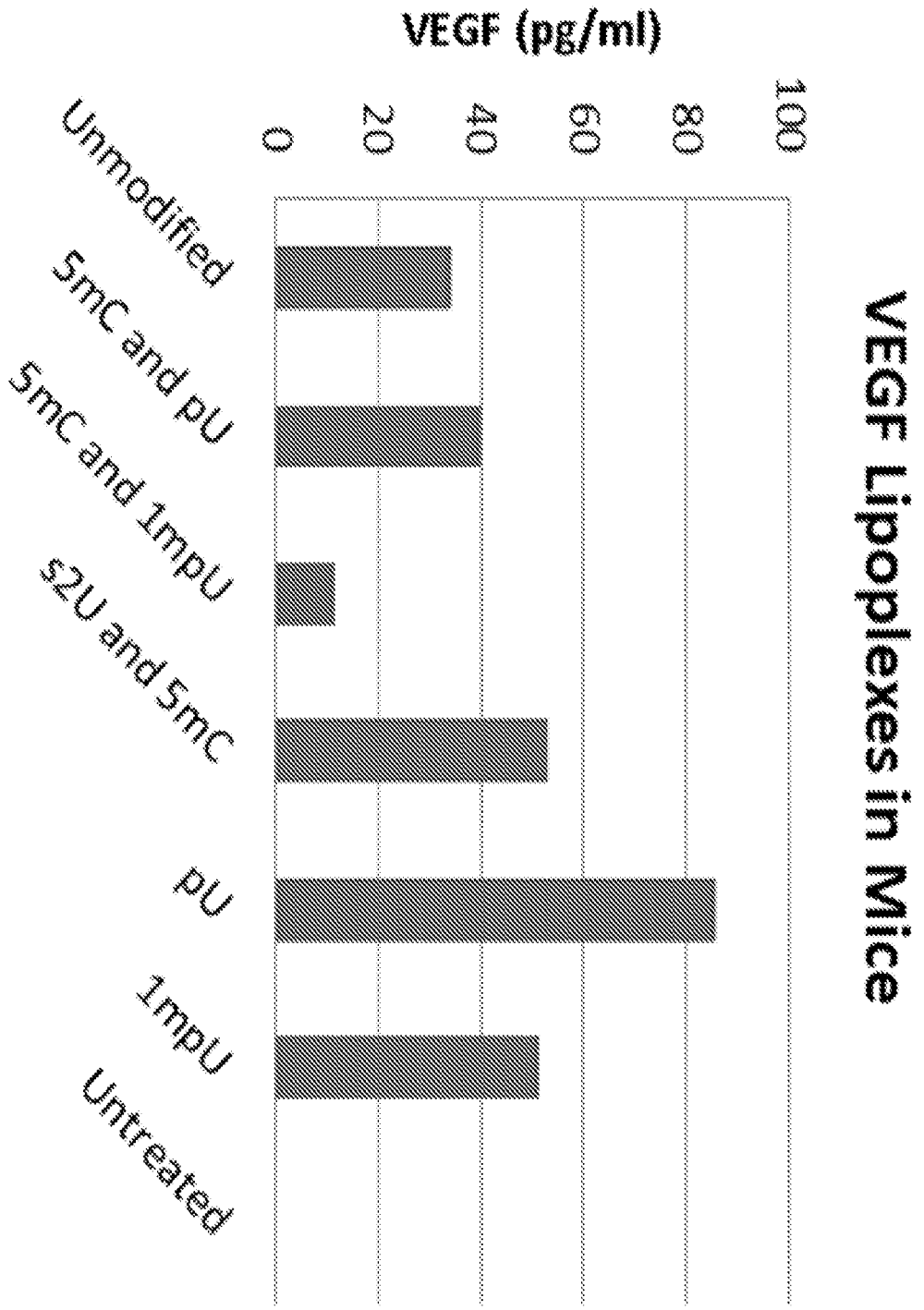

VEGF (pg/ml)
0
20
40
60
80
100
Unmodified
5mC and pU
5mC and 1mpU
s2U and 5mC
pU
1mpU
Untreated
VEGF Lipoplexes in Mice

FIGURE 11

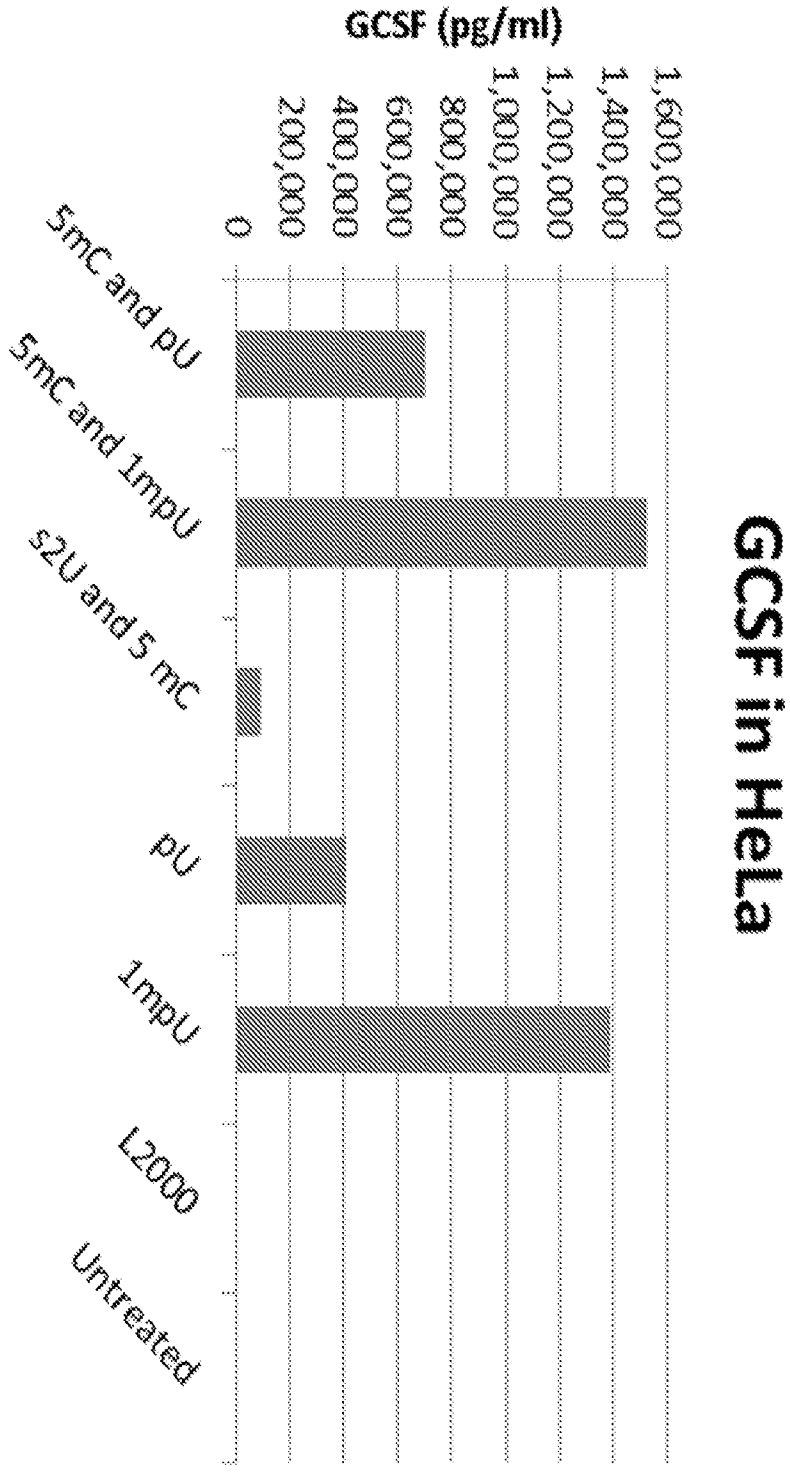
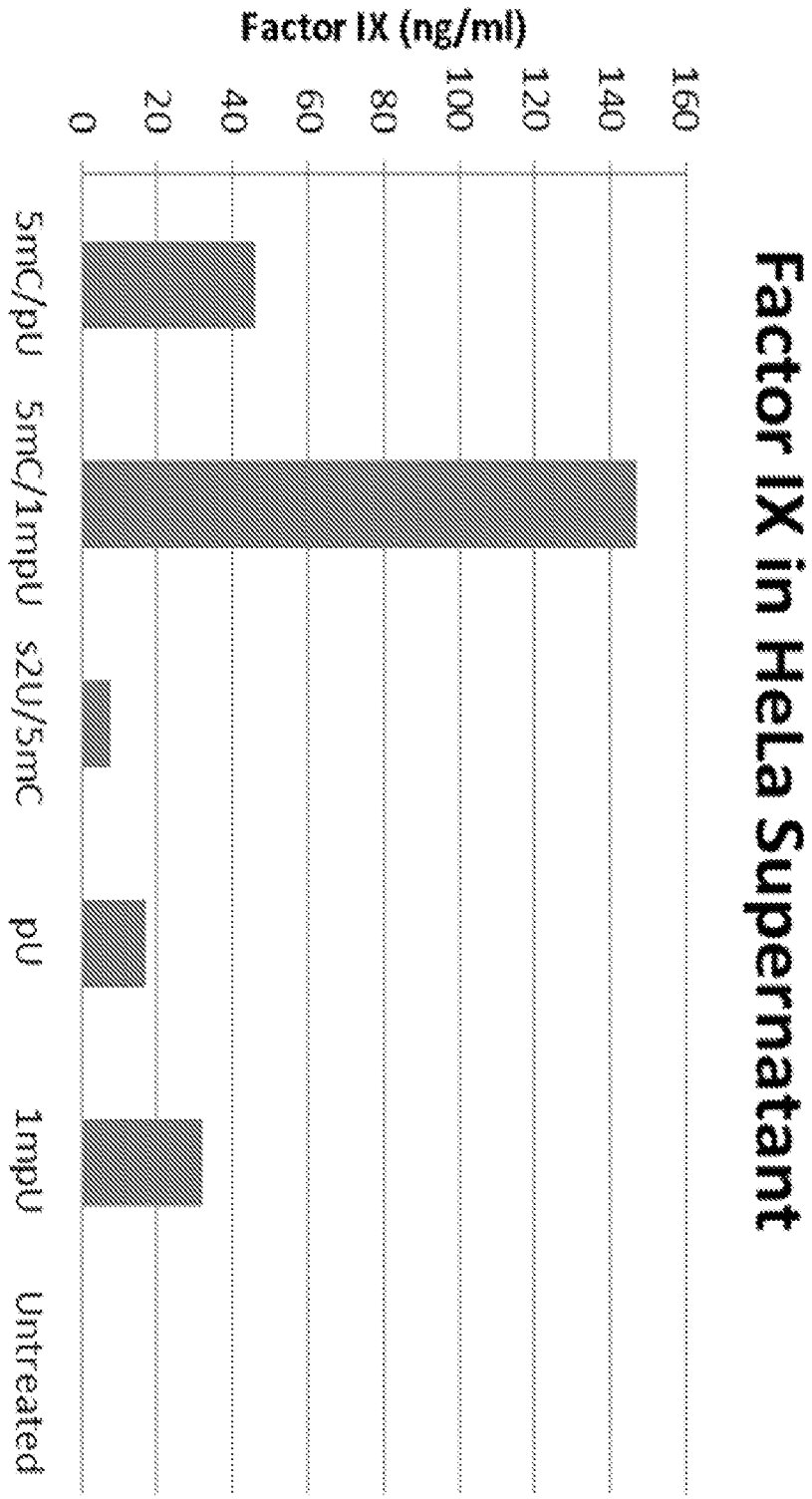

GCSF (pg/ml)
0
200,000
400,000
600,000
800,000
1,000,000
1,200,000
1,400,000
1,600,000
5mC and pU
5mC and 1mpU
s2U and 5 mC
pU
1mpU
L2000
Untreated
GCSF in HeLa

FIGURE 12


Factor IX in HeLa Supernatant
Factor IX (ng/ml)
0
20
40
60
80
100
120
140
160
5mC/pU
5mC/1mpU
s2U/5mC
pU
1mpU
Untreated

EDITORIAL NOTE

2013243946

Gene sequence for his application has 55974 pages. A copy can be obtained from WIPO Patenscope