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(54) **Title:** CORONAVIRUS VACCINE COMPOSITIONS AND METHODS

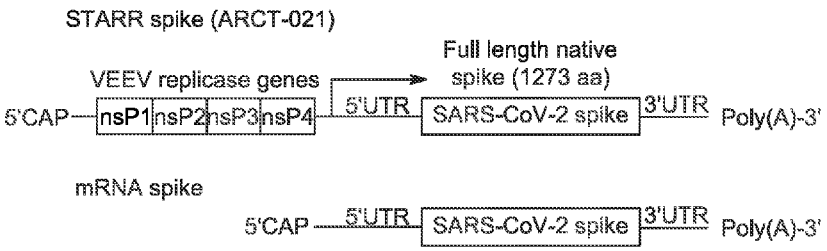


FIG. 1A

(57) **Abstract:** Provided herein are nucleic acid molecules encoding viral replication proteins and antigenic coronavirus proteins or fragments thereof. Also provided herein are compositions that include nucleic acid molecules encoding viral replication and antigenic proteins, and lipids. Nucleic acid molecules provided herein are useful for inducing immune responses.

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COMPOSITIONS AND METHODS FOR INDUCING IMMUNE RESPONSES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/987,191, filed March 9, 2020 and U.S. Provisional Application No. 63/073,900, filed September 2, 2020.

REFERENCE TO A SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on March 8, 2021 is named 049386-538001WO_SequenceListing_ST25.txt and is 481,150 bytes in size.

TECHNICAL FIELD

[0003] The present disclosure relates generally to inducing immune responses against infectious agents and tumor antigens and more specifically to self-transcribing and replicating RNA for antigen expression.

BACKGROUND

[0004] Infectious diseases and cancer represent significant burdens on health worldwide. According to the World Health Organization (WHO), lower respiratory tract infection was the deadliest infectious disease worldwide in 2016, causing approximately 3 million deaths. The impact of infectious diseases is illustrated by the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). SARS-CoV-2 is a novel coronavirus that was first identified in December 2019 in Wuhan, China and that has caused more than 20 million confirmed infections with more than 700,000 deaths worldwide as of August 2020. Current control measures to curb the rapid worldwide spread of SARS-CoV-2, such as national lockdowns, closure of work places and schools, and reduction of international travel are threatening to result in a global economic recession to an extent not seen since the Great Depression.

[0005] Cancer is the second leading cause of death globally, accounting for approximately 9.6 million deaths worldwide in 2018. Cancer is a large group of diseases that can affect almost

any organ or tissue in the body. Cancer burden continues to grow globally, exerting physical, emotional, and financial strains on patients and health care providers.

[0006] Self-replicating ribonucleic acids (RNAs), e.g., derived from viral replicons, are useful for expression of proteins, such as heterologous proteins, for a variety of purposes, such as expression of therapeutic proteins and expression of antigens for vaccines. A desirable property of such replicons is the ability for sustained expression of the protein.

[0007] Few treatments for infections caused by viruses and eukaryotic organisms are available, and resistance to antibiotics for the treatment of bacterial infections is increasing. In addition, rapid responses, including rapid vaccine development, are required to effectively control emerging infectious diseases and pandemics. Moreover, many cancer treatments include costly and painful surgeries and chemotherapies that are often unsuccessful or only modestly prolong life despite serious side effects. Thus, there exists a need for the prevention and/or treatment of infectious diseases and cancer.

SUMMARY

[0008] In one aspect, the present disclosure provides a nucleic acid molecule comprising (i) a first polynucleotide encoding one or more viral replication proteins, wherein the first polynucleotide is codon-optimized as compared to a wild-type polynucleotide encoding the one or more viral replication proteins; and (ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof, wherein the first antigenic protein is a coronavirus protein.

[0009] In some embodiments, the one or more viral replication proteins are alphavirus proteins or rubivirus proteins.

[0010] In some embodiments, the alphavirus proteins are from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus

(HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), Buggy Creek Virus (BCRV), or any combination thereof.

[0011] In some embodiments, the first polynucleotide encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, an alphavirus nsP4 protein, or any combination thereof.

[0012] In some embodiments, the first polynucleotide encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and an alphavirus nsP4 protein.

[0013] In some embodiments, the nucleic acid molecule further comprises a first intergenic region between a sequence encoding the polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and a sequence encoding an alphavirus nsP4 protein.

[0014] In some embodiments, the first intergenic region comprises an alphavirus sequence.

[0015] In some embodiments, the first polynucleotide comprises a sequence having at least 80% identity to a sequence of SEQ ID NO:72.

[0016] In some embodiments, the nucleic acid molecule further comprises a 5' untranslated region (UTR).

[0017] In some embodiments, the 5' UTR comprises a viral 5' UTR, a non-viral 5' UTR, or a combination of viral and non-viral 5' UTR sequences.

[0018] In some embodiments, the 5' UTR comprises an alphavirus 5' UTR.

[0019] In some embodiments, the alphavirus 5' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus

(HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 5' UTR sequence.

[0020] In some embodiments, the 5' UTR comprises a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75.

[0021] In some embodiments, the nucleic acid molecule further comprises a 3' untranslated region (UTR).

[0022] In some embodiments, the 3' UTR comprises a viral 3' UTR, a non-viral 3' UTR, or a combination of viral and non-viral 3' UTR sequences. In some embodiments, the 3' UTR comprises an alphavirus 3' UTR.

[0023] In some embodiments, the alphavirus 3' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 3' UTR sequence.

[0024] In some embodiments, the 3' UTR comprises a poly-A sequence.

[0025] In some embodiments, the 3' UTR comprises a sequence of SEQ ID NO:76.

[0026] In some embodiments, the antigenic protein is a SARS-CoV-2 protein.

[0027] In some embodiments, the antigenic protein is a SARS-CoV-2 spike glycoprotein.

[0028] In some embodiments, the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein having an amino acid sequence of SEQ ID NO:123.

[0029] In some embodiments, the second polynucleotide comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

[0030] In some embodiments, the second polynucleotide comprises at least two transgenes.

[0031] In some embodiments, a second transgene encodes a second antigenic protein or a fragment thereof or an immunomodulatory protein.

[0032] In some embodiments, the second polynucleotide further comprises a sequence encoding a 2A peptide, an internal ribosomal entry site (IRES), or a combination thereof, located between transgenes.

[0033] In some embodiments, the immunomodulatory protein is a cytokine, a chemokine, or an interleukin.

[0034] In some embodiments, the second transgene encodes a second coronavirus protein.

[0035] In some embodiments, the first polynucleotide is located 5' of the second polynucleotide.

[0036] In some embodiments, the nucleic acid molecule further comprises a second intergenic region located between the first polynucleotide and the second polynucleotide.

[0037] In some embodiments, the second intergenic region comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:77.

[0038] In some embodiments, the nucleic acid molecule is

(a) a DNA molecule; or

(b) an RNA molecule, wherein T is substituted with U.

[0039] In some embodiments, the DNA molecule further comprises a promoter.

[0040] In some embodiments, the promoter is located 5' of the 5'UTR.

[0041] In some embodiments, the promoter is a T7 promoter, a T3 promoter, or an SP6 promoter.

[0042] In some embodiments, the RNA molecule is a self-replicating RNA molecule.

[0043] In some embodiments, the RNA molecule further comprises a 5' cap.

[0044] In some embodiments, the 5' cap has a Cap 1 structure, a Cap 1 (^{m6}A) structure, a Cap 2 structure, a Cap 0 structure, or any combination thereof.

[0045] In another aspect, the disclosure provides a nucleic acid molecule comprising

(a) a sequence of SEQ ID NO:124;

(b) a sequence of SEQ ID NO:124, wherein T is substituted with U;

(c) a sequence of SEQ ID NO:125; or

(d) a sequence of SEQ ID NO:125, wherein T is substituted with U.

[0046] In some embodiments, the nucleic acid molecule is an RNA molecule.

[0047] In some embodiments, the nucleic acid molecule further comprises a 5' cap having a Cap 1 structure.

[0048] In yet another aspect the disclosure provides a nucleic acid molecule comprising:

(i) a first polynucleotide comprising a sequence having at least 80% identity to a sequence of SEQ ID NO:72; and

(ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof, wherein the first antigenic protein is a coronavirus protein.

[0049] In some embodiments, the nucleic acid molecule further comprises a 5' untranslated region (UTR).

[0050] In some embodiments, the 5' UTR comprises a viral 5' UTR, a non-viral 5' UTR, or a combination of viral and non-viral 5' UTR sequences.

[0051] In some embodiments, the 5' UTR comprises an alphavirus 5' UTR.

[0052] In some embodiments, the alphavirus 5' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 5' UTR sequence.

[0053] In some embodiments, the 5' UTR comprises a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75.

[0054] In some embodiments, the nucleic acid molecule further comprises a 3' untranslated region (UTR).

[0055] In some embodiments, the 3' UTR comprises a viral 3' UTR, a non-viral 3' UTR, or a combination of viral and non-viral 3' UTR sequences.

[0056] In some embodiments, the 3' UTR comprises an alphavirus 3' UTR.

[0057] In some embodiments, the alphavirus 3' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 3' UTR sequence.

[0058] In some embodiments, the 3' UTR comprises a poly-A sequence.

[0059] In some embodiments, the 3' UTR comprises a sequence of SEQ ID NO:76.

[0060] In some embodiments, the antigenic protein is a SARS-CoV-2 protein.

[0061] In some embodiments, the antigenic protein is a SARS-CoV-2 spike glycoprotein.

[0062] In some embodiments, the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein having an amino acid sequence of SEQ ID NO:123.

[0063] In some embodiments, the second polynucleotide comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

[0064] In some embodiments, the second polynucleotide comprises at least two transgenes.

[0065] In some embodiments, a second transgene encodes a second antigenic protein or a fragment thereof or an immunomodulatory protein.

[0066] In some embodiments, the second polynucleotide further comprises a sequence encoding a 2A peptide, an internal ribosomal entry site (IRES), or a combination thereof, located between transgenes.

[0067] In some embodiments, the immunomodulatory protein is a cytokine, a chemokine, or an interleukin.

[0068] In some embodiments, the second transgene encodes a second coronavirus protein.

[0069] In some embodiments, the first polynucleotide is located 5' of the second polynucleotide.

[0070] In some embodiments, the nucleic acid molecule further comprises a second intergenic region located between the first polynucleotide and the second polynucleotide.

[0071] In some embodiments, the second intergenic region comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:77.

[0072] In some embodiments, the nucleic acid molecule is

(a) a DNA molecule; or

(b) an RNA molecule, wherein T is substituted with U.

[0073] In some embodiments, the DNA molecule further comprises a promoter.

[0074] In some embodiments, the promoter is located 5' of the 5'UTR.

[0075] In some embodiments, the promoter is a T7 promoter, a T3 promoter, or an SP6 promoter.

[0076] In some embodiments, the RNA molecule is a self-replicating RNA molecule.

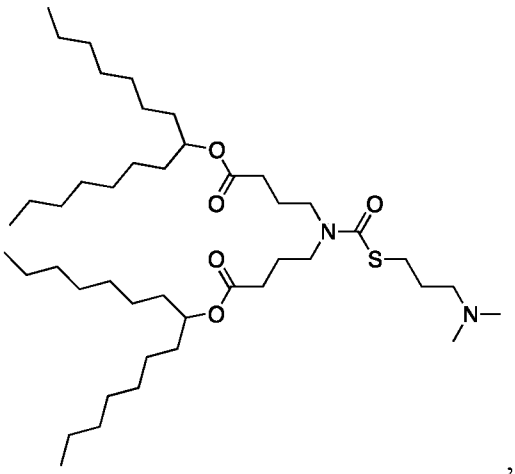
[0077] In some embodiments, the RNA molecule further comprises a 5' cap.

[0078] In some embodiments, the 5' cap has a Cap 1 structure, a Cap 1 (^{m6}A) structure, a Cap 2 structure, a Cap 0 structure, or any combination thereof.

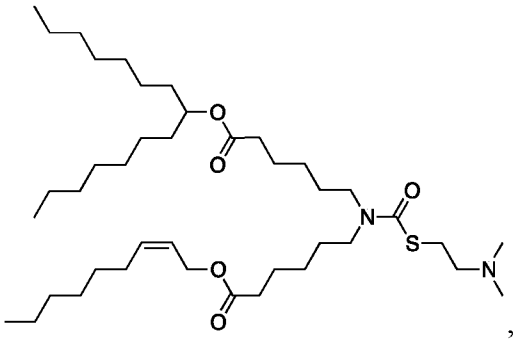
[0079] In yet another aspect, the disclosure provides a composition comprising any of the nucleic acid molecules provided herein. In some embodiments, the composition further comprises a lipid.

[0080] In some embodiments, the lipid comprises an ionizable cationic lipid.

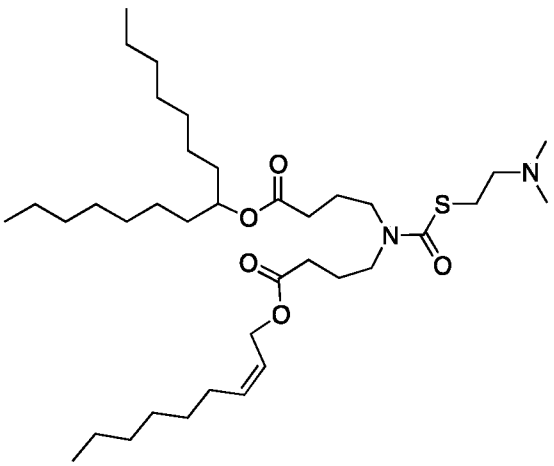
[0081] In some embodiments, the ionizable cationic lipid has a structure of



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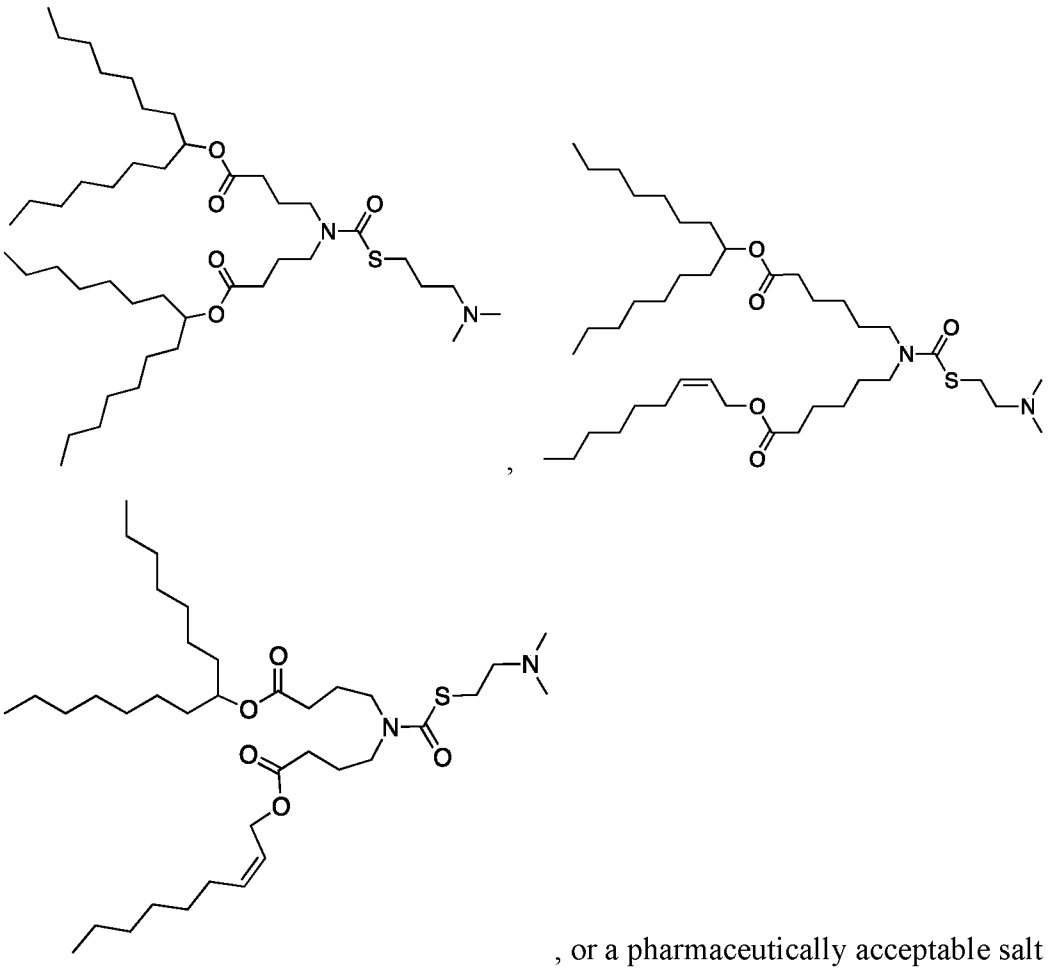


, or a pharmaceutically acceptable salt thereof.

[0082] In yet another aspect, the disclosure provides a composition comprising any of the nucleic acid molecules described herein and a lipid formulation.

[0083] In some embodiments, the lipid formulation comprises an ionizable cationic lipid.

[0084] In some embodiments, the ionizable cationic lipid has a structure of



, or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments, the lipid formulation is selected from a lipoplex, a liposome, a lipid nanoparticle, a polymer-based carrier, an exosome, a lamellar body, a micelle, and an emulsion.

[0086] In some embodiments, the lipid formulation is a liposome selected from a cationic liposome, a nanoliposome, a proteoliposome, a unilamellar liposome, a multilamellar liposome, a ceramide-containing nanoliposome, and a multivesicular liposome.

[0087] In some embodiments, the lipid formulation is a lipid nanoparticle.

[0088] In some embodiments, the lipid nanoparticle has a size of less than about 200 nm. In some embodiments, the lipid nanoparticle has a size of less than about 150 nm. In some embodiments, the lipid nanoparticle has a size of less than about 100 nm. In some embodiments, the lipid nanoparticle has a size of about 55 nm to about 90 nm.

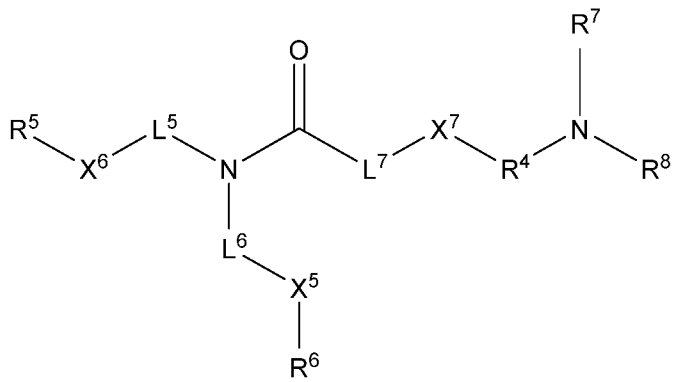
[0089] In some embodiments, the lipid formulation comprises one or more cationic lipids.

[0090] In some embodiments, the one or more cationic lipids is selected from 5-carboxyspermylglycinedioctadecylamide (DOGS), 2,3-dioleyloxy-N-[2(spermine-

carboxamido)ethyl]-N,N-dimethyl-1-propanaminium (DOSPA), 1,2-Dioleoyl-3-Dimethylammonium-Propane (DODAP), 1,2-Dioleoyl-3-Trimethylammonium-Propane (DOTAP), 1,2-distearyloxy-N,N-dimethyl-3-aminopropane (DSDMA), 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane (DODMA), 1,2-dilinoleyloxy-N,N-dimethyl-3-aminopropane (DLinDMA), 1,2-dilinolenyloxy-N,N-dimethyl-3-aminopropane (DLenDMA), N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), 3-dimethylamino-2-(cholest-5-en-3-beta-oxybutan-4-oxy)-1-(cis,cis-9,12-oc-tadecadienoxy)propane (CLinDMA), 2-[5′-(cholest-5-en-3-beta-oxy)-3′-oxapentoxy)-3-dimethy 1-1-(cis,cis-9′,1-2′-octadecadienoxy)propane (CpLinDMA), N,N-dimethyl-3,4-dioleyloxybenzylamine (DMOBA), 1,2-N,N′-dioleylcarbamyl-3-dimethylaminopropane (DOcarbDAP), 2,3-Dilinoleoyloxy-N,N-dimethylpropylamine (DLinDAP), 1,2-N,N′-Dilinoleylcarbamyl-3-dimethylaminopropane (DLincarbDAP), 1,2-Dilinoleoylcarbamyl-3-dimethylaminopropane (DLinCDAP), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), and 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane or (DLin-K-XTC2-DMA).

[0091] In some embodiments, the lipid formulation comprises an ionizable cationic lipid.

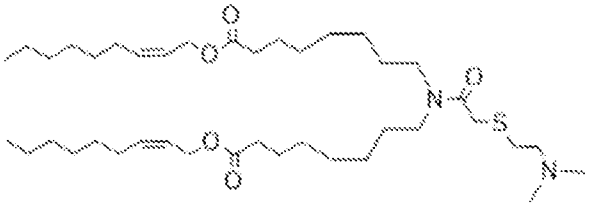
[0092] In some embodiments, the ionizable cationic lipid has a structure of Formula I:



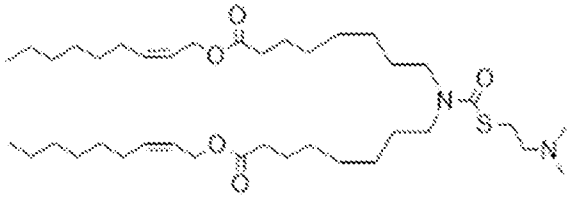
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 and R^6 are each independently selected from the group consisting of a linear or branched C_1-C_{31} alkyl, C_2-C_{31} alkenyl or C_2-C_{31} alkynyl and cholesteryl; L^5 and L^6 are each independently selected from the group consisting of a linear C_1-C_{20} alkyl and C_2-C_{20} alkenyl; X^5 is -C(O)O-, whereby -C(O)O-R^6 is formed or -OC(O)- whereby -OC(O)-R^6 is formed; X^6 is -C(O)O- whereby -C(O)O-R^5 is formed or -OC(O)- whereby -OC(O)-R^5 is formed; X^7 is S or O; L^7 is absent or lower alkyl; R^4 is a linear or branched C_1-C_6 alkyl; and R^7 and R^8 are each independently selected from the group consisting of a hydrogen and a linear or branched C_1-C_6 alkyl.

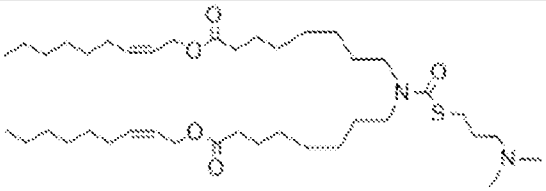
[0093] In some embodiments, the ionizable cationic lipid is selected from



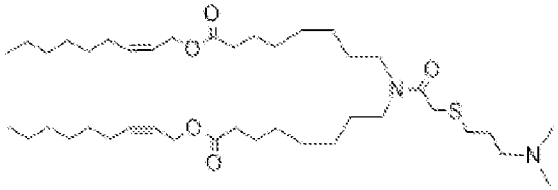
ATX-001



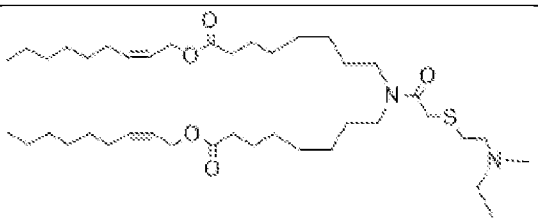
ATX-002



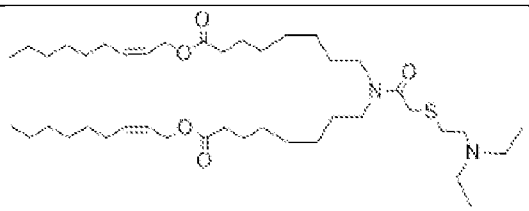
ATX-003



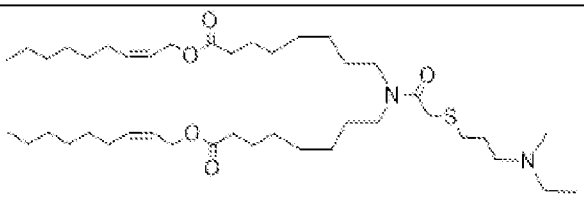
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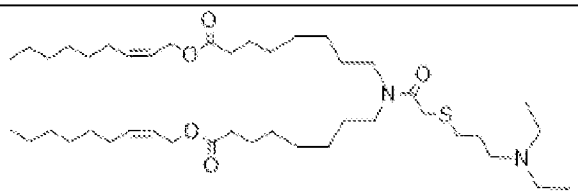
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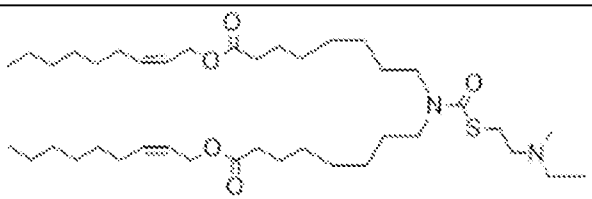
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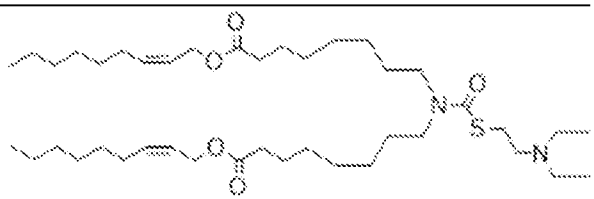
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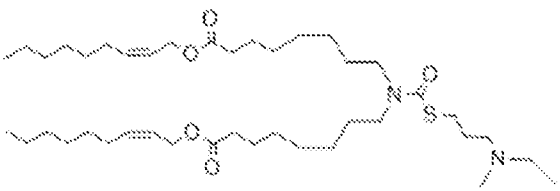
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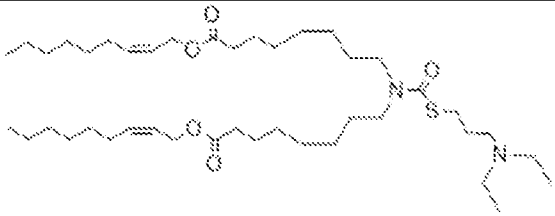
ATX-009



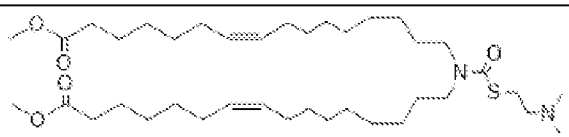
ATX-010



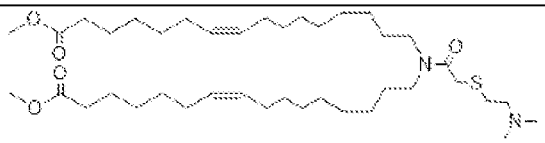
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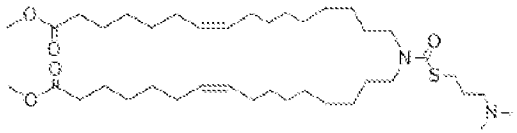
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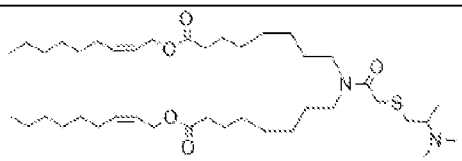
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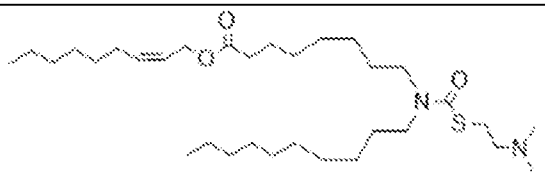
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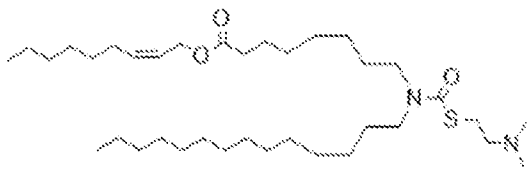
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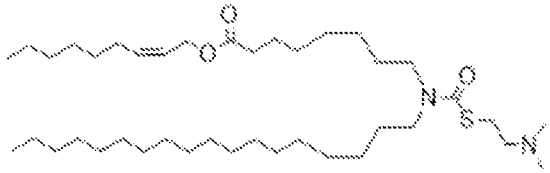
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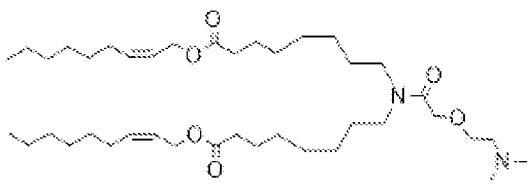
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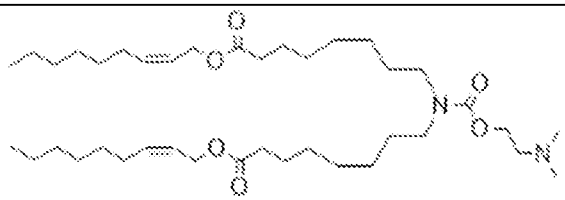
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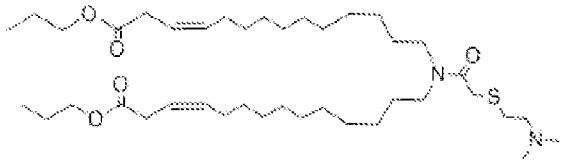
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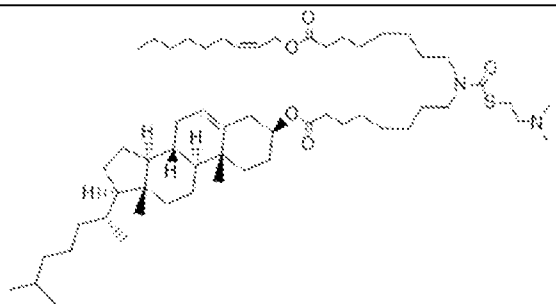
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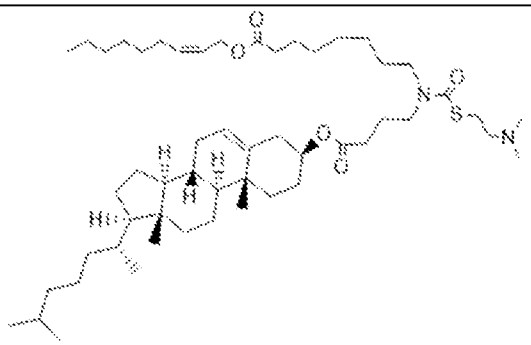
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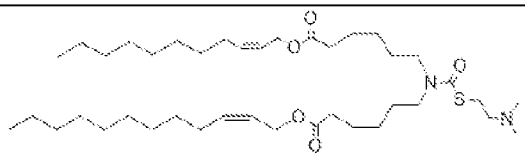
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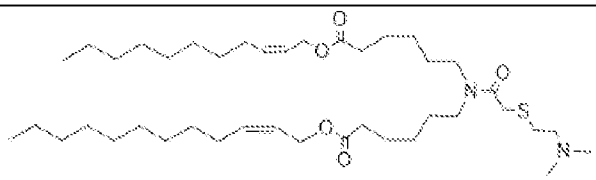
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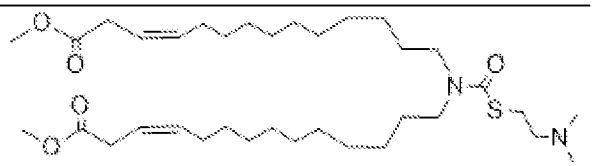
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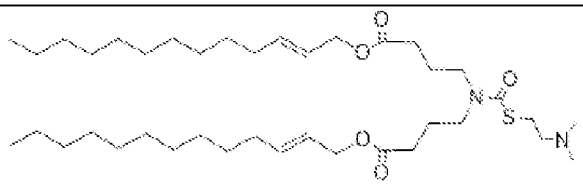
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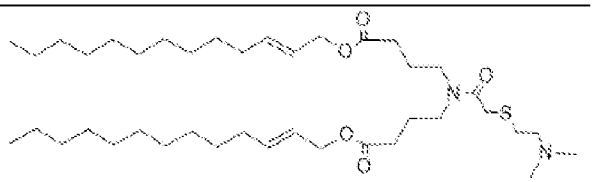
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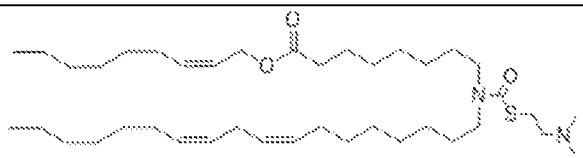
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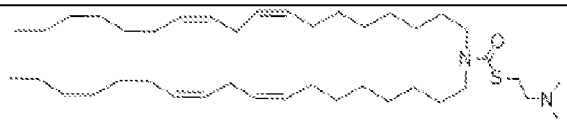
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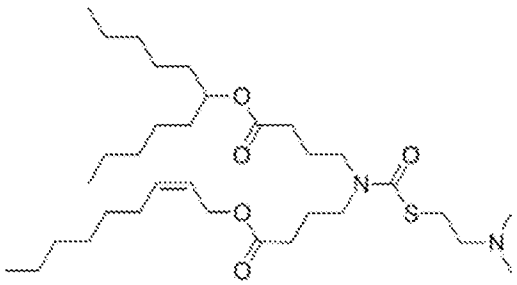
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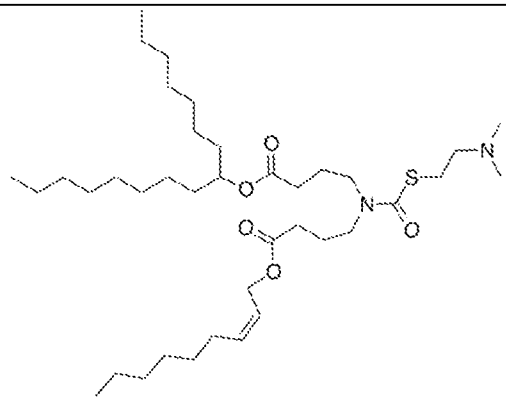
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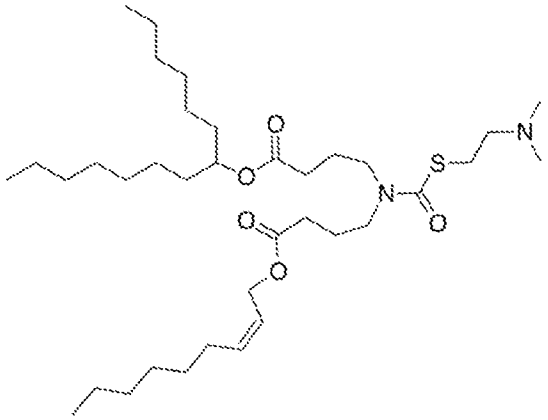
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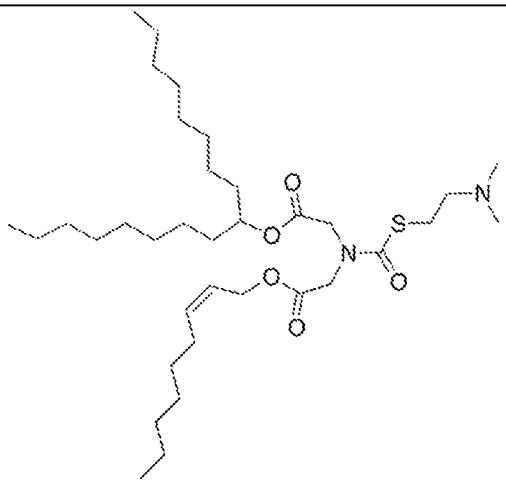
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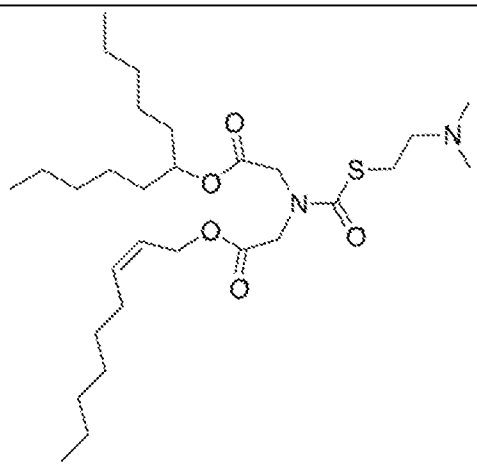
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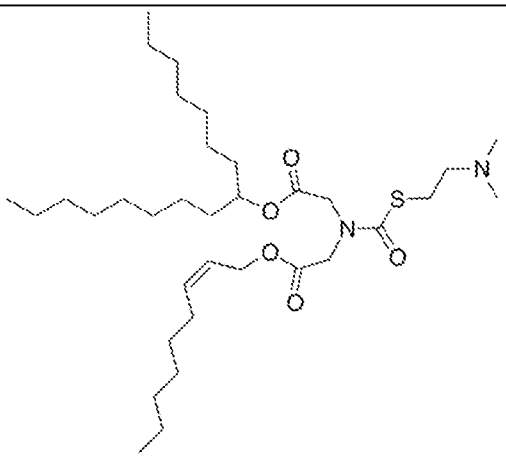
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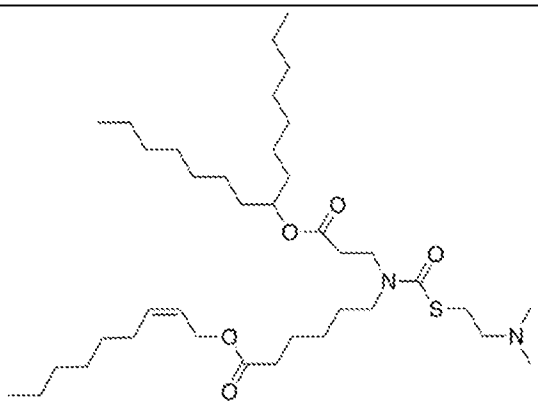
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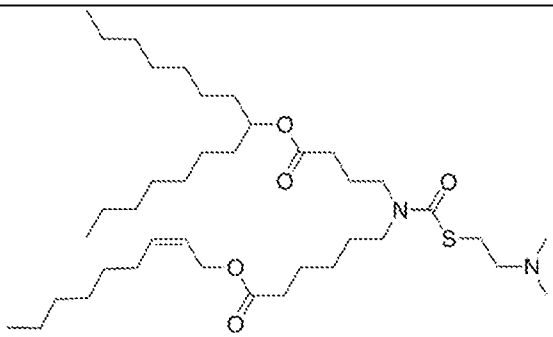
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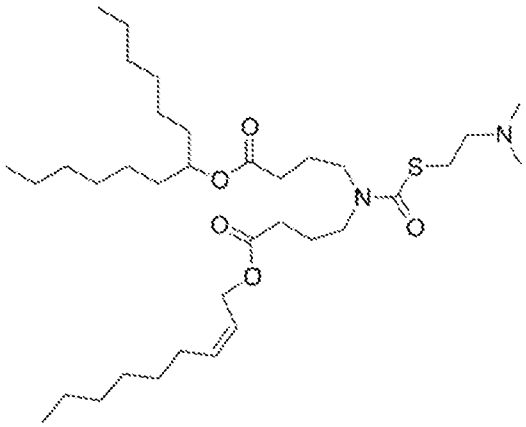
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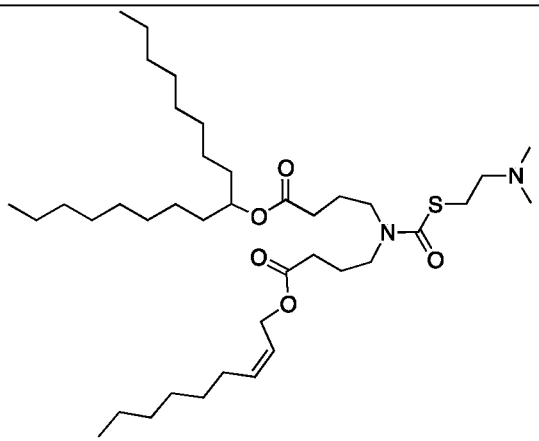
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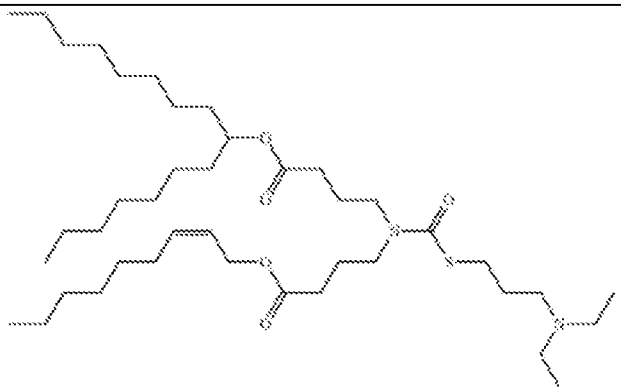
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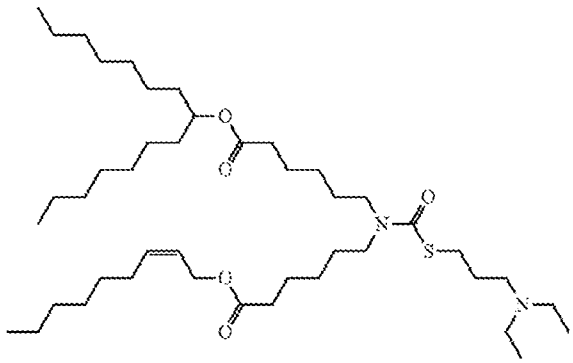
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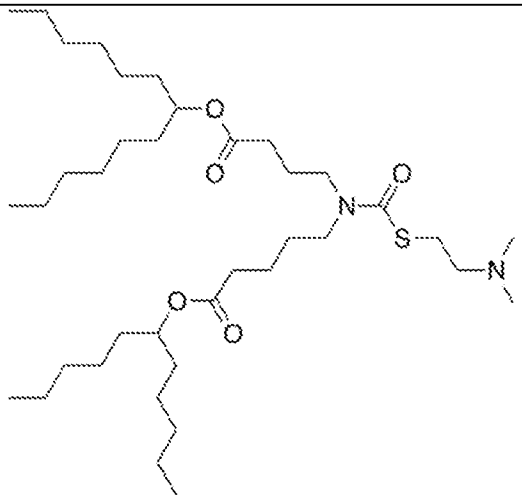
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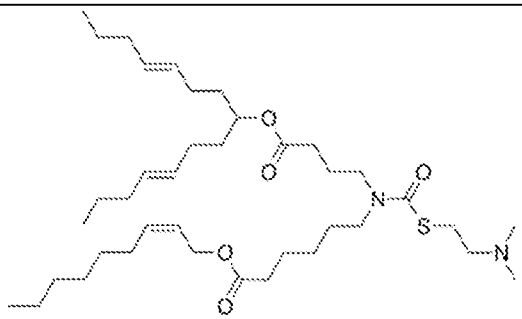
ATX-088



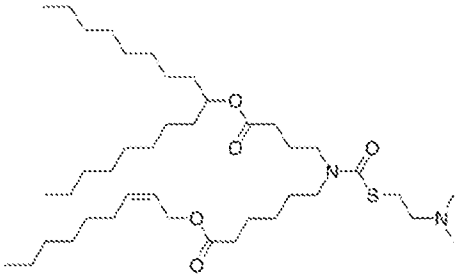
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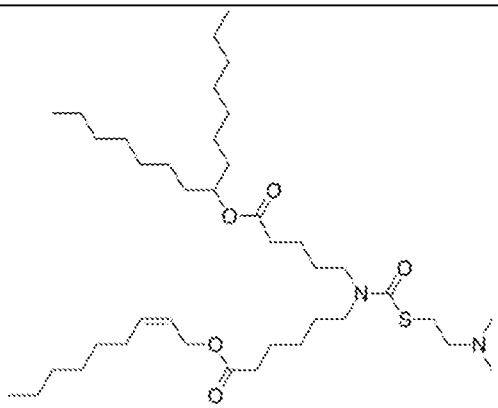
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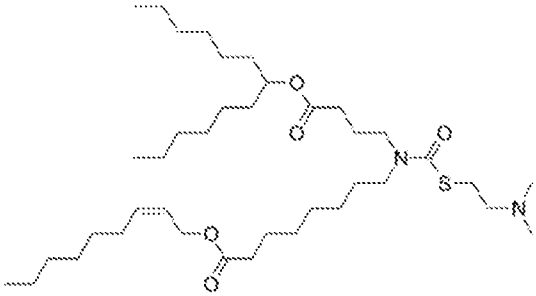
ATX-0121



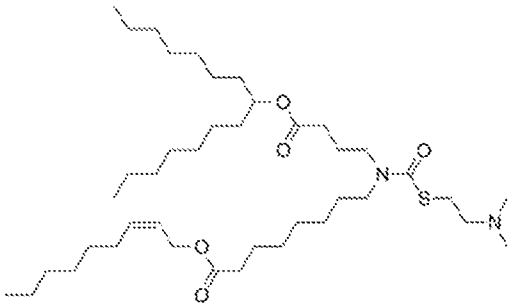
ATX-091



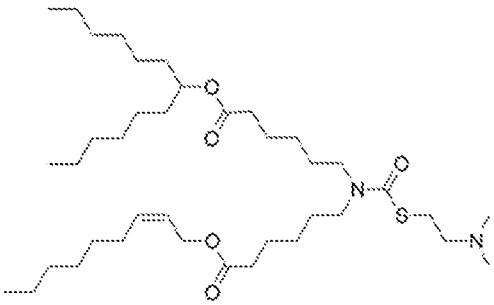
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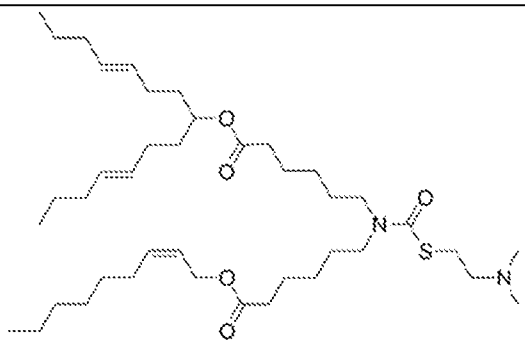
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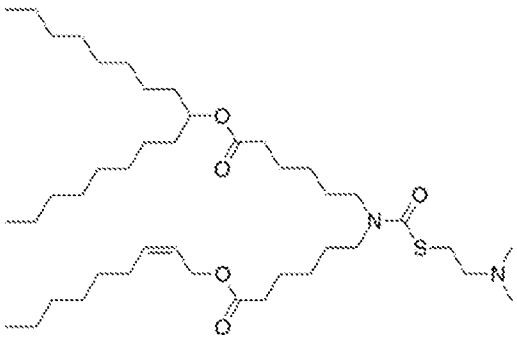
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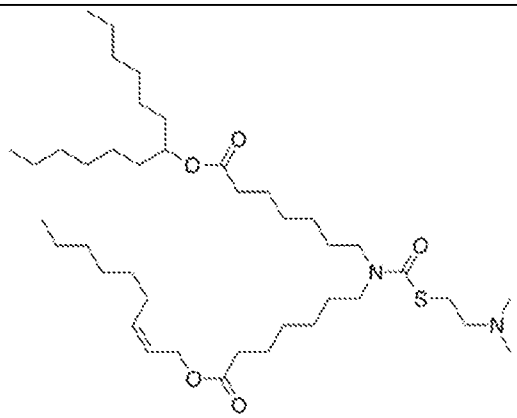
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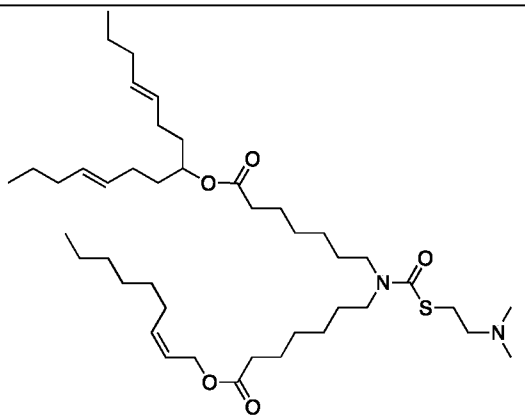
ATX-0125



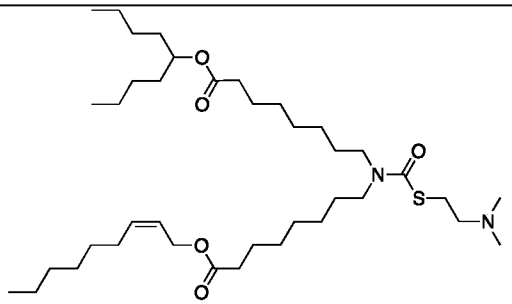
ATX-094



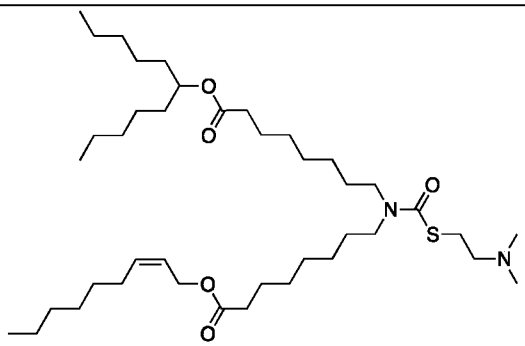
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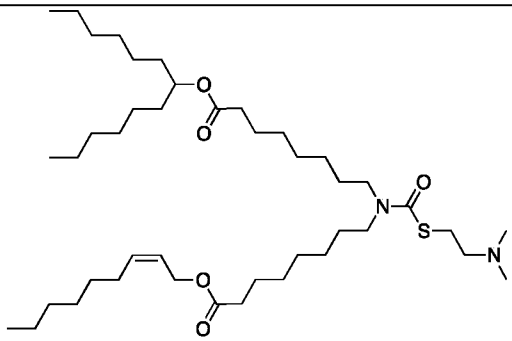
ATX-0118



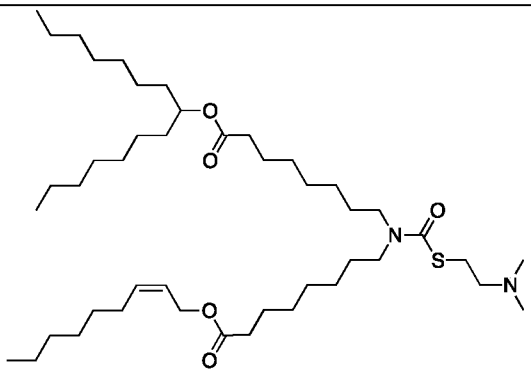
ATX-0108



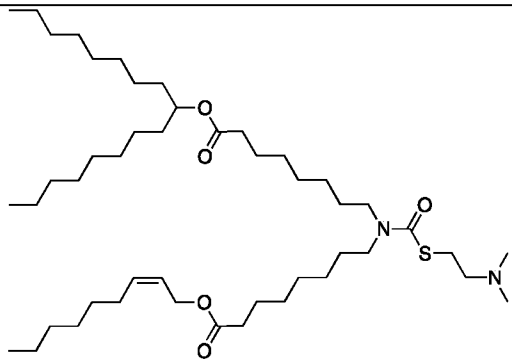
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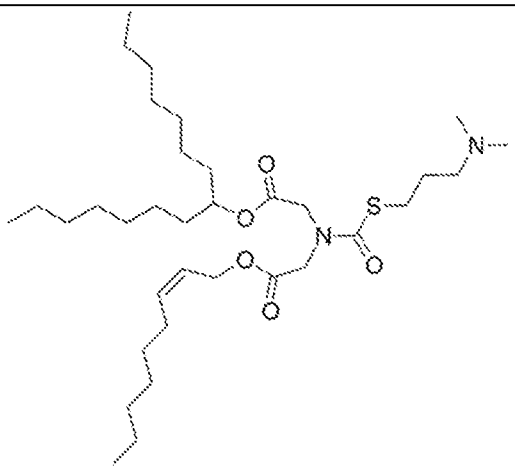
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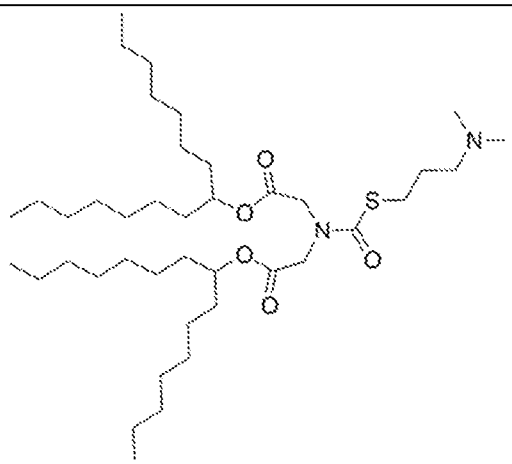


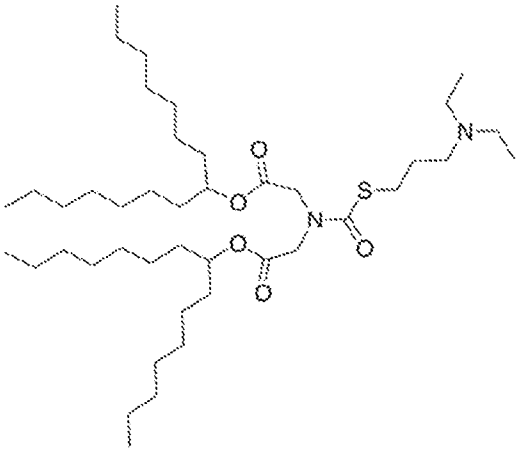
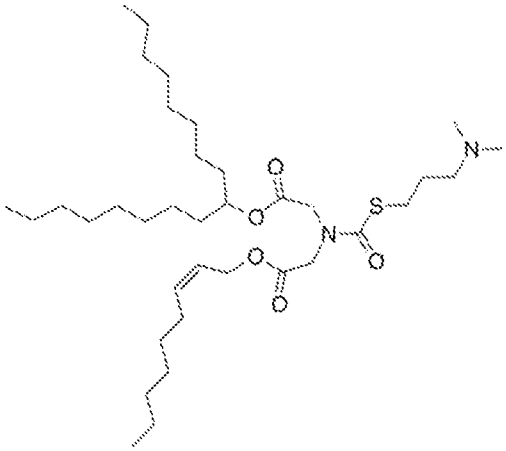
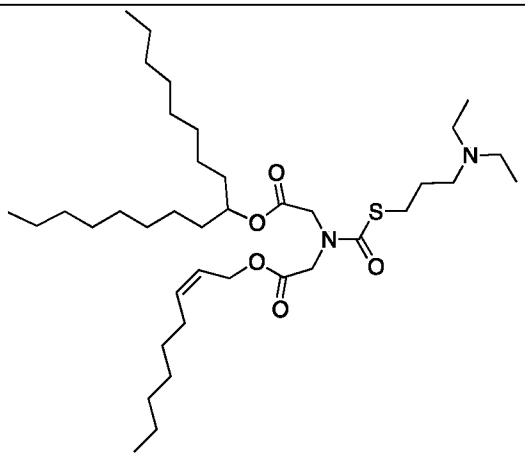
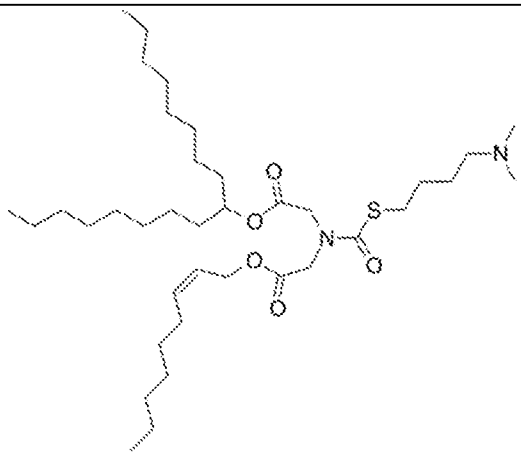
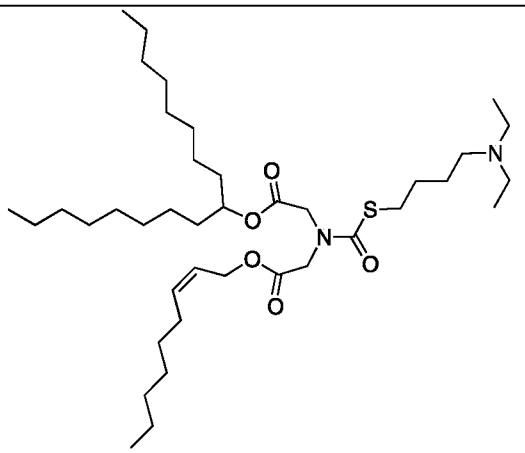
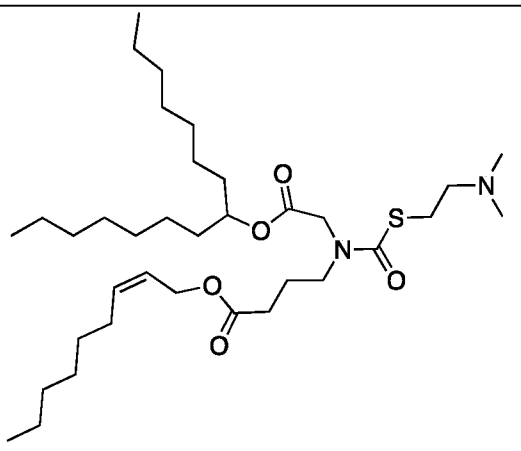
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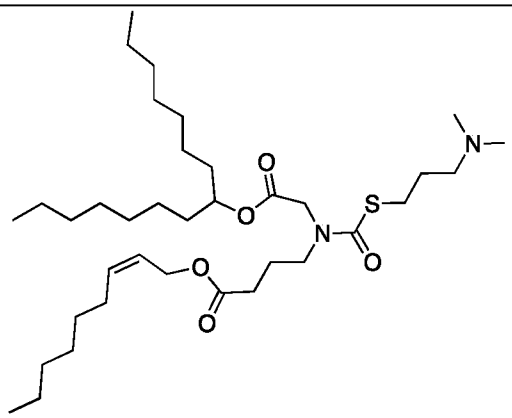


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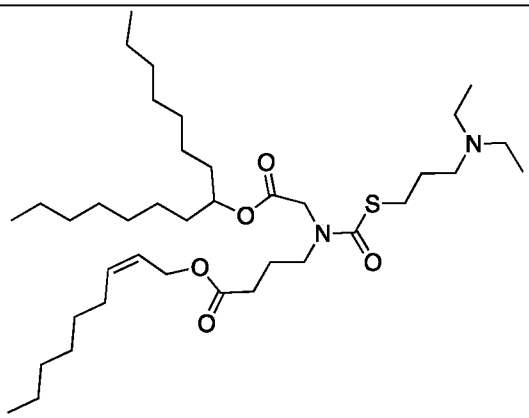




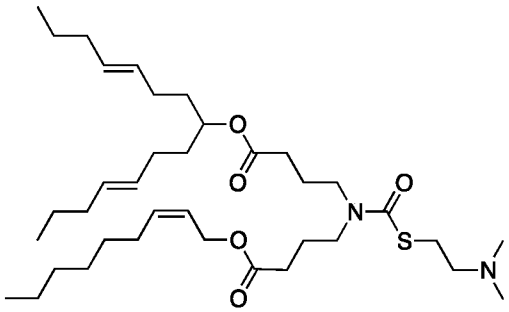
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ATX-0117	ATX-0114
	
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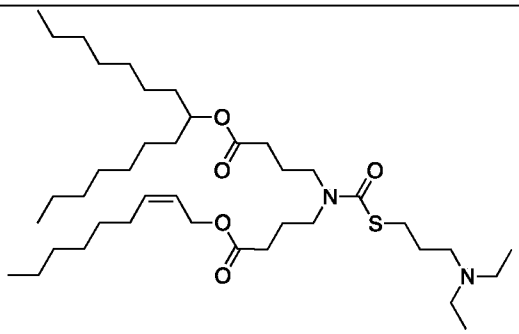
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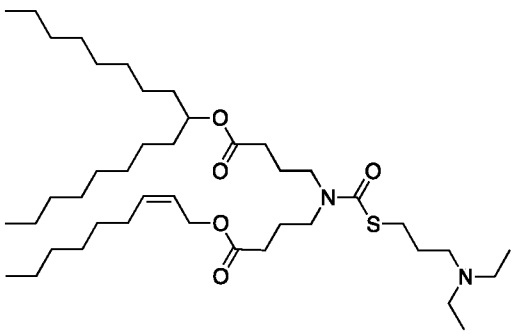
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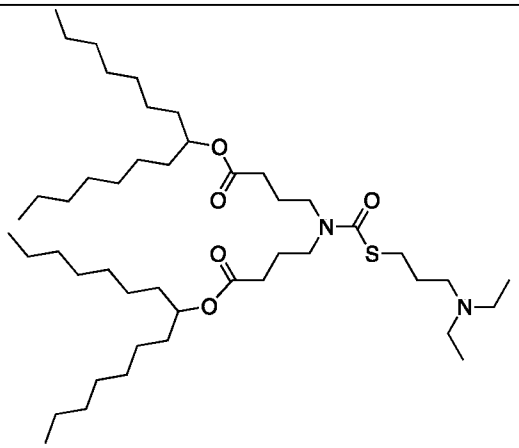
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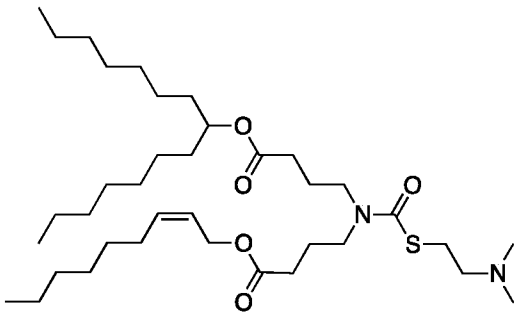
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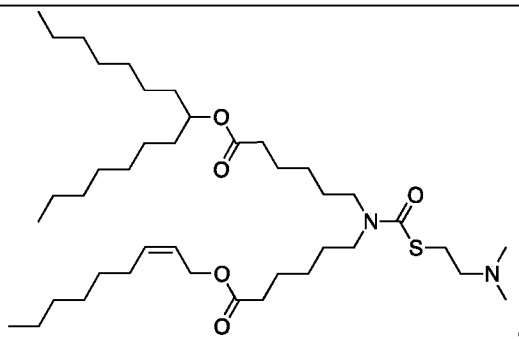
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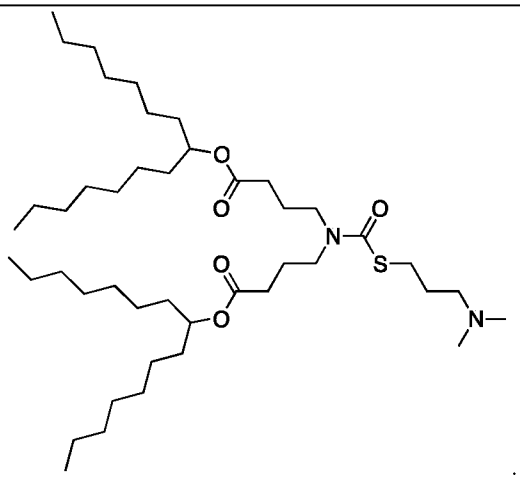


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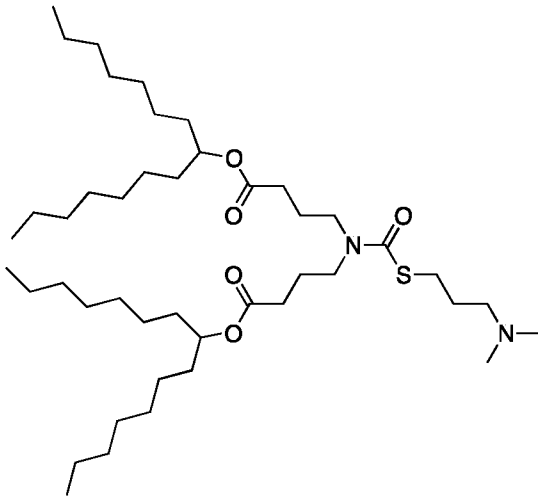
ATX-095

and



ATX-0126

[0094] In some embodiments, the ionizable cationic lipid is ATX-126:



ATX-126.

[0095] In some embodiments, the lipid formulation encapsulates the nucleic acid molecule.

[0096] In some embodiments, the lipid formulation is complexed to the nucleic acid molecule.

[0097] In some embodiments, the lipid formulation further comprises a helper lipid. In some embodiments, the helper lipid is a phospholipid. In some embodiments, the helper lipid is selected from dioleoylphosphatidyl ethanolamine (DOPE), dimyristoylphosphatidyl choline (DMPC), distearoylphosphatidyl choline (DSPC), dimyristoylphosphatidyl glycerol (DMPG), dipalmitoyl phosphatidylcholine (DPPC), and phosphatidylcholine (PC). In specific embodiments, the helper lipid is distearoylphosphatidylcholine (DSPC).

[0098] In some embodiments, the lipid formulation further comprises cholesterol.

[0099] In some embodiments, the lipid formulation further comprises a polyethylene glycol (PEG)-lipid conjugate. In some embodiments, the PEG-lipid conjugate is PEG-DMG. In some embodiments, the PEG-DMG is PEG2000-DMG.

[0100] In some embodiments, the lipid portion of the lipid formulation comprises about 40 mol% to about 60 mol% of the ionizable cationic lipid, about 4 mol% to about 16 mol% DSPC, about 30 mol% to about 47 mol% cholesterol, and about 0.5 mol% to about 3 mol% PEG2000-DMG.

[0101] In some embodiments, the lipid portion of the lipid formulation comprises about 42 mol% to about 58 mol% of the ionizable cationic lipid, about 6 mol% to about 14 mol% DSPC, about 32 mol% to about 44 mol% cholesterol, and about 1 mol% to about 2 mol% PEG2000-DMG.

[0102] In some embodiments, the lipid portion of the lipid formulation comprises about 45 mol% to about 55 mol% of the ionizable cationic lipid, about 8 mol% to about 12 mol% DSPC, about 35 mol% to about 42 mol% cholesterol, and about 1.25 mol% to about 1.75 mol% PEG2000-DMG.

[0103] In some embodiments, the composition has a total lipid:nucleic acid molecule weight ratio of about 50:1 to about 10:1. In some embodiments, the composition has a total lipid:nucleic acid molecule weight ratio of about 44:1 to about 24:1. In some embodiments, the composition has a total lipid: nucleic acid molecule weight ratio of about 40:1 to about 28:1. In some embodiments, the composition has a total lipid: nucleic acid molecule weight ratio of about 38:1 to about 30:1. In some embodiments, the composition has a total lipid: nucleic acid molecule weight ratio of about 37:1 to about 33:1. In some embodiments, the composition comprises a HEPES or TRIS buffer at a pH of about 7.0 to about 8.5.

[0104] In some embodiments, the HEPES or TRIS buffer is at a concentration of about 7 mg/mL to about 15 mg/mL.

[0105] In some embodiments, the composition further comprises about 2.0 mg/mL to about 4.0 mg/mL of NaCl.

[0106] In some embodiments, the composition further comprises one or more cryoprotectants.

[0107] In some embodiments, the one or more cryoprotectants are selected from sucrose, glycerol, or a combination of sucrose and glycerol.

[0108] In some embodiments, the composition comprises a combination of sucrose at a concentration of about 70 mg/mL to about 110 mg/mL of sucrose and glycerol at a concentration of about 50 mg/mL to about 70 mg/mL.

SUBSTITUTE SHEET (RULE 26)

[0109] In some embodiments, the composition is a lyophilized composition.

[0110] In some embodiments, the lyophilized composition comprises one or more lyoprotectants.

[0111] In some embodiments, the lyophilized composition comprises a poloxamer, potassium sorbate, sucrose, or any combination thereof.

[0112] In some embodiments, the poloxamer is poloxamer 188.

[0113] In some embodiments, the lyophilized composition comprises about 0.01 to about 1.0 % w/w of the nucleic acid molecule.

[0114] In some embodiments, the lyophilized composition comprises about 1.0 to about 5.0 % w/w lipids.

[0115] In some embodiments, the lyophilized composition comprises about 0.5 to about 2.5 % w/w of TRIS buffer.

[0116] In some embodiments, the lyophilized composition comprises about 0.75 to about 2.75 % w/w of NaCl.

[0117] In some embodiments, the lyophilized composition comprises about 85 to about 95 % w/w of a sugar. In some embodiments, the sugar is sucrose.

[0118] In some embodiments, the lyophilized composition comprises about 0.01 to about 1.0 % w/w of a poloxamer. In some embodiments, the poloxamer is poloxamer 188.

[0119] In some embodiments, the lyophilized composition comprises about 1.0 to about 5.0 % w/w of potassium sorbate.

[0120] In some embodiments, the nucleic acid molecule comprises

(a) a sequence of SEQ ID NO:124;

(b) a sequence of SEQ ID NO:124, wherein T is substituted with U;

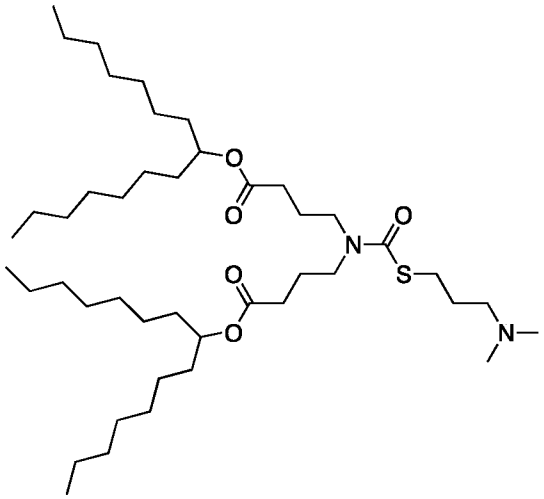
(c) a sequence of SEQ ID NO:125; or

(d) a sequence of SEQ ID NO:125, wherein T is substituted with U.

[0121] In yet another aspect, the disclosure provides a lipid nanoparticle composition comprising

a. a lipid formulation comprising

i. about 45 mol% to about 55 mol% of an ionizable cationic lipid having the structure of ATX-126:



ATX-126;

ii. about 8 mol% to about 12 mol% DSPC;

iii. about 35 mol% to about 42 mol% cholesterol; and

iv. about 1.25 mol% to about 1.75 mol% PEG2000-DMG; and

b. a nucleic acid molecule having at least 85% sequence identity to SEQ ID NO:125; wherein the lipid formulation encapsulates the nucleic acid molecule and the lipid nanoparticle has a size of about 60 to about 90 nm.

[0122] In yet another aspect, the disclosure provides a method for administering any of the compositions described herein to a subject in need thereof, wherein the composition is administered intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route. In specific embodiments, n the composition is administered intramuscularly.

[0123] In yet another aspect, the disclosure provides a method of administering any of the compositions described herein to a subject in need thereof, wherein the composition is lyophilized and is reconstituted prior to administration.

[0124] In yet another aspect, the disclosure provides a method of ameliorating COVID-19, comprising administering any of the compositions described herein to a subject in need thereof.

[0125] In some embodiments, the composition is administered one time. In some embodiments, the composition is administered two times.

[0126] In yet another aspect, the dislocusre provides a method of administering a booster dose to a vaccinated subject, comprising administering any of the compositions described herein to a subject who was previously vaccinated against coronavirus.

[0127] In some embodiments, the composition is administered at a dosage of about 0.01 μg to about 1,000 μg of nucleic acid.

[0128] In some embodiments, the composition is administered at a dosage of about 1, 2, 5, 7.5, or 10 μg of nucleic acid.

[0129] In yet another aspect, the disclosure provides a method of inducing an immune response in a subject comprising administering to the subject an effective amount of any of the nucleic acid molecules described herein.

[0130] In some embodiments, the nucleic acid molecule may be administered intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route.

[0131] In yet another aspect, the disclosure provides a method of inducing an immune response in a subject comprising administering to the subject an effective amount of any of the compositions described herein.

[0132] In some embodiments, the composition may be administered intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route.

[0133] In some embodiments, the nucleic acid molecules described herein may be used in inducing an immune response to the first antigenic protein or fragment thereof.

[0134] In some embodiments, the nucleic acid molecules described herein may be used in the manufacture of a medicament for inducing an immune response to the first antigenic protein or fragment thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0135] **FIGs. 1A-1D** show design and expression of a SARS-CoV-2 vaccine in mRNA and self-replicating RNA (STARR™) platforms. (1A) Schematic diagram of the SARS-CoV-2 self-replicating STARR™ RNA and mRNA vaccine constructs. The STARR™ construct encodes for the four non-structural proteins, ns1-ns4, from Venezuelan equine encephalitis virus (VEEV) and the SARS-CoV-2 full length spike (S) protein. The mRNA construct codes for the SARS-CoV-2 full length spike S protein. (1B) Physical characteristics and RNA trapping efficiency of the LNP in the mRNA and STARR™ (self-replicating RNA corresponding to SEQ ID NO:125; referred to herein as "STARR™ SARS-CoV-2 RNA") vaccines. (1C) Western blot detection of SARS-CoV-2 S protein following transfection of HEK293 cells with the STARR™ RNA and mRNA constructs. (1D) In vivo comparison of protein expression following intramuscular (IM) administration of LNP containing luciferase-

expressing STARR™ RNA or mRNA. Balb/c mice (n=3/group) were injected IM with 0.2 μg, 2.0 μg and 10.0 μg of STARR™ RNA or mRNA in lipid formulation. Luciferase expression was measured by in vivo bioluminescence on days 1, 3 and 7 post-IM administration. S domain 1 = S1, S domain 2 = S2, transmembrane domain = TM, cytoplasmic domain = CP.

[0136] **FIGs. 2A-2I** show clinical scores, mouse weights and transcriptomic analysis of immune genes following vaccination with STARR™ RNA or mRNA SARS-CoV-2 vaccine candidates. (2A) C57BL/6 mice were immunized with either PBS, mRNA or STARR™ SARS-CoV-2 RNA (doses 0.2 μg, 2 μg or 10 μg), weight and clinical scores assessed every day, bled at day 1 post-immunization, sacrificed at 7 days post-vaccination and lymph nodes harvested. Gene expression of inflammatory genes and immune genes were measured in whole blood (at day 1) and lymph nodes (at day 7), respectively. (2B) Expression of IFN and inflammatory response genes in whole blood presented as heatmap of z scores. (2C) Lymph node weights at 7 days post-vaccination. Principal component analysis (PCA) of immune gene expression following vaccination with mRNA or STARR™ SARS-CoV-2 RNA at doses (2D) 0.2 μg, (2E) 2 μg and (2F) 10 μg. Volcano plots of fold change of STARR™ SARS-CoV-2 RNA versus mRNA (x-axis) and Log10 P-value of STARR™ SARS-CoV-2 RNA versus mRNA (y-axis) for doses (2G) 0.2 μg, (2H) 2 μg and (2I) 10 μg.

[0137] **FIGs. 3A-3J** show cellular immune responses following vaccination with SARS-CoV-2 STARR™ RNA and mRNA. C57BL/6 mice (n=5 per group) were immunized with 0.2 μg, 2 μg, or 10 μg of STARR™ RNA or mRNA via IM, sacrificed at day 7 post-vaccination and spleens analyzed for cellular T cell responses by flow-cytometry and ELISPOT. (3A-3B) CD8+ and C) CD4+ T effector cells were assessed in vaccinated animals using surface staining for T cell markers and flow-cytometry. (3D-3E) IFNγ+ CD8+ T cells and (3F) Ratio of IFNγ+/ IL4+ CD4+ T cells in spleens of immunized mice were assessed following ex vivo stimulation with PMA/ionomycin (IO) and intracellular staining. (3G-3I) SARS-CoV-2 S protein-specific responses to pooled S protein peptides were assessed using IFNγ ELISPOT assays following vaccination with mRNA (3H) or STARR™ RNA (3I). A schematic of S protein domains is shown in (3J).

[0138] **FIGs. 4A-4G** show humoral responses in multiple mouse strains following immunization with mRNA and STARR™ vaccine candidates. (4A) BALB/c and C57BL/6J mice were immunized via IM with 0.2 μg, 2 μg, or 10 μg of STARR™ RNA or mRNA (n=5/group). Blood sampling was conducted at baseline, and days 10, 19, 30, 40, 50 and 60

post-vaccination for BALB/c and days 10, 20 and 30 for C57BL/6J. (4B-4C) IgM and (4D-4E) IgG against the SARS-CoV-2 S protein over time, assessed using insect cell-derived whole S protein in a Luminex immuno-assay (measured as MFI). IgG endpoint titers to mammalian-derived whole S protein, S1, S2 and receptor binding domain (RBD) proteins at day 30 post-vaccination were assessed in (4F) BALB/c and (4G) C57BL/6J.

[0139] **FIGs. 5A-5D** show that STARR™ SARS-CoV-2 RNA elicits Th1 skewed immune responses. SARS-CoV-2 spike-specific IgG subclasses and the ratio of IgG2a/c/IgG1 at 30 days post-vaccination with STARR™ RNA and mRNA in (5A) BALB/c and (5B) C57BL/6J mice. Th2 cytokine and Th1/Th2 skew in CD4 T cells at day 7 post-vaccination in C57BL/6J mice measured by ICS as (5C) percentage of IL4+ CD4 T cells and (5D) ratio of IFNγ+/IL4+ CD4+ T cells.

[0140] **FIGs. 6A-6E** show that STARR™ SARS-CoV-2 RNA elicits a higher quality humoral response than mRNA platform. (6A) Avidity of SARS-CoV-2 S protein-specific IgG at day 30 post-immunization was measured using 8M urea washes. (6B) Neutralizing antibody (PRNT50 titers) at day 30 post-vaccination against a clinically isolated live SARS-CoV-2 virus measured in both BALB/c and C57BL/6J. Dashed lines depict the serum dilution range (i.e. from 1:20 to 1:320) tested by PRNT. (6C) PRNT50 and (6D) PRNT70 of SARS-CoV-2 neutralization at day 60 post-vaccination and convalescent sera from COVID-19 patients. (6E) Correlation analysis of Spike-specific IgG endpoint titers against SARS-CoV-2 neutralization (PRNT50). PRNT – plaque reduction neutralization test.

[0141] **FIGs. 7A-7E** show clinical scores, body weight and immune responses to STARR™ SARS-CoV-2 RNA and mRNA following boost at day 30 post-prime in C57BL/6J. (7A) Clinical scores and (7B) percentage of initial body weight following boost vaccinations. (7C) Anti-Spike IgG responses following boost by mRNA and STARR™ SARS-CoV-2 RNA. Grey dashed line marks the experimental assay saturation point. IFN γ+ CD8+ T effector cells responses (fold change over PBS) in animals either primed or prime & boosted with either (7D) mRNA or (7E) STARR™ SARS-CoV-2 RNA vaccine candidates.

[0142] **FIGs. 8A-8B** show whole blood transcriptomic data at 1-day post-prime vaccination showing Nanostring counts per 50ng RNA of selected (8A) IFN and (8B) inflammatory genes.

[0143] **FIGs. 9A-9B** show correlation analysis of live SARS-CoV-2 neutralization against binding IgG and IgG subclasses in BALB/c and C57BL/6J mouse strains. (9A) Spearman

correlation analysis of SARS-CoV-2 neutralization (PRNT50) against total IgG specific to several SARS-CoV-2 antigens, including S, S1, and RBD recombinant proteins. (9B) Spearman correlation analysis of SARS-CoV-2 neutralization (PRNT50) against SARS-CoV-2 S-specific IgG subclasses (IgG1 and IgG2a or IgG2c).

[0144] **FIG. 10** shows Kaplan-Meier survival curves for unvaccinated mice (PBS) and mice vaccinated with STARR™ SARS-CoV-2 RNA following challenge with a lethal dose of SARS-CoV-2 virus. Upper line – STARR™ SARS-CoV-2 RNA (2μg, 10μg); dropping line – PBS.

[0145] **FIG. 11** shows that STARR™ SARS-CoV-2 RNA vaccination protects against lung and brain SARS-CoV-2 infection. Viral RNA levels in lungs (FIG. 11, left) and in brains (FIG. 11, right) of unvaccinated mice (PBS) and mice vaccinated with the indicated dose of STARR™ SARS-CoV-2 RNA are shown.

[0146] **FIG. 12** shows viral titers in lungs of unvaccinated mice (PBS) and mice vaccinated with the indicated dose of STARR™ SARS-CoV-2 RNA following challenge with SARS-CoV-2.

[0147] **FIG. 13** shows an RNA dose-dependent immunogenicity comparison between G614 and D614 SARS CoV-2 glycoprotein expressed from self-replicating RNA.

[0148] **FIG. 14** shows a schematic illustrating one aspect of STARR™ technology and lipid-mediated delivery.

[0149] **FIGs. 15A-15C** show duration of luciferase reporter gene expression for self-replicating (replicon) RNA (STARR™), such as (15A) STARR™ FLuc, (15B) STARR™ FLuc IRES-E3L, and (15C) STARR™ FLuc IRES E3L (short 3' UTR) as compared to mRNA.

[0150] **FIG. 16A-16D** show results of Luminex Assay for anti-SARS-Cov-2 Spike Glycoprotein IgG in two pre-clinical studies. BALB/c mice were vaccinated with increasing RNA doses of self-replicating RNA (SEQ ID NO:125) formulated as lyophilized lipid nanoparticles (LYO-LNP) and liquid (frozen) lipid nanoparticles (Liquid-LNP). (16A) First Study 0.2 μg, (16B) First Study 2 μg, (16C) Second Study 0.2 μg, and (16D) Second Study 2 μg. Blood was collected and processed to serum at various times post-vaccination and evaluated for anti-SARS-CoV-2 spike glycoprotein IgG. Two way ANOVA, Tukey's multiple

comparison post-test compared LYO-LNP to Liquid-LNP where * $p < 0.0332$, ** $p < 0.0021$, *** $p < 0.0002$, **** $p < 0.0001$.

[0151] **FIGs. 17A-17B** show the Area Under the Curve (AUC) Analysis for anti-SARS-Cov-2 Spike Glycoprotein IgG (First and Second Study combined data). IgG assay results were combined from two studies to evaluate self-replicating RNA (SEQ ID NO:125) formulated as lyophilized lipid nanoparticles (LYO-LNP) and liquid (frozen) lipid nanoparticles (Liquid-LNP) at (17A) 0.2 μg, and (17B) 2 μg. N=10/group. First Study Day 19 and 31 results were combined with Second Study Day 20 and 30 results, respectively, and an Area Under the Curve (AUC) analysis was performed. One way ANOVA, Sidak's multiple comparison post-test compared LYO-LNP to Liquid-LNP and resulted in no statistical differences.

[0152] **FIGs. 18A-18D** shows characterization of STARR™ technology with firefly luciferase transgene expression. (18A) Firefly luciferase (FLuc) expression from STARR™ Fluc, SINV FLuc, and mRNA FLuc was monitored up to day 28 by In Vivo Imaging System (IVIS). The average of total flux (p/s) from 6 injection sites in a mouse group was plotted at each time point with a standard error of mean, SEM. (18B) IVIS picture of three mice (6 injection sites) per group on day 14 is shown for each group that was administered with the test article labeled below the picture. (18C) Luciferase expression from mice that were intramuscularly injected with STARR™ FLuc was monitored by IVIS up to 63 days post administration. (18D) Effect of prior administration of replicon backbone was examined for STARR™ (upper panel) and SINV (lower panel). Replicon encoding FLuc was IM injected at 7 days post dose of replicon with homologous backbone with an irrelevant gene/sequence (labeled STARR™ irr or SINV irr) at day 0. As a reference, a mouse group with PBS administration at day 0 was included in each of STARR™ and SINV group.

[0153] **FIG. 19** shows that STARR™ elicits antigen-specific IFN-gamma response. Enzyme-linked immune absorbent spot ELISpot was used to count the number of splenocytes that were specifically stimulated by an antigen peptide of the same amino acid sequence encoded in TA STARR™. Neither no peptide (cell only) nor irrelevant peptide (Bgal) did not elicit significant IFN-gamma from splenocytes from mice vaccinated with STARR™ FLuc or TA STARR™. Stimulation with AH1-A5 peptide resulted in the detection of IFN-gamma-producing cells specifically from the mice that were vaccinated with TASTARR™. Concanavalin A (ConA) was used as a positive control of IFN-gamma production.

[0154] **FIGs. 20A-20F** illustrate reduced tumor growth rate by TA STARR™ vaccination in a CT26 syngeneic mouse model. CT26 murine colorectal carcinoma cells ($5x10^5$) were subcutaneously implanted in 10-week old female BALB/c mice (n=8 per group). On days 1 and 8, the mice were vaccinated with STARR™ FLuc, a negative control, or TA STARR™, which encodes AH1A5 epitope. Tumor growth was monitored in mice vaccinated with (20A) STARR™ FLuc without checkpoint inhibitor treatment; (20B) STARR™ FLuc with a combination anti-PD1/PDL1 treatment; (20C) STARR™ FLuc with a combination anti-CTLA4 treatment; (20D) STARR™ vaccine without checkpoint inhibitor treatment; (20E) STARR™ vaccine with a combination treatment of anti-PD1 and anti-PDL1; and (20F) STARR™ vaccine with a combination treatment of anti-CTLA4. The individual tumor growth curves from a mouse group that were administered with STARR™ FLuc and TA STARR™ are shown in upper and lower panels, respectively.

[0155] **FIG. 21** illustrates prolonged protection by combination treatment of TA STARR™ Vaccine with checkpoint inhibitors. Mice that were treated with TA STARR™ combined with anti-PD1/PDL1 or anti-CTLA4 were found to be resistant to tumor growth following the CT26 challenge at day 25 to 42. Naïve mice were used as a control for the CT26 tumor growth.

[0156] **FIGs. 22A-22C** show results from AH1-tetramer staining of CD8+ T-cells in the form of (22A) a graph and (22B and 22C) plots. Splenocytes from the mice group with combination treatment of TA STARR™ and anti-PD1/PDL1 at day 42 were stained with AH1 (H-2Ld)-tetramer. The staining was specific to CD8+ T cells from the mouse group with TA STARR™ treatment, and the population represented 9-17% of total CD8+ T cells from the splenocytes.

[0157] **FIG. 23** shows HAI titers obtained for self-replicating RNA (STARR™) and mRNA constructs encoding the hemagglutinin of influenza virus A/California/07/2009 (H1N1).

[0158] **FIGs. 24A-24B** show RNA replication levels (FIG. 24A) and luciferase reporter gene expression levels (FIG. 24B) for the indicated self-replicating (replicon) RNAs as compared to mRNA.

DETAILED DESCRIPTION

[0159] The present disclosure relates to self-replicating RNAs and nucleic acids encoding the same for expression of transgenes such as antigenic proteins and tumor antigens, for example. Also provided herein are methods of administration (e.g., to a host, such as a

mammalian subject) of self-replicating RNAs, whereby the self-replicating RNA is translated in vivo and the heterologous protein-coding sequence is expressed and, e.g., can elicit an immune response to the heterologous protein-coding sequence in the recipient or provide a therapeutic effect, where the heterologous protein-coding sequence is a therapeutic protein. Self-replicating RNAs provided herein are useful as vaccines that can be rapidly generated and that can be effective at low and/or single doses. The present disclosure further relates to methods of inducing an immune response using self-replicating RNAs provided herein.

[0160] In some embodiments, an immune response can be elicited against Coronavirus: immunogens that include, but are not limited to, those derived from a SARS coronavirus, avian infectious bronchitis (IBV), Mouse hepatitis virus (MHV), and Porcine transmissible gastroenteritis virus (TGEV). The coronavirus immunogen may be a spike polypeptide.

[0161] Self-replicating RNAs are described, for example, in U.S. 2018/0036398, the contents of which are incorporated by reference in their entirety.

Definitions

[0162] As used herein, the term "fragment," when referring to a protein or nucleic acid, for example, means any shorter sequence than the full-length protein or nucleic acid. Accordingly, any sequence of a nucleic acid or protein other than the full-length nucleic acid or protein sequence can be a fragment. In some aspects, a protein fragment includes an epitope. In other aspects, a protein fragment is an epitope.

[0163] As used herein, the term "nucleic acid" refers to any deoxyribonucleic acid (DNA) molecule, ribonucleic acid (RNA) molecule, or nucleic acid analogues. A DNA or RNA molecule can be double-stranded or single-stranded and can be of any size. Exemplary nucleic acids include, but are not limited to, chromosomal DNA, plasmid DNA, cDNA, cell-free DNA (cfDNA), mitochondrial DNA, chloroplast DNA, viral DNA, mRNA, tRNA, rRNA, long non-coding RNA, siRNA, micro RNA (miRNA or miR), hnRNA, and viral RNA. Exemplary nucleic analogues include peptide nucleic acid, morpholino- and locked nucleic acid, glycol nucleic acid, and threose nucleic acid. As used herein, the term "nucleic acid molecule" is meant to include fragments of nucleic acid molecules as well as any full-length or non-fragmented nucleic acid molecule, for example. As used herein, the terms "nucleic acid" and "nucleic acid molecule" can be used interchangeably, unless context clearly indicates otherwise.

[0164] As used herein, the term "protein" refers to any polymeric chain of amino acids. The terms "peptide" and "polypeptide" can be used interchangeably with the term protein, unless context clearly indicates otherwise, and can also refer to a polymeric chain of amino acids. The term "protein" encompasses native or artificial proteins, protein fragments and polypeptide analogs of a protein sequence. A protein may be monomeric or polymeric. The term "protein" encompasses fragments and variants (including fragments of variants) thereof, unless otherwise contradicted by context.

[0165] In general, "sequence identity" or "sequence homology," which can be used interchangeably, refer to an exact nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Typically, techniques for determining sequence identity include determining the nucleotide sequence of a polynucleotide and/or determining the amino acid sequence encoded thereby or the amino acid sequence of a polypeptide, and comparing these sequences to a second nucleotide or amino acid sequence. As used herein, the term "percent (%) sequence identity" or "percent (%) identity," also including "homology," refers to the percentage of amino acid residues or nucleotides in a sequence that are identical with the amino acid residues or nucleotides in a reference sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Thus, two or more sequences (polynucleotide or amino acid) can be compared by determining their "percent identity," also referred to as "percent homology." The percent identity to a reference sequence (e.g., nucleic acid or amino acid sequences), which may be a sequence within a longer molecule (e.g., polynucleotide or polypeptide), may be calculated as the number of exact matches between two optimally aligned sequences divided by the length of the reference sequence and multiplied by 100. Percent identity may also be determined, for example, by comparing sequence information using the advanced BLAST computer program, including version 2.2.9, available from the National Institutes of Health. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul et al., J. Mol. Biol. 215:403-410 (1990); Karlin and Altschul, Proc. Natl. Acad. sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997). Briefly, the BLAST program defines identity as the number of identical aligned symbols (i.e., nucleotides or amino acids), divided by the total number of symbols in the shorter of the two sequences. The program may be used to determine percent identity over the entire length of the sequences being compared. Default

parameters are provided to optimize searches with short query sequences, for example, with the blastp program. The program also allows use of an SEG filter to mask-off segments of the query sequences as determined by the SEG program of Wootton and Federhen, Computers and Chemistry 17: 149-163 (1993). Ranges of desired degrees of sequence identity are approximately 80% to 100% and integer values in between. Percent identities between a reference sequence and a claimed sequence can be at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, or at least 99.9%. In general, an exact match indicates 100% identity over the length of the reference sequence. Additional programs and methods for comparing sequences and/or assessing sequence identity include the Needleman-Wunsch algorithm (see, e.g., the EMBOSS Needle aligner available at ebi.ac.uk/Tools/psa/emboss needle/, optionally with default settings), the Smith-Waterman algorithm (see, e.g., the EMBOSS Water aligner available at ebi.ac.uk/Tools/psa/emboss water/, optionally with default settings), the similarity search method of Pearson and Lipman, 1988, Proc. Natl. Acad. Sci. USA 85, 2444, or computer programs which use these algorithms (GAP, BESTFIT, FASTA, BLAST P, BLAST N and TFASTA in Wisconsin Genetics Software Package, Genetics Computer Group. 575 Science Drive, Madison, Wis.). In some aspects, reference to percent sequence identity refers to sequence identity as measured using BLAST (Basic Local Alignment Search Tool). In other aspects, ClustalW is used for multiple sequence alignment. Optimal alignment may be assessed using any suitable parameters of a chosen algorithm, including default parameters.

[0166] As used herein, the term “drug” or “medicament,” means a pharmaceutical formulation or composition as described herein.

[0167] As used herein, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. Thus, for example, references to "the method" includes one or more methods, and/or steps of the type described herein which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0168] “About” as used herein when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of +20%, or ±10%, or ±5%, or even ±1% from the specified value, as such variations are appropriate for the disclosed methods or to perform the disclosed methods.

[0169] The term “expression” refers to the process by which a nucleic acid sequence or a polynucleotide is transcribed from a DNA template (such as into mRNA or other RNA

transcript) and/or the process by which a transcribed mRNA or other RNA is subsequently translated into peptides, polypeptides, or proteins. Transcripts and encoded polypeptides may be collectively referred to as "gene product."

[0170] As used herein, the terms "self-replicating RNA," "self-transcribing and self-replicating RNA," "self-amplifying RNA (saRNA)," and "replicon" may be used interchangeably, unless context clearly indicates otherwise. Generally, the term "replicon" or "viral replicon" refers to a self-replicating subgenomic RNA derived from a viral genome that includes viral genes encoding non-structural proteins important for viral replication and that lacks viral genes encoding structural proteins. A self-replicating RNA can encode further subgenomic RNAs that are not able to self-replicate.

[0171] As used herein, "operably linked," "operable linkage," "operatively linked," or grammatical equivalents thereof refer to juxtaposition of genetic elements, e.g., a promoter, an enhancer, a polyadenylation sequence, etc., wherein the elements are in a relationship permitting them to operate in the expected manner. For instance, a regulatory element, which can comprise promoter and/or enhancer sequences, is operatively linked to a coding region if the regulatory element helps initiate transcription of the coding sequence. There may be intervening residues between the regulatory element and coding region so long as this functional relationship is maintained.

Nucleic Acid Molecules

[0172] In some embodiments, provided herein are nucleic acid molecules comprising: (i) a first polynucleotide encoding one or more viral replication proteins, wherein the first polynucleotide is codon-optimized as compared to a wild-type polynucleotide encoding the one or more viral replication proteins; and (ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof, wherein the first antigenic protein is a coronavirus protein.

[0173] An RNA molecule can encode a single polypeptide immunogen or multiple polypeptides. Multiple immunogens can be presented as a single polypeptide immunogen (fusion polypeptide) or as separate polypeptides. If immunogens are expressed as separate polypeptides from a replicon then one or more of these may be provided with an upstream IRES or an additional viral promoter element. Alternatively, multiple immunogens may be expressed from a polyprotein that encodes individual immunogens fused to a short autocatalytic protease (e.g. foot-and-mouth disease virus 2A protein), or as inteins.

[0174] Also provided herein, in some embodiments, are nucleic acid molecules comprising: (i) a first polynucleotide comprising a sequence having at least 80% identity to a sequence of SEQ ID NO:72; and (ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof.

Codon Optimization

[0175] In some embodiments, first polynucleotides of nucleic acid molecules provided herein encoding one or more viral replication proteins include codon-optimized sequences. As used herein, the term "codon-optimized" means a polynucleotide, nucleic acid sequence, or coding sequence has been redesigned as compared to a wild-type or reference polynucleotide, nucleic acid sequence, or coding sequence by choosing different codons without altering the amino acid sequence of the encoded protein. Accordingly, codon-optimization generally refers to replacement of codons with synonymous codons to optimize expression of a protein while keeping the amino acid sequence of the translated protein the same. Codon optimization of a sequence can increase protein expression levels (Gustafsson et al., Codon bias and heterologous protein expression. 2004, Trends Biotechnol 22: 346-53) of the encoded proteins, for example, and provide other advantages. Variables such as codon usage preference as measured by codon adaptation index (CAI), for example, the presence or frequency of U and other nucleotides, mRNA secondary structures, cis-regulatory sequences, GC content, and other variables may correlate with protein expression levels (Villalobos et al., Gene Designer: a synthetic biology tool for constructing artificial DNA segments. 2006, BMC Bioinformatics 7:285).

[0176] Any method of codon optimization can be used to codon optimize polynucleotides and nucleic acid molecules provided herein, and any variable can be altered by codon optimization. Accordingly, any combination of codon optimization methods can be used. Exemplary methods include the high codon adaptation index (CAI) method, the Low U method, and others. The CAI method chooses a most frequently used synonymous codon for an entire protein coding sequence. As an example, the most frequently used codon for each amino acid can be deduced from 74,218 protein-coding genes from a human genome. The Low U method targets U-containing codons that can be replaced with a synonymous codon with fewer U moieties, generally without changing other codons. If there is more than one choice for replacement, the more frequently used codon can be selected. Any polynucleotide, nucleic acid sequence, or codon sequence provided herein can be codon-optimized.

[0177] In some embodiments, the nucleotide sequence of any region of the RNA or DNA templates described herein may be codon optimized. Preferably, the primary cDNA template may include reducing the occurrence or frequency of appearance of certain nucleotides in the template strand. For example, the occurrence of a nucleotide in a template may be reduced to a level below 25% of said nucleotides in the template. In further examples, the occurrence of a nucleotide in a template may be reduced to a level below 20% of said nucleotides in the template. In some examples, the occurrence of a nucleotide in a template may be reduced to a level below 16% of said nucleotides in the template. Preferably, the occurrence of a nucleotide in a template may be reduced to a level below 15%, and preferably may be reduced to a level below 12% of said nucleotides in the template.

[0178] In some embodiments, the nucleotide reduced is uridine. For example, the present disclosure provides nucleic acids with altered uracil content wherein at least one codon in the wild-type sequence has been replaced with an alternative codon to generate a uracil-altered sequence. Altered uracil sequences can have at least one of the following properties:

(i) an increase or decrease in global uracil content (i.e., the percentage of uracil of the total nucleotide content in the nucleic acid of a section of the nucleic acid, e.g., the open reading frame);

(ii) an increase or decrease in local uracil content (i.e., changes in uracil content are limited to specific subsequences);

(iii) a change in uracil distribution without a change in the global uracil content;

(iv) a change in uracil clustering (e.g., number of clusters, location of clusters, or distance between clusters); or

(v) combinations thereof.

[0179] In some embodiments, the percentage of uracil nucleobases in the nucleic acid sequence is reduced with respect to the percentage of uracil nucleobases in the wild-type nucleic acid sequence. For example, 30% of nucleobases may be uracil in the wild-type sequence but the nucleobases that are uracil are preferably lower than 15%, preferably lower than 12% and preferably lower than 10% of the nucleobases in the nucleic acid sequences of the disclosure. The percentage uracil content can be determined by dividing the number of uracil in a sequence by the total number of nucleotides and multiplying by 100.

[0180] In some embodiments, the percentage of uracil nucleobases in a subsequence of the nucleic acid sequence is reduced with respect to the percentage of uracil nucleobases in the corresponding subsequence of the wild-type sequence. For example, the wild-type sequence may have a 5′-end region (e.g., 30 codons) with a local uracil content of 30%, and the uracil content in that same region could be reduced to preferably 15% or lower, preferably 12% or lower and preferably 10% or lower in the nucleic acid sequences of the disclosure. These subsequences can also be part of the wild-type sequences of the heterologous 5' and 3' UTR sequences of the present disclosure.

[0181] In some embodiments, codons in the nucleic acid sequence of the disclosure reduce or modify, for example, the number, size, location, or distribution of uracil clusters that could have deleterious effects on protein translation. Although lower uracil content is desirable in certain aspects, the uracil content, and in particular the local uracil content, of some subsequences of the wild-type sequence can be greater than the wild-type sequence and still maintain beneficial features (e.g., increased expression).

[0182] In some embodiments, the uracil-modified sequence induces a lower Toll-Like Receptor (TLR) response when compared to the wild-type sequence. Several TLRs recognize and respond to nucleic acids. Double-stranded (ds)RNA, a frequent viral constituent, has been shown to activate TLR3. Single-stranded (ss)RNA activates TLR7. RNA oligonucleotides, for example RNA with phosphorothioate internucleotide linkages, are ligands of human TLR8. DNA containing unmethylated CpG motifs, characteristic of bacterial and viral DNA, activate TLR9.

[0183] As used herein, the term "TLR response" is defined as the recognition of single-stranded RNA by a TLR7 receptor, and preferably encompasses the degradation of the RNA and/or physiological responses caused by the recognition of the single-stranded RNA by the receptor. Methods to determine and quantify the binding of an RNA to a TLR7 are known in the art. Similarly, methods to determine whether an RNA has triggered a TLR7-mediated physiological response (e.g., cytokine secretion) are well known in the art. In some embodiments, a TLR response can be mediated by TLR3, TLR8, or TLR9 instead of TLR7. Suppression of TLR7-mediated response can be accomplished via nucleoside modification. RNA undergoes over a hundred different nucleoside modifications in nature. Human rRNA, for example, has ten times more pseudouracil (Ψ) and 25 times more 2′-O-methylated nucleosides than bacterial rRNA. Bacterial RNA contains no nucleoside modifications,

whereas mammalian RNAs have modified nucleosides such as 5-methylcytidine (m5C), N6-methyladenosine (m6A), inosine and many 2′-O-methylated nucleosides in addition to N7-methylguanosine (m7G).

[0184] In some embodiments, the uracil content of polynucleotides disclosed herein is less than about 50%, 49%, 48%, 47%, 46%, 45%, 44%, 43%, 42%, 41%, 40%, 39%, 38%, 37%, 36%, 35%, 34%, 33%, 32%, 31%, 30%, 29%, 28%, 27%, 26%, 25%, 24%, 23%, 22%, 21%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% of the total nucleobases in the sequence in the reference sequence. In some embodiments, the uracil content of polynucleotides disclosed herein is between about 5% and about 25%. In some embodiments, the uracil content of polynucleotides disclosed herein is between about 15% and about 25%.

[0185] In some embodiments, first polynucleotides of nucleic acid molecules provided herein comprise a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to a sequence of SEQ ID NO:72. In some embodiments, first polynucleotides of nucleic acid molecules provided herein comprise a sequence of SEQ ID NO:72.

[0186] In some aspects, first polynucleotides and second polynucleotides of nucleic acid molecules provided herein are included in the same (i.e., a single) or in separate nucleic acid molecules. Generally, first polynucleotides and second polynucleotides of nucleic acid molecules provided herein are included in a single nucleic acid molecule. In one aspect, the first polynucleotide is located 5’ of the second polynucleotide. In one aspect, first polynucleotides and second polynucleotides of nucleic acid molecules provided herein are included in separate nucleic acid molecules. In yet another aspect, first polynucleotides and second polynucleotides are included in two separate nucleic acid molecules.

[0187] In some aspects, first polynucleotides and second polynucleotides are included in the same (i.e., a single) nucleic acid molecule. First polynucleotides and second polynucleotides of nucleic acid molecules provided herein can be contiguous, i.e., adjacent to each other without nucleotides in between. In one aspect, an intergenic region is located between the first polynucleotide and the second polynucleotide. In another aspect, the intergenic region located between the first polynucleotide and the second polynucleotide is a

second intergenic region, with a first intergenic region included in the first polynucleotide as described below. As used herein, the terms "intergenic region" and intergenic sequence" can be used interchangeably, unless context clearly indicates otherwise.

[0188] An intergenic region located between the first polynucleotide and the second polynucleotide can be of any length and can have any nucleotide sequence. As an example, the intergenic region between the first polynucleotide and the second polynucleotide can include about one nucleotide, about two nucleotides, about three nucleotides, about four nucleotides, about five nucleotides, about six nucleotides, about seven nucleotides, about eight nucleotides, about nine nucleotides, about ten nucleotides, about 11 nucleotides, about 12 nucleotides, about 13 nucleotides, about 14 nucleotides, about 15 nucleotides, about 16 nucleotides, about 17 nucleotides, about 18 nucleotides, about 19 nucleotides, about 20 nucleotides, about 21 nucleotides, about 22 nucleotides, about 23 nucleotides, about 24 nucleotides, about 25 nucleotides, about 26 nucleotides, about 27 nucleotides, about 28 nucleotides, about 29 nucleotides, about 30 nucleotides, about 31 nucleotides, about 32 nucleotides, about 33 nucleotides, about 34 nucleotides, about 35 nucleotides, about 36 nucleotides, about 37 nucleotides, about 38 nucleotides, about 39 nucleotides, about 40 nucleotides, about 41 nucleotides, about 42 nucleotides, about 43 nucleotides, about 44 nucleotides, about 45 nucleotides, about 46 nucleotides, about 47 nucleotides, about 48 nucleotides, about 49 nucleotides, about 50 nucleotides, about 60 nucleotides, about 70 nucleotides, about 80 nucleotides, about 90 nucleotides, about 100 nucleotides, about 125 nucleotides, about 150 nucleotides, about 175 nucleotides, about 200 nucleotides, about 250 nucleotides, about 300 nucleotides, about 350 nucleotides, about 400 nucleotides, about 450 nucleotides, about 500 nucleotides, about 600 nucleotides, about 700 nucleotides, about 800 nucleotides, about 1,000 nucleotides, about 1,500 nucleotides, about 2,000 nucleotides, about 2,500 nucleotides, about 3,000 nucleotides, about 3,500 nucleotides, about 4,000 nucleotides, about 4,500 nucleotides, about 5,000 nucleotides, about 6,000 nucleotides, about 7,000 nucleotides, about 8,000 nucleotides, about 9,000 nucleotides, about 10,000 nucleotides, and any number or range in between. In one aspect, the intergenic region between first and second polynucleotides includes about 10-100 nucleotides, about 10-200 nucleotides, about 10-300 nucleotides, about 10-400 nucleotides, or about 10-500 nucleotides. In another aspect, the intergenic region between first and second polynucleotides includes about 1-10 nucleotides, about 1-20 nucleotides, about 1-30 nucleotides, about 1-40 nucleotides, or about 1- 50 nucleotides. In yet another aspect, the

region includes about 44 nucleotides. In one aspect, the intergenic region between first and second polynucleotides of nucleic acid molecules provided herein is a second intergenic region.

[0189] In one aspect, the intergenic region between first and second polynucleotides includes a viral sequence. The intergenic region between first and second polynucleotides can include a sequence from any virus, such as alphaviruses and rubiviruses, for example. In one aspect, the intergenic region between the first polynucleotide and the second polynucleotide comprises an alphavirus sequence, such as a sequence from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), Buggy Creek Virus (BCRV), or any combination thereof. In another aspect, the intergenic region between first and second polynucleotides comprises a sequence from Venezuelan Equine Encephalitis Virus (VEEV). In yet another aspect, the intergenic region between first and second polynucleotides comprises a sequence having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to SEQ ID NO:77. In a further aspect, the intergenic region between first and second polynucleotides comprises a sequence of SEQ ID NO:77. In yet a further aspect, the intergenic region between first and second polynucleotides is a second intergenic region comprising a sequence having at least 85% identity to SEQ ID NO:77.

Natural and Modified Nucleotides

[0190] A self-replicating RNA of the disclosure can comprise one or more chemically modified nucleotides. Examples of nucleic acid monomers include non-natural, modified, and chemically-modified nucleotides, including any such nucleotides known in the art. Nucleotides can be artificially modified at either the base portion or the sugar portion. In nature, most polynucleotides comprise nucleotides that are “unmodified” or “natural” nucleotides, which include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T),

cytosine (C) and uracil (U). These bases are typically fixed to a ribose or deoxy ribose at the 1' position. The use of RNA polynucleotides comprising chemically modified nucleotides have been shown to improve RNA expression, expression rates, half-life and/or expressed protein concentrations. RNA polynucleotides comprising chemically modified nucleotides have also been useful in optimizing protein localization thereby avoiding deleterious bio-responses such as immune responses and/or degradation pathways.

[0191] Examples of modified or chemically-modified nucleotides include 5-hydroxycytidines, 5-alkylcytidines, 5-hydroxyalkylcytidines, 5-carboxycytidines, 5-formylcytidines, 5-alkoxycytidines, 5-alkynylcytidines, 5-halocytidines, 2-thiocytidines, N4-alkylcytidines, N4-aminocytidines, N4-acetylcytidines, and N4,N4-dialkylcytidines.

[0192] Examples of modified or chemically-modified nucleotides include 5-hydroxycytidine, 5-methylcytidine, 5-hydroxymethylcytidine, 5-carboxycytidine, 5-formylcytidine, 5-methoxycytidine, 5-propynylcytidine, 5-bromocytidine, 5-iodocytidine, 2-thiocytidine; N4-methylcytidine, N4-aminocytidine, N4-acetylcytidine, and N4,N4-dimethylcytidine.

[0193] Examples of modified or chemically-modified nucleotides include 5-hydroxyuridines, 5-alkyluridines, 5-hydroxyalkyluridines, 5-carboxyuridines, 5-carboxyalkylesteruridines, 5-formyluridines, 5-alkoxyuridines, 5-alkynyluridines, 5-halouridines, 2-thiouridines, and 6-alkyluridines.

[0194] Examples of modified or chemically-modified nucleotides include 5-hydroxyuridine, 5-methyluridine, 5-hydroxymethyluridine, 5-carboxyuridine, 5-carboxymethylesteruridine, 5-formyluridine, 5-methoxyuridine (also referred to herein as "5MeOU"), 5-propynyluridine, 5-bromouridine, 5-fluorouridine, 5-iodouridine, 2-thiouridine, and 6-methyluridine.

[0195] Examples of modified or chemically-modified nucleotides include 5-methoxycarbonylmethyl-2-thiouridine, 5-methylaminomethyl-2-thiouridine, 5-carbamoylmethyluridine, 5-carbamoylmethyl-2'-O-methyluridine, 1-methyl-3-(3-amino-3-carboxypropy)pseudouridine, 5-methylaminomethyl-2-selenouridine, 5-carboxymethyluridine, 5-methyldihydrouridine, 5-taurinomethyluridine, 5-taurinomethyl-2-thiouridine, 5-(isopentenylaminomethyl)uridine, 2'-O-methylpseudouridine, 2-thio-2'O-methyluridine, and 3,2'-O-dimethyluridine.

[0196] Examples of modified or chemically-modified nucleotides include N6-methyladenosine, 2-aminoadenosine, 3-methyladenosine, 8-azaadenosine, 7-deazaadenosine, 8-oxoadenosine, 8-bromoadenosine, 2-methylthio-N6-methyladenosine, N6-isopentenyladenosine, 2-methylthio-N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyl-adenosine, N6-methyl-N6-threonylcarbamoyl-adenosine, 2-methylthio-N6-threonylcarbamoyl-adenosine, N6,N6-dimethyladenosine, N6-hydroxynorvalylcarbamoyladenosine, 2-methylthio-N6-hydroxynorvalylcarbamoyl-adenosine, N6-acetyl-adenosine, 7-methyl-adenine, 2-methylthio-adenine, 2-methoxy-adenine, alpha-thio-adenosine, 2'-O-methyl-adenosine, N6,2'-O-dimethyl-adenosine, N6,N6,2'-O-trimethyl-adenosine, 1,2'-O-dimethyl-adenosine, 2'-O-ribosyladenosine, 2-amino-N6-methyl-purine, 1-thio-adenosine, 2'-F-ara-adenosine, 2'-F-adenosine, 2'-OH-ara-adenosine, and N6-(19-amino-pentaoxanonadecyl)-adenosine.

[0197] Examples of modified or chemically-modified nucleotides include Nl-alkylguanosines, N2-alkylguanosines, thienoguanosines, 7-deazaguanosines, 8-oxoguanosines, 8-bromoguanosines, O6-alkylguanosines, xanthosines, inosines, and Nl-alkylinosines.

[0198] Examples of modified or chemically-modified nucleotides include Nl-methylguanosine, N2-methylguanosine, thienoguanosine, 7-deazaguanosine, 8-oxoguanosine, 8-bromoguanosine, O6-methylguanosine, xanthosine, inosine, and Nl-methylinosine.

[0199] Examples of modified or chemically-modified nucleotides include pseudouridines. Examples of pseudouridines include Nl-alkylpseudouridines, Nl-cycloalkylpseudouridines, N1-hydroxypseudouridines, N1-hydroxyalkylpseudouridines, Nl-phenylpseudouridines, Nl-phenylalkylpseudouridines, Nl-aminoalkylpseudouridines, N3-alkylpseudouridines, N6-alkylpseudouridines, N6-alkoxypseudouridines, N6-hydroxypseudouridines, N6-hydroxyalkylpseudouridines, N6-morpholinopseudouridines, N6-phenylpseudouridines, and N6-halopseudouridines. Examples of pseudouridines include Nl-alkyl-N6-alkylpseudouridines, Nl-alkyl-N6-alkoxypseudouridines, Nl-alkyl-N6-hydroxypseudouridines, Nl-alkyl-N6-hydroxyalkylpseudouridines, Nl-alkyl-N6-morpholinopseudouridines, Nl-alkyl-N6-phenylpseudouridines, and Nl-alkyl-N6-halopseudouridines. In these examples, the alkyl, cycloalkyl, and phenyl substituents may be unsubstituted, or further substituted with alkyl, halo, haloalkyl, amino, or nitro substituents.

[0200] Examples of pseudouridines include Nl-methylpseudouridine (also referred to herein as "N1MPU"), Nl-ethylpseudouridine, Nl-propylpseudouridine, Nl-cyclopropylpseudouridine, Nl-phenylpseudouridine, Nl-aminomethylpseudouridine, N3-methylpseudouridine, N1-hydroxypseudouridine, and N1-hydroxymethylpseudouridine.

[0201] Examples of nucleic acid monomers include modified and chemically-modified nucleotides, including any such nucleotides known in the art.

[0202] Examples of modified and chemically-modified nucleotide monomers include any such nucleotides known in the art, for example, 2'-O-methyl ribonucleotides, 2'-O-methyl purine nucleotides, 2'-deoxy-2'-fluoro ribonucleotides, 2'-deoxy-2'-fluoro pyrimidine nucleotides, 2'-deoxy ribonucleotides, 2'-deoxy purine nucleotides, universal base nucleotides, 5-C-methyl-nucleotides, and inverted deoxyabasic monomer residues.

[0203] Examples of modified and chemically-modified nucleotide monomers include 3'-end stabilized nucleotides, 3'-glyceryl nucleotides, 3'-inverted abasic nucleotides, and 3'-inverted thymidine.

[0204] Examples of modified and chemically-modified nucleotide monomers include locked nucleic acid nucleotides (LNA), 2'-O,4'-C-methylene-(D-ribofuranosyl) nucleotides, 2'-methoxyethoxy (MOE) nucleotides, 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro nucleotides, and 2'-O-methyl nucleotides. In an exemplary embodiment, the modified monomer is a locked nucleic acid nucleotide (LNA).

[0205] Examples of modified and chemically-modified nucleotide monomers include 2′,4′-constrained 2′-O-methoxyethyl (cMOE) and 2′-O-Ethyl (cEt) modified DNAs.

[0206] Examples of modified and chemically-modified nucleotide monomers include 2'-amino nucleotides, 2'-O-amino nucleotides, 2'-C-allyl nucleotides, and 2'-O-allyl nucleotides.

[0207] Examples of modified and chemically-modified nucleotide monomers include N6-methyladenosine nucleotides.

[0208] Examples of modified and chemically-modified nucleotide monomers include nucleotide monomers with modified bases 5-(3-amino)propyluridine, 5-(2-mercapto)ethyluridine, 5-bromouridine; 8-bromoguanosine, or 7-deazaadenosine.

[0209] Examples of modified and chemically-modified nucleotide monomers include 2'-O-aminopropyl substituted nucleotides.

[0210] Examples of modified and chemically-modified nucleotide monomers include replacing the 2'-OH group of a nucleotide with a 2'-R, a 2'-OR, a 2'-halogen, a 2'-SR, or a 2'-amino, where R can be H, alkyl, alkenyl, or alkynyl.

[0211] Example of base modifications described above can be combined with additional modifications of nucleoside or nucleotide structure, including sugar modifications and linkage modifications. Certain modified or chemically-modified nucleotide monomers may be found in nature.

[0212] Preferred nucleotide modifications include N1-methylpseudouridine and 5-methoxyuridine.

Viral Replication Proteins and Polynucleotides Encoding Them

[0213] Provided herein, in some embodiments, are nucleic acid molecules comprising a first polynucleotide encoding one or more viral replication proteins. As used herein, the term "replication protein" or "viral replication protein" refers to any protein or any protein subunit of a protein complex that functions in replication of a viral genome. Generally, viral replication proteins are non-structural proteins. Viral replication proteins encoded by nucleic acid molecules provided herein can function in the replication of any viral genome. The viral genome can be a single-stranded positive-sense RNA genome, a single-stranded negative-sense RNA genome, a double-stranded RNA genome, a single-stranded positive-sense DNA genome, a single-stranded negative-sense DNA genome, or a double-stranded DNA genome. Viral genomes can include a single nucleic acid molecule or more than one nucleic acid molecule. Nucleic acid molecules provided herein can encode one or more viral replication proteins from any virus or virus family, including animal viruses and plant viruses, for example. Viral replication proteins encoded by first polynucleotides included in nucleic acid molecules provided herein can be expressed from self-replicating RNA.

[0214] First polynucleotide sequences of nucleic acid molecules provided herein can encode one or more togavirus replication proteins. In some aspects, the one or more viral replication proteins encoded by first polynucleotides of nucleic acid molecules provided herein are alphavirus proteins. In some embodiments, the one or more viral replication proteins encoded by first polynucleotides of nucleic acid molecules provided herein are rubivirus

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proteins. First polynucleotide sequences of nucleic acid molecules provided herein can encode any alphavirus replication protein and any rubivirus replication protein. Exemplary replication proteins from alphaviruses include proteins from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), Buggy Creek Virus (BCRV), and any combination thereof. Exemplary rubivirus replication proteins include proteins from rubella virus.

[0215] Viral replication proteins encoded by first polynucleotides of nucleic acid molecules provided herein can be expressed as one or more polyproteins or as separate or single proteins. Generally, polyproteins are precursor proteins that are cleaved to generate individual or separate proteins. Accordingly, proteins derived from a precursor polyprotein can be expressed from a single open reading frame (ORF). As used herein, the term “ORF” refers to a nucleotide sequence that begins with a start codon, generally ATG, and that ends with a stop codon, such as TAA, TAG, or TGA, for example. It will be appreciated that T is present in DNA, while U is present in RNA. Accordingly, a start codon of ATG in DNA corresponds to AUG in RNA, and the stop codons TAA, TAG, and TGA in DNA correspond to UAA, UAG, and UGA in RNA. It will further be appreciated that for any sequence provided in the present disclosure, T is present in DNA, while U is present in RNA. Accordingly, for any sequence provided herein, T present in DNA is substituted with U for an RNA molecule, and U present in RNA is substituted with T for a DNA molecule.

[0216] The protease cleaving a polyprotein can be a viral protease or a cellular protease. In some aspects, the first polynucleotide of nucleic acid molecules provided herein encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, an alphavirus nsP4 protein, or any combination thereof. In other aspects, the first polynucleotide of nucleic acid molecules provided herein encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and an alphavirus nsP4 protein. In some aspects, the polyprotein is a

VEEV polyprotein. In other aspects, the alphavirus nsP1, nsP2, nsP3, and nsP4 proteins are VEEV proteins.

[0217] In one aspect, first polynucleotides of nucleic acid molecules provided herein lack a stop codon between sequences encoding an nsP3 protein and an nsP4 protein. Accordingly, in some aspects, first polynucleotides of nucleic acid molecules provided herein encode a P1234 polyprotein comprising nsP1, nsP2, nsP3, and nsP4. First polynucleotides of nucleic acid molecules provided herein can also include a stop codon between sequences encoding an nsP3 and an nsP4 protein. Accordingly, in some aspects, first polynucleotides of nucleic acid molecules provided herein encode a P123 polyprotein comprising nsP1, nsP2, and nsP3 and a P1234 polyprotein comprising nsP1, nsP2, nsP3, and nsP4 as a result of stop codon readthrough, for example. In other aspects, first polynucleotides of nucleic acid molecules provided herein encode a polyprotein having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to a sequence of SEQ ID NO:79. In some embodiments, first polynucleotides of nucleic acid molecules provided herein encode a polyprotein having a sequence of SEQ ID NO:79. Further exemplary polyproteins comprise a sequence of SEQ ID NO:80 or SEQ ID NO:81. In one aspect, nsP2 and nsP3 proteins include mutations. Exemplary mutations include G1309R and S1583G mutations of VEEV proteins. In another aspect, the nsP1, nsP2, and nsP4 proteins are VEEV proteins, and the nsP3 protein is a chikungunya virus (CHIKV) nsP3 protein.

[0218] In some aspects, first polynucleotides of nucleic acid molecules provided herein can include a first intergenic region. In some aspects, the first intergenic region is located between a sequence encoding a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and a sequence encoding an alphavirus nsP4 protein. A first intergenic region can comprise any sequence, such as any viral or non-viral sequence. In one aspect, the first intergenic region comprises a viral sequence. In another aspect, the first intergenic region comprises an alphavirus sequence. In yet another aspect, the alphavirus is VEEV. In one aspect, nsP2 and nsP3 proteins include mutations. Exemplary mutations include G1309R and S1583G mutations of VEEV proteins. In another aspect, the nsP1, nsP2, and nsP4 proteins are VEEV proteins, and the nsP3 protein is a chikungunya virus (CHIKV) nsP3 protein.

[0219] In some embodiments, the first polynucleotide may comprise a sequence having at least 80% identity to a sequence of SEQ ID NO:72.

[0220] In some embodiments, the nucleic acid molecule described herein may further comprise a second polynucleotide comprising a first transgene encoding a first antigenic protein or fragment thereof, wherein the first antigenic protein is a coronavirus protein. In specific embodiments, the antigenic protein may be a SARS-CoV-2 protein. In specific embodiments, the antigenic protein is a SARS-CoV-2 spike glycoprotein. In specific embodiments, the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein having an amino acid sequence of SEQ ID NO:123.

[0221] In some embodiments, the second polynucleotide comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

5' Untranslated Region (5' UTR)

[0222] Nucleic acid molecules provided herein can further comprise untranslated regions (UTRs). Untranslated regions, including 5' UTRs and 3' UTRs, for example, can affect RNA stability and/or efficiency of RNA translation, such as translation of cellular and viral mRNAs, for example. 5' UTRs and 3' UTRs can also affect stability and translation of viral genomic RNAs and self-replicating RNAs, including virally derived self-replicating RNAs or replicons. Exemplary viral genomic RNAs whose stability and/or efficiency of translation can be affected by 5' UTRs and 3' UTRs include the genome nucleic acid of positive-sense RNA viruses. Both genome nucleic acid of positive-sense RNA viruses and self-replicating RNAs, including virally derived self-replicating RNAs or replicons, can be translated upon infection or introduction into a cell.

[0223] In some aspects, nucleic acid molecules provided herein further include a 5' untranslated region (5' UTR). Any 5' UTR sequence can be included in nucleic acid molecules provided herein. In some embodiments, nucleic acid molecules provided herein include a viral 5' UTR. In one aspect, nucleic acid molecules provided herein include a non-viral 5' UTR. Any non-viral 5' UTR can be included in nucleic acid molecules provided herein, such as 5' UTRs of transcripts expressed in any cell or organ, including muscle, skin, subcutaneous tissue, liver, spleen, lymph nodes, antigen-presenting cells, and others. In another aspect, nucleic acid molecules provided herein include a 5' UTR comprising viral and non-viral sequences. Accordingly, a 5' UTR included in nucleic acid molecules provided herein can comprise a combination of viral and non-viral 5' UTR sequences. In some aspects, the 5' UTR included

in nucleic acid molecules provided herein is located upstream of or 5' of the first polynucleotide that encodes one or more viral replication proteins. In other aspects, the 5' UTR is located 5' of or upstream of the first polynucleotide of nucleic acid molecules provided herein that encodes one or more viral replication proteins, and the first polynucleotide is located 5' of or upstream of the second polynucleotide of nucleic acid molecules provided herein.

[0224] In one aspect, the 5' UTR of nucleic acid molecules provided herein comprises an alphavirus 5' UTR. A 5' UTR from any alphavirus can be included in nucleic acid molecules provided herein, including 5' UTR sequences from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV). In another aspect, the 5' UTR comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75. In yet another aspect, the 5' UTR comprises a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75.

[0225] In some embodiments, the 5' UTR comprises a sequence selected from the 5' UTRs of human IL-6, alanine aminotransferase 1, human apolipoprotein E, human fibrinogen alpha chain, human transthyretin, human haptoglobin, human alpha-1-antichymotrypsin, human antithrombin, human alpha-1-antitrypsin, human albumin, human beta globin, human complement C3, human complement C5, SynK (thylakoid potassium channel protein derived from the cyanobacteria, Synechocystis sp.), mouse beta globin, mouse albumin, and a tobacco etch virus, or fragments of any of the foregoing. Preferably, the 5' UTR is derived from a tobacco etch virus (TEV). Preferably, an mRNA described herein comprises a 5' UTR sequence that is derived from a gene expressed by Arabidopsis thaliana. Preferably, the 5' UTR sequence of a gene expressed by Arabidopsis thaliana is AT1G58420. Examples of 5 UTRs and 3' UTRs are described in PCT/US2018/035419, the contents of which are herein

incorporated by reference. Preferred 5' UTR sequences comprise SEQ ID NOs: 5-10 and 25-45: as shown in Table 1.

Table 1. 5' UTR Sequences

Name	Sequence	Seq ID No.:
EV	UCAACACAACAUAUACAAAACAAACGAAUCUCAAGCAAUC AAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCAUUUCU UUUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUU ACGAACGAUAG	SEQ ID NO: 5
AT1G58420	AUUAUUACAUCAAAACAAAAAGCCGCCA	SEQ ID NO: 6
ARC5-2	CUUAAGGGGGCGCUGCCUACGGAGGUGGCAGCCAUCUCCU UCUCGGCAUCAAGCUUACCAUGGUGCCCCAGGCCCUGCUC UUGGUCCCGCUGCUGGUGUUCCCCCUCUGCUUCGGCAAGU UCCCCAUCUACACCAUCCCCGACAAGCUGGGGCCGUGGAG CCCCAUCGACAUCCACCACCUGUCCUGCCCCAACAACCUCG UGGUCGAGGACGAGGGCUGCACCAACCUGAGCGGGUUCUC CUAC	SEQ ID NO: 7
HCV	UGAGUGUCGU ACAGCCUCCA GGCCCCCCCC UCCCGGGAGA GCCAUAGUGG UCUGCGGAACCGGUGAGUAC ACCGGAAUUG CCGGGAAGAC UGGGUCCUUU CUUGGAUAAA CCCACUCUAUGCCCGGCCAU UUGGGCGUGC CCCCGCAAGA CUGCUAGCCG AGUAGUGUUG GGUUGCG	SEQ ID NO: 8
HUMAN ALBUMIN	AAUUAUUGGUUAAAGAAGUAUAUUAGUGCUAAUUUCCCU CCGUUUGUCCUAGCUUUUCUCUUCUGUCAACCCCACACGC CUUUGGCACA	SEQ ID NO: 9
EMCV	CUCCCUCCCC CCCCCCUAAC GUUACUGGCC GAAGCCGCUU GGAAUAAGGC CGGUGUGCGU UUGUCUAUAU GUUAUUUUCC ACCAUAUUGC CGUCUUUUGG CAAUGUGAGG GCCCGGAAAC CUGGCCCUGU CUUCUUGACG AGCAUUCCUA GGGGUCUUUC CCCUCUCGCC AAAGGAAUGC AAGGUCUGUU GAAUGUCGUG AAGGAAGCAG UUCCUCUGGA AGCUUCUUGA AGACAAACAA CGUCUGUAGC GACCCUUUGC AGGCAGCGGA ACCCCCCACC UGGCGACAGG UGCCUCUGCG GCCAAAAGCC ACGUGUAUAA GAUACACCUG CAAAGGCGGC ACAACCCCAG UGCCACGUUG UGAGUUGGAU AGUUGUGGAA AGAGUCAAAU GGCUCUCCUC AAGCGUAUUC AACAAGGGGC UGAAGGAUGC CCAGAAGGUA CCCCAUUGUA UGGGAUCUGA UCUGGGGCCU CGGUGCACAU GCUUUACGUG UGUUUAGUCG AGGUUAAAAA ACGUCUAGGC CCCCCGAACC ACGGGGACGU GGUUUUCCUU UGAAAAACAC GAUGAUAAU	SEQ ID NO: 10
AT1G67090	CACAAAGAGUAAAGAAGAACA	SEQ ID NO: 25
AT1G35720	AACACUAAAAGUAGAAGAAAA	SEq ID NO: 26
AT5G45900	CUCAGAAAGAUAAGAUCAGCC	SEQ ID NO: 27
AT5G61250	AACCAAUCGAAAGAAACCAAA	SEQ ID NO: 28

Name	Sequence	Seq ID No.:
AT5G46430	CUCUAAUCACCAGGAGUAAAA	SEQ ID NO: 29
AT5G47110	GAGAGAGAUCUUAACAAAAAA	SEQ ID NO: 30
AT1G03110	UGUGUAACAACAACAACAACA	SEQ ID NO: 31
AT3G12380	CCGCAGUAGGAAGAGAAAGCC	SEQ ID NO: 32
AT5G45910	AAAAAAAAAAGAAAUCAUAAA	SEQ ID NO: 33
AT1G07260	GAGAGAAGAAAGAAGAAGACG	SEQ ID NO: 34
AT3G55500	CAAUUAAAAAUACUUACCAAA	SEQ ID NO: 35
AT3G46230	GCAAACAGAGUAAGCGAAACG	SEQ ID NO: 36
AT2G36170	GCGAAGAAGACGAACGCAAAG	SEQ ID NO: 37
AT1G10660	UUAGGACUGUAUUGACUGGCC	SEQ ID NO: 38
AT4G14340	AUCAUCGGAAUUCGGAAAAAG	SEQ ID NO: 39
AT1G49310	AAAACAAAAGUUAAAGCAGAC	SEQ ID NO: 40
AT4G14360	UUUAUCUCAAAUAAGAAGGCA	SEQ ID NO: 41
AT1G28520	GGUGGGGAGGUGAGAUUUCUU	SEQ ID NO: 42
AT1G20160	UGAUUAGGAAACUACAAAGCC	SEQ ID NO: 43
AT5G37370	CAUUUUUCAAUUUCAUAAAAC	SEQ ID NO: 44
AT4G11320	UUACUUUUAAGCCCAACAAAA	SEQ ID NO: 45
AT5G40850	GGCGUGUGUGUGUGUUGUUGA	SEQ ID NO: 46
AT1G06150	GUGGUGAAGGGGAAGGUUUAG	SEQ ID NO: 47
AT2G26080	UUGUUUUUUUUUGGUUUGGUU	SEQ ID NO:48

3' Untranslated Region (3' UTR)

[0226] In some aspects, nucleic acid molecules provided herein further include a 3' untranslated region (3' UTR). Any 3' UTR sequence can be included in nucleic acid molecules provided herein. In one aspect, nucleic acid molecules provided herein include a viral 3' UTR. In another aspect, nucleic acid molecules provided herein include a non-viral 3' UTR. Any non-viral 3' UTR can be included in nucleic acid molecules provided herein, such as 3' UTRs of transcripts expressed in any cell or organ, including muscle, skin, subcutaneous tissue, liver, spleen, lymph nodes, antigen-presenting cells, and others. In some aspects, nucleic acid

molecules provided herein include a 3' UTR comprising viral and non-viral sequences. Accordingly, a 3' UTR included in nucleic acid molecules provided herein can comprise a combination of viral and non-viral 3' UTR sequences. In one aspect, the 3' UTR is located 3' of or downstream of the second polynucleotide of nucleic acid molecules provided herein that comprises a first transgene encoding a first antigenic protein or a fragment thereof. In another aspect, the 3' UTR is located 3' of or downstream of the second polynucleotide of nucleic acid molecules provided herein that comprises a first transgene encoding a first antigenic protein or a fragment thereof, and the second polynucleotide is located 3' of or downstream of the first polynucleotide of nucleic acid molecules provided herein.

[0227] In one aspect, the 3' UTR of nucleic acid molecules provided herein comprises an alphavirus 3' UTR. A 3' UTR from any alphavirus can be included in nucleic acid molecules provided herein, including 3' UTR sequences from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV). In another aspect, the 3' UTR comprises a sequence having at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to a sequence of SEQ ID NO:76. In yet another aspect, the 3' UTR comprises a poly-A sequence. In a further aspect, the 3' UTR comprises a sequence of SEQ ID NO:76.

[0228] In some embodiments, the 3' UTR comprises a sequence selected from the 3' UTRs of alanine aminotransferase 1, human apolipoprotein E, human fibrinogen alpha chain, human haptoglobin, human antithrombin, human alpha globin, human beta globin, human complement C3, human growth factor, human hepcidin, MALAT-1, mouse beta globin, mouse albumin, and Xenopus beta globin, or fragments of any of the foregoing. In some embodiments, the 3' UTR is derived from Xenopus beta globin. Exemplary 3' UTR sequences include SEQ ID NOs: 16-22 as shown in Table 2.

Table 2. 3' UTR sequences.

Name	Sequence	Seq ID No.:
XBG	CUAGUGACUGACUAGGAUCUGGUUACCACUAAACCAG CCUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUA AUACCAACUUACACUUACAAAAUGUUGUCCCCCAAAA UGUAGCCAUUCGUAUCUGCUCCUAAUAAAAAGAAAGU UUCUUCACAU	SEQ ID NO: 16
HUMAN HAPTOGLOBIN	UGCAAGGCUGGCCGGAAGCCCUUGCCUGAAAGCAAGA UUUCAGCCUGGAAGAGGGCAAAGUGGACGGGAGUGG ACAGGAGUGGAUGCGAUAAGAUGUGGUUUGAAGCUG AUGGGUGCCAGCCCUGCAUUGCUGAGUCAAUCAAUAA AGAGCUUUCUUUUGACCCAU	SEQ ID NO: 17
HUMAN APOLIPOPROTEIN E	ACGCCGAAGCCUGCAGCCAUGCGACCCCACGCCACCCC GUGCCUCCUGCCUCCGCGCAGCCUGCAGCGGGAGACC CUGUCCCCGCCCCAGCCGUCCUCCUGGGGUGGACCCU AGUUUAAUAAAGAUUCACCAAGUUUCACGCA	SEQ ID NO: 18
HCV	UAGAGCGGCAAACCCUAGCUACACUCCAUAGCUAGUU UCUUUUUUUUUUGUUUUUUUUUUUUUUUUUUUUU UUUUUUUUUUUUUUUUCCUUUCUUUUCCUUCUUUUU UUCCUCUUUUCUUGGUGGCUCCAUCUUAGCCCUAGUC ACGGCUAGCUGUGAAAGGUCCGUGAGCCGCAUGACUG CAGAGAGUGCCGUAACUGGUCUCUCUGCAGAUCAUGU	SEQ ID NO: 19
MOUSE ALBUMIN	ACACAUCACAACCACAACCUUCUCAGGCUACCCUGAG AAAAAAAGACAUGAAGACUCAGGACUCAUCUUUUCUG UUGGUGUAAAAUCAACACCCUAAGGAACACAAAUUUC UUUAAACAUUUGACUUCUUGUCUCUGUGCUGCAAUUA AUAAAAAAUGGAAAGAAUCUAC	SEQ ID NO: 20
HUMAN ALPHA GLOBIN	GCUGGAGCCUCGGUAGCCGUUCCUCCUGCCCGCUGGG CCUCCCAACGGGCCCUCCUCCCCCUCCUUGCACCGGCCC UUCCUGGUCUUUGAAUAAAGUCUGAGUGGGCAGCA	SEQ ID NO: 21
EMCV	UAGUGCAGUCAC UGGCACAACG CGUUGCCCGG UAAGCCAAUC GGGUAUACAC GGUCGUCAUACUGCAGACAG GGUUCUUCUA CUUUGCAAGA UAGUCUAGAG UAGUAAAAUA AAUAGUAUAAG	SEQ ID NO: 22

Triple Stop Codon

[0229] In some embodiments, the self-replicating RNA may comprise a sequence immediately downstream of a coding region (i.e., ORF) that creates a triple stop codon. A triple stop codon is a sequence of three consecutive stop codons. The triple stop codon can ensure total insulation of an expression cassette and may be incorporated to enhance the efficiency of translation. In some embodiments, a self-replicating RNA of the disclosure may comprise a triple combination of any of the sequences UAG, UGA, or UAA immediately downstream of a ORF described herein. The triple combination can be three of the same codons, three different codons, or any other permutation of the three stop codons.

Translation Enhancers and Kozak Sequences

[0230] For translation initiation, proper interactions between ribosomes and mRNAs must be established to determine the exact position of the translation initiation region. However, ribosomes also must dissociate from the translation initiation region to slide toward the downstream sequence during mRNA translation. Translation enhancers upstream from initiation sequences of mRNAs enhance the yields of protein biosynthesis. Several studies have investigated the effects of translation enhancers. In some embodiments, an mRNA described herein comprises a translation enhancer sequence. These translation enhancer sequences enhance the translation efficiency of a self-replicating RNA of the disclosure and thereby provide increased production of the protein encoded by the mRNA. The translation enhancer region may be located in the 5' or 3' UTR of an mRNA sequence. Examples of translation enhancer regions include naturally-occurring enhancer regions from the TEV 5' UTR and the Xenopus beta-globin 3' UTR. Exemplary 5' UTR enhancer sequences include but are not limited to those derived from mRNAs encoding human heat shock proteins (HSP) including HSP70-P2, HSP70-M1 HSP72-M2, HSP17.9 and HSP70-P1. Preferred translation enhancer sequences used in accordance with the embodiments of the present disclosure are represented by SEQ ID Nos: 11-15 as shown in Table 3.

Table 3. 5' UTR Enhancers

Name	Sequence	Seq ID No.:
HSP70-P2	GUCAGCUUUCAAACUCUUUGUUUCUUGUUUGUUGAUUGAGAA UA	SEQ ID NO: 11
HSP70-M1	CUCUCGCCUGAGAAAAAAAAUCCACGAACCAAUUUCUCAGCA ACCAGCAGCACG	SEQ ID NO: 12
HSP72-M2	ACCUGUGAGGGUUCGAAGGAAGUAGCAGUGUUUUUUGUUCCU AGAGGAAGAG	SEQ ID NO: 13
HSP17.9	ACACAGAAACAUUCGCAAAAACAAAAUCCCAGUAUCAAAAUU CUUCUCUUUUUUUCAUAUUUCGCAAAGAC	SEQ ID NO: 14
HSP70-P1	CAGAAAAAUUUGCUACAUUGUUUCACAAACUUCAAAUAUUAU UCAUUUAUUU	SEQ ID NO: 15

[0231] In some embodiments, a self-replicating RNA of the disclosure comprises a Kozak sequence. As is understood in the art, a Kozak sequence is a short consensus sequence centered around the translational initiation site of eukaryotic mRNAs that allows for efficient initiation of translation of the mRNA. See, for example, Kozak, Marilyn (1988) Mol. and Cell Biol, 8:2737-2744; Kozak, Marilyn (1991) J. Biol. Chem, 266: 19867-19870; Kozak, Marilyn (1990) Proc Natl. Acad. Sci. USA, 87:8301-8305; and Kozak, Marilyn (1989) J. Cell Biol, 108:229-241. It ensures that a protein is correctly translated from the genetic message, mediating ribosome assembly and translation initiation. The ribosomal translation machinery recognizes

the AUG initiation codon in the context of the Kozak sequence. A Kozak sequence may be inserted upstream of the coding sequence for the protein of interest, downstream of a 5' UTR or inserted upstream of the coding sequence for the protein of interest and downstream of a 5' UTR. In some embodiments, a self-replicating RNA described herein comprises a Kozak sequence having the amino acid sequence GCCACC (SEQ ID NO: 23). Preferably a self-replicating RNA described herein comprises a partial Kozak sequence "p" having the amino acid sequence GCCA (SEQ ID NO: 24).

Transgenes

[0232] Transgenes included in nucleic acid molecules provided herein can encode an antigenic protein or a fragment thereof. In some embodiments, second polynucleotides of nucleic acid molecules provided herein comprise a first transgene. A first transgene included in second polynucleotides of nucleic acid molecules provided herein can encode a first antigenic protein or a fragment thereof. A transgene included in second polynucleotides of nucleic acid molecules provided herein can comprise a sequence encoding the full amino acid sequence of an antigenic protein or a sequence encoding any suitable portion or fragment of the full amino acid sequence of an antigenic protein. In some embodiments, the antigenic protein is a coronavirus protein.

[0233] In another embodiment, the antigenic protein, when administered to a mammalian subject, raises an immune response to a pathogen, such as a coronavirus. In some more particular embodiments, the antigenic protein is expressed on the outer surface of the coronavirus; while in other more particular embodiments, the antigen may be a non-surface antigen, e.g., useful as a T-cell epitope. The immunogen may elicit an immune response against a coronavirus. The immune response may comprise an antibody response (usually including IgG) and/or a cell mediated immune response. The polypeptide immunogen will typically elicit an immune response that recognizes the corresponding coronavirus The immunogen will typically be a surface polypeptide e.g. an envelope glycoprotein, a spike glycoprotein, etc.

[0234] In some aspects, the viral protein encoded by transgenes included in nucleic acid molecules provided herein is a coronavirus protein. In some embodiments, the antigenic protein is a SARS-CoV-2 protein.

[0235] In one aspect, the antigenic protein is a SARS-CoV-2 spike glycoprotein or a fragment thereof. In another aspect, the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein. In some aspects, the wild-type SARS-CoV-2 spike glycoprotein has

an amino acid sequence of SEQ ID NO:123. In yet another aspect, the second polynucleotide of nucleic acid molecules provided herein comprises a sequence having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122. In another aspect, the second polynucleotide of nucleic acid molecules provided herein comprises a sequence of SEQ ID NO:121 or SEQ ID NO:122. Accordingly, in some aspects, first transgenes included in second polynucleotides of nucleic acid molecules provided herein comprise a sequence having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, or 100% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

[0236] In one aspect, the second polynucleotide of nucleic acid molecules provided herein encodes a wild-type SARS-CoV-2 spike glycoprotein or a fragment thereof. In some aspects, a wild-type SARS-CoV-2 spike glycoprotein comprises a sequence of SEQ ID NO:123. In another aspect, the second polynucleotide of nucleic acid molecules provided herein encodes a SARS-CoV-2 spike protein comprising one or more mutations as compared to a wild-type SARS-CoV-2 spike glycoprotein sequence. Mutations can include substitutions, deletions, insertions, and others. Mutations can be present at any position or at any combination of positions of a SARS-CoV-2 spike glycoprotein. Any number of substitutions, insertions, deletions, or combinations thereof, can be present at any one or more positions of a SARS-CoV-2 spike glycoprotein. As an example, substitutions can include a change of a wild-type amino acid at any position or at any combination of positions to any other amino acid or combination of any other amino acids. Exemplary mutations include mutations at positions 614, 936, 320, 477, 986, 987, or any combination thereof. In one aspect, a SARS-CoV-2 spike glycoprotein or a fragment thereof encoded by transgenes of second polynucleotides included in nucleic acid molecules provided herein includes a D614G mutation, a D936Y mutation, a D936H mutation, a V320G mutation, an S477N mutation, an S477I mutation, an S477T mutation, a K986P mutation, a V987P mutation, or any combination thereof. Additional mutations and variants can be found in the National Bioinformatics Center 2019 Novel Coronavirus Information Database (2019nCoVR), National Genomics Data Center, China National Center for Bioinformation / Beijing Institute of Genomics, Chinese Academy of

Science at bigd.big.ac.cn/ncov/variation/annotation. In another aspect, the second polynucleotide includes a transgene encoding a SARS-CoV-2 glycoprotein having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 97.5%, at least 98%, at least 98.5%, at least 99%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, and any number or range in between, or 100% identity to a sequence of SEQ ID NO:123.

[0237] In some aspects, the second polynucleotide of nucleic acid molecules provided herein comprises at least two transgenes, such as a second coronavirus protein. Any number of transgenes can be included in second polynucleotides of nucleic acid molecules provided herein, such as one, two, three, four, five, six, seven, eight, nine, ten, or more transgenes. In one aspect, the second polynucleotide of nucleic acid molecules provided herein includes a second transgene encoding a second antigenic protein or a fragment thereof or an immunomodulatory protein. In one aspect, the second polynucleotide further comprises an internal ribosomal entry site (IRES), a sequence encoding a 2A peptide, or a combination thereof, located between transgenes. As used herein, the term "2A peptide" refers to a small (generally 18-22 amino acids) sequence that allows for efficient, stoichiometric production of discrete protein products within a single reading frame through a ribosomal skipping event within the 2A peptide sequence. As used herein, the term "internal ribosomal entry site" or "IRES" refers to a nucleotide sequence that allows for the initiation of protein translation of a messenger RNA (mRNA) sequence in the absence of an AUG start codon or without using an AUG start codon. An IRES can be found anywhere in an mRNA sequence, such as at or near the beginning, at or near the middle, or at or near the end of the mRNA sequence, for example.

[0238] Any number of transgenes included in second polynucleotides of nucleic acid molecules provided herein can be expressed via any combination of 2A peptide and IRES sequences. For example, a second transgene located 3' of a first transgene can be expressed via a 2A peptide sequence or via an IRES sequence. As another example, a second transgene located 3' of a first transgene and a third transgene located 3' of the second transgene can be expressed via 2A peptide sequences located between the first and second transgenes and the second and third transgenes, via an IRES sequence located between the first and second transgenes and the second and third transgenes, via a 2A peptide sequence located between the first and second transgenes and an IRES located between the second and third transgenes, or via an IRES sequence located between the first and second transgenes and a 2A peptide sequence located between the second and third transgenes. Similar configurations and

combinations of 2A peptide and IRES sequences located between transgenes are contemplated for any number of transgenes included in second polynucleotides of nucleic acid molecules provided herein. In addition to expression via 2A peptide and IRES sequences, two or more transgenes included in nucleic acid molecules provided herein can also be expressed from separate subgenomic RNAs.

[0239] A second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, etc., transgene included in second polynucleotides of nucleic acid molecules provided herein can encode an immunomodulatory protein or a functional fragment or functional variant thereof. Any immunomodulatory protein or a functional fragment or functional variant thereof can be encoded by a transgene included in second polynucleotides.

[0240] As used herein, the terms "functional variant" or "functional fragment" refer to a molecule, including a nucleic acid or protein, for example, that comprises a nucleotide and/or amino acid sequence that is altered by one or more nucleotides and/or amino acids compared to the nucleotide and/or amino acid sequences of the parent or reference molecule. For a protein, a functional variant is still able to function in a manner that is similar to the parent molecule. In other words, the modifications in the amino acid and/or nucleotide sequence of the parent molecule do not significantly affect or alter the functional characteristics of the molecule encoded by the nucleotide sequence or containing the amino acid sequence. The functional variant may have conservative sequence modifications including nucleotide and amino acid substitutions, additions and deletions. These modifications can be introduced by standard techniques known in the art, such as site-directed mutagenesis and random PCR-mediated mutagenesis. Functional variants can also include, but are not limited to, derivatives that are substantially similar in primary structural sequence, but which contain, e.g., in vitro or in vivo modifications, chemical and/or biochemical, that are not found in the parent molecule. Such modifications include, inter alia, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI-anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-

RNA-mediated addition of amino acids to proteins such as arginylation, ubiquitination, and the like.

[0241] In one aspect, a second transgene included in second polynucleotides of nucleic acid molecules provided herein encodes a cytokine, a chemokine, or an interleukin. Exemplary cytokines include interferons, TNF- α , TGF-β, G-CSF, and GM-CSF. Exemplary chemokines include CCL3, CCL26, and CXCL7. Exemplary interleukins include IL-I, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IL-18, IL-21, and IL-23. Any transgene or combination of transgenes encoding any cytokine, chemokine, interleukin, or combinations thereof, can be included in second polynucleotides of nucleic acid molecules provided herein.

[0242] In some embodiments, the second transgene encodes a second coronavirus protein.

DNA and RNA Molecules

[0243] Nucleic acid molecules provided herein can be DNA molecules or RNA molecules. It will be appreciated that T present in DNA is substituted with U in RNA, and vice versa. In one aspect, nucleic acid molecules provided herein are DNA molecules. In another aspect, DNA molecules provided herein further comprise a promoter. As used herein, the term "promoter" refers to a regulatory sequence that initiates transcription. A promoter can be operably linked to first and second polynucleotides of nucleic acid molecules provided herein. Generally, promoters included in DNA molecules provided herein include promoters for in vitro transcription (IVT). Any suitable promoter for in vitro transcription can be included in DNA molecules provided herein, such as a T7 promoter, a T3 promoter, an SP6 promoter, and others. In one aspect, DNA molecules provided herein comprise a T7 promoter. In another aspect, the promoter is located 5' of the 5' UTR included in DNA molecules provided herein. In yet another aspect, the promoter is a T7 promoter located 5' of the 5' UTR included in DNA molecules provided herein. In yet another aspect, the promoter overlaps with the 5' UTR. A promoter and a 5' UTR can overlap by about one nucleotide, about two nucleotides, about three nucleotides, about four nucleotides, about five nucleotides, about six nucleotides, about seven nucleotides, about eight nucleotides, about nine nucleotides, about ten nucleotides, about 11 nucleotides, about 12 nucleotides, about 13 nucleotides, about 14 nucleotides, about 15 nucleotides, about 16 nucleotides, about 17 nucleotides, about 18 nucleotides, about 19 nucleotides, about 20 nucleotides, about 21 nucleotides, about 22 nucleotides, about 23 nucleotides, about 24 nucleotides, about 25 nucleotides, about 26 nucleotides, about 27 nucleotides, about 28 nucleotides, about 29 nucleotides, about 30 nucleotides, about 31

nucleotides, about 32 nucleotides, about 33 nucleotides, about 34 nucleotides, about 35 nucleotides, about 36 nucleotides, about 37 nucleotides, about 38 nucleotides, about 39 nucleotides, about 40 nucleotides, about 41 nucleotides, about 42 nucleotides, about 43 nucleotides, about 44 nucleotides, about 45 nucleotides, about 46 nucleotides, about 47 nucleotides, about 48 nucleotides, about 49 nucleotides, about 50 nucleotides, or more nucleotides.

[0244] In some aspects, DNA molecules provided herein include a promoter for in vivo transcription. Generally, the promoter for in vivo transcription is an RNA polymerase II (RNA pol II) promoter. Any RNA pol II promoter can be included in DNA molecules provided herein, including constitutive promoters, inducible promoters, and tissue-specific promoters. Exemplary constitutive promoters include a cytomegalovirus (CMV) promoter, an EF1α promoter, an SV40 promoter, a PGK1 promoter, a Ubc promoter, a human beta actin promoter, a CAG promoter, and others. Any tissue-specific promoter can be included in DNA molecules provided herein. In one aspect, the RNA pol II promoter is a muscle-specific promoter, skin-specific promoter, subcutaneous tissue-specific promoter, liver-specific promoter, spleen-specific promoter, lymph node-specific promoter, or a promoter with any other tissue specificity. DNA molecules provided herein can also include an enhancer. Any enhancer that increases transcription can be included in DNA molecules provided herein.

[0245] In some aspects, nucleic acid molecules provided herein are RNA molecules. An RNA molecule provided herein can be generated by in vitro transcription (IVT) of DNA molecules provided herein. In one aspect, RNA molecules provided herein are self-replicating RNA molecules. In another aspect, RNA molecules provided herein further comprise a 5' cap. Any 5' cap can be included in RNA molecules provided herein, including 5' caps having a Cap 1 structure, a Cap 1 (m6A) structure, a Cap 2 structure, a Cap 0 structure, or any combination thereof. In one aspect, RNA molecules provided herein include a 5' cap having Cap 1 structure. In yet another aspect, RNA molecules provided herein are self-replicating RNA molecules comprising a 5' cap having a Cap 1 structure. In a further aspect, RNA molecules provided herein comprise a cap having a Cap 1 structure, wherein a m7G is linked via a 5'-5' triphosphate to the 5' end of the 5' UTR. In yet a further aspect, RNA molecules provided herein comprise a cap having a Cap 1 structure, wherein a m7G is linked via a 5'-5' triphosphate to the 5' end of the 5' UTR comprising a sequence of SEQ ID NO:73. Any method of capping can be used, including, but not limited to using a Vaccinia Capping enzyme (New England Biolabs, Ipswich, Mass.) and co-transcriptional capping or capping at or shortly after

initiation of in vitro transcription (IVT), by for example, including a capping agent as part of an in vitro transcription (IVT) reaction. (Nuc. Acids Symp. (2009) 53:129).

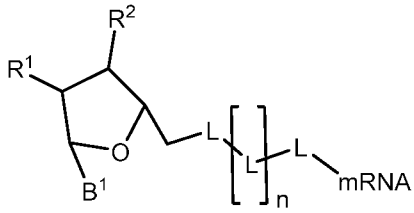
[0246] Provided herein, in some embodiments, are nucleic acid molecules comprising (a) a sequence of SEQ ID NO:10; (b) a sequence of SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:76, and SEQ ID NO:77, wherein T is substituted with U; (c) a sequence of SEQ ID NO:124; (d) a sequence of SEQ ID NO:124, wherein T is substituted with U; (e) a sequence of SEQ ID NO:125; or (f) a sequence of SEQ ID NO:125, wherein T is substituted with U. In one aspect, nucleic acid molecules provided herein are RNA molecules. In another aspect, RNA molecules provided herein further comprise a 5' cap having a Cap 1 structure. Any RNA molecules provided herein can be self-replicating RNA molecules.

[0247] Only those mRNAs that carry the Cap structure are active in Cap dependent translation; "decapitation" of mRNA results in an almost complete loss of their template activity for protein synthesis (Nature, 255:33-37, (1975); J. Biol. Chem., vol. 253:5228-5231, (1978); and Proc. Natl. Acad. Sci. USA, 72:1189-1193, (1975)).

[0248] Another element of eukaryotic mRNA is the presence of 2′-O-methyl nucleoside residues at transcript position 1 (Cap 1), and in some cases, at transcript positions 1 and 2 (Cap 2). The 2′-O-methylation of mRNA provides higher efficacy of mRNA translation in vivo (Proc. Natl. Acad. Sci. USA, 77:3952-3956 (1980)) and further improves nuclease stability of the 5′-capped mRNA. The mRNA with Cap 1 (and Cap 2) is a distinctive mark that allows cells to recognize the bona fide mRNA 5′ end, and in some instances, to discriminate against transcripts emanating from infectious genetic elements (Nucleic Acid Research 43: 482-492 (2015)).

[0249] Some examples of 5' cap structures and methods for preparing mRNAs comprising the same are given in WO2015/051169A2, WO/2015/061491, US 2018/0273576, and US Patent Nos. 8,093,367, 8,304,529, and U.S. 10,487,105. In some embodiments, the 5' cap is m7GpppAmpG, which is known in the art. In some embodiments, the 5' cap is m7GpppG or m7GpppGm, which are known in the art. Structural formulas for embodiments of 5' cap structures are provided below.

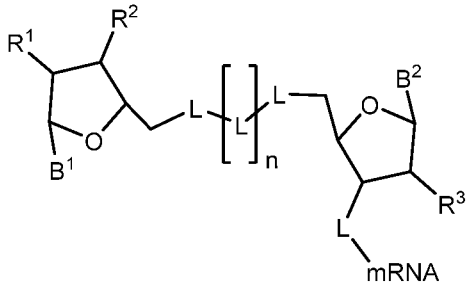
[0250] In some embodiments, a self-replicating RNA of the disclosure comprises a 5' cap having the structure of Formula (Cap I).



(Cap I)

wherein B^1 is a natural or modified nucleobase; R^1 and R^2 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phophorothioate, and boranophosphate wherein each L is linked by diester bonds; n is 0 or 1. and mRNA represents an mRNA of the present disclosure linked at its 5' end. In some embodiments B^1 is G, m^7G, or A. In some embodiments, n is 0. In some embodiments n is 1. In some embodiments, B^1 is A or m^6A and R^1 is OCH_3; wherein G is guanine, m^7G is 7-methylguanine, A is adenine, and m^6A is N^6-methyladenine.

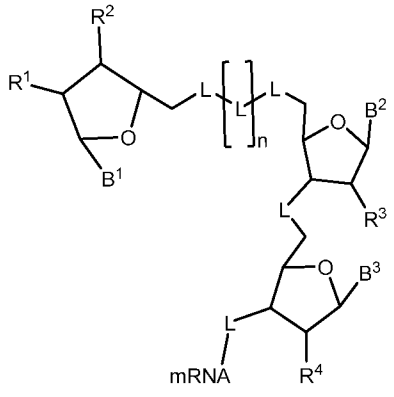
[0251] In some embodiments, a self-replicating RNA of the disclosure comprises a 5' cap having the structure of Formula (Cap II).



(Cap II)

wherein B^1 and B^2 are each independently a natural or modified nucleobase; R^1, R^2, and R^3 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phophorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1.. In some embodiments B^1 is G, m^7G, or A. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, B^1 is A or m^6A and R^1 is OCH_3; wherein G is guanine, m^7G is 7-methylguanine, A is adenine, and m^6A is N^6-methyladenine.

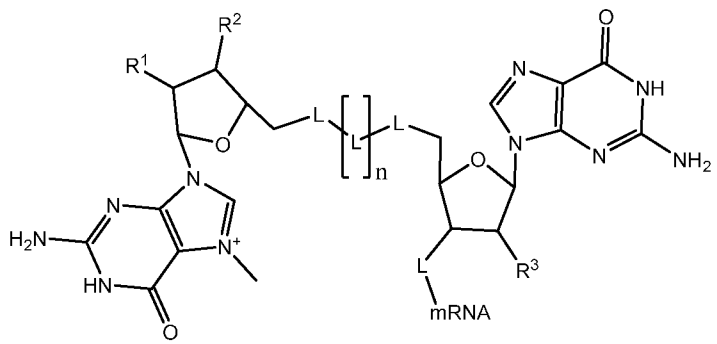
[0252] In some embodiments, a self-replicating RNA of the disclosure comprises a 5' cap having the structure of Formula (Cap III).



(Cap III)

wherein B1, B2, and B3 are each independently a natural or modified nucleobase; R1, R2, R3, and R4 are each independently selected from a halogen, OH, and OCH3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1.In some embodiments, at least one of R1, R2, R3, and R4 is OH. In some embodiments B1 is G, m7G, or A. In some embodiments, B1 is A or m6A and R1 is OCH3; wherein G is guanine, m7G is 7-methylguanine, A is adenine, and m6A is N6-methyladenine. In some embodiments, n is 1.

[0253] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppG 5' cap analog having the structure of Formula (Cap IV).

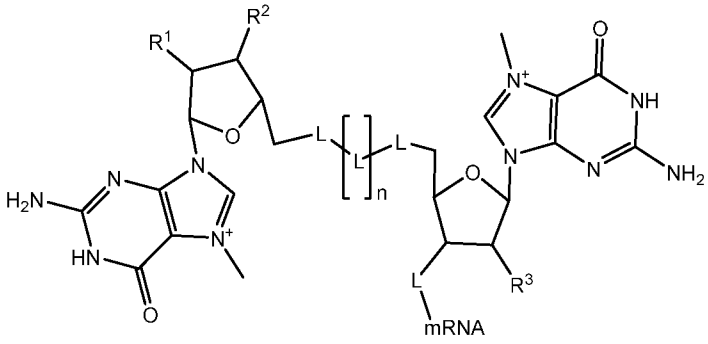


(Cap IV)

wherein, R^1, R^2, and R^3 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; n is 0 or 1. In some embodiments, at least one of R^1, R^2, and R^3 is OH. In some embodiments, the 5' cap is m^7GpppG wherein R^1, R^2, and R^3 are each OH, n is 1, and each L is a phosphate. In some embodiments, n is 1. In some embodiments,

the 5' cap is m7GpppGm, wherein R^1 and R^2 are each OH, R^3 is OCH_3, each L is a phosphate, mRNA is the mRNA encoding an enzyme having OTC activity linked at its 5' end, and n is 1.

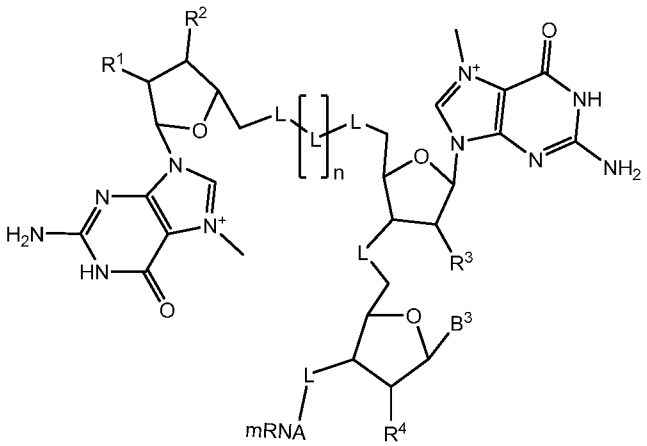
[0254] In some embodiments, a self-replicating RNA of the disclosure comprises a m7Gpppm7G 5' cap analog having the structure of Formula (Cap V).



(Cap V)

wherein, R^1, R^2, and R^3 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, and R^3 is OH. In some embodiments, n is 1.

[0255] In some embodiments, a self-replicating RNA of the disclosure comprises a m7Gpppm7GpN, 5' cap analog, wherein N is a natural or modified nucleotide, the 5' cap analog having the structure of Formula (Cap VI).

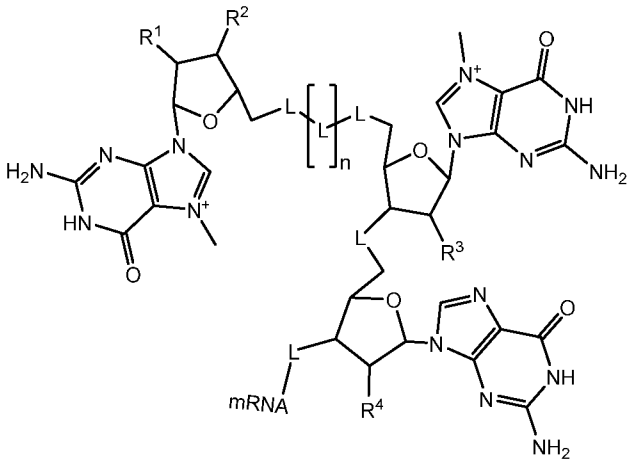


(Cap VI)

wherein B^3 is a natural or modified nucleobase; R^1, R^2, R^3, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 3. In some embodiments, at least one of R^1, R^2, R^3, and R^4 is OH. In some embodiments

B^1 is G, m^7G, or A. In some embodiments, B^1 is A or m^6A and R^1 is OCH_3; wherein G is guanine, m^7G is 7-methylguanine, A is adenine, and m^6A is N^6-methyladenine. In some embodiments, n is 1.

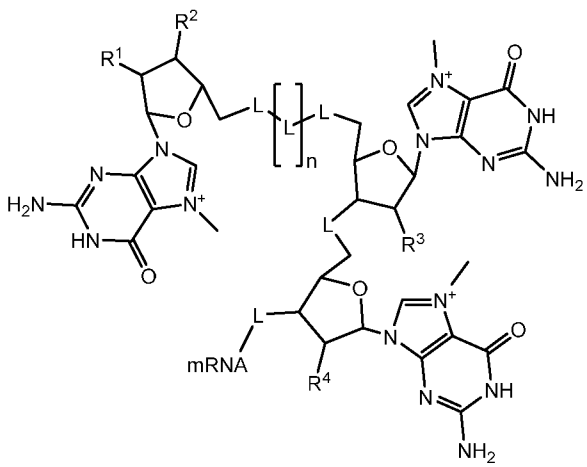
[0256] In some embodiments, a self-replicating RNA of the disclosure comprises a m7Gpppm7GpG 5' cap analog having the structure of Formula (Cap VII).



(Cap VII)

wherein, R^1, R^2, R^3, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, R^3, and R^4 is OH. In some embodiments, n is 1.

[0257] In some embodiments, a self-replicating RNA of the disclosure comprises a m7Gpppm7Gpm7G 5' cap analog having the structure of Formula (Cap VIII).

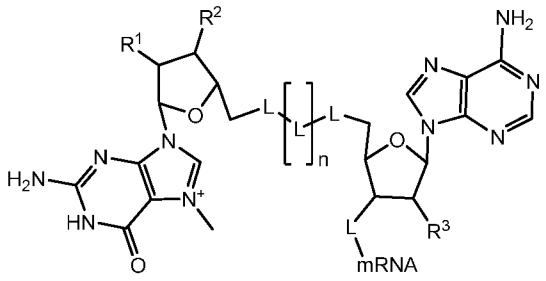


(Cap VIII)

wherein, R^1, R^2, R^3, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate,

and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; n is 0 or 1. In some embodiments, at least one of R^1, R^2, R^3, and R^4 is OH. In some embodiments, n is 1.

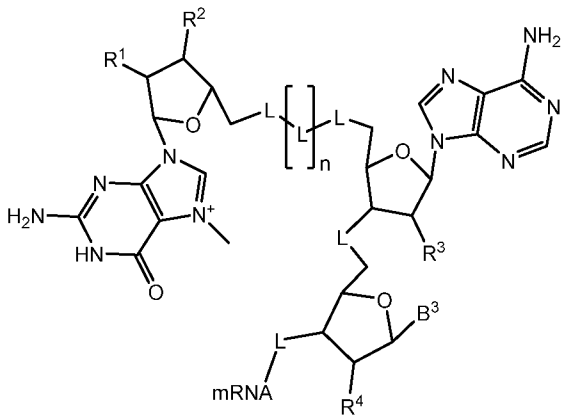
[0258] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppA 5' cap analog having the structure of Formula (Cap IX).



(Cap IX)

wherein, R^1, R^2, and R^3 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, and R^3 is OH. In some embodiments, n is 1.

[0259] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppApN 5' cap analog, wherein N is a natural or modified nucleotide, and the 5' cap has the structure of Formula (Cap X).

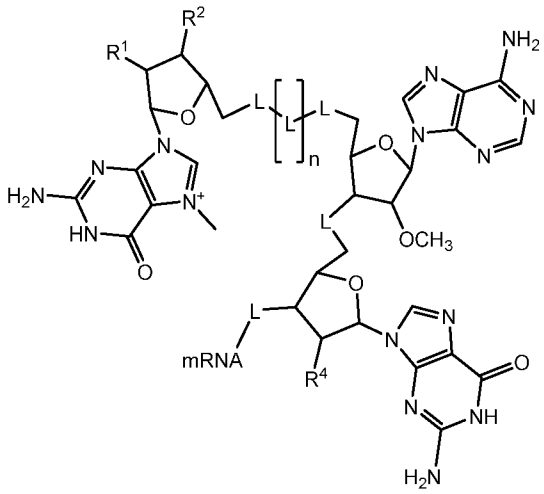


(Cap X)

wherein B^3 is a natural or modified nucleobase; R^1, R^2, R^3, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, R^3, and R^4 is OH. In some embodiments

B^3 is G, m^7G, A or m^6A; wherein G is guanine, m^7G is 7-methylguanine, A is adenine, and m^6A is N^6-methyladenine. In some embodiments, n is 1.

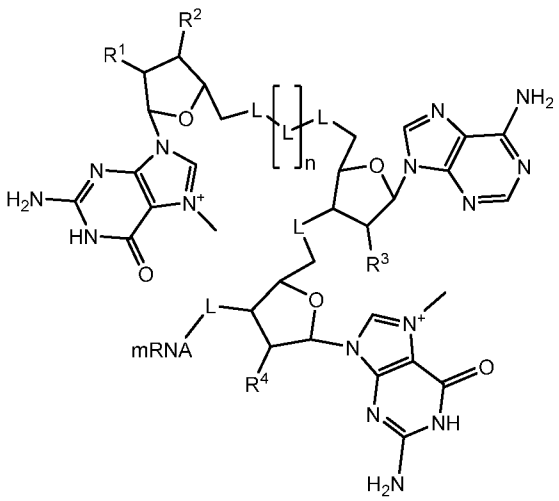
[0260] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppAmpG 5' cap analog having the structure of Formula (Cap XI).



(Cap XI)

wherein, R^1, R^2, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, and R^4 is OH. In some embodiments, the compound of Formula Cap XI is $m^7GpppAmpG$, wherein R^1, R^2, and R^4 are each OH, n is 1, and each L is a phosphate linkage. In some embodiments, n is 1.

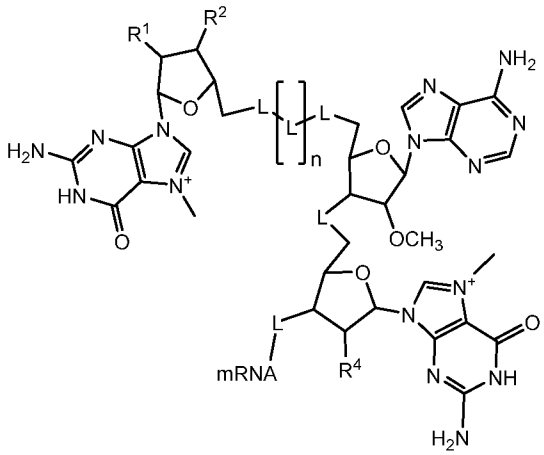
[0261] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppApm7G 5' cap analog having the structure of Formula (Cap XII).



(Cap XII)

wherein, R^1, R^2, R^3, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or1. In some embodiments,at least one of R^1, R^2, R^3, and R^4 is OH. In some embodiments, n is 1.

[0262] In some embodiments, a self-replicating RNA of the disclosure comprises a m7GpppApm7G 5' cap analog having the structure of Formula (Cap XIII).



(Cap XIII)

wherein, R^1, R^2, and R^4 are each independently selected from a halogen, OH, and OCH_3; each L is independently selected from the group consisting of phosphate, phosphorothioate, and boranophosphate wherein each L is linked by diester bonds; mRNA represents an mRNA of the present disclosure linked at its 5' end; and n is 0 or 1. In some embodiments, at least one of R^1, R^2, and R^4 is OH. In some embodiments, n is 1.

Poly-Adenine (Poly-A) Tail

[0263] Polyadenylation is the addition of a poly(A) tail, a chain of adenine nucleotides usually about 100-120 monomers in length, to a mRNA. In eukaryotes, polyadenylation is part of the process that produces mature mRNA for translation and begins as the transcription of a gene terminates. The 3′-most segment of a newly made pre-mRNA is first cleaved off by a set of proteins; these proteins then synthesize the poly(A) tail at the 3′ end. The poly(A) tail is important for the nuclear export, translation, and stability of mRNA. The tail is shortened over time, and, when it is short enough, the mRNA is enzymatically degraded. However, in a few cell types, mRNAs with short poly(A) tails are stored for later activation by re-polyadenylation in the cytosol.

[0264] Preferably, a self-replicating RNA of the disclosure comprises a 3' tail region, which can serve to protect the RNA from exonuclease degradation. The tail region may be a 3'poly(A) and/or 3'poly(C) region. Preferably, the tail region is a 3' poly(A) tail. As used herein a "3' poly(A) tail" is a polymer of sequential adenine nucleotides that can range in size from, for example: 10 to 250 sequential adenine nucleotides; 60-125 sequential adenine nucleotides, 90-125 sequential adenine nucleotides, 95-125 sequential adenine nucleotides, 95-121 sequential adenine nucleotides, 100 to 121 sequential adenine nucleotides, 110-121 sequential adenine nucleotides; 112-121 sequential adenine nucleotides; 114-121 adenine sequential nucleotides; or 115 to 121 sequential adenine nucleotides. Preferably, a 3' poly(A) tail as described herein comprise 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, or 125 sequential adenine nucleotides. 3' Poly(A) tails can be added using a variety of methods known in the art, e.g., using poly(A) polymerase to add tails to synthetic or in vitro transcribed RNA. Other methods include the use of a transcription vector to encode poly(A) tails or the use of a ligase (e.g., via splint ligation using a T4 RNA ligase and/or T4 DNA ligase), wherein poly(A) may be ligated to the 3' end of a sense RNA. In some embodiments, a combination of any of the above methods is utilized.

Design and Synthesis of Self-Replicating RNA

[0265] The constructs for exemplary self-replicating RNA sequences of the present disclosure are provided in Tables 4-5.

Table 4: Comparison of STARR™ self-replicating RNA of the disclosure with comparative self-replicating RNA as described

Construct	Position	Sequence Type	Sequence
STARR™ (SEQ ID NO:49)	5' UTR	nucleotide	ATGGGCGGCGCATGAGAGAAGCCCAGACCAATTACCT ACCCAAA

Construct	Position	Sequence Type	Sequence
STARR™ (SEQ ID NO:50)	non-structural gene ORF	nucleotide	ATGGAGAAAGTTCACGTTGACATCGAGGAAGACAGCC CATTCCTCAGAGCTTTGCAGCGGAGCTTCCCGCAGTTT GAGGTAGAAGCCAAGCAGGTCACTGATAATGACCATG CTAATGCCAGAGCGTTTTCGCATCTGGCTTCAAAACTG ATCGAAACGGAGGTGGACCCATCCGACACGATCCTTG ACATTGGAAGTGCGCCCGCCCGCAGAATGTATTCTAA GCACAAGTATCATTGTATCTGTCCGATGAGATGTGCGG AAGATCCGGACAGATTGTATAAGTATGCAACTAAGCT GAAGAAAAACTGTAAGGAAATAACTGATAAGGAATTG GACAAGAAAATGAAGGAGCTGGCCGCCGTCATGAGCG ACCCTGACCTGGAAACTGAGACTATGTGCCTCCACGA CGACGAGTCGTGTCGCTACGAAGGGCAAGTCGCTGTT TACCAGGATGTATACGCCGTCGACGGCCCCACCAGCC TGTACCACCAGGCCAACAAGGGCGTGAGGGTGGCCTA CTGGATCGGCTTCGACACCACACCCTTCATGTTCAAGA ACCTGGCCGGCGCCTACCCCAGCTACAGCACCAACTG GGCCGACGAGACCGTGCTGACCGCCAGGAACATCGGC CTGTGCAGCAGCGACGTGATGGAGAGGAGCCGGAGAG GCATGAGCATCCTGAGGAAGAAATACCTGAAGCCCAG CAACAACGTGCTGTTCAGCGTGGGCAGCACCATCTAC CACGAGAAGAGGGACCTGCTCAGGAGCTGGCACCTGC CCAGCGTGTTCCACCTGAGGGGCAAGCAGAACTACAC CTGCAGGTGCGAGACCATCGTGAGCTGCGACGGCTAC GTGGTGAAGAGGATCGCCATCAGCCCCGGCCTGTACG GCAAGCCCAGCGGCTACGCCGCTACAATGCACAGGGA GGGCTTCCTGTGCTGCAAGGTGACCGACACCCTGAAC GGCGAGAGGGTGAGCTTCCCCGTGTGCACCTACGTGC CCGCCACCCTGTGCGACCAGATGACCGGCATCCTGGC CACCGACGTGAGCGCCGACGACGCCCAGAAGCTGCTC GTGGGCCTGAACCAGAGGATCGTGGTCAACGGCAGGA CCCAGAGGAACACCAACACAATGAAGAACTACCTGCT GCCCGTGGTGGCCCAGGCTTTCGCCAGGTGGGCCAAG GAGTACAAGGAGGACCAGGAAGACGAGAGGCCCCTG GGCCTGAGGGACAGGCAGCTGGTGATGGGCTGCTGCT GGGCCTTCAGGCGGCACAAGATCACCAGCATCTACAA GAGGCCCGACACCCAGACCATCATCAAGGTGAACAGC GACTTCCACAGCTTCGTGCTGCCCAGGATCGGCAGCA ACACCCTGGAGATCGGCCTGAGGACCCGGATCAGGAA

Construct	Position	Sequence Type	Sequence
			GATGCTGGAGGAACACAAGGAGCCCAGCCCACTGATC
			ACCGCCGAGGACGTGCAGGAGGCCAAGTGCGCTGCCG
			ACGAGGCCAAGGAGGTGAGGGAGGCCGAGGAACTGA
			GGGCCGCCCTGCCACCCCTGGCTGCCGACGTGGAGGA
			ACCCACCCTGGAAGCCGACGTGGACCTGATGCTGCAG
			GAGGCCGGCGCCGGAAGCGTGGAGACACCCAGGGGC
			CTGATCAAGGTGACCAGCTACGACGGCGAGGACAAGA
			TCGGCAGCTACGCCGTGCTGAGCCCACAGGCCGTGCT
			GAAGTCCGAGAAGCTGAGCTGCATCCACCCACTGGCC
			GAGCAGGTGATCGTGATCACCCACAGCGGCAGGAAGG
			GCAGGTACGCCGTGGAGCCCTACCACGGCAAGGTGGT
			CGTGCCCGAGGGCCACGCCATCCCCGTGCAGGACTTC
			CAGGCCCTGAGCGAGAGCGCCACCATCGTGTACAACG
			AGAGGGAGTTCGTGAACAGGTACCTGCACCATATCGC
			CACCCACGGCGGAGCCCTGAACACCGACGAGGAATAC
			TACAAGACCGTGAAGCCCAGCGAGCACGACGGCGAGT
			ACCTGTACGACATCGACAGGAAGCAGTGCGTGAAGAA
			AGAGCTGGTGACCGGCCTGGGACTGACCGGCGAGCTG
			GTGGACCCACCCTTCCACGAGTTCGCCTACGAGAGCCT
			GAGGACCAGACCCGCCGCTCCCTACCAGGTGCCCACC
			ATCGGCGTGTACGGCGTGCCCGGCAGCGGAAAGAGCG
			GCATCATCAAGAGCGCCGTGACCAAGAAAGACCTGGT
			GGTCAGCGCCAAGAAAGAGAACTGCGCCGAGATCATC
			AGGGACGTGAAGAAGATGAAAGGCCTGGACGTGAAC
			GCGCGCACCGTGGACAGCGTGCTGCTGAACGGCTGCA
			AGCACCCCGTGGAGACCCTGTACATCGACGAGGCCTT
			CGCTTGCCACGCCGGCACCCTGAGGGCCCTGATCGCC
			ATCATCAGGCCCAAGAAAGCCGTGCTGTGCGGCGACC
			CCAAGCAGTGCGGCTTCTTCAACATGATGTGCCTGAAG
			GTGCACTTCAACCACGAGATCTGCACCCAGGTGTTCCA
			CAAGAGCATCAGCAGGCGGTGCACCAAGAGCGTGACC
			AGCGTCGTGAGCACCCTGTTCTACGACAAGAAAATGA
			GGACCACCAACCCCAAGGAGACCAAAATCGTGATCGA
			CACCACAGGCAGCACCAAGCCCAAGCAGGACGACCTG
			ATCCTGACCTGCTTCAGGGGCTGGGTGAAGCAGCTGC
			AGATCGACTACAAGGGCAACGAGATCATGACCGCCGC
			TGCCAGCCAGGGCCTGACCAGGAAGGGCGTGTACGCC
			GTGAGGTACAAGGTGAACGAGAACCCACTGTACGCTC

Construct	Position	Sequence Type	Sequence
			CCACCAGCGAGCACGTGAACGTGCTGCTGACCAGGAC
			CGAGGACAGGATCGTGTGGAAGACCCTGGCCGGCGAC
			CCCTGGATCAAGACCCTGACCGCCAAGTACCCCGGCA
			ACTTCACCGCCACCATCGAAGAGTGGCAGGCCGAGCA
			CGACGCCATCATGAGGCACATCCTGGAGAGGCCCGAC
			CCCACCGACGTGTTCCAGAACAAGGCCAACGTGTGCT
			GGGCCAAGGCCCTGGTGCCCGTGCTGAAGACCGCCGG
			CATCGACATGACCACAGAGCAGTGGAACACCGTGGAC
			TACTTCGAGACCGACAAGGCCCACAGCGCCGAGATCG
			TGCTGAACCAGCTGTGCGTGAGGTTCTTCGGCCTGGAC
			CTGGACAGCGGCCTGTTCAGCGCCCCCACCGTGCCACT
			GAGCATCAGGAACAACCACTGGGACAACAGCCCCAGC
			CCAAACATGTACGGCCTGAACAAGGAGGTGGTCAGGC
			AGCTGAGCAGGCGGTACCCACAGCTGCCCAGGGCCGT
			GGCCACCGGCAGGGTGTACGACATGAACACCGGCACC
			CTGAGGAACTACGACCCCAGGATCAACCTGGTGCCCG
			TGAACAGGCGGCTGCCCCACGCCCTGGTGCTGCACCA
			CAACGAGCACCCACAGAGCGACTTCAGCTCCTTCGTG
			AGCAAGCTGAAAGGCAGGACCGTGCTGGTCGTGGGCG
			AGAAGCTGAGCGTGCCCGGCAAGATGGTGGACTGGCT
			GAGCGACAGGCCCGAGGCCACCTTCCGGGCCAGGCTG
			GACCTCGGCATCCCCGGCGACGTGCCCAAGTACGACA
			TCATCTTCGTGAACGTCAGGACCCCATACAAGTACCAC
			CATTACCAGCAGTGCGAGGACCACGCCATCAAGCTGA
			GCATGCTGACCAAGAAGGCCTGCCTGCACCTGAACCC
			CGGAGGCACCTGCGTGAGCATCGGCTACGGCTACGCC
			GACAGGGCCAGCGAGAGCATCATTGGCGCCATCGCCA
			GGCTGTTCAAGTTCAGCAGGGTGTGCAAACCCAAGAG
			CAGCCTGGAGGAAACCGAGGTGCTGTTCGTGTTCATC
			GGCTACGACCGGAAGGCCAGGACCCACAACCCCTACA
			AGCTGAGCAGCACCCTGACAAACATCTACACCGGCAG
			CAGGCTGCACGAGGCCGGCTGCGCCCCCAGCTACCAC
			GTGGTCAGGGGCGATATCGCCACCGCCACCGAGGGCG
			TGATCATCAACGCTGCCAACAGCAAGGGCCAGCCCGG
			AGGCGGAGTGTGCGGCGCCCTGTACAAGAAGTTCCCC
			GAGAGCTTCGACCTGCAGCCCATCGAGGTGGGCAAGG
			CCAGGCTGGTGAAGGGCGCCGCTAAGCACATCATCCA
			CGCCGTGGGCCCCAACTTCAACAAGGTGAGCGAGGTG

Construct	Position	Sequence Type	Sequence
			GAAGGCGACAAGCAGCTGGCCGAAGCCTACGAGAGC
			ATCGCCAAGATCGTGAACGACAATAACTACAAGAGCG
			TGGCCATCCCACTGCTCAGCACCGGCATCTTCAGCGGC
			AACAAGGACAGGCTGACCCAGAGCCTGAACCACCTGC
			TCACCGCCCTGGACACCACCGATGCCGACGTGGCCAT
			CTACTGCAGGGACAAGAAGTGGGAGATGACCCTGAAG
			GAGGCCGTGGCCAGGCGGGAGGCCGTGGAAGAGATCT
			GCATCAGCGACGACTCCAGCGTGACCGAGCCCGACGC
			CGAGCTGGTGAGGGTGCACCCCAAGAGCTCCCTGGCC
			GGCAGGAAGGGCTACAGCACCAGCGACGGCAAGACCT
			TCAGCTACCTGGAGGGCACCAAGTTCCACCAGGCCGC
			TAAGGACATCGCCGAGATCAACGCTATGTGGCCCGTG
			GCCACCGAGGCCAACGAGCAGGTGTGCATGTACATCC
			TGGGCGAGAGCATGTCCAGCATCAGGAGCAAGTGCCC
			CGTGGAGGAAAGCGAGGCCAGCACACCACCCAGCACC
			CTGCCCTGCCTGTGCATCCACGCTATGACACCCGAGAG
			GGTGCAGCGGCTGAAGGCCAGCAGGCCCGAGCAGATC
			ACCGTGTGCAGCTCCTTCCCACTGCCCAAGTACAGGAT
			CACCGGCGTGCAGAAGATCCAGTGCAGCCAGCCCATC
			CTGTTCAGCCCAAAGGTGCCCGCCTACATCCACCCCAG
			GAAGTACCTGGTGGAGACCCCACCCGTGGACGAGACA
			CCCGAGCCAAGCGCCGAGAACCAGAGCACCGAGGGC
			ACACCCGAGCAGCCACCCCTGATCACCGAGGACGAGA
			CAAGGACCCGGACCCCAGAGCCCATCATTATCGAGGA
			AGAGGAAGAGGACAGCATCAGCCTGCTGAGCGACGGC
			CCCACCCACCAGGTGCTGCAGGTGGAGGCCGACATCC
			ACGGCCCACCCAGCGTGTCCAGCTCCAGCTGGAGCAT
			CCCACACGCCAGCGACTTCGACGTGGACAGCCTGAGC
			ATCCTGGACACCCTGGAGGGCGCCAGCGTGACCTCCG
			GCGCCACCAGCGCCGAGACCAACAGCTACTTCGCCAA
			GAGCATGGAGTTCCTGGCCAGGCCCGTGCCAGCTCCC
			AGGACCGTGTTCAGGAACCCACCCCACCCAGCTCCCA
			GGACCAGGACCCCAAGCCTGGCTCCCAGCAGGGCCTG
			CAGCAGGACCAGCCTGGTGAGCACCCCACCCGGCGTG
			AACAGGGTGATCACCAGGGAGGAACTGGAGGCCCTGA
			CACCCAGCAGGACCCCCAGCAGGTCCGTGAGCAGGAC
			TAGTCTGGTGTCCAACCCACCCGGCGTGAACAGGGTG
			ATCACCAGGGAGGAATTCGAGGCCTTCGTGGCCCAGC

Construct	Position	Sequence Type	Sequence
			AACAGAGACGGTTCGACGCCGGCGCCTACATCTTCAG
			CAGCGACACCGGCCAGGGACACCTGCAGCAAAAGAGC
			GTGAGGCAGACCGTGCTGAGCGAGGTGGTGCTGGAGA
			GGACCGAGCTGGAAATCAGCTACGCCCCCAGGCTGGA
			CCAGGAGAAGGAGGAACTGCTCAGGAAGAAACTGCA
			GCTGAACCCCACCCCAGCCAACAGGAGCAGGTACCAG
			AGCAGGAAGGTGGAGAACATGAAGGCCATCACCGCCA
			GGCGGATCCTGCAGGGCCTGGGACACTACCTGAAGGC
			CGAGGGCAAGGTGGAGTGCTACAGGACCCTGCACCCC
			GTGCCACTGTACAGCTCCAGCGTGAACAGGGCCTTCTC
			CAGCCCCAAGGTGGCCGTGGAGGCCTGCAACGCTATG
			CTGAAGGAGAACTTCCCCACCGTGGCCAGCTACTGCA
			TCATCCCCGAGTACGACGCCTACCTGGACATGGTGGA
			CGGCGCCAGCTGCTGCCTGGACACCGCCAGCTTCTGCC
			CCGCCAAGCTGAGGAGCTTCCCCAAGAAACACAGCTA
			CCTGGAGCCCACCATCAGGAGCGCCGTGCCCAGCGCC
			ATCCAGAACACCCTGCAGAACGTGCTGGCCGCTGCCA
			CCAAGAGGAACTGCAACGTGACCCAGATGAGGGAGCT
			GCCCGTGCTGGACAGCGCTGCCTTCAACGTGGAGTGCT
			TCAAGAAATACGCCTGCAACAACGAGTACTGGGAGAC
			CTTCAAGGAGAACCCCATCAGGCTGACCGAAGAGAAC
			GTGGTGAACTACATCACCAAGCTGAAGGGCCCCAAGG
			CCGCTGCCCTGTTCGCTAAGACCCACAACCTGAACATG
			CTGCAGGACATCCCAATGGACAGGTTCGTGATGGACC
			TGAAGAGGGACGTGAAGGTGACACCCGGCACCAAGCA
			CACCGAGGAGAGGCCCAAGGTGCAGGTGATCCAGGCC
			GCTGACCCACTGGCCACCGCCTACCTGTGCGGCATCCA
			CAGGGAGCTGGTGAGGCGGCTGAACGCCGTGCTGCTG
			CCCAACATCCACACCCTGTTCGACATGAGCGCCGAGG
			ACTTCGACGCCATCATCGCCGAGCACTTCCAGCCCGGC
			GACTGCGTGCTGGAGACCGACATCGCCAGCTTCGACA
			AGAGCGAGGATGACGCTATGGCCCTGACCGCTCTGAT
			GATCCTGGAGGACCTGGGCGTGGACGCCGAGCTGCTC
			ACCCTGATCGAGGCTGCCTTCGGCGAGATCAGCTCCAT
			CCACCTGCCCACCAAGACCAAGTTCAAGTTCGGCGCT
			ATGATGAAAAGCGGAATGTTCCTGACCCTGTTCGTGA
			ACACCGTGATCAACATTGTGATCGCCAGCAGGGTGCT
			GCGGGAGAGGCTGACCGGCAGCCCCTGCGCTGCCTTC

Construct	Position	Sequence Type	Sequence
			ATCGGCGACGACAACATCGTGAAGGGCGTGAAAAGCG ACAAGCTGATGGCCGACAGGTGCGCCACCTGGCTGAA CATGGAGGTGAAGATCATCGACGCCGTGGTGGGCGAG AAGGCCCCCTACTTCTGCGGCGGATTCATCCTGTGCGA CAGCGTGACCGGCACCGCCTGCAGGGTGGCCGACCCC CTGAAGAGGCTGTTCAAGCTGGGCAAGCCACTGGCCG CTGACGATGAGCACGACGATGACAGGCGGAGGGCCCT GCACGAGGAAAGCACCAGGTGGAACAGGGTGGGCAT CCTGAGCGAGCTGTGCAAGGCCGTGGAGAGCAGGTAC GAGACCGTGGGCACCAGCATCATCGTGATGGCTATGA CCACACTGGCCAGCTCCGTCAAGAGCTTCTCCTACCTG AGGGGGGCCCCTATAACTCTCTACGGCTAA

Construct	Position	Sequence Type	Sequence
STARR™ (SEQ ID NO:51)	non-structural gene ORF	amino acid	MEKVHVDIEEDSPFLRALQRSFPQFEVEAKQVTDNDHAN ARAFSHLASKLIETEVDPSDTILDIGSAPARRMYSKHKYH CICPMRCAEDPDRLYKYATKLKKNCKEITDKELDKKMK ELAAVMSDPDLETETMCLHDDESCRYEGQVAVYQDVY AVDGPTSLYHQANKGVRVAYWIGFDTTPFMFKNLAGAY PSYSTNWADETVLTARNIGLCSSDVMERSRRGMSILRKK YLKPSNNVLFSVGSTIYHEKRDLLRSWHLPSVFHLRGKQ NYTCRCETIVSCDGYVVKRIAISPGLYGKPSGYAATMHR EGFLCCKVTDTLNGERVSFPVCTYVPATLCDQMTGILAT DVSADDAQKLLVGLNQRIVVNGRTQRNTNTMKNYLLPV VAQAFARWAKEYKEDQEDERPLGLRDRQLVMGCCWAF RRHKITSIYKRPDTQTIIKVNSDFHSFVLPRIGSNTLEIGLR TRIRKMLEEHKEPSPLITAEDVQEAKCAADEAKEVREAE ELRAALPPLAADVEEPTLEADVDLMLQEAGAGSVETPRG LIKVTSYDGEDKIGSYAVLSPQAVLKSEKLSCIHPLAEQVI VITHSGRKGRYAVEPYHGKVVVPEGHAIPVQDFQALSES ATIVYNEREFVNRYLHHIATHGGALNTDEEYYKTVKPSE HDGEYLYDIDRKQCVKKELVTGLGLTGELVDPPFHEFAY ESLRTRPAAPYQVPTIGVYGVPGSGKSGIIKSAVTKKDLV VSAKKENCAEIIRDVKKMKGLDVNARTVDSVLLNGCKH PVETLYIDEAFACHAGTLRALIAIIRPKKAVLCGDPKQCG FFNMMCLKVHFNHEICTQVFHKSISRRCTKSVTSVVSTLF YDKKMRTTNPKETKIVIDTTGSTKPKQDDLILTCFRGWV KQLQIDYKGNEIMTAAASQGLTRKGVYAVRYKVNENPL YAPTSEHVNVLLTRTEDRIVWKTLAGDPWIKTLTAKYPG NFTATIEEWQAEHDAIMRHILERPDPTDVFQNKANVCWA KALVPVLKTAGIDMTTEQWNTVDYFETDKAHSAEIVLN QLCVRFFGLDLDSGLFSAPTVPLSIRNNHWDNSPSPNMY GLNKEVVRQLSRRYPQLPRAVATGRVYDMNTGTLRNYD PRINLVPVNRRLPHALVLHHNEHPQSDFSSFVSKLKGRTV LVVGEKLSVPGKMVDWLSDRPEATFRARLDLGIPGDVP KYDIIFVNVRTPYKYHHYQQCEDHAIKLSMLTKKACLHL NPGGTCVSIGYGYADRASESIIGAIARLFKFSRVCKPKSSL EETEVLFVFIGYDRKARTHNPYKLSSTLTNIYTGSRLHEA GCAPSYHVVRGDIATATEGVIINAANSKGQPGGGVCGAL YKKFPESFDLQPIEVGKARLVKGAAKHIIHAVGPNFNKVS EVEGDKQLAEAYESIAKIVNDNNYKSVAIPLLSTGIFSGN KDRLTQSLNHLLTALDTTDADVAIYCRDKKWEMTLKEA

Construct	Position	Sequence Type	Sequence
			VARREAVEEICISDDSSVTEPDAELVRVHPKSSLAGRKGY STSDGKTFSYLEGTKFHQAAKDIAEINAMWPVATEANEQ VCMYILGESMSSIRSKCPVEESEASTPPSTLPCLCIHAMTP ERVQRLKASRPEQITVCSSFPLPKYRITGVQKIQCSQPILFS PKVPAYIHPRKYLVETPPVDETPEPSAENQSTEGTPEQPPL ITEDETRTRTPEPIIIEEEEEDSISLLSDGPTHQVLQVEADIH GPPSVSSSSWSIPHASDFDVDSLSILDTLEGASVTSGATSA ETNSYFAKSMEFLARPVPAPRTVFRNPPHPAPRTRTPSLA PSRACSRTSLVSTPPGVNRVITREELEALTPSRTPSRSVSR TSLVSNPPGVNRVITREEFEAFVAQQQRRFDAGAYIFSSD TGQGHLQQKSVRQTVLSEVVLERTELEISYAPRLDQEKE ELLRKKLQLNPTPANRSRYQSRKVENMKAITARRILQGL GHYLKAEGKVECYRTLHPVPLYSSSVNRAFSSPKVAVEA CNAMLKENFPTVASYCIIPEYDAYLDMVDGASCCLDTAS FCPAKLRSFPKKHSYLEPTIRSAVPSAIQNTLQNVLAAAT KRNCNVTQMRELPVLDSAAFNVECFKKYACNNEYWETF KENPIRLTEENVVNYITKLKGPKAAALFAKTHNLNMLQD IPMDRFVMDLKRDVKVTPGTKHTEERPKVQVIQAADPL ATAYLCGIHRELVRRLNAVLLPNIHTLFDMSAEDFDAIIA EHFQPGDCVLETDIASFDKSEDDAMALTALMILEDLGVD AELLTLIEAAFGEISSIHLPTKTKFKFGAMMKSGMFLTLF VNTVINIVIASRVLRERLTGSPCAAFIGDDNIVKGVKSDK LMADRCATWLNMEVKIIDAVVGEKAPYFCGGFILCDSVT GTACRVADPLKRLFKLGKPLAADDEHDDDRRRALHEES TRWNRVGILSELCKAVESRYETVGTSIIVMAMTTLASSV KSFSYLRGAPITLYG*
STARR™ (SEQ ID NO:52)	intergenic region	nucleotide	CCTGAATGGACTACGACATAGTCTAGTCCGCCAAGGC CGCCACC
STARR™	transgene ORF	nucleotide	n/a (depends on gene of our interest)

Construct	Position	Sequence Type	Sequence
STARR™ (SEQ ID NO:53)	3' UTR	nucleotide	ACTCGAGTATGTTACGTGCAAAGGTGATTGTCACCCCC CGAAAGACCATATTGTGACACACCCTCAGTATCACGC CCAAACATTTACAGCCGCGGTGTCAAAAACCGCGTGG ACGTGGTTAACATCCCTGCTGGGAGGATCAGCCGTAA TTATTATAATTGGCTTGGTGCTGGCTACTATTGTGGCC ATGTACGTGCTGACCAACCAGAAACATAATTGAATAC AGCAGCAATTGGCAAGCTGCTTACATAGAACTCGCGG CGATTGGCATGCCGCCTTAAAATTTTTATTTTATTTTTT CTTTTCTTTTCCGAATCGGATTTTGTTTTTAATATTTCA AAAAAAAAAAAAAAAAAAAAAAAAATCTAGAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAA
Comparitive	5' UTR	nucleotide	unknown

Construct	Position	Sequence Type	Sequence
Original (SEQ ID NO:54)	non-structural gene ORF	nucleotide	ATGCCCGAGAAGGTGCACGTGGACATCGAGGAGGACA GCCCCTTCCTGAGGGCCCTGCAGAGGAGCTTCCCACA GTTCGAAGTGGAGGCCAAGCAGGTGACCGACAACGAC CACGCCAACGCCAGGGCCTTCAGCCACCTGGCCAGCA AGCTGATCGAGACCGAGGTGGACCCCAGCGACACCAT CCTGGACATCGGCAGCGCCCCAGCCAGGAGAATGTAC AGCAAGCACAAGTACCACTGCATCTGCCCCATGAGGT GCGCCGAGGACCCCGACAGGCTGTACAAGTACGCCAC CAAACTGAAGAAGAACTGCAAGGAGATCACCGACAA GGAGCTGGACAAGAAAATGAAGGAGCTGGCCGCCGTG ATGAGCGACCCCGACCTGGAGACCGAGACAATGTGCC TGCACGACGACGAGAGCTGCAGGTACGAGGGCCAGGT GGCCGTCTACCAGGACGTGTACGCCGTCGACGGCCCC ACCAGCCTGTACCACCAGGCCAACAAGGGCGTGAGGG TGGCCTACTGGATCGGCTTCGACACCACACCCTTCATG TTCAAGAACCTGGCCGGCGCCTACCCCAGCTACAGCA CCAACTGGGCCGACGAGACCGTGCTGACCGCCAGGAA CATCGGCCTGTGCAGCAGCGACGTGATGGAGAGGAGC CGGAGAGGCATGAGCATCCTGAGGAAGAAATACCTGA AGCCCAGCAACAACGTGCTGTTCAGCGTGGGCAGCAC CATCTACCACGAGAAGAGGGACCTGCTCAGGAGCTGG CACCTGCCCAGCGTGTTCCACCTGAGGGGCAAGCAGA ACTACACCTGCAGGTGCGAGACCATCGTGAGCTGCGA CGGCTACGTGGTGAAGAGGATCGCCATCAGCCCCGGC CTGTACGGCAAGCCCAGCGGCTACGCCGCTACAATGC ACAGGGAGGGCTTCCTGTGCTGCAAGGTGACCGACAC CCTGAACGGCGAGAGGGTGAGCTTCCCCGTGTGCACC TACGTGCCCGCCACCCTGTGCGACCAGATGACCGGCA TCCTGGCCACCGACGTGAGCGCCGACGACGCCCAGAA GCTGCTCGTGGGCCTGAACCAGAGGATCGTGGTCAAC GGCAGGACCCAGAGGAACACCAACACAATGAAGAAC TACCTGCTGCCCGTGGTGGCCCAGGCTTTCGCCAGGTG GGCCAAGGAGTACAAGGAGGACCAGGAAGACGAGAG GCCCCTGGGCCTGAGGGACAGGCAGCTGGTGATGGGC TGCTGCTGGGCCTTCAGGCGGCACAAGATCACCAGCA TCTACAAGAGGCCCGACACCCAGACCATCATCAAGGT GAACAGCGACTTCCACAGCTTCGTGCTGCCCAGGATC GGCAGCAACACCCTGGAGATCGGCCTGAGGACCCGGA

Construct	Position	Sequence Type	Sequence
			TCAGGAAGATGCTGGAGGAACACAAGGAGCCCAGCCC
			ACTGATCACCGCCGAGGACGTGCAGGAGGCCAAGTGC
			GCTGCCGACGAGGCCAAGGAGGTGAGGGAGGCCGAG
			GAACTGAGGGCCGCCCTGCCACCCCTGGCTGCCGACG
			TGGAGGAACCCACCCTGGAAGCCGACGTGGACCTGAT
			GCTGCAGGAGGCCGGCGCCGGAAGCGTGGAGACACCC
			AGGGGCCTGATCAAGGTGACCAGCTACGACGGCGAGG
			ACAAGATCGGCAGCTACGCCGTGCTGAGCCCACAGGC
			CGTGCTGAAGTCCGAGAAGCTGAGCTGCATCCACCCA
			CTGGCCGAGCAGGTGATCGTGATCACCCACAGCGGCA
			GGAAGGGCAGGTACGCCGTGGAGCCCTACCACGGCAA
			GGTGGTCGTGCCCGAGGGCCACGCCATCCCCGTGCAG
			GACTTCCAGGCCCTGAGCGAGAGCGCCACCATCGTGT
			ACAACGAGAGGGAGTTCGTGAACAGGTACCTGCACCA
			TATCGCCACCCACGGCGGAGCCCTGAACACCGACGAG
			GAATACTACAAGACCGTGAAGCCCAGCGAGCACGACG
			GCGAGTACCTGTACGACATCGACAGGAAGCAGTGCGT
			GAAGAAAGAGCTGGTGACCGGCCTGGGACTGACCGGC
			GAGCTGGTGGACCCACCCTTCCACGAGTTCGCCTACGA
			GAGCCTGAGGACCAGACCCGCCGCTCCCTACCAGGTG
			CCCACCATCGGCGTGTACGGCGTGCCCGGCAGCGGAA
			AGAGCGGCATCATCAAGAGCGCCGTGACCAAGAAAGA
			CCTGGTGGTCAGCGCCAAGAAAGAGAACTGCGCCGAG
			ATCATCAGGGACGTGAAGAAGATGAAAGGCCTGGACG
			TGAACGCGCGCACCGTGGACAGCGTGCTGCTGAACGG
			CTGCAAGCACCCCGTGGAGACCCTGTACATCGACGAG
			GCCTTCGCTTGCCACGCCGGCACCCTGAGGGCCCTGAT
			CGCCATCATCAGGCCCAAGAAAGCCGTGCTGTGCGGC
			GACCCCAAGCAGTGCGGCTTCTTCAACATGATGTGCCT
			GAAGGTGCACTTCAACCACGAGATCTGCACCCAGGTG
			TTCCACAAGAGCATCAGCAGGCGGTGCACCAAGAGCG
			TGACCAGCGTCGTGAGCACCCTGTTCTACGACAAGAA
			AATGAGGACCACCAACCCCAAGGAGACCAAAATCGTG
			ATCGACACCACAGGCAGCACCAAGCCCAAGCAGGACG
			ACCTGATCCTGACCTGCTTCAGGGGCTGGGTGAAGCA
			GCTGCAGATCGACTACAAGGGCAACGAGATCATGACC
			GCCGCTGCCAGCCAGGGCCTGACCAGGAAGGGCGTGT
			ACGCCGTGAGGTACAAGGTGAACGAGAACCCACTGTA

Construct	Position	Sequence Type	Sequence
			CGCTCCCACCAGCGAGCACGTGAACGTGCTGCTGACC
			AGGACCGAGGACAGGATCGTGTGGAAGACCCTGGCCG
			GCGACCCCTGGATCAAGACCCTGACCGCCAAGTACCC
			CGGCAACTTCACCGCCACCATCGAAGAGTGGCAGGCC
			GAGCACGACGCCATCATGAGGCACATCCTGGAGAGGC
			CCGACCCCACCGACGTGTTCCAGAACAAGGCCAACGT
			GTGCTGGGCCAAGGCCCTGGTGCCCGTGCTGAAGACC
			GCCGGCATCGACATGACCACAGAGCAGTGGAACACCG
			TGGACTACTTCGAGACCGACAAGGCCCACAGCGCCGA
			GATCGTGCTGAACCAGCTGTGCGTGAGGTTCTTCGGCC
			TGGACCTGGACAGCGGCCTGTTCAGCGCCCCCACCGT
			GCCACTGAGCATCAGGAACAACCACTGGGACAACAGC
			CCCAGCCCAAACATGTACGGCCTGAACAAGGAGGTGG
			TCAGGCAGCTGAGCAGGCGGTACCCACAGCTGCCCAG
			GGCCGTGGCCACCGGCAGGGTGTACGACATGAACACC
			GGCACCCTGAGGAACTACGACCCCAGGATCAACCTGG
			TGCCCGTGAACAGGCGGCTGCCCCACGCCCTGGTGCT
			GCACCACAACGAGCACCCACAGAGCGACTTCAGCTCC
			TTCGTGAGCAAGCTGAAAGGCAGGACCGTGCTGGTCG
			TGGGCGAGAAGCTGAGCGTGCCCGGCAAGATGGTGGA
			CTGGCTGAGCGACAGGCCCGAGGCCACCTTCCGGGCC
			AGGCTGGACCTCGGCATCCCCGGCGACGTGCCCAAGT
			ACGACATCATCTTCGTGAACGTCAGGACCCCATACAA
			GTACCACCATTACCAGCAGTGCGAGGACCACGCCATC
			AAGCTGAGCATGCTGACCAAGAAGGCCTGCCTGCACC
			TGAACCCCGGAGGCACCTGCGTGAGCATCGGCTACGG
			CTACGCCGACAGGGCCAGCGAGAGCATCATTGGCGCC
			ATCGCCAGGCTGTTCAAGTTCAGCAGGGTGTGCAAAC
			CCAAGAGCAGCCTGGAGGAAACCGAGGTGCTGTTCGT
			GTTCATCGGCTACGACCGGAAGGCCAGGACCCACAAC
			CCCTACAAGCTGAGCAGCACCCTGACAAACATCTACA
			CCGGCAGCAGGCTGCACGAGGCCGGCTGCGCCCCCAG
			CTACCACGTGGTCAGGGGCGATATCGCCACCGCCACC
			GAGGGCGTGATCATCAACGCTGCCAACAGCAAGGGCC
			AGCCCGGAGGCGGAGTGTGCGGCGCCCTGTACAAGAA
			GTTCCCCGAGAGCTTCGACCTGCAGCCCATCGAGGTG
			GGCAAGGCCAGGCTGGTGAAGGGCGCCGCTAAGCACA
			TCATCCACGCCGTGGGCCCCAACTTCAACAAGGTGAG

Construct	Position	Sequence Type	Sequence
			CGAGGTGGAAGGCGACAAGCAGCTGGCCGAAGCCTAC
			GAGAGCATCGCCAAGATCGTGAACGACAATAACTACA
			AGAGCGTGGCCATCCCACTGCTCAGCACCGGCATCTTC
			AGCGGCAACAAGGACAGGCTGACCCAGAGCCTGAACC
			ACCTGCTCACCGCCCTGGACACCACCGATGCCGACGT
			GGCCATCTACTGCAGGGACAAGAAGTGGGAGATGACC
			CTGAAGGAGGCCGTGGCCAGGCGGGAGGCCGTGGAA
			GAGATCTGCATCAGCGACGACTCCAGCGTGACCGAGC
			CCGACGCCGAGCTGGTGAGGGTGCACCCCAAGAGCTC
			CCTGGCCGGCAGGAAGGGCTACAGCACCAGCGACGGC
			AAGACCTTCAGCTACCTGGAGGGCACCAAGTTCCACC
			AGGCCGCTAAGGACATCGCCGAGATCAACGCTATGTG
			GCCCGTGGCCACCGAGGCCAACGAGCAGGTGTGCATG
			TACATCCTGGGCGAGAGCATGTCCAGCATCAGGAGCA
			AGTGCCCCGTGGAGGAAAGCGAGGCCAGCACACCACC
			CAGCACCCTGCCCTGCCTGTGCATCCACGCTATGACAC
			CCGAGAGGGTGCAGCGGCTGAAGGCCAGCAGGCCCGA
			GCAGATCACCGTGTGCAGCTCCTTCCCACTGCCCAAGT
			ACAGGATCACCGGCGTGCAGAAGATCCAGTGCAGCCA
			GCCCATCCTGTTCAGCCCAAAGGTGCCCGCCTACATCC
			ACCCCAGGAAGTACCTGGTGGAGACCCCACCCGTGGA
			CGAGACACCCGAGCCAAGCGCCGAGAACCAGAGCACC
			GAGGGCACACCCGAGCAGCCACCCCTGATCACCGAGG
			ACGAGACAAGGACCCGGACCCCAGAGCCCATCATTAT
			CGAGGAAGAGGAAGAGGACAGCATCAGCCTGCTGAG
			CGACGGCCCCACCCACCAGGTGCTGCAGGTGGAGGCC
			GACATCCACGGCCCACCCAGCGTGTCCAGCTCCAGCT
			GGAGCATCCCACACGCCAGCGACTTCGACGTGGACAG
			CCTGAGCATCCTGGACACCCTGGAGGGCGCCAGCGTG
			ACCTCCGGCGCCACCAGCGCCGAGACCAACAGCTACT
			TCGCCAAGAGCATGGAGTTCCTGGCCAGGCCCGTGCC
			AGCTCCCAGGACCGTGTTCAGGAACCCACCCCACCCA
			GCTCCCAGGACCAGGACCCCAAGCCTGGCTCCCAGCA
			GGGCCTGCAGCAGGACCAGCCTGGTGAGCACCCCACC
			CGGCGTGAACAGGGTGATCACCAGGGAGGAACTGGAG
			GCCCTGACACCCAGCAGGACCCCCAGCAGGTCCGTGA
			GCAGGACTAGTCTGGTGTCCAACCCACCCGGCGTGAA
			CAGGGTGATCACCAGGGAGGAATTCGAGGCCTTCGTG

Construct	Position	Sequence Type	Sequence
			GCCCAGCAACAGAGACGGTTCGACGCCGGCGCCTACA
			TCTTCAGCAGCGACACCGGCCAGGGACACCTGCAGCA
			AAAGAGCGTGAGGCAGACCGTGCTGAGCGAGGTGGTG
			CTGGAGAGGACCGAGCTGGAAATCAGCTACGCCCCCA
			GGCTGGACCAGGAGAAGGAGGAACTGCTCAGGAAGA
			AACTGCAGCTGAACCCCACCCCAGCCAACAGGAGCAG
			GTACCAGAGCAGGAAGGTGGAGAACATGAAGGCCATC
			ACCGCCAGGCGGATCCTGCAGGGCCTGGGACACTACC
			TGAAGGCCGAGGGCAAGGTGGAGTGCTACAGGACCCT
			GCACCCCGTGCCACTGTACAGCTCCAGCGTGAACAGG
			GCCTTCTCCAGCCCCAAGGTGGCCGTGGAGGCCTGCA
			ACGCTATGCTGAAGGAGAACTTCCCCACCGTGGCCAG
			CTACTGCATCATCCCCGAGTACGACGCCTACCTGGACA
			TGGTGGACGGCGCCAGCTGCTGCCTGGACACCGCCAG
			CTTCTGCCCCGCCAAGCTGAGGAGCTTCCCCAAGAAA
			CACAGCTACCTGGAGCCCACCATCAGGAGCGCCGTGC
			CCAGCGCCATCCAGAACACCCTGCAGAACGTGCTGGC
			CGCTGCCACCAAGAGGAACTGCAACGTGACCCAGATG
			AGGGAGCTGCCCGTGCTGGACAGCGCTGCCTTCAACG
			TGGAGTGCTTCAAGAAATACGCCTGCAACAACGAGTA
			CTGGGAGACCTTCAAGGAGAACCCCATCAGGCTGACC
			GAAGAGAACGTGGTGAACTACATCACCAAGCTGAAGG
			GCCCCAAGGCCGCTGCCCTGTTCGCTAAGACCCACAA
			CCTGAACATGCTGCAGGACATCCCAATGGACAGGTTC
			GTGATGGACCTGAAGAGGGACGTGAAGGTGACACCCG
			GCACCAAGCACACCGAGGAGAGGCCCAAGGTGCAGGT
			GATCCAGGCCGCTGACCCACTGGCCACCGCCTACCTGT
			GCGGCATCCACAGGGAGCTGGTGAGGCGGCTGAACGC
			CGTGCTGCTGCCCAACATCCACACCCTGTTCGACATGA
			GCGCCGAGGACTTCGACGCCATCATCGCCGAGCACTT
			CCAGCCCGGCGACTGCGTGCTGGAGACCGACATCGCC
			AGCTTCGACAAGAGCGAGGATGACGCTATGGCCCTGA
			CCGCTCTGATGATCCTGGAGGACCTGGGCGTGGACGC
			CGAGCTGCTCACCCTGATCGAGGCTGCCTTCGGCGAG
			ATCAGCTCCATCCACCTGCCCACCAAGACCAAGTTCAA
			GTTCGGCGCTATGATGAAAAGCGGAATGTTCCTGACC
			CTGTTCGTGAACACCGTGATCAACATTGTGATCGCCAG
			CAGGGTGCTGCGGGAGAGGCTGACCGGCAGCCCCTGC

Construct	Position	Sequence Type	Sequence
			GCTGCCTTCATCGGCGACGACAACATCGTGAAGGGCG TGAAAAGCGACAAGCTGATGGCCGACAGGTGCGCCAC CTGGCTGAACATGGAGGTGAAGATCATCGACGCCGTG GTGGGCGAGAAGGCCCCCTACTTCTGCGGCGGATTCA TCCTGTGCGACAGCGTGACCGGCACCGCCTGCAGGGT GGCCGACCCCCTGAAGAGGCTGTTCAAGCTGGGCAAG CCACTGGCCGCTGACGATGAGCACGACGATGACAGGC GGAGGGCCCTGCACGAGGAAAGCACCAGGTGGAACA GGGTGGGCATCCTGAGCGAGCTGTGCAAGGCCGTGGA GAGCAGGTACGAGACCGTGGGCACCAGCATCATCGTG ATGGCTATGACCACACTGGCCAGCTCCGTCAAGAGCTT CTCCTACCTGAGGGGGGCCCCTATAACTCTCTACGGCT AA

Construct	Position	Sequence Type	Sequence
Comparitive (SEQ ID NO:55)	non-structural gene ORF	amino acid	MPEKVHVDIEEDSPFLRALQRSFPQFEVEAKQVTDNDHA NARAFSHLASKLIETEVDPSDTILDIGSAPARRMYSKHKY HCICPMRCAEDPDRLYKYATKLKKNCKEITDKELDKKM KELAAVMSDPDLETETMCLHDDESCRYEGQVAVYQDV YAVDGPTSLYHQANKGVRVAYWIGFDTTPFMFKNLAGA YPSYSTNWADETVLTARNIGLCSSDVMERSRRGMSILRK KYLKPSNNVLFSVGSTIYHEKRDLLRSWHLPSVFHLRGK QNYTCRCETIVSCDGYVVKRIAISPGLYGKPSGYAATMH REGFLCCKVTDTLNGERVSFPVCTYVPATLCDQMTGILA TDVSADDAQKLLVGLNQRIVVNGRTQRNTNTMKNYLLP VVAQAFARWAKEYKEDQEDERPLGLRDRQLVMGCCWA FRRHKITSIYKRPDTQTIIKVNSDFHSFVLPRIGSNTLEIGL RTRIRKMLEEHKEPSPLITAEDVQEAKCAADEAKEVREA EELRAALPPLAADVEEPTLEADVDLMLQEAGAGSVETPR GLIKVTSYDGEDKIGSYAVLSPQAVLKSEKLSCIHPLAEQ VIVITHSGRKGRYAVEPYHGKVVVPEGHAIPVQDFQALS ESATIVYNEREFVNRYLHHIATHGGALNTDEEYYKTVKP SEHDGEYLYDIDRKQCVKKELVTGLGLTGELVDPPFHEF AYESLRTRPAAPYQVPTIGVYGVPGSGKSGIIKSAVTKKD LVVSAKKENCAEIIRDVKKMKGLDVNARTVDSVLLNGC KHPVETLYIDEAFACHAGTLRALIAIIRPKKAVLCGDPKQ CGFFNMMCLKVHFNHEICTQVFHKSISRRCTKSVTSVVS TLFYDKKMRTTNPKETKIVIDTTGSTKPKQDDLILTCFRG WVKQLQIDYKGNEIMTAAASQGLTRKGVYAVRYKVNE NPLYAPTSEHVNVLLTRTEDRIVWKTLAGDPWIKTLTAK YPGNFTATIEEWQAEHDAIMRHILERPDPTDVFQNKANV CWAKALVPVLKTAGIDMTTEQWNTVDYFETDKAHSAEI VLNQLCVRFFGLDLDSGLFSAPTVPLSIRNNHWDNSPSPN MYGLNKEVVRQLSRRYPQLPRAVATGRVYDMNTGTLR NYDPRINLVPVNRRLPHALVLHHNEHPQSDFSSFVSKLK GRTVLVVGEKLSVPGKMVDWLSDRPEATFRARLDLGIP GDVPKYDIIFVNVRTPYKYHHYQQCEDHAIKLSMLTKKA CLHLNPGGTCVSIGYGYADRASESIIGAIARLFKFSRVCKP KSSLEETEVLFVFIGYDRKARTHNPYKLSSTLTNIYTGSRL HEAGCAPSYHVVRGDIATATEGVIINAANSKGQPGGGVC GALYKKFPESFDLQPIEVGKARLVKGAAKHIIHAVGPNF NKVSEVEGDKQLAEAYESIAKIVNDNNYKSVAIPLLSTGI FSGNKDRLTQSLNHLLTALDTTDADVAIYCRDKKWEMT

Construct	Position	Sequence Type	Sequence
			LKEAVARREAVEEICISDDSSVTEPDAELVRVHPKSSLAG RKGYSTSDGKTFSYLEGTKFHQAAKDIAEINAMWPVATE ANEQVCMYILGESMSSIRSKCPVEESEASTPPSTLPCLCIH AMTPERVQRLKASRPEQITVCSSFPLPKYRITGVQKIQCS QPILFSPKVPAYIHPRKYLVETPPVDETPEPSAENQSTEGT PEQPPLITEDETRTRTPEPIIIEEEEEDSISLLSDGPTHQVLQ VEADIHGPPSVSSSSWSIPHASDFDVDSLSILDTLEGASVT SGATSAETNSYFAKSMEFLARPVPAPRTVFRNPPHPAPRT RTPSLAPSRACSRTSLVSTPPGVNRVITREELEALTPSRTP SRSVSRTSLVSNPPGVNRVITREEFEAFVAQQQRRFDAGA YIFSSDTGQGHLQQKSVRQTVLSEVVLERTELEISYAPRL DQEKEELLRKKLQLNPTPANRSRYQSRKVENMKAITARR ILQGLGHYLKAEGKVECYRTLHPVPLYSSSVNRAFSSPK VAVEACNAMLKENFPTVASYCIIPEYDAYLDMVDGASC CLDTASFCPAKLRSFPKKHSYLEPTIRSAVPSAIQNTLQNV LAAATKRNCNVTQMRELPVLDSAAFNVECFKKYACNNE YWETFKENPIRLTEENVVNYITKLKGPKAAALFAKTHNL NMLQDIPMDRFVMDLKRDVKVTPGTKHTEERPKVQVIQ AADPLATAYLCGIHRELVRRLNAVLLPNIHTLFDMSAED FDAIIAEHFQPGDCVLETDIASFDKSEDDAMALTALMILE DLGVDAELLTLIEAAFGEISSIHLPTKTKFKFGAMMKSGM FLTLFVNTVINIVIASRVLRERLTGSPCAAFIGDDNIVKGV KSDKLMADRCATWLNMEVKIIDAVVGEKAPYFCGGFIL CDSVTGTACRVADPLKRLFKLGKPLAADDEHDDDRRRA LHEESTRWNRVGILSELCKAVESRYETVGTSIIVMAMTTL ASSVKSFSYLRGAPITLYG*
Comparitive	intergenic region	nucleotide	unknown
Comparitive	3' UTR	nucleotide	unknown

Table 5: ORF of Peptide of Interest for Self-Replicating RNAs of the Disclosure

ORF Identity	Sequence Type	Sequence
2019-nCoV Spike gene (SEQ ID NO:117)	nucleotide	ATGTTTGTTTTTCTTGTTTTATTGCCACTAGTCTCTAGTCAGTGTGT TAATCTTACAACCAGAACTCAATTACCCCCTGCATACACTAATTC TTTCACACGTGGTGTTTATTACCCTGACAAAGTTTTCAGATCCTCA GTTTTACATTCAACTCAGGACTTGTTCTTACCTTTCTTTTCCAATGT TACTTGGTTCCATGCTATACATGTCTCTGGGACCAATGGTACTAA GAGGTTTGATAACCCTGTCCTACCATTTAATGATGGTGTTTATTTT GCTTCCACTGAGAAGTCTAACATAATAAGAGGCTGGATTTTTGGT ACTACTTTAGATTCGAAGACCCAGTCCCTACTTATTGTTAATAAC GCTACTAATGTTGTTATTAAAGTCTGTGAATTTCAATTTTGTAATG ATCCATTTTTGGGTGTTTATTACCACAAAAACAACAAAAGTTGGA TGGAAAGTGAGTTCAGAGTTTATTCTAGTGCGAATAATTGCACTT TTGAATATGTCTCTCAGCCTTTTCTTATGGACCTTGAAGGAAAAC AGGGTAATTTCAAAAATCTTAGGGAATTTGTGTTTAAGAATATTG ATGGTTATTTTAAAATATATTCTAAGCACACGCCTATTAATTTAGT GCGTGATCTCCCTCAGGGTTTTTCGGCTTTAGAACCATTGGTAGAT TTGCCAATAGGTATTAACATCACTAGGTTTCAAACTTTACTTGCTT TACATAGAAGTTATTTGACTCCTGGTGATTCTTCTTCAGGTTGGAC AGCTGGTGCTGCAGCTTATTATGTGGGTTATCTTCAACCTAGGAC TTTTCTATTAAAATATAATGAAAATGGAACCATTACAGATGCTGT AGACTGTGCACTTGACCCTCTCTCAGAAACAAAGTGTACGTTGAA ATCCTTCACTGTAGAAAAAGGAATCTATCAAACTTCTAACTTTAG AGTCCAACCAACAGAATCTATTGTTAGATTTCCTAATATTACAAA CTTGTGCCCTTTTGGTGAAGTTTTTAACGCCACCAGATTTGCATCT GTTTATGCTTGGAACAGGAAGAGAATCAGCAACTGTGTTGCTGAT TATTCTGTCCTATATAATTCCGCATCATTTTCCACTTTTAAGTGTT ATGGAGTGTCTCCTACTAAATTAAATGATCTCTGCTTTACTAATGT CTATGCAGATTCATTTGTAATTAGAGGTGATGAAGTCAGACAAAT CGCTCCAGGGCAAACTGGAAAGATTGCTGATTATAATTATAAATT ACCAGATGATTTTACAGGCTGCGTTATAGCTTGGAATTCTAACAA TCTTGATTCTAAGGTTGGTGGTAATTATAATTACCTGTATAGATTG TTTAGGAAGTCTAATCTCAAACCTTTTGAGAGAGATATTTCAACT GAAATCTATCAGGCCGGTAGCACACCTTGTAATGGTGTTGAAGGT

ORF Identity	Sequence Type	Sequence
		TTTAATTGTTACTTTCCTTTACAATCATATGGTTTCCAACCCACTA ATGGTGTTGGTTACCAACCATACAGAGTAGTAGTACTTTCTTTTG AACTTCTACATGCACCAGCAACTGTTTGTGGACCTAAAAAGTCTA CTAATTTGGTTAAAAACAAATGTGTCAATTTCAACTTCAATGGTTT AACAGGCACAGGTGTTCTTACTGAGTCTAACAAAAAGTTTCTGCC TTTCCAACAATTTGGCAGAGACATTGCTGACACTACTGATGCTGT CCGTGATCCACAGACACTTGAGATTCTTGACATTACACCATGTTC TTTTGGTGGTGTCAGTGTTATAACACCAGGAACAAATACTTCTAA CCAGGTTGCTGTTCTTTATCAGGATGTTAACTGCACAGAAGTCCC TGTTGCTATTCATGCAGATCAACTTACTCCTACTTGGCGTGTTTAT TCTACAGGTTCTAATGTTTTTCAAACACGTGCAGGCTGTTTAATAG GGGCTGAACATGTCAACAACTCATATGAGTGTGACATACCCATTG GTGCAGGTATATGCGCTAGTTATCAGACTCAGACTAATTCTCCTC GGCGGGCACGTAGTGTAGCTAGTCAATCCATCATTGCCTACACTA TGTCACTTGGTGCAGAAAATTCAGTTGCTTACTCTAATAACTCTAT TGCCATACCCACAAATTTTACTATTAGTGTTACCACAGAAATTCT ACCAGTGTCTATGACCAAGACATCAGTAGATTGTACAATGTACAT TTGTGGTGATTCAACTGAATGCAGCAATCTTTTGTTGCAATATGG CAGTTTTTGTACACAATTAAACCGTGCTTTAACTGGAATAGCTGTT GAACAAGACAAAAACACCCAAGAAGTTTTTGCACAAGTCAAACA AATTTACAAAACACCACCAATTAAAGATTTTGGTGGTTTTAATTTT TCACAAATATTACCAGATCCATCAAAACCAAGCAAGAGGTCATTT ATTGAAGATCTACTTTTCAACAAAGTGACACTTGCAGATGCTGGC TTCATCAAACAATATGGTGATTGCCTTGGTGATATTGCTGCTAGA GACCTCATTTGTGCACAAAAGTTTAACGGCCTTACTGTTTTGCCAC CTTTGCTCACAGATGAAATGATTGCTCAATACACTTCTGCACTGTT AGCGGGTACAATCACTTCTGGTTGGACCTTTGGTGCAGGTGCTGC ATTACAAATACCATTTGCTATGCAAATGGCTTATAGGTTTAATGG TATTGGAGTTACACAGAATGTTCTCTATGAGAACCAAAAATTGAT TGCCAACCAATTTAATAGTGCTATTGGCAAAATTCAAGACTCACT TTCTTCCACAGCAAGTGCACTTGGAAAACTTCAAGATGTGGTCAA CCAAAATGCACAAGCTTTAAACACGCTTGTTAAACAACTTAGCTC CAATTTTGGTGCAATTTCAAGTGTTTTAAATGATATCCTTTCACGT CTTGACAAAGTTGAGGCTGAAGTGCAAATTGATAGGTTGATCACA

ORF Identity	Sequence Type	Sequence
		GGCAGACTTCAAAGTTTGCAGACATATGTGACTCAACAATTAATT AGAGCTGCAGAAATCAGAGCTTCTGCTAATCTTGCTGCTACTAAA ATGTCAGAGTGTGTACTTGGACAATCAAAAAGAGTTGATTTTTGT GGAAAGGGCTATCATCTTATGTCCTTCCCTCAGTCAGCACCTCAT GGTGTAGTCTTCTTGCATGTGACTTATGTCCCTGCACAAGAAAAG AACTTCACAACTGCTCCTGCCATTTGTCATGATGGAAAAGCACAC TTTCCTCGTGAAGGTGTCTTTGTTTCAAATGGCACACACTGGTTTG TAACACAAAGGAATTTTTATGAACCACAAATCATTACTACAGACA ACACATTTGTGTCTGGTAACTGTGATGTTGTAATAGGAATTGTCA ACAACACAGTTTATGATCCTTTGCAACCTGAATTAGACTCATTCA AGGAGGAGTTAGATAAATATTTTAAGAATCATACATCACCAGATG TTGATTTAGGTGACATCTCTGGCATTAATGCTTCAGTTGTAAACAT TCAAAAAGAAATTGACCGCCTCAATGAGGTTGCCAAGAATTTAA ATGAATCTCTCATCGATCTCCAAGAACTTGGAAAGTATGAGCAGT ATATAAAATGGCCATGGTACATTTGGCTAGGTTTTATAGCTGGCT TGATTGCCATAGTAATGGTGACAATTATGCTTTGCTGTATGACCA GTTGCTGTAGTTGTCTCAAGGGCTGTTGTTCTTGTGGATCCTGCTG CAAATTTGATGAAGACGACTCTGAGCCAGTGCTCAAAGGAGTCA AATTACATTACACATAA

ORF Identity	Sequence Type	Sequence
2019-nCoV Spike gene (SEQ ID NO:118)	amino acid	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSV LHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFAS TEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLG VYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFK NLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITR FQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENG TITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNI TNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKC YGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLP DDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIY QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQF GRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQ DVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNS YECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAY SNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY GSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFS QILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICA QKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALG KLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQI DRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGK AHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVN NTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKE IDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVM VTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT*

ORF Identity	Sequence Type	Sequence
2019-nCoV Spike gene (SEQ ID NO:119)	nucleotide	ATGTTCGTCTTCCTGGTCCTGCTGCCTCTGGTCTCCTCACAGTGCG TCAATCTGACAACTCGGACTCAGCTGCCACCTGCTTATACTAATA GCTTCACCAGAGGCGTGTACTATCCTGACAAGGTGTTTAGAAGCT CCGTGCTGCACTCTACACAGGATCTGTTTCTGCCATTCTTTAGCAA CGTGACCTGGTTCCACGCCATCCACGTGAGCGGCACCAATGGCAC AAAGCGGTTCGACAATCCCGTGCTGCCTTTTAACGATGGCGTGTA CTTCGCCTCTACCGAGAAGAGCAACATCATCAGAGGCTGGATCTT TGGCACCACACTGGACTCCAAGACACAGTCTCTGCTGATCGTGAA CAATGCCACCAACGTGGTCATCAAGGTGTGCGAGTTCCAGTTTTG TAATGATCCCTTCCTGGGCGTGTACTATCACAAGAACAATAAGAG CTGGATGGAGTCCGAGTTTAGAGTGTATTCTAGCGCCAACAACTG CACATTTGAGTACGTGAGCCAGCCTTTCCTGATGGACCTGGAGGG CAAGCAGGGCAATTTCAAGAACCTGAGGGAGTTCGTGTTTAAGA ATATCGACGGCTACTTCAAAATCTACTCTAAGCACACCCCCATCA ACCTGGTGCGCGACCTGCCTCAGGGCTTCAGCGCCCTGGAGCCCC TGGTGGATCTGCCTATCGGCATCAACATCACCCGGTTTCAGACAC TGCTGGCCCTGCACAGAAGCTACCTGACACCCGGCGACTCCTCTA GCGGATGGACCGCCGGCGCTGCCGCCTACTATGTGGGCTACCTCC AGCCCCGGACCTTCCTGCTGAAGTACAACGAGAATGGCACCATCA CAGACGCAGTGGATTGCGCCCTGGACCCCCTGAGCGAGACAAAG TGTACACTGAAGTCCTTTACCGTGGAGAAGGGCATCTATCAGACA TCCAATTTCAGGGTGCAGCCAACCGAGTCTATCGTGCGCTTTCCT AATATCACAAACCTGTGCCCATTTGGCGAGGTGTTCAACGCAACC CGCTTCGCCAGCGTGTACGCCTGGAATAGGAAGCGGATCAGCAA CTGCGTGGCCGACTATAGCGTGCTGTACAACTCCGCCTCTTTCAG CACCTTTAAGTGCTATGGCGTGTCCCCCACAAAGCTGAATGACCT GTGCTTTACCAACGTCTACGCCGATTCTTTCGTGATCAGGGGCGA CGAGGTGCGCCAGATCGCCCCCGGCCAGACAGGCAAGATCGCAG ACTACAATTATAAGCTGCCAGACGATTTCACCGGCTGCGTGATCG CCTGGAACAGCAACAATCTGGATTCCAAAGTGGGCGGCAACTAC AATTATCTGTACCGGCTGTTTAGAAAGAGCAATCTGAAGCCCTTC GAGAGGGACATCTCTACAGAAATCTACCAGGCCGGCAGCACCCC TTGCAATGGCGTGGAGGGCTTTAACTGTTATTTCCCACTCCAGTCC TACGGCTTCCAGCCCACAAACGGCGTGGGCTATCAGCCTTACCGC

ORF Identity	Sequence Type	Sequence
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		GAACTTCAACTTCAACGGCCTGACCGGCACAGGCGTGCTGACCGA
		GTCCAACAAGAAGTTCCTGCCATTTCAGCAGTTCGGCAGGGACAT
		CGCAGATACCACAGACGCCGTGCGCGACCCACAGACCCTGGAGA
		TCCTGGACATCACACCCTGCTCTTTCGGCGGCGTGAGCGTGATCA
		CACCCGGCACCAATACAAGCAACCAGGTGGCCGTGCTGTATCAG
		GACGTGAATTGTACCGAGGTGCCCGTGGCTATCCACGCCGATCAG
		CTGACCCCAACATGGCGGGTGTACAGCACCGGCTCCAACGTCTTC
		CAGACAAGAGCCGGATGCCTGATCGGAGCAGAGCACGTGAACAA
		TTCCTATGAGTGCGACATCCCAATCGGCGCCGGCATCTGTGCCTC
		TTACCAGACCCAGACAAACTCTCCCAGAAGAGCCCGGAGCGTGG
		CCTCCCAGTCTATCATCGCCTATACCATGTCCCTGGGCGCCGAGA
		ACAGCGTGGCCTACTCTAACAATAGCATCGCCATCCCAACCAACT
		TCACAATCTCTGTGACCACAGAGATCCTGCCCGTGTCCATGACCA
		AGACATCTGTGGACTGCACAATGTATATCTGTGGCGATTCTACCG
		AGTGCAGCAACCTGCTGCTCCAGTACGGCAGCTTTTGTACCCAGC
		TGAATAGAGCCCTGACAGGCATCGCCGTGGAGCAGGATAAGAAC
		ACACAGGAGGTGTTCGCCCAGGTGAAGCAAATCTACAAGACCCC
		CCCTATCAAGGACTTTGGCGGCTTCAATTTTTCCCAGATCCTGCCT
		GATCCATCCAAGCCTTCTAAGCGGAGCTTTATCGAGGACCTGCTG
		TTCAACAAGGTGACCCTGGCCGATGCCGGCTTCATCAAGCAGTAT
		GGCGATTGCCTGGGCGACATCGCAGCCAGGGACCTGATCTGCGCC
		CAGAAGTTTAATGGCCTGACCGTGCTGCCACCCCTGCTGACAGAT
		GAGATGATCGCACAGTACACAAGCGCCCTGCTGGCCGGCACCAT
		CACATCCGGATGGACCTTCGGCGCAGGAGCCGCCCTCCAGATCCC
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		CCAGAATGTGCTGTACGAGAACCAGAAGCTGATCGCCAATCAGTT
		TAACTCCGCCATCGGCAAGATCCAGGACAGCCTGTCCTCTACAGC
		CAGCGCCCTGGGCAAGCTCCAGGATGTGGTGAATCAGAACGCCC
		AGGCCCTGAATACCCTGGTGAAGCAGCTGAGCAGCAACTTCGGC
		GCCATCTCTAGCGTGCTGAATGACATCCTGAGCCGGCTGGACAAG
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ORF Identity	Sequence Type	Sequence
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ORF Identity	Sequence Type	Sequence
2019-nCoV Spike gene (SEQ ID NO:120)	amino acid	MFVFLVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSV LHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFAS TEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLG VYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFK NLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITR FQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENG TITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNI TNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKC YGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLP DDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIY QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLH APATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQF GRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQ DVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNS YECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAY SNNSIAIPTNFTISVTTEILPVSMTKTSVDCTMYICGDSTECSNLLLQY GSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFS QILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICA QKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA MQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALG KLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLDKVEAEVQI DRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRV DFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGK AHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVN NTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKE IDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVM VTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT*

[0266] RNA sequences can include any combination of the RNA sequences listed in Tables 4 and 5. In some embodiments, RNA sequences of the present disclosure include any combination of the RNA sequences listed in Tables 4 and 5 in which 0% to 100%, 1% to 100%, 25% to 100%, 50% to 100% and 75% to 100% of the uracil nucleotides of the mRNA sequences are modified. In some embodiments, 1% to 100% of the uracil nucleotides are N1-methylpseudouridine or 5-methoxyuridine. In some embodiments,100% of the uracil

nucleotides are N1-methylpseudouridine. In some embodiments, 100% of the uracil nucleotides are 5-methoxyuridine.

[0267] A self-replicating RNA of the disclosure may be obtained by any suitable means. Methods for the manufacture of self-replicating RNA are known in the art and would be readily apparent to a person of ordinary skill. A self-replicating RNA of the disclosure may be prepared according to any available technique including, but not limited to chemical synthesis, in vitro transcription (IVT) or enzymatic or chemical cleavage of a longer precursor, etc.

[0268] In some embodiments, a self-replicating RNA of the disclosure is produced from a primary complementary DNA (cDNA) construct. The cDNA constructs can be produced on an RNA template by the action of a reverse transcriptase (e.g., RNA-dependent DNA-polymerase). The process of design and synthesis of the primary cDNA constructs described herein generally includes the steps of gene construction, RNA production (either with or without modifications) and purification. In the IVT method, a target polynucleotide sequence encoding a self-replicating RNA of the disclosure 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 a self-replicating RNA of the disclosure through in vitro transcription (IVT). After production, the self-replicating RNA of the disclosure may undergo purification and clean-up processes. The steps of which are provided in more detail below.

[0269] 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. Once a protein of interest 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.

[0270] The cDNA templates may be transcribed to produce a self-replicating RNA of the disclosure 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 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.

[0271] The primary cDNA template or transcribed RNA sequence 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, Mass.) or capping at initiation of in vitro transcription, by for example, including a capping agent as part of the IVT reaction. (Nuc. Acids Symp. (2009) 53:129). 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.

[0272] Codon optimized cDNA constructs encoding the non-structural proteins and the transgene for a self-replicating RNA protein are particularly suitable for generating self-replicating RNA sequences described herein. For example, such cDNA constructs may be used as the basis to transcribe, in vitro, a polyribonucleotide encoding a protein of interest as part of a self-replicating RNA.

[0273] The present disclosure also provides expression vectors comprising a nucleotide sequence encoding a self-replicating RNA that is preferably operably linked to at least one regulatory sequence. Regulatory sequences are art-recognized and are selected to direct expression of the encoded polypeptide.

[0274] Accordingly, the term regulatory sequence includes promoters, enhancers, and other expression control elements. The design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed.

[0275] The present disclosure also provides polynucleotides (e.g. DNA, RNA, cDNA, mRNA, etc.) directed to a self-replicating RNA of the disclosure that may be operably linked to one or more regulatory nucleotide sequences in an expression construct, such as a vector or plasmid. In certain embodiments, such constructs are DNA constructs. Regulatory nucleotide

sequences will generally be appropriate for a host cell used for expression. Numerous types of appropriate expression vectors and suitable regulatory sequences are known in the art for a variety of host cells.

[0276] Typically, said one or more regulatory nucleotide sequences may include, but are not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and termination sequences, translational start and termination sequences, and enhancer or activator sequences. Constitutive or inducible promoters as known in the art are contemplated by the embodiments of the present disclosure. The promoters may be either naturally occurring promoters, or hybrid promoters that combine elements of more than one promoter.

[0277] An expression construct may be present in a cell on an episome, such as a plasmid, or the expression construct may be inserted in a chromosome. In some embodiments, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selectable marker genes are well known in the art and will vary with the host cell used.

[0278] The present disclosure also provides a host cell transfected with a self-replicating RNA or DNA described herein. The self-replicating RNA or DNA can encode any coronavirus protein of interest, for example an antigen, including the S-antigen of the COVID-19 virus. The host cell may be any prokaryotic or eukaryotic cell. For example, a polypeptide encoded by a self-replicating RNA may be expressed in bacterial cells such as E. coli, insect cells (e.g., using a baculovirus expression system), yeast, or mammalian cells. Other suitable host cells are known to those skilled in the art.

[0279] A host cell transfected with an expression vector comprising a self-replicating RNA of the disclosure can be cultured under appropriate conditions to allow expression of the amplification of the self-replicating RNA and translation of the polypeptide to occur. The polypeptide may be secreted and isolated from a mixture of cells and medium containing the polypeptides. Alternatively, the polypeptides may be retained in the cytoplasm or in a membrane fraction and the cells harvested, lysed and the protein isolated. A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art.

[0280] The expressed proteins described herein can be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins, including ion-

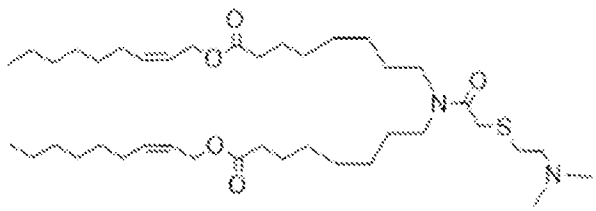
exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for particular epitopes of the polypeptide.

Compositions and Pharmaceutical Compositions

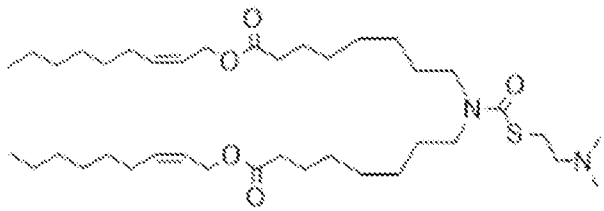
[0281] Provided herein, in some embodiments, are compositions comprising any of the nucleic acid molecules provided herein. Compositions provided herein can include a lipid. Any lipid can be included in compositions provided herein. In one aspect, the lipid is an ionizable cationic lipid. Any ionizable cationic lipid can be included in compositions comprising nucleic acid molecules provided herein.

[0282] The compositions and polynucleotides of the present disclosure may be used to immunize or vaccinate a subject against a viral infection. In some embodiments, the compositions and polynucleotides of the present disclosure may be used to vaccinate or immunize a subject against COVID-19 virus.

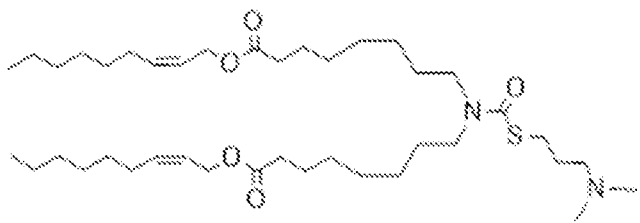
[0283] Also provided herein, in some embodiments, are pharmaceutical compositions comprising any of the nucleic acid molecules provided herein and a lipid formulation. Any lipid can be included in lipid formulations of pharmaceutical compositions provided herein. In one aspect, lipid formulations of pharmaceutical compositions provided herein include an ionizable cationic lipid. Exemplary ionizable cationic lipids of compositions and pharmaceutical compositions provided herein include the following:



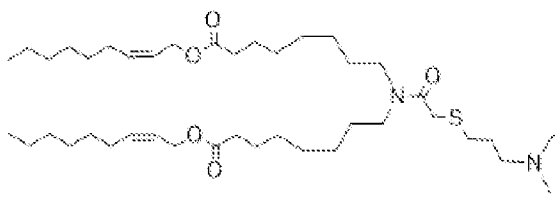
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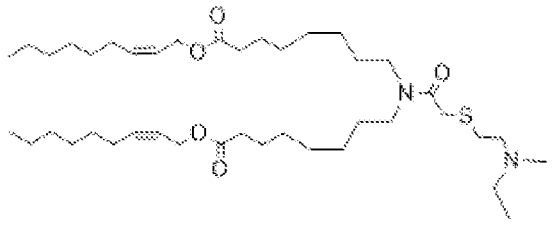
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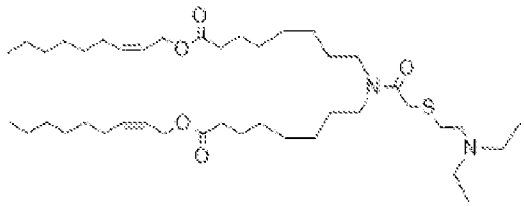
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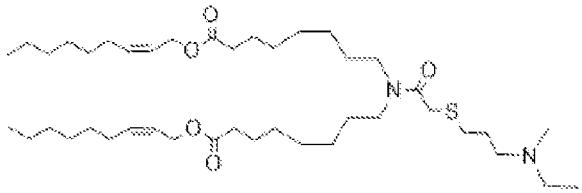
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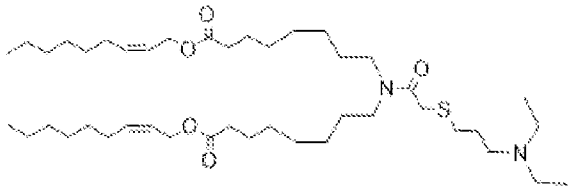
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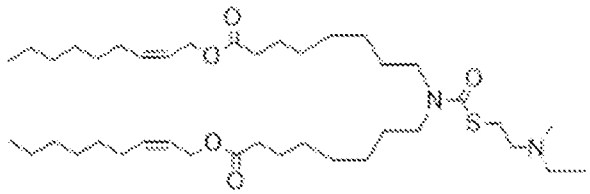
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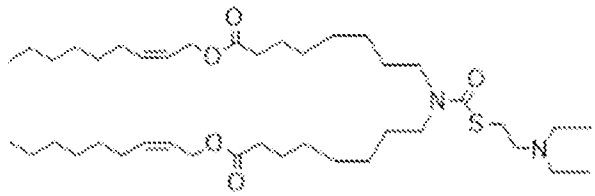
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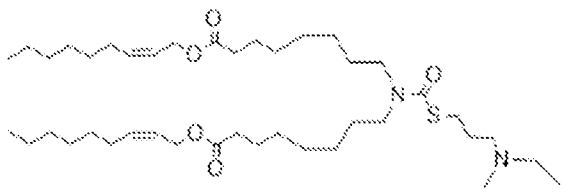
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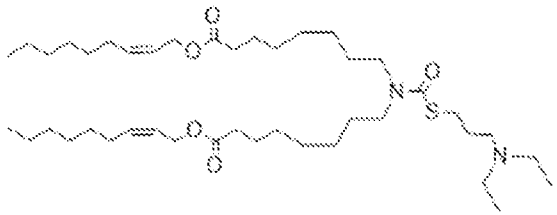
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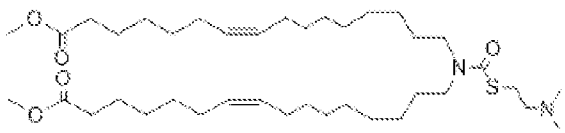
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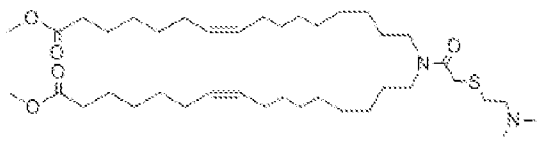
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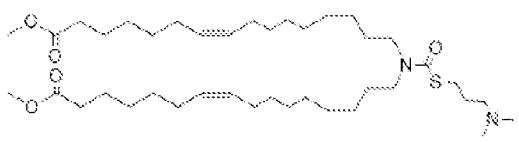
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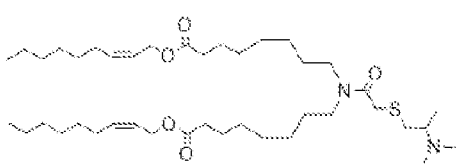
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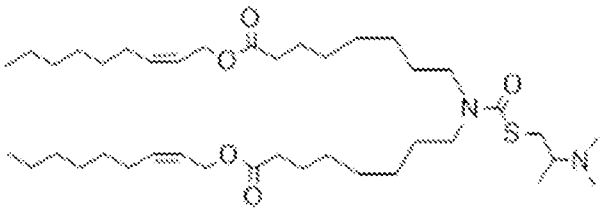
ATX-014

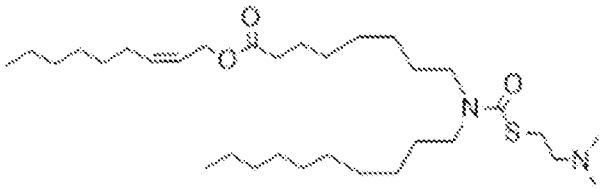


ATX-015

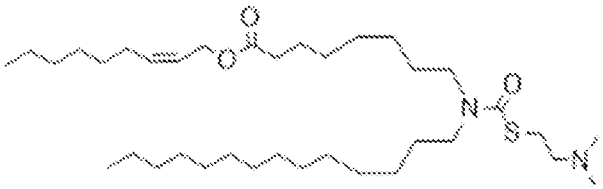


ATX-016

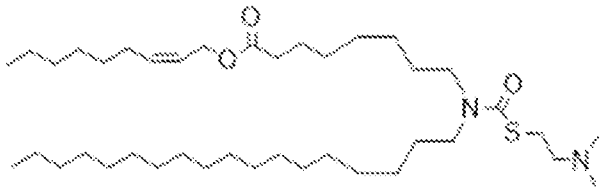




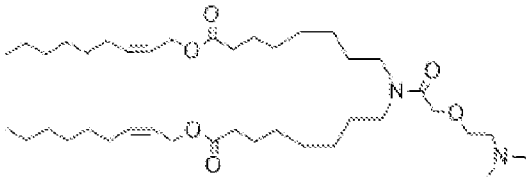
ATX-018



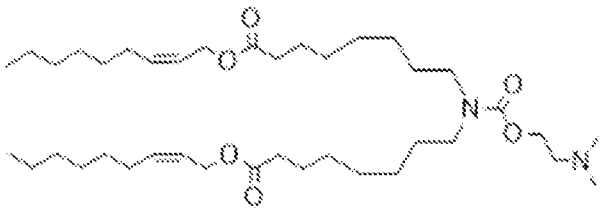
ATX-019



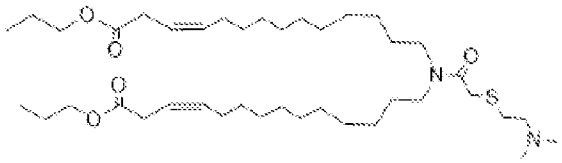
ATX-020



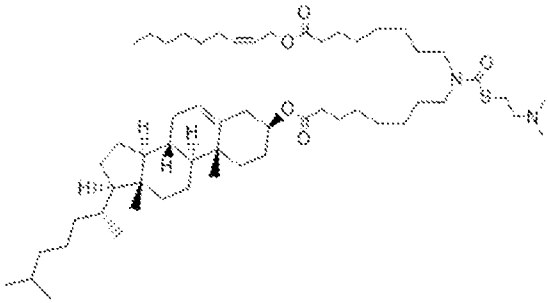
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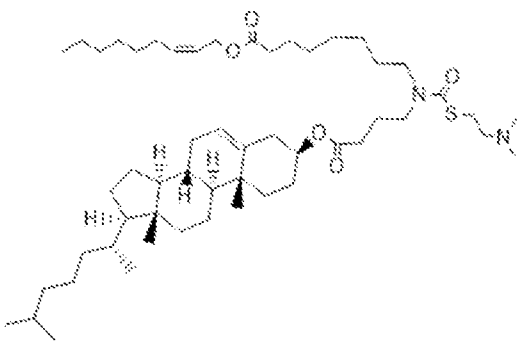
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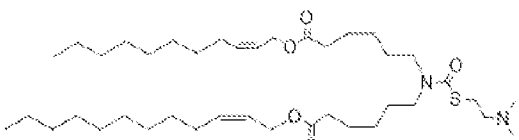
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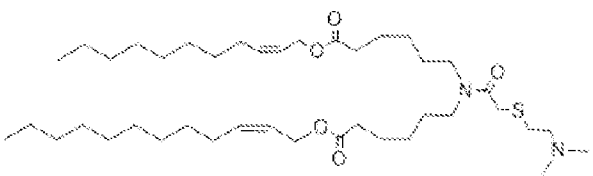
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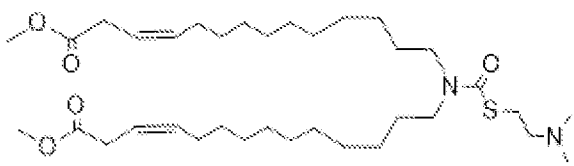


ATX-025

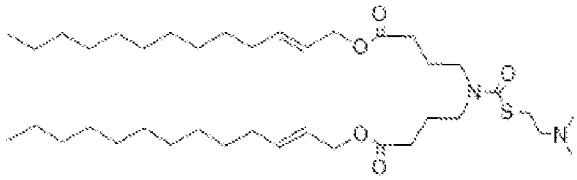


ATX-026

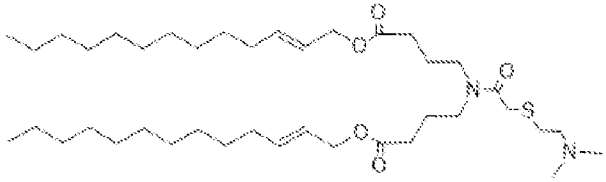




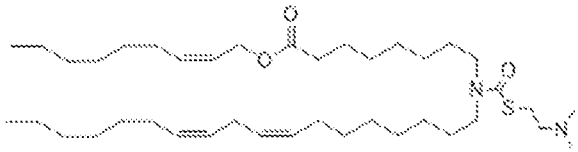
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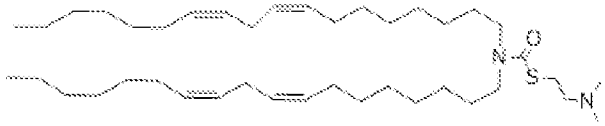
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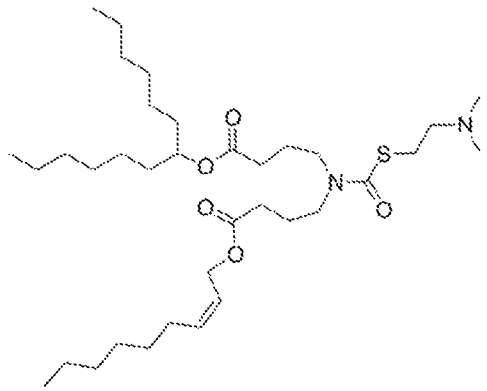
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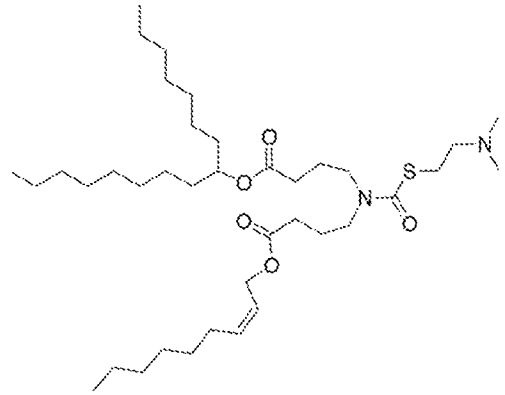
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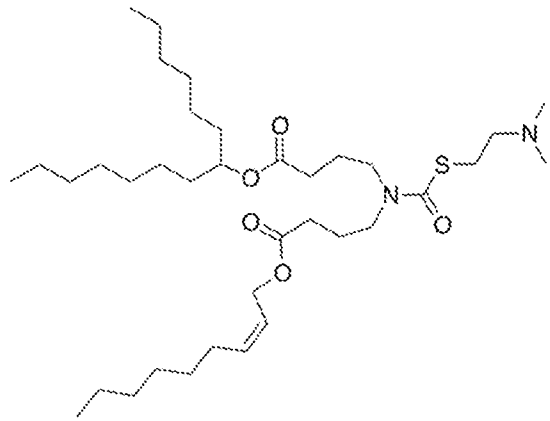
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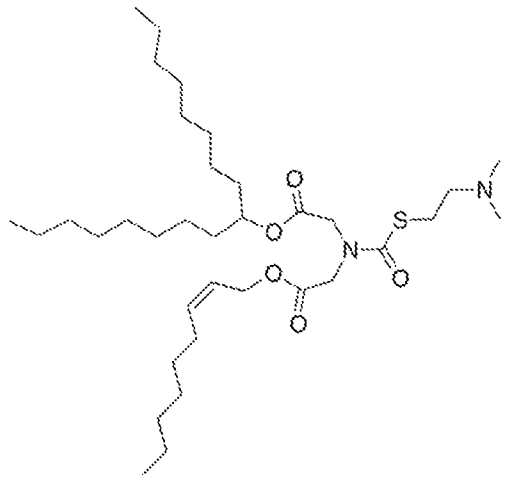
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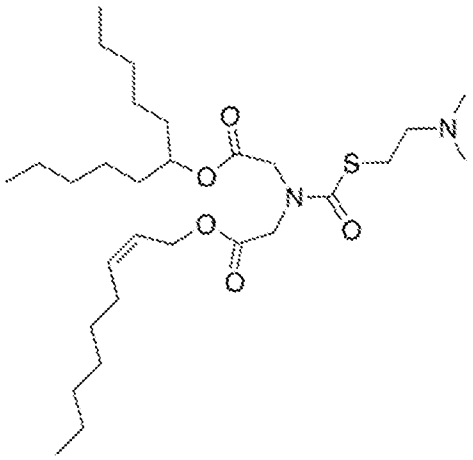
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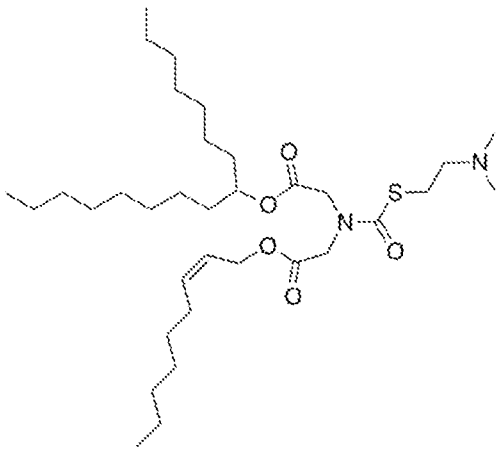
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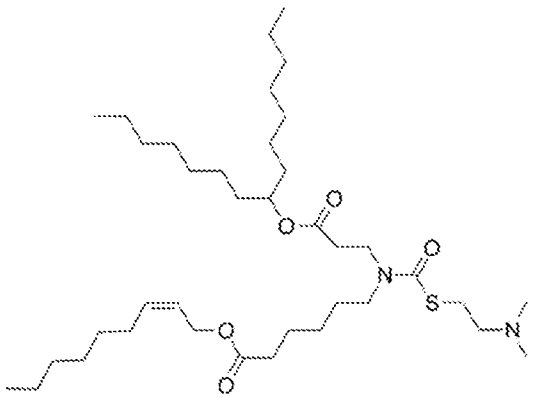
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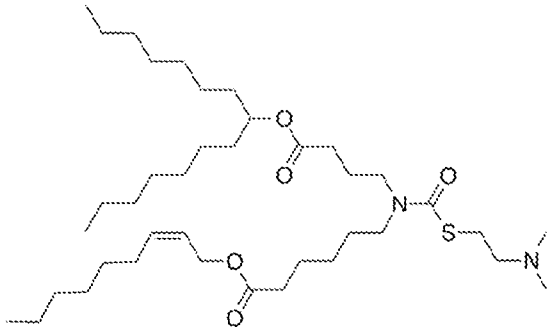
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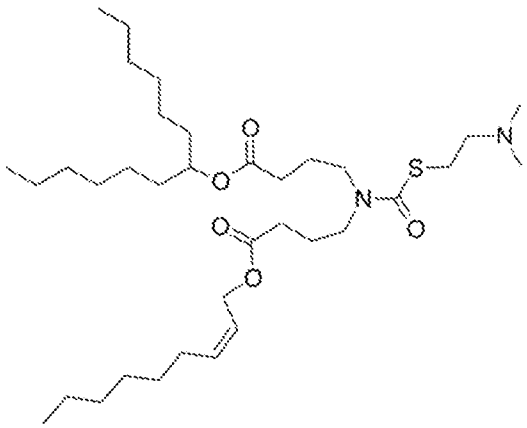
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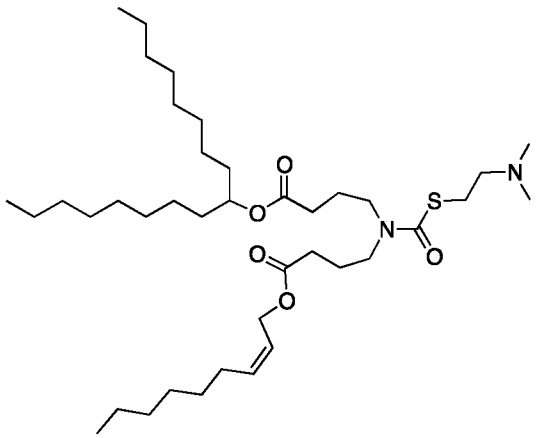
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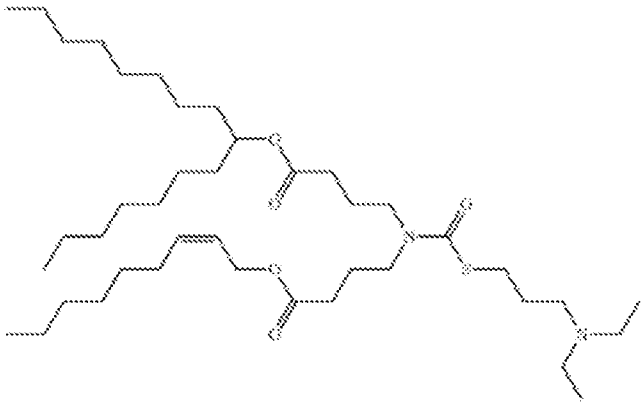
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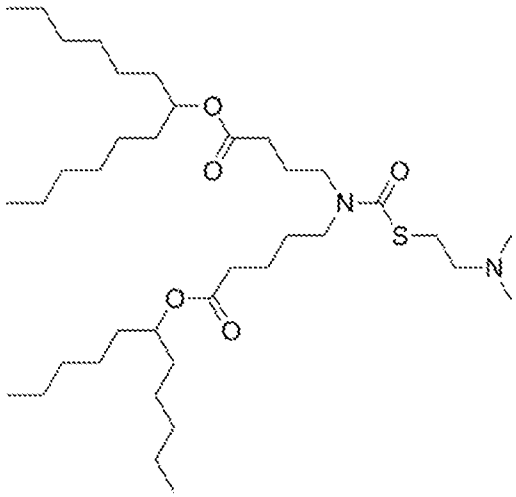
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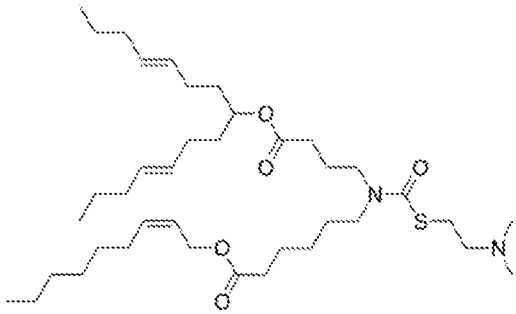
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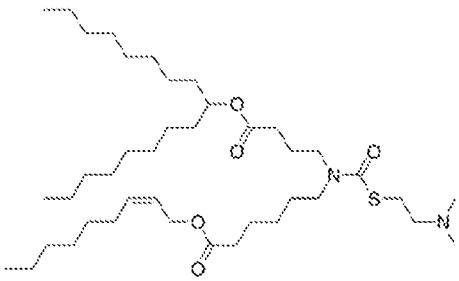
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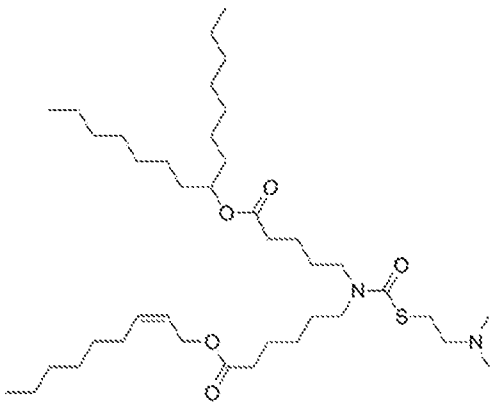
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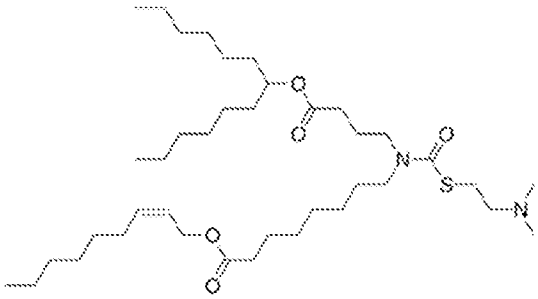
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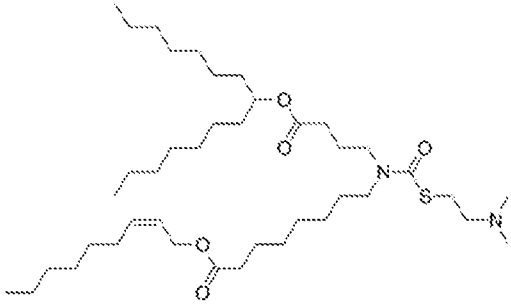
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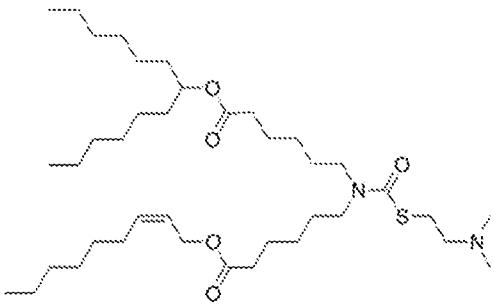
ATX-0102



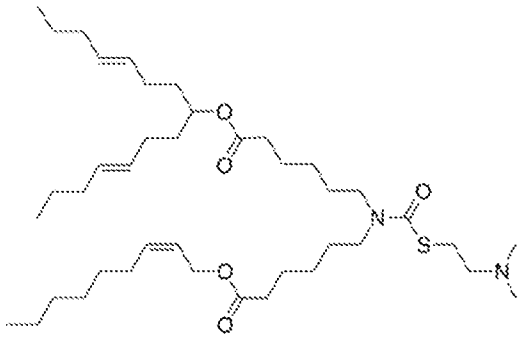
ATX-098



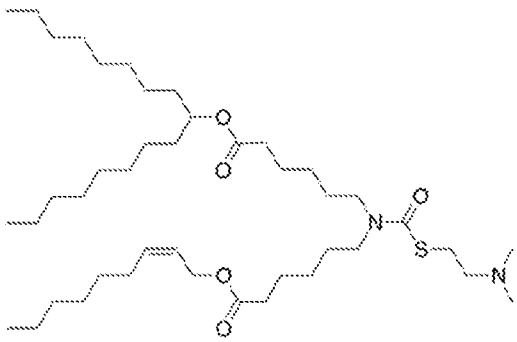
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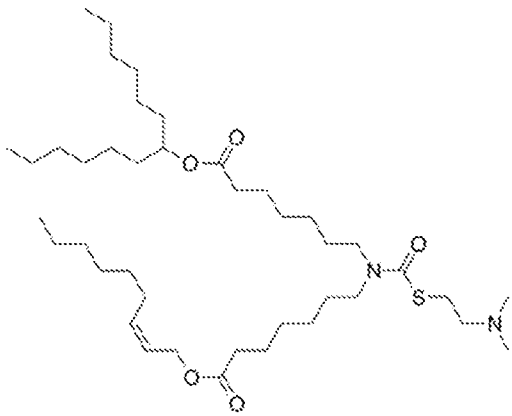
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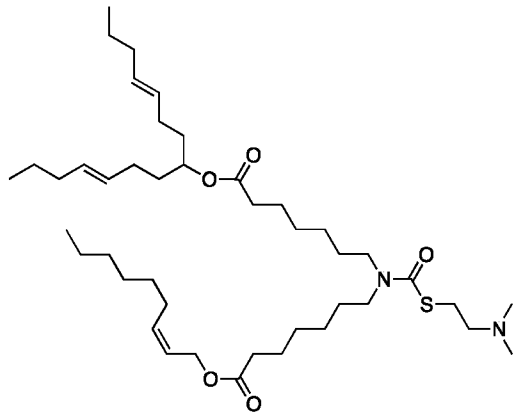
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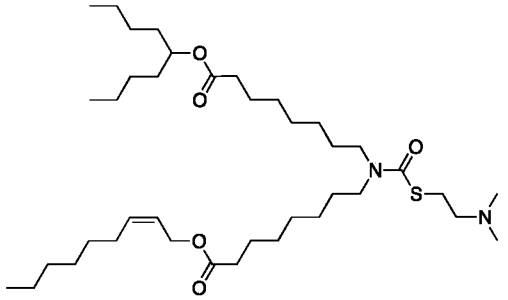
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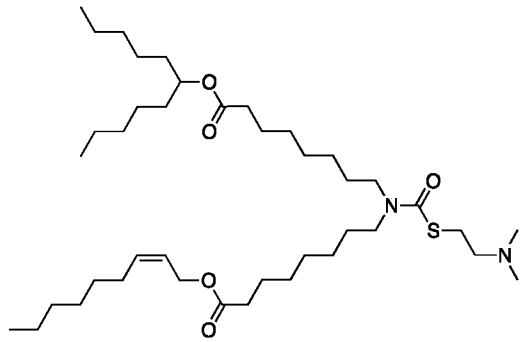
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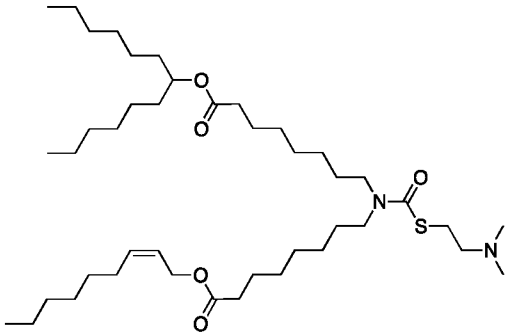
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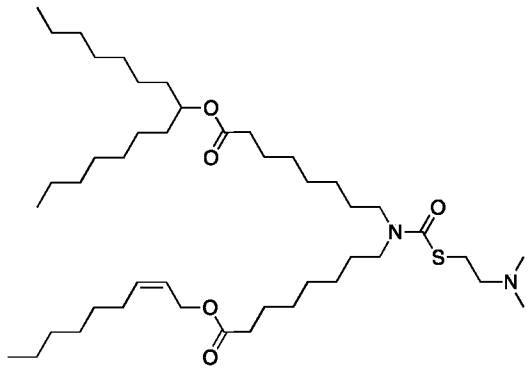
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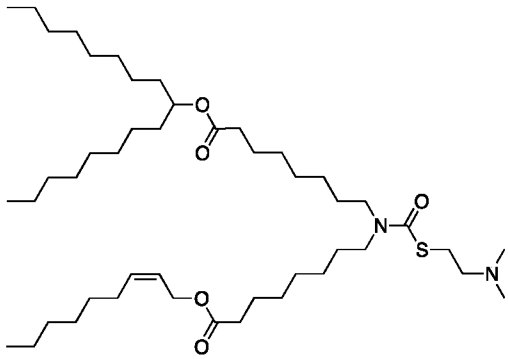
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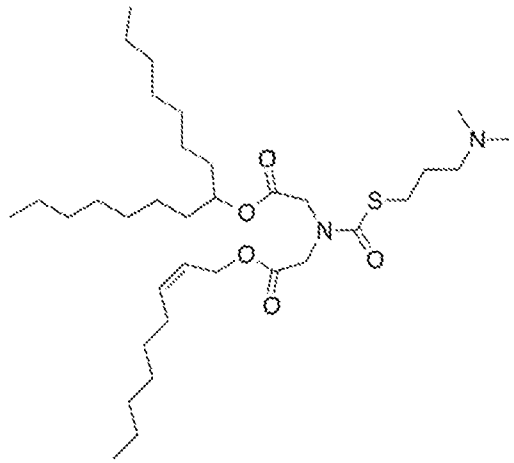
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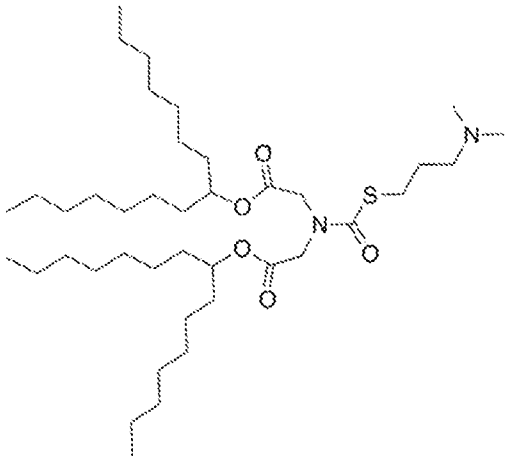


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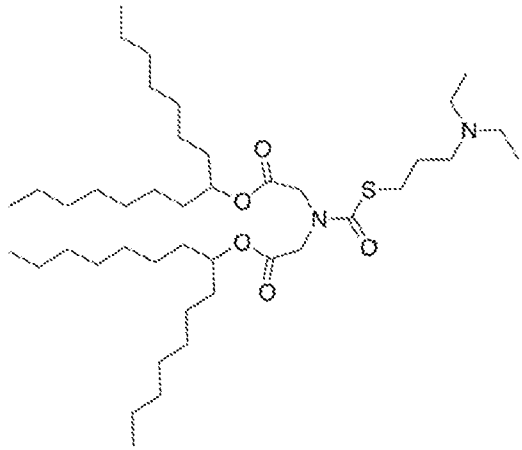


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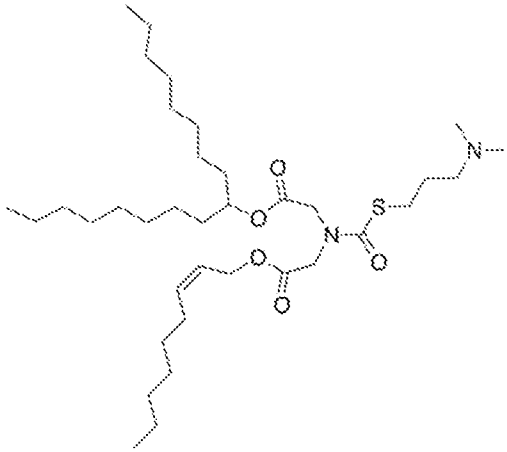




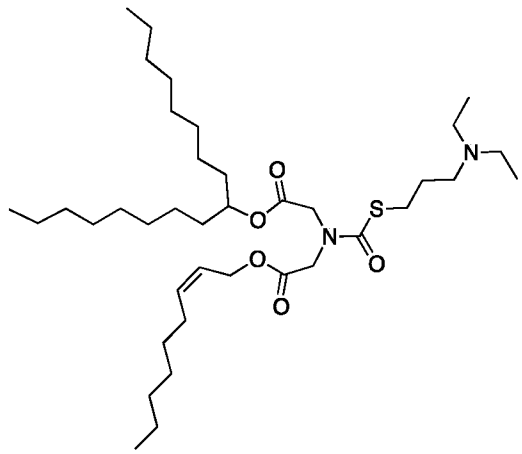
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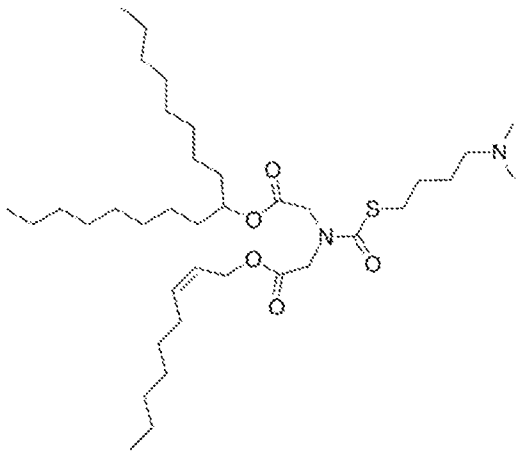
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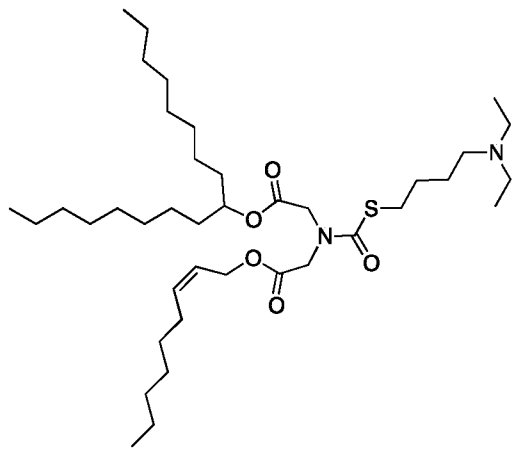
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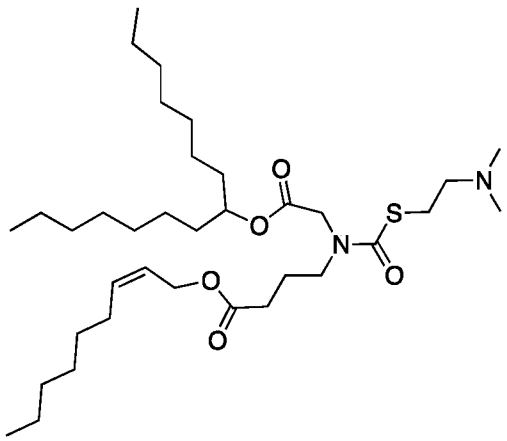
ATX-0100



ATX-0117

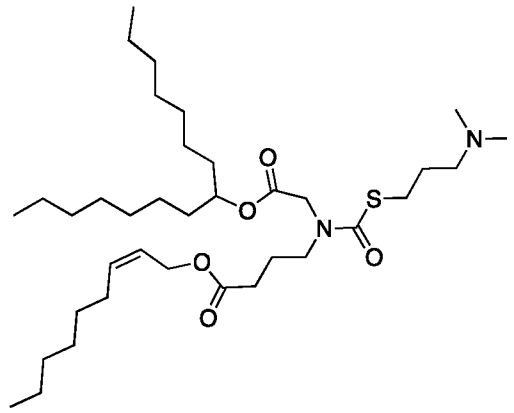


ATX-0114

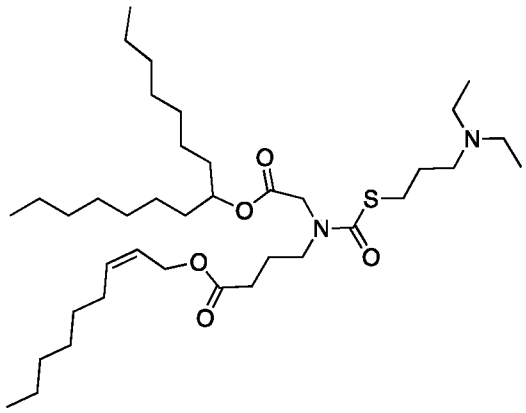


ATX-0115

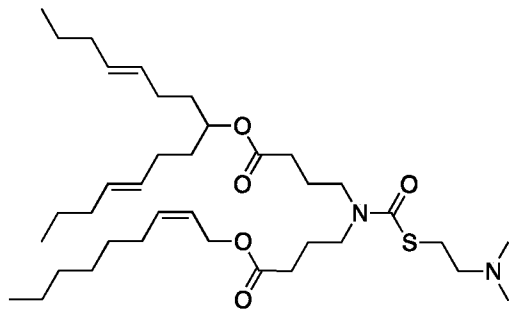
ATX-0101



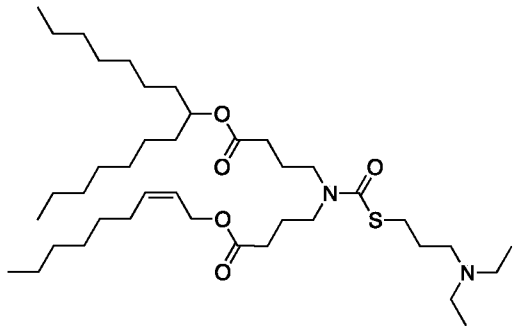
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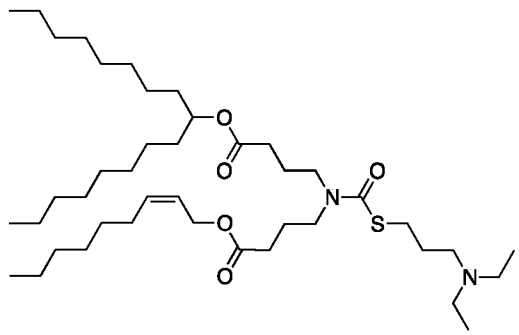
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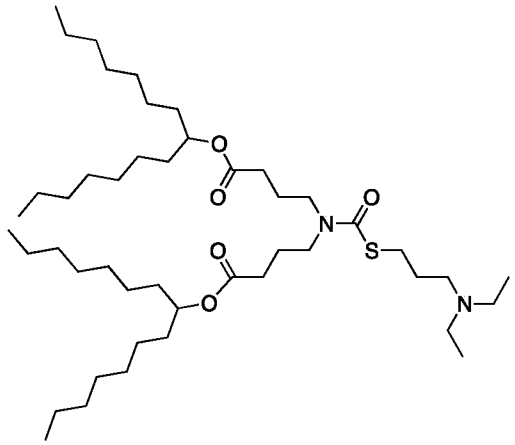
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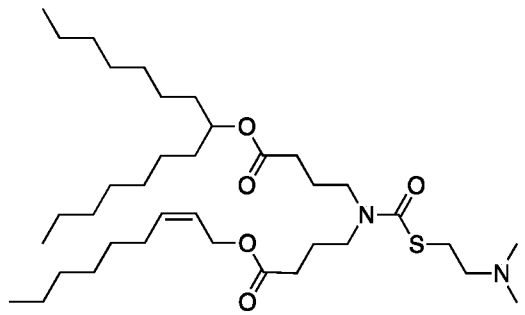
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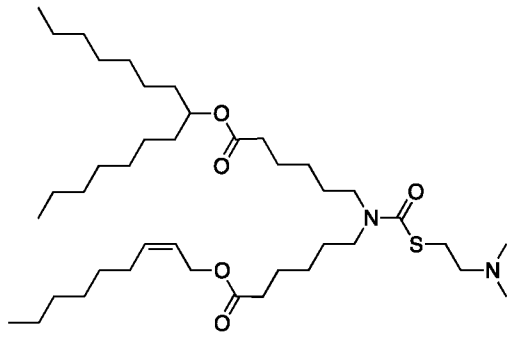
ATX-0124



ATX-0129

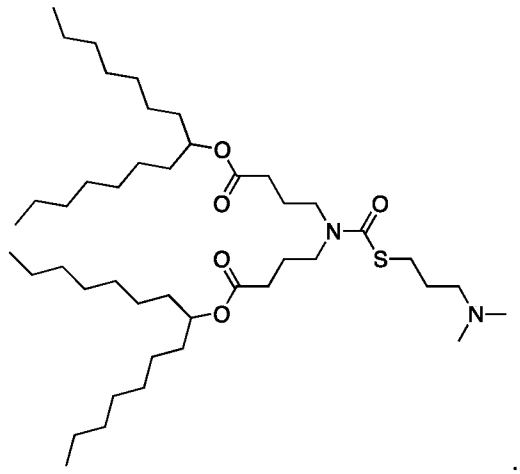


ATX-081



and

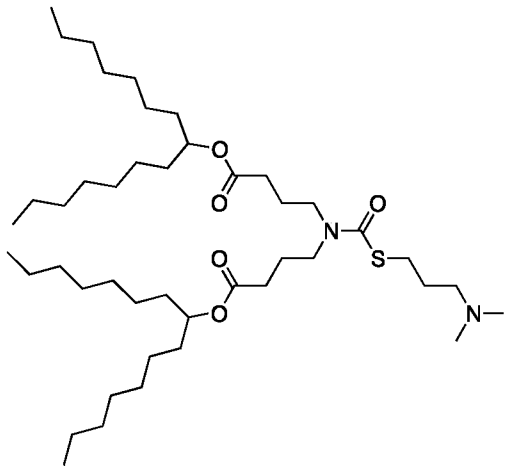
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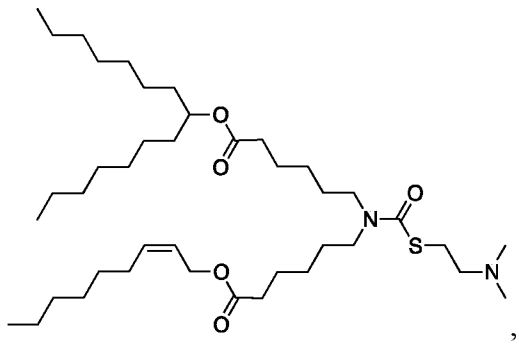
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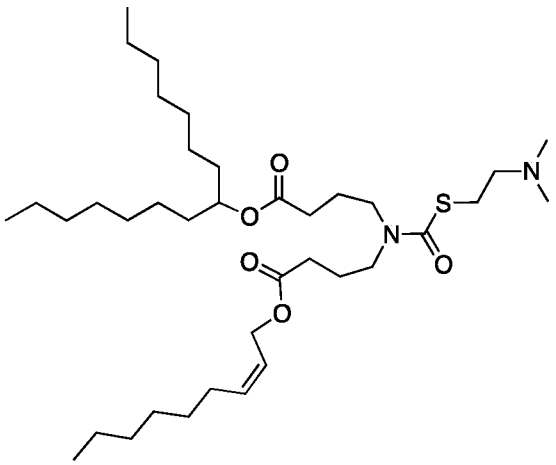
[0284] In one aspect, the ionizable cationic lipid of compositions provided herein has a structure of



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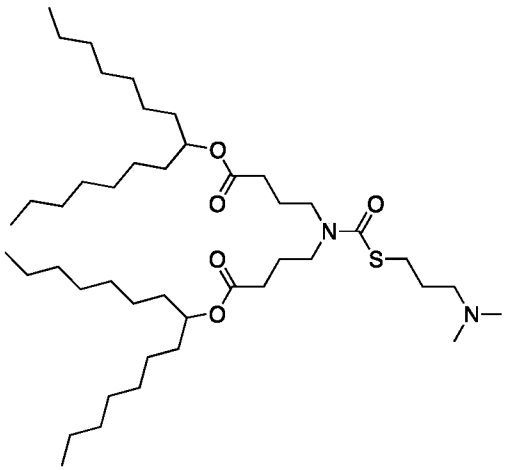


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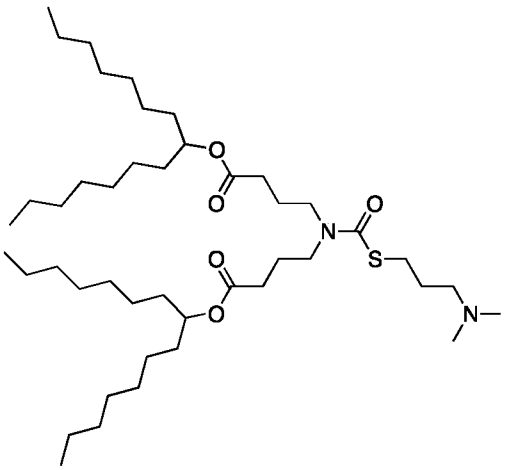
, or a pharmaceutically acceptable salt thereof.

[0285] In another aspect, the ionizable cationic lipid of compositions provided herein has a structure of

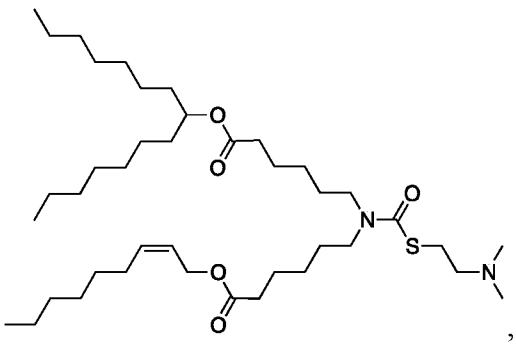


, or a pharmaceutically acceptable salt thereof.

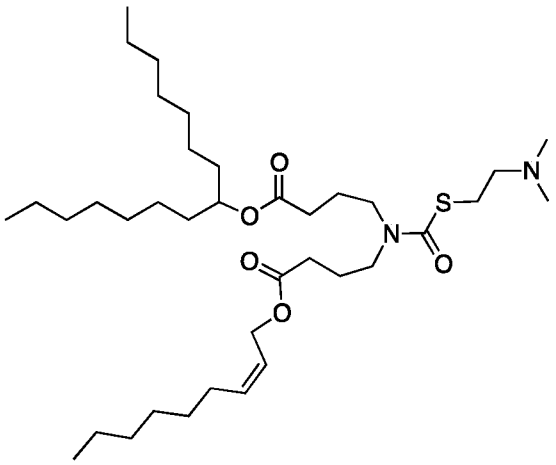
[0286] In one aspect, the ionizable cationic lipid included in lipid formulations of pharmaceutical compositions provided herein has a structure of



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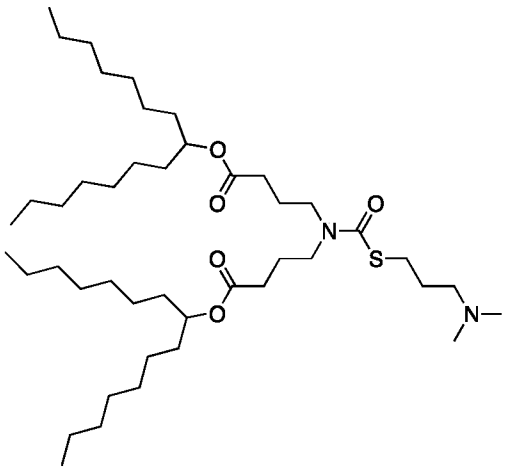


,



, or a pharmaceutically acceptable salt thereof.

[0287] In another aspect, the ionizable cationic lipid included in lipid formulations of pharmaceutical compositions provided herein has a structure of



, or a pharmaceutically acceptable salt thereof.

Lipid Formulations/LNPs

[0288] Therapies based on the intracellular delivery of nucleic acids to target cells face both extracellular and intracellular barriers. Indeed, naked nucleic acid materials cannot be easily systemically administered due to their toxicity, low stability in serum, rapid renal clearance, reduced uptake by target cells, phagocyte uptake and their ability in activating the immune response, all features that preclude their clinical development. When exogenous nucleic acid material (e.g., mRNA) enters the human biological system, it is recognized by the reticuloendothelial system (RES) as foreign pathogens and cleared from blood circulation before having the chance to encounter target cells within or outside the vascular system. It has been reported that the half-life of naked nucleic acid in the blood stream is around several minutes (Kawabata K, Takakura Y, Hashida MPharm Res. 1995 Jun; 12(6):825-30). Chemical

modification and a proper delivery method can reduce uptake by the RES and protect nucleic acids from degradation by ubiquitous nucleases, which increase stability and efficacy of nucleic acid-based therapies. In addition, RNAs or DNAs are anionic hydrophilic polymers that are not favorable for uptake by cells, which are also anionic at the surface. The success of nucleic acid-based therapies thus depends largely on the development of vehicles or vectors that can efficiently and effectively deliver genetic material to target cells and obtain sufficient levels of expression in vivo with minimal toxicity.

[0289] Moreover, upon internalization into a target cell, nucleic acid delivery vectors are challenged by intracellular barriers, including endosome entrapment, lysosomal degradation, nucleic acid unpacking from vectors, translocation across the nuclear membrane (for DNA), release at the cytoplasm (for RNA), and so on. Successful nucleic acid-based therapy thus depends upon the ability of the vector to deliver the nucleic acids to the target sites inside of the cells in order to obtain sufficient levels of a desired activity such as expression of a gene.

[0290] While several gene therapies have been able to successfully utilize a viral delivery vector (e.g., AAV), lipid-based formulations have been increasingly recognized as one of the most promising delivery systems for RNA and other nucleic acid compounds due to their biocompatibility and their ease of large-scale production. One of the most significant advances in lipid-based nucleic acid therapies happened in August 2018 when Patisiran (ALN-TTR02) was the first siRNA therapeutic approved by the Food and Drug Administration (FDA) and by the European Commission (EC). ALN-TTR02 is an siRNA formulation based upon the so-called Stable Nucleic Acid Lipid Particle (SNALP) transfecting technology. Despite the success of Patisiran, the delivery of nucleic acid therapeutics, including mRNA, via lipid formulations is still under ongoing development.

[0291] Some art-recognized lipid-formulated delivery vehicles for nucleic acid therapeutics include, according to various embodiments, polymer based carriers, such as polyethyleneimine (PEI), lipid nanoparticles and liposomes, nanoliposomes, ceramide-containing nanoliposomes, multivesicular liposomes, proteoliposomes, both natural and synthetically-derived exosomes, natural, synthetic and semi-synthetic lamellar bodies, nanoparticulates, micelles, and emulsions. These lipid formulations can vary in their structure and composition, and as can be expected in a rapidly evolving field, several different terms have been used in the art to describe a single type of delivery vehicle. At the same time, the terms for lipid formulations have varied as to their intended meaning throughout the scientific literature, and this inconsistent use has

caused confusion as to the exact meaning of several terms for lipid formulations. Among the several potential lipid formulations, liposomes, cationic liposomes, and lipid nanoparticles are specifically described in detail and defined herein for the purposes of the present disclosure.

Liposomes

[0292] Conventional liposomes are vesicles that consist of at least one bilayer and an internal aqueous compartment. Bilayer membranes of liposomes are typically formed by amphiphilic molecules, such as lipids of synthetic or natural origin that comprise spatially separated hydrophilic and hydrophobic domains (Lasic, Trends Biotechnol., 16: 307-321, 1998). Bilayer membranes of the liposomes can also be formed by amphiphilic polymers and surfactants (e.g., polymerosomes, niosomes, etc.). They generally present as spherical vesicles and can range in size from 20 nm to a few microns. Liposomal formulations can be prepared as a colloidal dispersion or they can be lyophilized to reduce stability risks and to improve the shelf-life for liposome-based drugs. Methods of preparing liposomal compositions are known in the art and would be within the skill of an ordinary artisan.

[0293] Liposomes that have only one bilayer are referred to as being unilamellar, and those having more than one bilayer are referred to as multilamellar. The most common types of liposomes are small unilamellar vesicles (SUV), large unilamellar vesicle (LUV), and multilamellar vesicles (MLV). In contrast to liposomes, lysosomes, micelles, and reversed micelles are composed of monolayers of lipids. Generally, a liposome is thought of as having a single interior compartment, however some formulations can be multivesicular liposomes (MVL), which consist of numerous discontinuous internal aqueous compartments separated by several nonconcentric lipid bilayers.

[0294] Liposomes have long been perceived as drug delivery vehicles because of their superior biocompatibility, given that liposomes are basically analogs of biological membranes, and can be prepared from both natural and synthetic phospholipids (Int J Nanomedicine. 2014; 9:1833-1843). In their use as drug delivery vehicles, because a liposome has an aqueous solution core surrounded by a hydrophobic membrane, hydrophilic solutes dissolved in the core cannot readily pass through the bilayer, and hydrophobic compounds will associate with the bilayer. Thus, a liposome can be loaded with hydrophobic and/or hydrophilic molecules. When a liposome is used to carry a nucleic acid such as RNA, the nucleic acid will be contained within the liposomal compartment in an aqueous phase.

Cationic Liposomes

[0295] Liposomes can be composed of cationic, anionic, and/or neutral lipids. As an important subclass of liposomes, cationic liposomes are liposomes that are made in whole or part from positively charged lipids, or more specifically a lipid that comprises both a cationic group and a lipophilic portion. In addition to the general characteristics profiled above for liposomes, the positively charged moieties of cationic lipids used in cationic liposomes provide several advantages and some unique structural features. For example, the lipophilic portion of the cationic lipid is hydrophobic and thus will direct itself away from the aqueous interior of the liposome and associate with other nonpolar and hydrophobic species. Conversely, the cationic moiety will associate with aqueous media and more importantly with polar molecules and species with which it can complex in the aqueous interior of the cationic liposome. For these reasons, cationic liposomes are increasingly being researched for use in gene therapy due to their favorability towards negatively charged nucleic acids via electrostatic interactions, resulting in complexes that offer biocompatibility, low toxicity, and the possibility of the large-scale production required for in vivo clinical applications. Cationic lipids suitable for use in cationic liposomes are listed herein below.

Lipid Nanoparticles

[0296] In contrast to liposomes and cationic liposomes, lipid nanoparticles (LNP) have a structure that includes a single monolayer or bilayer of lipids that encapsulates a compound in a solid phase. Thus, unlike liposomes, lipid nanoparticles do not have an aqueous phase or other liquid phase in its interior, but rather the lipids from the bilayer or monolayer shell are directly complexed to the internal compound thereby encapsulating it in a solid core. Lipid nanoparticles are typically spherical vesicles having a relatively uniform dispersion of shape and size. While sources vary on what size qualifies a lipid particle as being a nanoparticle, there is some overlap in agreement that a lipid nanoparticle can have a diameter in the range of from 10 nm to 1000 nm. However, more commonly they are considered to be smaller than 120 nm or even 100 nm.

[0297] For lipid nanoparticle nucleic acid delivery systems, the lipid shell is formulated to include an ionizable cationic lipid which can complex to and associate with the negatively charged backbone of the nucleic acid core. Ionizable cationic lipids with apparent pKa values below about 7 have the benefit of providing a cationic lipid for complexing with the nucleic acid's negatively charged backbone and loading into the lipid nanoparticle at pH values below

the pKa of the ionizable lipid where it is positively charged. Then, at physiological pH values, the lipid nanoparticle can adopt a relatively neutral exterior allowing for a significant increase in the circulation half-lives of the particles following i.v. administration. In the context of nucleic acid delivery, lipid nanoparticles offer many advantages over other lipid-based nucleic acid delivery systems including high nucleic acid encapsulation efficiency, potent transfection, improved penetration into tissues to deliver therapeutics, and low levels of cytotoxicity and immunogenicity.

[0298] Prior to the development of lipid nanoparticle delivery systems for nucleic acids, cationic lipids were widely studied as synthetic materials for delivery of nucleic acid medicines. In these early efforts, after mixing together at physiological pH, nucleic acids were condensed by cationic lipids to form lipid-nucleic acid complexes known as lipoplexes. However, lipoplexes proved to be unstable and characterized by broad size distributions ranging from the submicron scale to a few microns. Lipoplexes, such as the Lipofectamine® reagent, have found considerable utility for in vitro transfection. However, these first-generation lipoplexes have not proven useful in vivo. The large particle size and positive charge (Imparted by the cationic lipid) result in rapid plasma clearance, hemolytic and other toxicities, as well as immune system activation.In some aspects, nucleic acid molecules provided herein and lipids or lipid formulations provided herein form a lipid nanoparticle (LNP).

[0299] In other aspects, nucleic acid molecules provided herein are incorporated into a lipid formulation (i.e., a lipid-based delivery vehicle).

[0300] In the context of the present disclosure, a lipid-based delivery vehicle typically serves to transport a desired RNA to a target cell or tissue. The lipid-based delivery vehicle can be any suitable lipid-based delivery vehicle known in the art. In some aspects, the lipid-based delivery vehicle is a liposome, a cationic liposome, or a lipid nanoparticle containing a self-replicating RNA of the disclosure. In some aspects, the lipid-based delivery vehicle comprises a nanoparticle or a bilayer of lipid molecules and a self-replicating RNA of the disclosure. In some aspects, the lipid bilayer further comprises a neutral lipid or a polymer. In some aspects, the lipid formulation comprises a liquid medium. In some aspects, the formulation further encapsulates a nucleic acid. In some aspects, the lipid formulation further comprises a nucleic acid and a neutral lipid or a polymer. In some aspects, the lipid formulation encapsulates the nucleic acid.

[0301] The description provides lipid formulations comprising one or more self-replicating RNA molecules encapsulated within the lipid formulation. In some aspects, the lipid formulation comprises liposomes. In some aspects, the lipid formulation comprises cationic liposomes. In some aspects, the lipid formulation comprises lipid nanoparticles.

[0302] In some aspects, the self-replicating RNA is fully encapsulated within the lipid portion of the lipid formulation such that the RNA in the lipid formulation is resistant in aqueous solution to nuclease degradation. In other aspects, the lipid formulations described herein are substantially non-toxic to animals such as humans and other mammals.

[0303] The lipid formulations of the disclosure also typically have a total lipid:RNA ratio (mass/mass ratio) of from about 1:1 to about 100:1, from about 1:1 to about 50:1, from about 2:1 to about 45:1, from about 3:1 to about 40:1, from about 5:1 to about 45:1, or from about 10:1 to about 40:1, or from about 15:1 to about 40:1, or from about 20:1 to about 40:1; or from about 25:1 to about 45:1; or from about 30:1 to about 45:1; or from about 32:1 to about 42:1; or from about 34:1 to about 42:1. In some aspects, the total lipid:RNA ratio (mass/mass ratio) is from about 30:1 to about 45:1. The ratio may be any value or subvalue within the recited ranges, including endpoints.

[0304] The lipid formulations of the present disclosure typically have a mean diameter of from about 30 nm to about 150 nm, from about 40 nm to about 150 nm, from about 50 nm to about 150 nm, from about 60 nm to about 130 nm, from about 70 nm to about 110 nm, from about 70 nm to about 100 nm, from about 80 nm to about 100 nm, from about 90 nm to about 100 nm, from about 70 to about 90 nm, from about 80 nm to about 90 nm, from about 70 nm to about 80 nm, or about 30 nm, about 35 nm, about 40 nm, about 45 nm, about 50 nm, about 55 nm, about 60 nm, about 65 nm, about 70 nm, about 75 nm, about 80 nm, about 85 nm, about 90 nm, about 95 nm, about 100 nm, about 105 nm, about 110 nm, about 115 nm, about 120 nm, about 125 nm, about 130 nm, about 135 nm, about 140 nm, about 145 nm, or about 150 nm, and are substantially non-toxic. The diameter may be any value or subvalue within the recited ranges, including endpoints. In addition, nucleic acids, when present in the lipid nanoparticles of the present disclosure, generally are resistant in aqueous solution to degradation with a nuclease.

[0305] In some embodiments, the lipid nanoparticle has a size of less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 200 nm, less than about 100

nm, or less than about 50 nm. In specific embodiments, the lipid nanoparticle has a size of about 55 nm to about 90 nm.

[0306] In some aspects, the lipid formulations comprise a self-replicating RNA, a cationic lipid (e.g., one or more cationic lipids or salts thereof described herein), a phospholipid, and a conjugated lipid that inhibits aggregation of the particles (e.g., one or more PEG-lipid conjugates). The lipid formulations can also include cholesterol. In one aspect, the cationic lipid is an ionizable cationic lipid.

[0307] In the nucleic acid-lipid formulations, the RNA may be fully encapsulated within the lipid portion of the formulation, thereby protecting the nucleic acid from nuclease degradation. In some aspects, a lipid formulation comprising an RNA is fully encapsulated within the lipid portion of the lipid formulation, thereby protecting the nucleic acid from nuclease degradation. In certain aspects, the RNA in the lipid formulation is not substantially degraded after exposure of the particle to a nuclease at 37°C for at least 20, 30, 45, or 60 minutes. In certain other aspects, the RNA in the lipid formulation is not substantially degraded after incubation of the formulation in serum at 37°C for at least 30, 45, or 60 minutes or at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, or 36 hours. In some aspects, the RNA is complexed with the lipid portion of the formulation. One of the benefits of the formulations of the present disclosure is that the nucleic acid-lipid compositions are substantially non-toxic to animals such as humans and other mammals.

[0308] In the context of nucleic acids, full encapsulation may be determined by performing a membrane-impermeable fluorescent dye exclusion assay, which uses a dye that has enhanced fluorescence when associated with nucleic acid. Encapsulation is determined by adding the dye to a lipid formulation, measuring the resulting fluorescence, and comparing it to the fluorescence observed upon addition of a small amount of nonionic detergent. Detergent-mediated disruption of the lipid layer releases the encapsulated nucleic acid, allowing it to interact with the membrane-impermeable dye. Nucleic acid encapsulation may be calculated as $E = (I0 - I)/I0$, where/and I0 refers to the fluorescence intensities before and after the addition of detergent.

[0309] In some aspects, the present disclosure provides a nucleic acid-lipid composition comprising a plurality of nucleic acid-liposomes, nucleic acid-cationic liposomes, or nucleic acid-lipid nanoparticles. In some aspects, the nucleic acid-lipid composition comprises a plurality of RNA-liposomes. In some aspects, the nucleic acid-lipid composition comprises a

plurality of RNA-cationic liposomes. In some aspects, the nucleic acid-lipid composition comprises a plurality of RNA-lipid nanoparticles.

[0310] In some aspects, the lipid formulations comprise RNA that is fully encapsulated within the lipid portion of the formulation, such that from about 30% to about 100%, from about 40% to about 100%, from about 50% to about 100%, from about 60% to about 100%, from about 70% to about 100%, from about 80% to about 100%, from about 90% to about 100%, from about 30% to about 95%, from about 40% to about 95%, from about 50% to about 95%, from about 60% to about 95%, from about 70% to about 95%, from about 80% to about 95%, from about 85% to about 95%, from about 90% to about 95%, from about 30% to about 90%, from about 40% to about 90%, from about 50% to about 90%, from about 60% to about 90%, from about 70% to about 90%, from about 80% to about 90%, or at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% (or any fraction thereof or range therein) of the particles have the RNA encapsulated therein. The amount may be any value or subvalue within the recited ranges, including endpoints. The RNA included in any RNA-lipid composition or RNA-lipid formulation provided herein can be a self-replicating RNA.

[0311] Depending on the intended use of the lipid formulation, the proportions of the components can be varied, and the delivery efficiency of a particular formulation can be measured using assays known in the art.

[0312] In some aspects, nucleic acid molecules provided herein are lipid formulated. The lipid formulation is preferably selected from, but not limited to, liposomes, cationic liposomes, and lipid nanoparticles. In one aspect, a lipid formulation is a cationic liposome or a lipid nanoparticle (LNP) comprising:

[0313] (a) an RNA of the present disclosure,

[0314] (b) a cationic lipid,

[0315] (c) an aggregation reducing agent (such as polyethylene glycol (PEG) lipid or PEG-modified lipid),

[0316] (d) optionally a non-cationic lipid (such as a neutral lipid), and

[0317] (e) optionally, a sterol.

[0318] In another aspect, the cationic lipid is an ionizable cationic lipid. Any ionizable cationic lipid can be included in lipid formulations, including exemplary cationic lipids provided herein.

Cationic Lipids

[0319] In one aspect, the lipid nanoparticle formulation comprises (i) at least one cationic lipid; (ii) a helper lipid; (iii) a sterol (e.g., cholesterol); and (iv) a PEG-lipid. In another aspect, the cationic lipid is an ionizable cationic lipid. In yet another aspect, the lipid nanoparticle formulation comprises (i) at least one cationic lipid; (ii) a helper lipid; (iii) a sterol (e.g., cholesterol); and (iv) a PEG-lipid, in a molar ratio of about 40-70% ionizable cationic lipid: about 2-15% helper lipid: about 20-45% sterol; about 0.5-5% PEG-lipid. In a further aspect, the cationic lipid is an ionizable cationic lipid.

[0320] In one aspect, the lipid nanoparticle formulation consists of (i) at least one cationic lipid; (ii) a helper lipid; (iii) a sterol (e.g., cholesterol); and (iv) a PEG-lipid. In another aspect, the cationic lipid is an ionizable cationic lipid. In yet another aspect, the lipid nanoparticle formulation consists of (i) at least one cationic lipid; (ii) a helper lipid; (iii) a sterol (e.g., cholesterol); and (iv) a PEG-lipid, in a molar ratio of about 40-70% ionizable cationic lipid: about 2-15% helper lipid: about 20-45% sterol; about 0.5-5% PEG-lipid. In a further aspect, the cationic lipid is an ionizable cationic lipid.

[0321] In the presently disclosed lipid formulations, the cationic lipid may be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), 1,2-dioleoyltrimethylammoniumpropane chloride (DOTAP) (also known as N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride and 1,2-Dioleyloxy-3-trimethylaminopropane chloride salt), N-(l-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-di-y-linolenyloxy-N,N-dimethylaminopropane (γ-DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-

TAP.Cl), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanediol (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N- dimethylamino)ethoxypropane (DLin-EG-DMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-5-amine, (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl4-(dimethylamino)butanoate (MC3), 1,1'-(2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl)piperazin-1-yl)ethylazanediyl)didodecan-2-ol (C12-200), 2,2-dilinoleyl-4-(2-dimethylaminoethyl)-[1,3]-dioxolane (DLin-K-C2-DMA), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28 31-tetraen-19-yl 4-(dimethylamino) butanoate (DLin-M-C3-DMA), 3-((6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,3 1-tetraen-19-yloxy)-N,N-dimethylpropan-1-amine (MC3 Ether), 4-((6Z,9Z,28Z,31 Z)-heptatriaconta-6,9,28,31-tetraen-19-yloxy)-N,N-dimethylbutan-1-amine (MC4 Ether), or any combination thereof. Other cationic lipids include, but are not limited to, N,N-distearyl-N,N-dimethylammonium bromide (DDAB), 3P-(N-(N',N'-dimethylaminoethane)- carbamoyl)cholesterol (DC-Choi), N-(1-(2,3-dioleyloxy)propyl)-N-2-(sperminecarboxamido)ethyl)-N,N-dimethylammonium trifluoracetate (DOSPA), dioctadecylamidoglycyl carboxyspermine (DOGS), 1,2-dileoyl-sn-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-dimethylammonium propane (DODAP), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), and 2,2-Dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (XTC). Additionally, commercial preparations of cationic lipids can be used, such as, e.g., LIPOFECTIN (including DOTMA and DOPE, available from GIBCO/BRL), and Lipofectamine (comprising DOSPA and DOPE, available from GIBCO/BRL).

[0322] Other suitable cationic lipids are disclosed in International Publication Nos. WO 09/086558, WO 09/127060, WO 10/048536, WO 10/054406, WO 10/088537, WO 10/129709, and WO 2011/153493; U.S. Patent Publication Nos. 2011/0256175, 2012/0128760, and 2012/0027803; U.S. Patent Nos. 8,158,601; and Love et al., PNAS, 107(5), 1864-69, 2010, the contents of which are herein incorporated by reference.

[0323] The RNA-lipid formulations of the present disclosure can comprise a helper lipid, which can be referred to as a neutral helper lipid, non-cationic lipid, non-cationic helper lipid, anionic lipid, anionic helper lipid, or a neutral lipid. It has been found that lipid formulations, particularly cationic liposomes and lipid nanoparticles have increased cellular uptake if helper

lipids are present in the formulation. (Curr. Drug Metab. 2014; 15(9):882-92). For example, some studies have indicated that neutral and zwitterionic lipids such as 1,2-dioleoylsn-glycero-3-phosphatidylcholine (DOPC), Di-Oleoyl-Phosphatidyl-Ethanoalamine (DOPE) and 1,2-DiStearoyl-sn-glycero-3-PhosphoCholine (DSPC), being more fusogenic (i.e., facilitating fusion) than cationic lipids, can affect the polymorphic features of lipid-nucleic acid complexes, promoting the transition from a lamellar to a hexagonal phase, and thus inducing fusion and a disruption of the cellular membrane. (Nanomedicine (Lond). 2014 Jan; 9(1):105-20). In addition, the use of helper lipids can help to reduce any potential detrimental effects from using many prevalent cationic lipids such as toxicity and immunogenicity.

[0324] Non-limiting examples of non-cationic lipids suitable for lipid formulations of the present disclosure include phospholipids such as lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidic acid, cerebrosides, dicetylphosphate, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoyl-phosphatidylcholine (POPC), palmitoyloleoyl-phosphatidylethanolamine (POPE), palmitoyloleyol-phosphatidylglycerol (POPG), dioleoylphosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (DOPE-mal), dipalmitoyl-phosphatidylethanolamine (DPPE), dimyristoyl-phosphatidylethanolamine (DMPE), distearoyl-phosphatidylethanolamine (DSPE), monomethyl-phosphatidylethanolamine, dimethyl-phosphatidylethanolamine, dielaidoyl-phosphatidylethanolamine (DEPE), stearoyloleoyl-phosphatidylethanolamine (SOPE), lysophosphatidylcholine, dilinoleoylphosphatidylcholine, and mixtures thereof. Other diacylphosphatidylcholine and diacylphosphatidylethanolamine phospholipids can also be used. The acyl groups in these lipids are preferably acyl groups derived from fatty acids having C10-C24 carbon chains, e.g., lauroyl, myristoyl, palmitoyl, stearoyl, or oleoyl.

[0325] Additional examples of non-cationic lipids include sterols such as cholesterol and derivatives thereof. As a helper lipid, cholesterol increases the spacing of the charges of the lipid layer interfacing with the nucleic acid making the charge distribution match that of the nucleic acid more closely. (J. R. Soc. Interface. 2012 Mar 7; 9(68): 548–561). Non-limiting examples of cholesterol derivatives include polar analogues such as 5α-cholestanol, 5α-coprostanol, cholesteryl-(2'-hydroxy)-ethyl ether, cholesteryl-(4'- hydroxy)-butyl ether, and 6-

ketocholestanol; non-polar analogues such as 5α-cholestane, cholestenone, 5α-cholestanone, 5α-cholestanone, and cholesteryl decanoate; and mixtures thereof. In some aspects, the cholesterol derivative is a polar analogue such as cholesteryl-(4'-hydroxy)-butyl ether.

[0326] In some aspects, the helper lipid present in the lipid formulation comprises or consists of a mixture of one or more phospholipids and cholesterol or a derivative thereof. In other aspects, the neutral lipid present in the lipid formulation comprises or consists of one or more phospholipids, e.g., a cholesterol-free lipid formulation. In yet other aspects, the neutral lipid present in the lipid formulation comprises or consists of cholesterol or a derivative thereof, e.g., a phospholipid-free lipid formulation.

[0327] Other examples of helper lipids include nonphosphorous containing lipids such as, e.g., stearylamine, dodecylamine, hexadecylamine, acetyl palmitate, glycerol ricinoleate, hexadecyl stearate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethyloxylated fatty acid amides, dioctadecyldimethyl ammonium bromide, ceramide, and sphingomyelin.

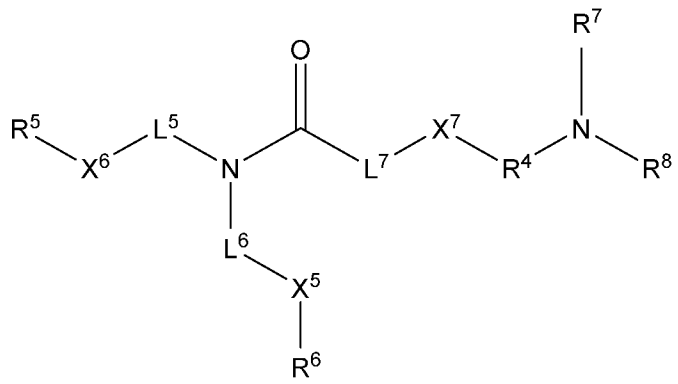
[0328] Other suitable cationic lipids include those having alternative fatty acid groups and other dialkylamino groups, including those, in which the alkyl substituents are different (e.g., N-ethyl- N-methylamino-, and N-propyl-N-ethylamino-). These lipids are part of a subcategory of cationic lipids referred to as amino lipids. In some embodiments of the lipid formulations described herein, the cationic lipid is an amino lipid. In general, amino lipids having less saturated acyl chains are more easily sized, particularly when the complexes must be sized below about 0.3 microns, for purposes of filter sterilization. Amino lipids containing unsaturated fatty acids with carbon chain lengths in the range of C14 to C22 may be used. Other scaffolds can also be used to separate the amino group and the fatty acid or fatty alkyl portion of the amino lipid.

[0329] In some embodiments, the lipid formulation comprises the cationic lipid with Formula I according to the patent application PCT/EP2017/064066. In this context, the disclosure of PCT/EP2017/064066 is also incorporated herein by reference.

[0330] In some embodiments, amino or cationic lipids of the present disclosure are ionizable and have at least one protonatable or deprotonatable group, such that the lipid is positively charged at a pH at or below physiological pH (e.g., pH 7.4), and neutral at a second pH, preferably at or above physiological pH. Of course, it will be understood that the addition

or removal of protons as a function of pH is an equilibrium process, and that the reference to a charged or a neutral lipid refers to the nature of the predominant species and does not require that all of the lipid be present in the charged or neutral form. Lipids that have more than one protonatable or deprotonatable group, or which are zwitterionic, are not excluded from use in the disclosure. In certain embodiments, the protonatable lipids have a pKa of the protonatable group in the range of about 4 to about 11. In some embodiments, the ionizable cationic lipid has a pKa of about 5 to about 7. In some embodiments, the pKa of an ionizable cationic lipid is about 6 to about 7.

[0331] In some embodiments, the lipid formulation comprises an ionizable cationic lipid of Formula I:



(I)

[0332] or a pharmaceutically acceptable salt or solvate thereof, wherein R5 and R6 are each independently selected from the group consisting of a linear or branched C1-C31 alkyl, C2-C31 alkenyl or C2-C31 alkynyl and cholesteryl; L5 and L6 are each independently selected from the group consisting of a linear C1-C20 alkyl and C2-C20 alkenyl; X5 is -C(O)O-, whereby -C(O)O-R6 is formed or -OC(O)- whereby -OC(O)-R6 is formed; X6 is -C(O)O- whereby -C(O)O-R5 is formed or -OC(O)- whereby -OC(O)-R5 is formed; X7 is S or O; L7 is absent or lower alkyl; R4 is a linear or branched C1-C6 alkyl; and R7 and R8 are each independently selected from the group consisting of a hydrogen and a linear or branched C1-C6 alkyl.

[0333] In some embodiments, X7 is S.

[0334] In some embodiments, X5 is -C(O)O-, whereby -C(O)O-R6 is formed and X6 is -C(O)O- whereby -C(O)O-R5 is formed.

[0335] In some embodiments, R7 and R8 are each independently selected from the group consisting of methyl, ethyl and isopropyl.

[0336] In some embodiments, L5 and L6 are each independently a C1-C10 alkyl. In some embodiments, L5 is C1-C3 alkyl, and L6 is C1-C5 alkyl. In some embodiments, L6 is C1-C2 alkyl. In some embodiments, L5 and L6 are each a linear C7 alkyl. In some embodiments, L5 and L6 are each a linear C9 alkyl.

[0337] In some embodiments, R5 and R6 are each independently an alkenyl. In some embodiments, R6 is alkenyl. In some embodiments, R6 is C2-C9 alkenyl. In some embodiments, the alkenyl comprises a single double bond. In some embodiments, R5 and R6 are each alkyl. In some embodiments, R5 is a branched alkyl. In some embodiments, R5 and R6 are each independently selected from the group consisting of a C9 alkyl, C9 alkenyl and C9 alkynyl. In some embodiments, R5 and R6 are each independently selected from the group consisting of a C11 alkyl, C11 alkenyl and C11 alkynyl. In some embodiments, R5 and R6 are each independently selected from the group consisting of a C7 alkyl, C7 alkenyl and C7 alkynyl. In some embodiments, R5 is –CH((CH2)pCH3)2 or –CH((CH2)pCH3)((CH2)p-1CH3), wherein p is 4-8. In some embodiments, p is 5 and L5 is a C1-C3 alkyl. In some embodiments, p is 6 and L5 is a C3 alkyl. In some embodiments, p is 7. In some embodiments, p is 8 and L5 is a C1-C3 alkyl. In some embodiments, R5 consists of –CH((CH2)pCH3)((CH2)p-1CH3), wherein p is 7 or 8.

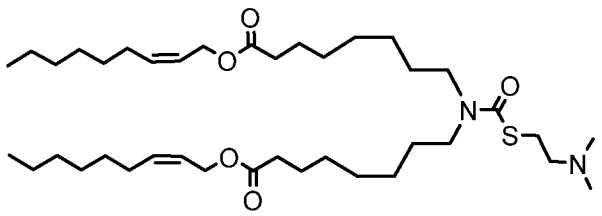
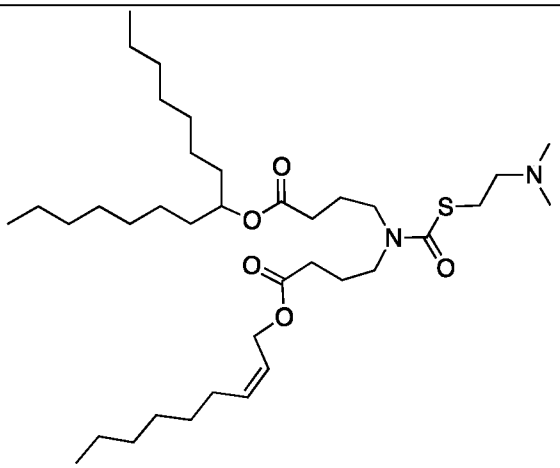
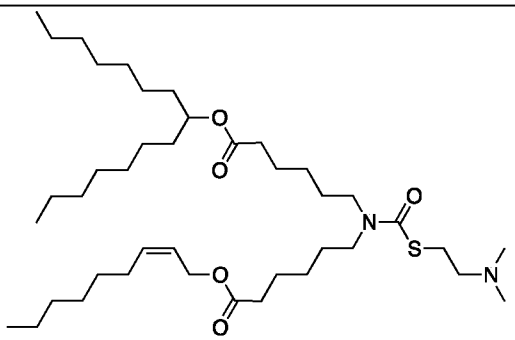
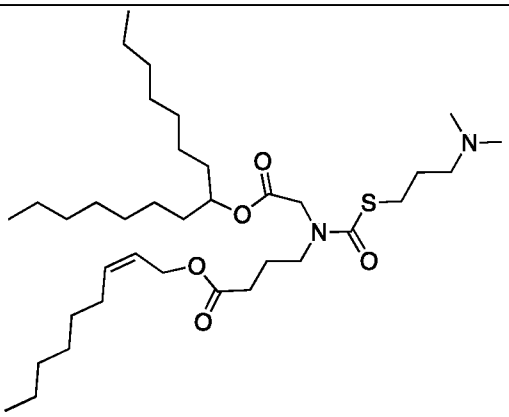
[0338] In some embodiments, R4 is ethylene or propylene. In some embodiments, R4 is n-propylene or isobutylene.

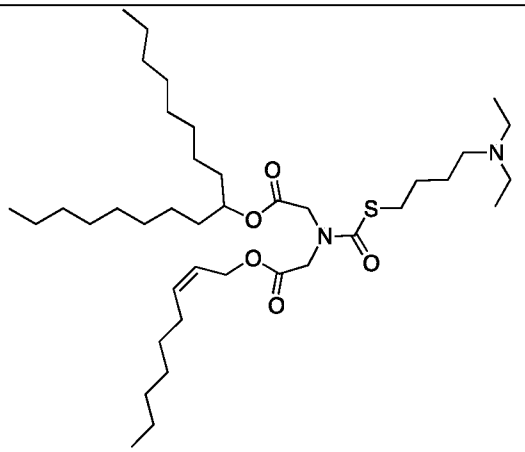
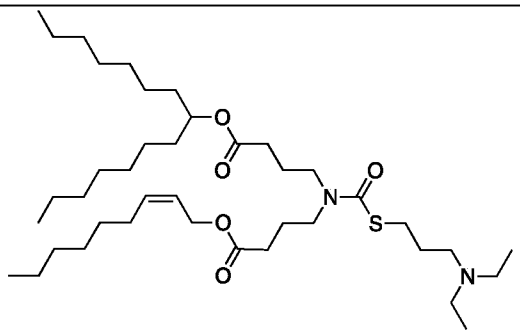
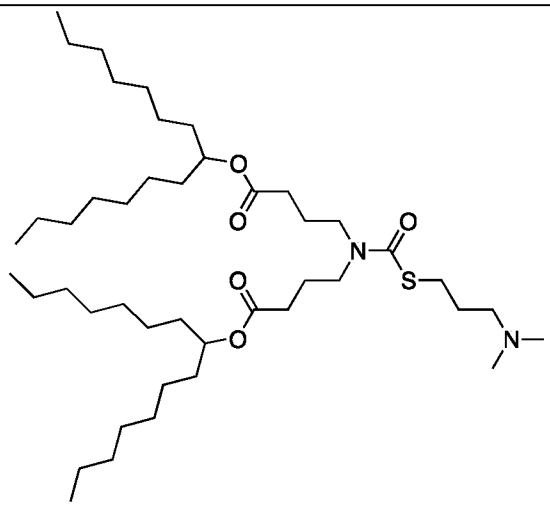
[0339] In some embodiments, L7 is absent, R4 is ethylene, X7 is S and R7 and R8 are each methyl. In some embodiments, L7 is absent, R4 is n-propylene, X7 is S and R7 and R8 are each methyl. In some embodiments, L7 is absent, R4 is ethylene, X7 is S and R7 and R8 are each ethyl.

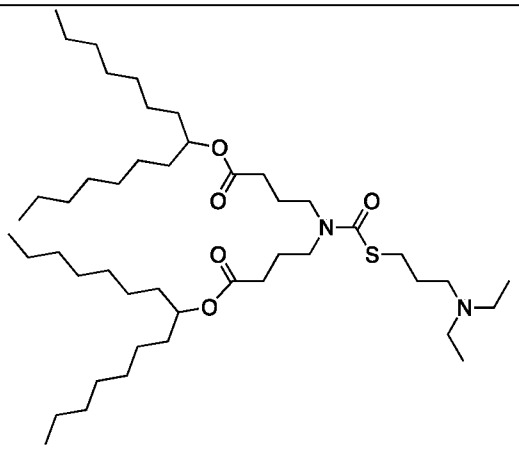
[0340] In some embodiments, X7 is S, X5 is -C(O)O-, whereby -C(O)O-R6 is formed, X6 is -C(O)O- whereby -C(O)O-R5 is formed, L5 and L6 are each independently a linear C3-C7 alkyl, L7 is absent, R5 is –CH((CH2)pCH3)2, and R6 is C7-C12 alkenyl. In some further embodiments, p is 6 and R6 is C9 alkenyl.

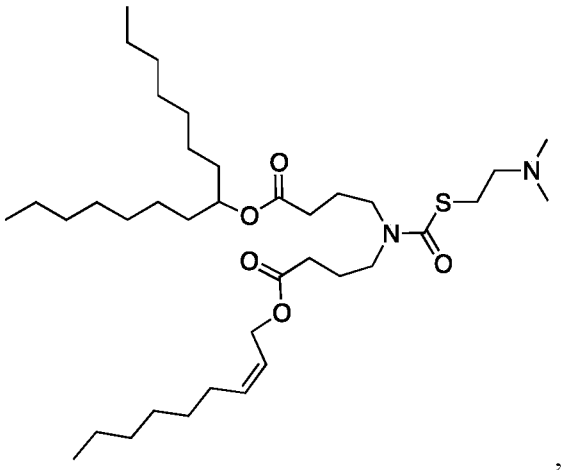
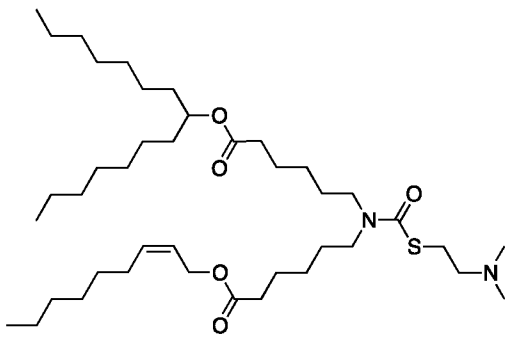
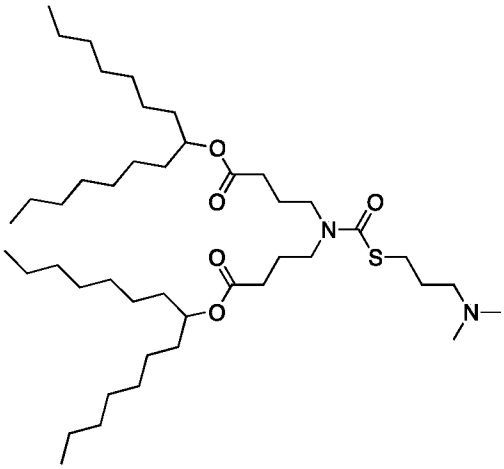
[0341] In some embodiments, the lipid formulation can comprise an ionizable cationic lipid selected from the group consisting of LIPID # 1 to LIPID # 8:

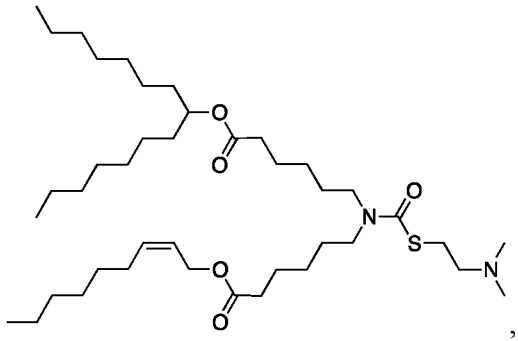
Table 6.

LIPID #	STRUCTURE
1	
2	
3	
4	

LIPID #	STRUCTURE
5	
6	
7	

LIPID #	STRUCTURE
8	

In some embodiments, the lipid formulation comprises an ionizable cationic lipid having a structure selected from  ,  , and  , or a pharmaceutically acceptable salt thereof.

In some preferred embodiments, the lipid formulation comprises an ionizable cationic lipid having the structure  , or a pharmaceutically acceptable salt thereof.

[0342] In embodiments, any one or more lipids recited herein may be expressly excluded.

[0343] In some aspects, the helper lipid comprises from about 2 mol% to about 20 mol%, from about 3 mol% to about 18 mol%, from about 4 mol% to about 16 mol%, about 5 mol% to about 14 mol%, from about 6 mol% to about 12 mol%, from about 5 mol% to about 10 mol%, from about 5 mol% to about 9 mol%, or about 2 mol%, about 3 mol%, about 4 mol%, about 5 mol%, about 6 mol%, about 7 mol%, about 8 mol%, about 9 mol%, about 10 mol%, about 11 mol%, or about 12 mol% (or any fraction thereof or the range therein) of the total lipid present in the lipid formulation.

[0344] The lipid portion, or the cholesterol or cholesterol derivative in the lipid formulation may comprise up to about 40 mol%, about 45 mol%, about 50 mol%, about 55 mol%, or about 60 mol% of the total lipid present in the lipid formulation. In some aspects, the cholesterol or cholesterol derivative comprises about 15 mol% to about 45 mol%, about 20 mol% to about 40 mol%, about 25 mol% to about 35 mol%, or about 28 mol% to about 35 mol%; or about 25 mol%, about 26 mol%, about 27 mol%, about 28 mol%, about 29 mol%, about 30 mol%, about 31 mol%, about 32 mol%, about 33 mol%, about 34 mol%, about 35 mol%, about 36 mol%, or about 37 mol% of the total lipid present in the lipid formulation.

[0345] In specific embodiments, the lipid portion of the lipid formulation is about 35 mol% to about 42 mol% cholesterol.

[0346] In some aspects, the phospholipid component in the mixture may comprise from about 2 mol% to about 20 mol%, from about 3 mol% to about 18 mol%, from about 4 mol % to about 16 mol %, about 5 mol % to about 14 mol %, from about 6 mol % to about 12 mol%, from about 5 mol% to about 10 mol%, from about 5 mol% to about 9 mol%, or about 2 mol%, about 3 mol%, about 4 mol%, about 5 mol%, about 6 mol%, about 7 mol%, about 8 mol%,

about 9 mol%, about 10 mol%, about 11 mol%, or about 12 mol% (or any fraction thereof or the range therein) of the total lipid present in the lipid formulation.

[0347] In certain embodiments, the lipid portion of the lipid formulation comprises about, but is not necessarily limited to, 40 mol% to about 60 mol% of the ionizable cationic lipid, about 4 mol% to about 16 mol% DSPC, about 30 mol% to about 47 mol% cholesterol, and about 0.5 mol% to about 3 mol% PEG2000-DMG.

[0348] In certain embodiments, the lipid portion of the lipid formulation may comprise, but is not necessarily limited to, about 42 mol% to about 58 mol% of the ionizable cationic lipid, about 6 mol% to about 14 mol% DSPC, about 32 mol% to about 44 mol% cholesterol, and about 1 mol% to about 2 mol% PEG2000-DMG.

[0349] In certain embodiments, the lipid portion of the lipid formulation may comprise, but is not necessarily limited to, about 45 mol% to about 55 mol% of the ionizable cationic lipid, about 8 mol% to about 12 mol% DSPC, about 35 mol% to about 42 mol% cholesterol, and about 1.25 mol% to about 1.75 mol% PEG2000-DMG.

[0350] The percentage of helper lipid present in the lipid formulation is a target amount, and the actual amount of helper lipid present in the formulation may vary, for example, by ± 5 mol%.

[0351] A lipid formulation that includes a cationic lipid compound or ionizable cationic lipid compound may be on a molar basis about 30-70% cationic lipid compound, about 25-40 % cholesterol, about 2-15% helper lipid, and about 0.5-5% of a polyethylene glycol (PEG) lipid, wherein the percent is of the total lipid present in the formulation. In some aspects, the composition is about 40-65% cationic lipid compound, about 25- 35% cholesterol, about 3-9% helper lipid, and about 0.5-3% of a PEG-lipid, wherein the percent is of the total lipid present in the formulation.

[0352] The formulation may be a lipid particle formulation, for example containing 8-30% nucleic acid compound, 5-30% helper lipid, and 0-20% cholesterol; 4-25% cationic lipid, 4-25% helper lipid, 2- 25% cholesterol, 10- 35% cholesterol-PEG, and 5% cholesterol-amine; or 2-30% cationic lipid, 2-30% helper lipid, 1-15% cholesterol, 2-35% cholesterol-PEG, and 1-20% cholesterol-amine; or up to 90% cationic lipid and 2-10% helper lipids, or even 100% cationic lipid.

Lipid Conjugates

[0353] The lipid formulations described herein may further comprise a lipid conjugate. The conjugated lipid is useful in that it prevents the aggregation of particles. Suitable conjugated lipids include, but are not limited to, PEG-lipid conjugates, cationic-polymer-lipid conjugates, and mixtures thereof. Furthermore, lipid delivery vehicles can be used for specific targeting by attaching ligands (e.g., antibodies, peptides, and carbohydrates) to its surface or to the terminal end of the attached PEG chains (Front Pharmacol. 2015 Dec 1; 6:286).

[0354] In some aspects, the lipid conjugate is a PEG-lipid. The inclusion of polyethylene glycol (PEG) in a lipid formulation as a coating or surface ligand, a technique referred to as PEGylation, helps to protect nanoparticles from the immune system and their escape from RES uptake (Nanomedicine (Lond). 2011 Jun; 6(4):715-28). PEGylation has been used to stabilize lipid formulations and their payloads through physical, chemical, and biological mechanisms. Detergent-like PEG lipids (e.g., PEG-DSPE) can enter the lipid formulation to form a hydrated layer and steric barrier on the surface. Based on the degree of PEGylation, the surface layer can be generally divided into two types, brush-like and mushroom-like layers. For PEG-DSPE-stabilized formulations, PEG will take on the mushroom conformation at a low degree of PEGylation (usually less than 5 mol%) and will shift to brush conformation as the content of PEG-DSPE is increased past a certain level (Journal of Nanomaterials. 2011;2011:12). PEGylation leads to a significant increase in the circulation half-life of lipid formulations (Annu. Rev. Biomed. Eng. 2011 Aug 15; 13():507-30; J. Control Release. 2010 Aug 3; 145(3):178-81).

[0355] Examples of PEG-lipids include, but are not limited to, PEG coupled to dialkyloxypropyls (PEG-DAA), PEG coupled to diacylglycerol (PEG-DAG), methoxypolyethyleneglycol (PEG-DMG or PEG2000-DMG), PEG coupled to phospholipids such as phosphatidylethanolamine (PEG-PE), PEG conjugated to ceramides, PEG conjugated to cholesterol or a derivative thereof, and mixtures thereof.

[0356] PEG is a linear, water-soluble polymer of ethylene PEG repeating units with two terminal hydroxyl groups. PEGs are classified by their molecular weights and include the following: monomethoxypolyethylene glycol (MePEG-OH), monomethoxypolyethylene glycol- succinate (MePEG-S), monomethoxypolyethylene glycol-succinimidyl succinate (MePEG-S-NHS), monomethoxypolyethylene glycol-amine (MePEG-NH2), monomethoxypolyethylene glycol-tresylate (MePEG-TRES), monomethoxypolyethylene

glycol-imidazolyl-carbonyl (MePEG-IM), as well as such compounds containing a terminal hydroxyl group instead of a terminal methoxy group (e.g., HO-PEG-S, HO-PEG-S-NHS, HO-PEG-NH2).

[0357] The PEG moiety of the PEG-lipid conjugates described herein may comprise an average molecular weight ranging from about 550 daltons to about 10,000 daltons. In certain aspects, the PEG moiety has an average molecular weight of from about 750 daltons to about 5,000 daltons (e.g., from about 1,000 daltons to about 5,000 daltons, from about 1,500 daltons to about 3,000 daltons, from about 750 daltons to about 3,000 daltons, from about 750 daltons to about 2,000 daltons). In some aspects, the PEG moiety has an average molecular weight of about 2,000 daltons or about 750 daltons. The average molecular weight may be any value or subvalue within the recited ranges, including endpoints.

[0358] In certain aspects, the PEG can be optionally substituted by an alkyl, alkoxy, acyl, or aryl group. The PEG can be conjugated directly to the lipid or may be linked to the lipid via a linker moiety. Any linker moiety suitable for coupling the PEG to a lipid can be used including, e.g., non-ester-containing linker moieties and ester-containing linker moieties. In one aspect, the linker moiety is a non-ester-containing linker moiety. Exemplary non-ester-containing linker moieties include, but are not limited to, amido (-C(O)NH-), amino (-NR-), carbonyl (-C(O)-), carbamate (-NHC(O)O-), urea (-NHC(O)NH-), disulfide (-S-S-), ether (-O-), succinyl (-(O)CCH2CH2C(O)-), succinamidyl (-NHC(O)CH2CH2C(O)NH-), ether, as well as combinations thereof (such as a linker containing both a carbamate linker moiety and an amido linker moiety). In one aspect, a carbamate linker is used to couple the PEG to the lipid.

[0359] In some aspects, an ester-containing linker moiety is used to couple the PEG to the lipid. Exemplary ester-containing linker moieties include, e.g., carbonate (-OC(O)O-), succinoyl, phosphate esters (-O-(O)POH-O-), sulfonate esters, and combinations thereof.

[0360] Phosphatidylethanolamines having a variety of acyl chain groups of varying chain lengths and degrees of saturation can be conjugated to PEG to form the lipid conjugate. Such phosphatidylethanolamines are commercially available or can be isolated or synthesized using conventional techniques known to those of skill in the art. Phosphatidylethanolamines containing saturated or unsaturated fatty acids with carbon chain lengths in the range of C_{10} to C_{20} are preferred. Phosphatidylethanolamines with mono- or di-unsaturated fatty acids and mixtures of saturated and unsaturated fatty acids can also be used. Suitable

phosphatidylethanolamines include, but are not limited to, dimyristoyl-phosphatidylethanolamine (DMPE), dipalmitoyl-phosphatidylethanolamine (DPPE), dioleoyl-phosphatidylethanolamine (DOPE), and distearoyl-phosphatidylethanolamine (DSPE).

[0361] In some aspects, the PEG-DAA conjugate is a PEG-didecyloxypropyl (C10) conjugate, a PEG-dilauryloxypropyl (C12) conjugate, a PEG-dimyristyloxypropyl (C14) conjugate, a PEG-dipalmityloxypropyl (C16) conjugate, or a PEG-distearyloxypropyl (C18) conjugate. In some aspects, the PEG has an average molecular weight of about 750 or about 2,000 daltons. In some aspects, the terminal hydroxyl group of the PEG is substituted with a methyl group.

[0362] In addition to the foregoing, other hydrophilic polymers can be used in place of PEG. Examples of suitable polymers that can be used in place of PEG include, but are not limited to, polyvinylpyrrolidone, polymethyloxazoline, polyethyloxazoline, polyhydroxypropyl, methacrylamide, polymethacrylamide, and polydimethylacrylamide, polylactic acid, polyglycolic acid, and derivatized celluloses such as hydroxymethylcellulose or hydroxyethylcellulose.

[0363] In some aspects, the lipid conjugate (e.g., PEG-lipid) comprises from about 0.1 mol% to about 2 mol%, from about 0.5 mol% to about 2 mol%, from about 1 mol% to about 2 mol%, from about 0.6 mol% to about 1.9 mol%, from about 0.7 mol% to about 1.8 mol%, from about 0.8 mol% to about 1.7 mol%, from about 0.9 mol% to about 1.6 mol%, from about 0.9 mol% to about 1.8 mol%, from about 1 mol% to about 1.8 mol%, from about 1 mol% to about 1.7 mol%, from about 1.2 mol% to about 1.8 mol%, from about 1.2 mol% to about 1.7 mol%, from about 1.3 mol% to about 1.6 mol%, or from about 1.4 mol% to about 1.6 mol% (or any fraction thereof or range therein) of the total lipid present in the lipid formulation. In other embodiments, the lipid conjugate (e.g., PEG-lipid) comprises about 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.2%, 1.3%, 1.4%, 1.5%, 1.6%, 1.7%, 1.8%, 1.9%, 2.0%, 2.5%, 3.0%, 3.5%, 4.0%, 4.5%, or 5%, (or any fraction thereof or range therein) of the total lipid present in the lipid formulation. The amount may be any value or subvalue within the recited ranges, including endpoints.

[0364] The percentage of lipid conjugate (e.g., PEG-lipid) present in the lipid formulations of the disclosure is a target amount, and the actual amount of lipid conjugate present in the formulation may vary, for example, by ± 0.5 mol%. One of ordinary skill in the art will

appreciate that the concentration of the lipid conjugate can be varied depending on the lipid conjugate employed and the rate at which the lipid formulation is to become fusogenic.

[0365] In some embodiments, the lipid formulation for any of the compositions described herein comprises a lipoplex, a liposome, a lipid nanoparticle, a polymer-based particle, an exosome, a lamellar body, a micelle, or an emulsion.

Mechanism of Action for Cellular Uptake of Lipid Formulations

[0366] In some aspects, lipid formulations for the intracellular delivery of nucleic acids, particularly liposomes, cationic liposomes, and lipid nanoparticles, are designed for cellular uptake by penetrating target cells through exploitation of the target cells' endocytic mechanisms where the contents of the lipid delivery vehicle are delivered to the cytosol of the target cell. (Nucleic Acid Therapeutics, 28(3):146-157, 2018). Prior to endocytosis, functionalized ligands such as PEG-lipid at the surface of the lipid delivery vehicle are shed from the surface, which triggers internalization into the target cell. During endocytosis, some part of the plasma membrane of the cell surrounds the vector and engulfs it into a vesicle that then pinches off from the cell membrane, enters the cytosol and ultimately enters and moves through the endolysosomal pathway. For ionizable cationic lipid-containing delivery vehicles, the increased acidity as the endosome ages results in a vehicle with a strong positive charge on the surface. Interactions between the delivery vehicle and the endosomal membrane then result in a membrane fusion event that leads to cytosolic delivery of the payload. For RNA payloads, the cell's own internal translation processes will then translate the RNA into the encoded protein. The encoded protein can further undergo postranslational processing, including transportation to a targeted organelle or location within the cell or excretion from the cell.

[0367] By controlling the composition and concentration of the lipid conjugate, one can control the rate at which the lipid conjugate exchanges out of the lipid formulation and, in turn, the rate at which the lipid formulation becomes fusogenic. In addition, other variables including, e.g., pH, temperature, or ionic strength, can be used to vary and/or control the rate at which the lipid formulation becomes fusogenic. Other methods which can be used to control the rate at which the lipid formulation becomes fusogenic will become apparent to those of skill in the art upon reading this disclosure. Also, by controlling the composition and concentration of the lipid conjugate, one can control the liposomal or lipid particle size.

Lipid Formulation Manufacture

[0368] There are many different methods for the preparation of lipid formulations comprising a nucleic acid. (Curr. Drug Metabol. 2014, 15, 882–892; Chem. Phys. Lipids 2014, 177, 8–18; Int. J. Pharm. Stud. Res. 2012, 3, 14–20). The techniques of thin film hydration, double emulsion, reverse phase evaporation, microfluidic preparation, dual assymetric centrifugation, ethanol injection, detergent dialysis, spontaneous vesicle formation by ethanol dilution, and encapsulation in preformed liposomes are briefly described herein.

Thin Film Hydration

[0369] In Thin Film Hydration (TFH) or the Bangham method, the lipids are dissolved in an organic solvent, then evaporated through the use of a rotary evaporator leading to a thin lipid layer formation. After the layer hydration by an aqueous buffer solution containing the compound to be loaded, Multilamellar Vesicles (MLVs) are formed, which can be reduced in size to produce Small or Large Unilamellar vesicles (LUV and SUV) by extrusion through membranes or by the sonication of the starting MLV.

Double Emulsion

[0370] Lipid formulations can also be prepared through the Double Emulsion technique, which involves lipids dissolution in a water/organic solvent mixture. The organic solution, containing water droplets, is mixed with an excess of aqueous medium, leading to a water-in-oil-in-water (W/O/W) double emulsion formation. After mechanical vigorous shaking, part of the water droplets collapse, giving Large Unilamellar Vesicles (LUVs).

Reverse Phase Evaporation

[0371] The Reverse Phase Evaporation (REV) method also allows one to achieve LUVs loaded with nucleic acid. In this technique a two-phase system is formed by phospholipids dissolution in organic solvents and aqueous buffer. The resulting suspension is then sonicated briefly until the mixture becomes a clear one-phase dispersion. The lipid formulation is achieved after the organic solvent evaporation under reduced pressure. This technique has been used to encapsulate different large and small hydrophilic molecules including nucleic acids.

Microfluidic Preparation

[0372] The Microfluidic method, unlike other bulk techniques, gives the possibility of controlling the lipid hydration process. The method can be classified in continuous-flow microfluidic and droplet-based microfluidic, according to the way in which the flow is manipulated. In the microfluidic hydrodynamic focusing (MHF) method, which operates in a continuous flow mode, lipids are dissolved in isopropyl alcohol which is hydrodynamically

focused in a microchannel cross junction between two aqueous buffer streams. Vesicles size can be controlled by modulating the flow rates, thus controlling the lipids solution/buffer dilution process. The method can be used for producing oligonucleotide (ON) lipid formulations by using a microfluidic device consisting of three-inlet and one-outlet ports.

Dual Asymmetric Centrifugation

[0373] Dual Asymmetric Centrifugation (DAC) differs from more common centrifugation as it uses an additional rotation around its own vertical axis. An efficient homogenization is achieved due to the two overlaying movements generated: the sample is pushed outwards, as in a normal centrifuge, and then it is pushed towards the center of the vial due to the additional rotation. By mixing lipids and an NaCl-solution a viscous vesicular phospholipid gel (VPC) is achieved, which is then diluted to obtain a lipid formulation dispersion. The lipid formulation size can be regulated by optimizing DAC speed, lipid concentration and homogenization time.

Ethanol Injection

[0374] The Ethanol Injection (EI) method can be used for nucleic acid encapsulation. This method provides the rapid injection of an ethanolic solution, in which lipids are dissolved, into an aqueous medium containing nucleic acids to be encapsulated, through the use of a needle. Vesicles are spontaneously formed when the phospholipids are dispersed throughout the medium.

Detergent Dialysis

[0375] The Detergent dialysis method can be used to encapsulate nucleic acids. Briefly lipid and plasmid are solubilized in a detergent solution of appropriate ionic strength, after removing the detergent by dialysis, a stabilized lipid formulation is formed. Unencapsulated nucleic acid is then removed by ion-exchange chromatography and empty vesicles by sucrose density gradient centrifugation. The technique is highly sensitive to the cationic lipid content and to the salt concentration of the dialysis buffer, and the method is also difficult to scale.

Spontaneous Vesicle Formation by Ethanol Dilution

[0376] Stable lipid formulations can also be produced through the Spontaneous Vesicle Formation by Ethanol Dilution method in which a stepwise or dropwise ethanol dilution provides the instantaneous formation of vesicles loaded with nucleic acid by the controlled addition of lipid dissolved in ethanol to a rapidly mixing aqueous buffer containing the nucleic acid.

Encapsulation in Preformed Liposomes

[0377] The entrapment of nucleic acids can also be obtained starting with preformed liposomes through two different methods: (1) A simple mixing of cationic liposomes with nucleic acids which gives electrostatic complexes called “lipoplexes”, where they can be successfully used to transfect cell cultures, but are characterized by their low encapsulation efficiency and poor performance in vivo; and (2) a liposomal destabilization, slowly adding absolute ethanol to a suspension of cationic vesicles up to a concentration of 40% v/v followed by the dropwise addition of nucleic acids achieving loaded vesicles; however, the two main steps characterizing the encapsulation process are too sensitive, and the particles have to be downsized.

Excipients

[0378] The pharmaceutical compositions disclosed herein can be formulated using one or more excipients to: (1) increase stability; (2) increase cell transfection; (3) permit a sustained or delayed release (e.g., from a depot formulation of the polynucleotide, primary construct, or RNA); (4) alter the biodistribution (e.g., target the polynucleotide, primary construct, or RNA 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.

[0379] 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 (i.e., nucleic acid) with an excipient and/or one or more other accessory ingredients. 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.

[0380] Pharmaceutical compositions 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.

[0381] 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 disclosure can include, without limitation, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell

nanoparticles, peptides, proteins, cells transfected with primary DNA construct, or RNA (e.g., for transplantation into a subject), hyaluronidase, nanoparticle mimics and combinations thereof.

[0382] Accordingly, the pharmaceutical compositions described herein can include one or more excipients, each in an amount that together increases the stability of the nucleic acid in the lipid formulation, increases cell transfection by the nucleic acid, increases the expression of the encoded protein, and/or alters the release profile of encoded proteins. Further, the RNA of the present disclosure may be formulated using self-assembled nucleic acid nanoparticles.

[0383] 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 embodiments 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.

[0384] The pharmaceutical compositions of this disclosure may further contain as pharmaceutically acceptable carriers substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, and wetting agents, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, and mixtures thereof. For solid compositions, conventional nontoxic pharmaceutically acceptable carriers can be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like.

[0385] In certain embodiments of the disclosure, the RNA-lipid formulation may be administered in a time release formulation, for example in a composition which includes a slow release polymer. The active agent can be prepared with carriers that will protect against rapid release, for example a controlled release vehicle such as a polymer, microencapsulated delivery system, or a bioadhesive gel. Prolonged delivery of the RNA, in various compositions of the disclosure can be brought about by including in the composition agents that delay absorption, for example, aluminum monostearate hydrogels and gelatin.

Methods of Inducing Immune Responses

[0386] Provided herein, in some embodiments, are methods of inducing an immune response in a subject. Any type of immune response can be induced using the methods provided herein, including adaptive and innate immune responses. In one aspect, immune responses induced using the methods provided herein include an antibody response, a cellular immune response, or both an antibody response and a cellular immune response.

[0387] Methods of inducing an immune response provided herein include administering to a subject an effective amount of any nucleic acid molecule provided herein. In one aspect, methods of inducing an immune response include administering to a subject an effective amount of any composition comprising a nucleic acid molecule and a lipid provided herein. In another aspect, methods of inducing an immune response include administering to a subject an effective amount of any pharmaceutical composition comprising a nucleic acid molecule and a lipid formulation provided herein. In some aspects, nucleic acid molecules, compositions, and pharmaceutical composition provided here are vaccines that can elicit a protective or a therapeutic immune response, for example.

[0388] As used herein, the term "subject" refers to any individual or patient on which the methods disclosed herein are performed. The term "subject" can be used interchangeably with the term "individual" or "patient." The subject can be a human, although the subject may be an animal, as will be appreciated by those in the art. Thus, other animals, including mammals such as rodents (including mice, rats, hamsters and guinea pigs), cats, dogs, rabbits, farm animals including cows, horses, goats, sheep, pigs, etc., and primates (including monkeys, chimpanzees, orangutans and gorillas) are included within the definition of subject. As used herein, the term "effective amount" or "therapeutically effective amount" refers to that amount of a nucleic acid molecule, composition, or pharmaceutical composition described herein that is sufficient to effect the intended application, including but not limited to inducing an immune response and/or disease treatment, as defined herein. The therapeutically effective amount may vary depending upon the intended application (e.g., inducing an immune response, treatment, application in vivo), or the subject or patient and disease condition being treated, e.g., the weight and age of the subject, the species, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in a target cell. The specific dose will vary depending on the particular nucleic acid molecule, composition, or pharmaceutical composition chosen, the dosing regimen to be followed, whether it is

administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

[0389] Exemplary doses of nucleic acid molecules that can be administered include about 0.01 μg, about 0.02 μg, about 0.03 μg, about 0.04 μg, about 0.05 μg, about 0.06 μg, about 0.07 μg, about 0.08 μg, about 0.09 μg, about 0.1 μg, about 0.2 μg, about 0.3 μg, about 0.4 μg, about 0.5 μg, about 0.6 μg, about 0.7 μg, about 0.8 μg, about 0.9 μg, about 1.0 μg, about 1.5 μg, about 2.0 μg, about 2.5 μg, about 3.0 μg, about 3.5 μg, about 4.0 μg, about 4.5 μg, about 5.0 μg, about 5.5 μg, about 6.0 μg, about 6.5 μg, about 7.0 μg, about 7.5 μg, about 8.0 μg, about 8.5 μg, about 9.0 μg, about 9.5 μg, about 10 μg, about 11 μg, about 12 μg, about 13 μ, about 14 μg, about 15 μg, about 16 μg, about 17 μg, about 18 μg, about 19 μg, about 20 μg, about 21 μg, about 22 μg, about 23 μg, about 24 μg, about 25 μg, about 26 μg, about 27 μg, about 28 μg, about 29 μg, about 30 μg, about 35 μg, about 40 μg, about 45 μg, about 50 μg, about 55 μg, about 60 μg, about 65 μg, about 70 μg, about 75 μg, about 80 μg, about 85 μg, about 90 μg, about 95 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 250 μg, about 300 μg, about 350 μg, about 400 μg, about 450 μg, about 500 μg, about 600 μg, about 700 μg, about 800 μg, about 900 μg, about 1,000 μg, or more, and any number or range in between. In one aspect, the nucleic acid molecules are RNA molecules. In another aspect, the nucleic acid molecules are DNA molecules. Nucleic acid molecules can have a unit dosage comprising about 0.01 μg to about 1,000 μg or more nucleic acid in a single dose.

[0390] In some aspects, compositions provided herein that can be administered include about 0.01 μg, about 0.02 μg, about 0.03 μg, about 0.04 μg, about 0.05 μg, about 0.06 μg, about 0.07 μg, about 0.08 μg, about 0.09 μg, about 0.1 μg, about 0.2 μg, about 0.3 μg, about 0.4 μg, about 0.5 μg, about 0.6 μg, about 0.7 μg, about 0.8 μg, about 0.9 μg, about 1.0 μg, about 1.5 μg, about 2.0 μg, about 2.5 μg, about 3.0 μg, about 3.5 μg, about 4.0 μg, about 4.5 μg, about 5.0 μg, about 5.5 μg, about 6.0 μg, about 6.5 μg, about 7.0 μg, about 7.5 μg, about 8.0 μg, about 8.5 μg, about 9.0 μg, about 9.5 μg, about 10 μg, about 11 μg, about 12 μg, about 13 μg, about 14 μg, about 15 μg, about 16 μg, about 17 μg, about 18 μg, about 19 μg, about 20 μg, about 21 μg, about 22 μg, about 23 μg, about 24 μg, about 25 μg, about 26 μg, about 27 μg, about 28 μg, about 29 μg, about 30 μg, about 35 μg, about 40 μg, about 45 μg, about 50 μg, about 55 μg, about 60 μg, about 65 μg, about 70 μg, about 75 μg, about 80 μg,

about 85 μg, about 90 μg, about 95 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 250 μg, about 300 μg, about 350 μg, about 400 μg, about 450 μg, about 500 μg, about 600 μg, about 700 μg, about 800 μg, about 900 μg, about 1,000 μg, or more, and any number or range in between, nucleic acid and lipid. In other aspects, pharmaceutical compositions provided herein that can be administered include about 0.01 μg, about 0.02 μg, about 0.03 μg, about 0.04 μg, about 0.05 μg, about 0.06 μg, about 0.07 μg, about 0.08 μg, about 0.09 μg, about 0.1 μg, about 0.2 μg, about 0.3 μg, about 0.4 μg, about 0.5 μg, about 0.6 μg, about 0.7 μg, about 0.8 μg, about 0.9 μg, about 1.0 μg, about 1.5 μg, about 2.0 μg, about 2.5 μg, about 3.0 μg, about 3.5 μg, about 4.0 μg, about 4.5 μg, about 5.0 μg, about 5.5 μg, about 6.0 μg, about 6.5 μg, about 7.0 μg, about 7.5 μg, about 8.0 μg, about 8.5 μg, about 9.0 μg, about 9.5 μg, about 10 μg, about 11 μg, about 12 μg, about 13 μg, about 14 μg, about 15 μg, about 16 μg, about 17 μg, about 18 μg, about 19 μg, about 20 μg, about 21 μg, about 22 μg, about 23 μg, about 24 μg, about 25 μg, about 26 μg, about 27 μg, about 28 μg, about 29 μg, about 30 μg, about 35 μg, about 40 μg, about 45 μg, about 50 μg, about 55 μg, about 60 μg, about 65 μg, about 70 μg, about 75 μg, about 80 μg, about 85 μg, about 90 μg, about 95 μg, about 100 μg, about 125 μg, about 150 μg, about 175 μg, about 200 μg, about 250 μg, about 300 μg, about 350 μg, about 400 μg, about 450 μg, about 500 μg, about 600 μg, about 700 μg, about 800 μg, about 900 μg, about 1,000 μg, or more, and any number or range in between, nucleic acid and lipid formulation.

[0391] In one aspect, compositions provided herein can have a unit dosage comprising about 0.01 μg to about 1,000 μg or more nucleic acid and lipid in a single dose. In another aspect, pharmaceutical compositions provided herein can have a unit dosage comprising about 0.01 μg to about 1,000 μg or more nucleic acid and lipid formulation in a single dose. A vaccine unit dosage can correspond to the unit dosage of nucleic acid molecules, compositions, or pharmaceutical compositions provided herein and that can be administered to a subject. In one aspect, vaccine compositions of the instant disclosure have a unit dosage comprising about 0.01 μg to about 1,000 μg or more nucleic acid and lipid formulation in a single dose. In another aspect, vaccine compositions of the instant disclosure have a unit dosage comprising about 0.01 μg to about 50 μg nucleic acid and lipid formulation in a single dose. In yet another aspect, vaccine compositions of the instant disclosure have a unit dosage comprising about 0.2 μg to about 20 μg nucleic acid and lipid formulation in a single dose.

[0392] A dosage form of the composition of this disclosure can be solid, which can be reconstituted in a liquid prior to administration. The solid can be administered as a powder. The solid can be in the form of a capsule, tablet, or gel. In some embodiments, the pharmaceutical composition comprises a nucleic acid lipid formulation that has been lyophilized. In some embodiments, the lyophilized composition may comprise one or more lyoprotectants, such as, including but not necessarily limited to, glucose, trehalose, sucrose, maltose, lactose, mannitol, inositol, hydroxypropyl-β-cyclodextrin, and/or polyethylene glycol. In some embodiments, the lyophilized composition comprises a poloxamer, potassium sorbate, sucrose, or any combination thereof. In specific embodiments, the poloxamer is poloxamer 188. In some embodiments, the lyophilized compositions described herein may comprise about 0.01 to about 1.0% w/w of a poloxamer. In some embodiments, the lyophilized compositions described herein may comprise about 1.0 to about 5.0% w/w of potassium sorbate. The percentages may be any value or subvalue within the recited ranges, including endpoints.

[0393] In some embodiments, the lyophilized composition may comprise about 0.01 to about 1.0 % w/w of the nucleic acid molecule. In some embodiments, the composition may comprise about 1.0 to about 5.0 % w/w lipids. In some embodiments, the composition may comprise about 0.5 to about 2.5 % w/w of TRIS buffer. In some embodiments, the composition may comprise about 0.75 to about 2.75 % w/w of NaCl. In some embodiments, the composition may comprise about 85 to about 95 % w/w of a sugar. The percentages may be any value or subvalue within the recited ranges, including endpoints.

[0394] In a preferred embodiment, the dosage form of the pharmaceutical compositions described herein can be a liquid suspension of self-replicating RNA lipid nanoparticles described herein. In some embodiments, the liquid suspension is in a buffered solution. In some embodiments, the buffered solution comprises a buffer selected from the group consisting of HEPES, MOPS, TES, and TRIS. In some embodiments, the buffer has a pH of about 7.4. In some preferred embodiments, the buffer is HEPES. In some further embodiments, the buffered solution further comprises a cryoprotectant. In some embodiments, the cryoprotectant is selected from a sugar and glycerol or a combination of a sugar and glycerol. In some embodiments, the sugar is a dimeric sugar. In some embodiments, the sugar is sucrose. In some preferred embodiments, the buffer comprises HEPES, sucrose, and glycerol at a pH of 7.4. In certain embodiments, the composition comprises a HEPES, MOPS, TES, or TRIS buffer at a pH of about 7.0 to about 8.5. In some embodiments, the HEPES, MOPS, TES, or TRIS buffer

may at a concentration ranging from 7 mg/ml to about 15 mg/ml. The pH or concentration may be any value or subvalue within the recited ranges, including endpoints.

[0395] In some embodiments, the suspension is frozen during storage and thawed prior to administration. In some embodiments, the suspension is frozen at a temperature below about 70 °C. In some embodiments, the suspension is diluted with sterile water during intravenous administration. In some embodiments, intravenous administration comprises diluting the suspension with about 2 volumes to about 6 volumes of sterile water. In some embodiments, the suspension comprises about 0.1 mg to about 3.0 mg self-replicating RNA/mL, about 15 mg/mL to about 25 mg/mL of an ionizable cationic lipid, about 0.5 mg/mL to about 2.5 mg/mL of a PEG-lipid, about 1.8 mg/mL to about 3.5 mg/mL of a helper lipid, about 4.5 mg/mL to about 7.5 mg/mL of a cholesterol, about 7 mg/mL to about 15 mg/mL of a buffer, about 2.0 mg/mL to about 4.0 mg/mL of NaCl, about 70 mg/mL to about 110 mg/mL of sucrose, and about 50 mg/mL to about 70 mg/mL of glycerol. In some embodiments, a lyophilized self-replicating RNA-lipid nanoparticle formulation can be resuspended in a buffer as described herein.

[0396] In some embodiments, the compositions of the disclosure are administered to a subject such that a self-replicating RNA concentration of at least about 0.05 mg/kg, at least about 0.1 mg/kg, at least about 0.5 mg/kg, at least about 1.0 mg/kg, at least about 2.0 mg/kg, at least about 3.0 mg/kg, at least about 4.0 mg/kg, at least about 5.0 mg/kg of body weight is administered in a single dose or as part of single treatment cycle. In some embodiments, the compositions of the disclosure are administered to a subject such that a total amount of at least about 0.1 mg, at least about 0.5 mg, at least about 1.0 mg, at least about 2.0 mg, at least about 3.0 mg, at least about 4.0 mg, at least about 5.0 mg, at least about 6.0 mg, at least about 7.0 mg, at least about 8.0 mg, at least about 9.0 mg, at least about 10 mg, at least about 15 mg, at least about 20 mg, at least about 25 mg, at least about 30 mg, at least about 35 mg, at least about 40 mg, at least about 45 mg, at least about 50 mg, at least about 55 mg, at least about 60 mg, at least about 65 mg, at least about 70 mg, at least about 75 mg, at least about 80 mg, at least about 85 mg, at least about 90 mg, at least about 95 mg, at least about 100 mg, at least about 105 mg, at least about 110 mg, at least about 115 mg, at least about 120 mg, or at least about 125 mg self-replicating RNA is administered in one or more doses up to a maximum dose of about 300 mg, about 350 mg, about 400 mg, about 450 mg, or about 500 mg self-replicating RNA.

[0397] Any route of administration can be included in methods provided herein. In some aspects, nucleic acid molecules, compositions, and pharmaceutical compositions provided herein are administered intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route, such as by inhalation or by nebulization, for example. In some embodiments, the pharmaceutical compositions described are administered systemically. Suitable routes of administration include, for example, oral, rectal, vaginal, transmucosal, pulmonary including intratracheal or inhaled, or intestinal administration; parenteral delivery, including intradermal, transdermal (topical), intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, or intranasal. In particular embodiments, the intramuscular administration is to a muscle selected from the group consisting of skeletal muscle, smooth muscle and cardiac muscle. In some embodiments, the pharmaceutical composition is administered intravenously.

[0398] Pharmaceutical compositions may be administered to any desired tissue. In some embodiments, the self-replicating RNA delivered is expressed in a tissue different from the tissue in which the lipid formulation or pharmaceutical composition was administered. In preferred embodiments, self-replicating RNA is delivered and expressed in the liver.

[0399] In other aspects, nucleic acid molecules, compositions, and pharmaceutical compositions provided herein are administered intramuscularly.

[0400] In some aspects, the subject in which an immune response is induced is a healthy subject. As used herein, the term “healthy subject” refers to a subject not having a condition or disease, including an infectious disease or cancer, for example, or not having a condition or disease against which an immune response is induced. Accordingly, in some aspects, a nucleic acid molecule, composition, or pharmaceutical composition provided herein is administered prophylactically to prevent an infectious disease or cancer, for example. In other aspects, the subject in which an immune response is induced has cancer. The subject may suffer from any cancer or have any tumor, including solid and liquid tumors. In one aspect, the cancer is kidney cancer, renal cancer, urinary bladder cancer, prostate cancer, uterine cancer, breast cancer, cervical cancer, ovarian cancer, lung cancer, liver cancer, stomach cancer, colon cancer, rectal cancer, oral cavity cancer, pharynx cancer, pancreatic cancer, thyroid cancer, melanoma, skin cancer, head and neck cancer, brain cancer, hematopoietic cancer, leukemia, lymphoma, bone cancer, or sarcoma. Accordingly, a nucleic acid molecule, composition, or pharmaceutical

composition provided herein can be administered therapeutically, i.e., to treat a condition or disease, such as cancer, after the onset of the condition or disease.

[0401] As used herein, the terms "treat," "treatment," "therapy," "therapeutic," and the like refer to obtaining a desired pharmacologic and/or physiologic effect, including, but not limited to, alleviating, delaying or slowing the progression, reducing the effects or symptoms, preventing onset, inhibiting, ameliorating the onset of a diseases or disorder, obtaining a beneficial or desired result with respect to a disease, disorder, or medical condition, such as a therapeutic benefit and/or a prophylactic benefit. "Treatment," as used herein, includes any treatment of a disease in a mammal, particularly in a human, and includes: (a) preventing the disease from occurring in a subject, including a subject which is predisposed to the disease or at risk of acquiring the disease but has not yet been diagnosed as having it; (b) inhibiting the disease, i.e., arresting its development; and (c) relieving the disease, i.e., causing regression of the disease. A therapeutic benefit includes eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder. In some aspects, for prophylactic benefit, treatment or compositions for treatment, including pharmaceutical compositions, are administered to a subject at risk of developing a particular disease, or to a subject reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made. The methods of the present disclosure may be used with any mammal or other animal. In some aspects, treatment results in a decrease or cessation of symptoms. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0402] Nucleic acid molecules, compositions, and pharmaceutical compositions provided herein can be administered once or multiple times. Accordingly, nucleic acid molecules, compositions, and pharmaceutical compositions provided herein can be administered one, two, three, four, five, six, seven, eight, nine, ten, or more times. Timing between two or more administrations can be one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, weeks, ten weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32

weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or more weeks, and any number or range in between. In some aspects, timing between two or more administrations is one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, or more months, and any number or range in between. In other aspects, timing between two or more administrations can be one year, two years, three years, four years, five years, six years, seven years, eight years, nine years, ten years, or more years, and any number or range in between, Timing between the first and any subsequent administration can be the same or different. In one aspect, nucleic acid molecules, compositions, or pharmaceutical compositions provided herein are administered once.

[0403] More than one nucleic acid molecule, composition, or pharmaceutical composition can be administered in the methods provided herein. In one aspect, two or more nucleic acid molecules, compositions, or pharmaceutical compositions provided herein are administered simultaneously. In another aspect, two or more nucleic acid molecules, compositions, or pharmaceutical compositions provided herein are administered sequentially. Simultaneous and sequential administrations can include any number and any combination of nucleic acid molecules, compositions, or pharmaceutical compositions provided herein. Multiple nucleic acid molecules, compositions, or pharmaceutical compositions that are administered together or sequentially can include transgenes encoding different antigenic proteins or fragments thereof. In this manner, immune responses against different antigenic targets can be induced. Two, three, four, five, six, seven, eight, nine, ten, or more nucleic acid molecules, compositions, or pharmaceutical compositions including transgenes encoding different antigenic proteins or fragments thereof can be administered simultaneously or sequentially. Any combination of nucleic acid molecules, compositions, and pharmaceutical compositions including any combination of transgenes can be administered simultaneously or sequentially. In some aspects, administration is simultaneous. In other aspects, administration is sequential. Timing between two or more administrations can be one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, weeks, ten weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 25 weeks, 26 weeks, 27 weeks, 28 weeks, 29

weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, or more weeks, and any number or range in between. In some aspects, timing between two or more administrations is one month, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, 11 months, 12 months, 13 months, 14 months, 15 months, months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, or more months, and any number or range in between. In other aspects, timing between two or more administrations can be one year, two years, three years, four years, five years, six years, seven years, eight years, nine years, ten years, or more years, and any number or range in between, Timing between the first and any subsequent administration can be the same or different. Nucleic acid molecules, compositions, and pharmaceutical compositions provided herein can be administered with any other vaccine or treatment.

[0404] Following administration of the composition to the subject, the protein product encoded by the self-replicating RNA of the disclosure (e.g., an antigen) is detectable in the target tissues for at least about one to seven days or longer. The amount of protein product necessary to achieve a therapeutic effect will vary depending on antibody titer necessary to generate an immunity to COVID-19 in the patient. For example, the protein product may be detectable in the target tissues at a concentration (e.g., a therapeutic concentration) of at least about 0.025-1.5 μg/ml (e.g., at least about 0.050 μg/ml, at least about 0.075 μg/ml, at least about 0.1 μg/ml, at least about 0.2 μg/ml, at least about 0.3 μg/ml, at least about 0.4 μg/ml, at least about 0.5 μg/ml, at least about 0.6 μg/ml, at least about 0.7 μg/ml, at least about 0.8 μg/ml, at least about 0.9 μg/ml, at least about 1.0 μg/ml, at least about 1.1 μg/ml, at least about 1.2 μg/ml, at least about 1.3 μg/ml, at least about 1.4 μg/ml, or at least about 1.5 μg/ml), for at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45 days or longer following administration of the composition to the subject.

[0405] In some embodiments, the composition described herein may be administered one time. In some embodiments, the composition described herein may be administered two times.

[0406] In some embodiments, the composition may be administered in the form of a booster dose, to a subject who was previously vaccinated against coronavirus.

[0407] In some embodiments, a pharmaceutical composition of the present disclosure is administered to a subject once per month. In some embodiments, a pharmaceutical composition of the present disclosure is administered to a subject twice per month. In some embodiments, a pharmaceutical composition of the present disclosure is administered to a subject three times per month. In some embodiments, a pharmaceutical composition of the present disclosure is administered to a subject four times per month.

[0408] Alternatively, the compositions of the present disclosure may be administered in a local rather than systemic manner, for example, via injection of the pharmaceutical composition directly into a targeted tissue, preferably in a depot or sustained release formulation. Local delivery can be affected in various ways, depending on the tissue to be targeted. For example, aerosols containing compositions of the present disclosure can be inhaled (for nasal, tracheal, or bronchial delivery); compositions of the present disclosure can be injected into the site of injury, disease manifestation, or pain, for example; compositions can be provided in lozenges for oral, tracheal, or esophageal application; can be supplied in liquid, tablet or capsule form for administration to the stomach or intestines, can be supplied in suppository form for rectal or vaginal application; or can even be delivered to the eye by use of creams, drops, or even injection. Formulations containing compositions of the present disclosure complexed with therapeutic molecules or ligands can even be surgically administered, for example in association with a polymer or other structure or substance that can allow the compositions to diffuse from the site of implantation to surrounding cells. Alternatively, they can be applied surgically without the use of polymers or supports.

Combinations

[0409] The self-replicating RNA, formulations thereof, or encoded proteins described herein 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. Preferably, the methods of treatment of the present disclosure encompass 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, a self-replicating RNA of the disclosure may be used in combination with a pharmaceutical agent for immunizing or vaccinating a subject. In general, it is expected that agents utilized in combination with the presently disclosed self-replicating RNA and formulations thereof 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 as are known in the art.

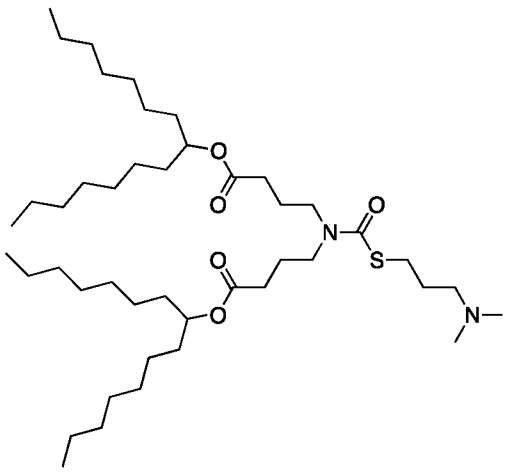
Ranges

[0410] Throughout this disclosure, various aspects can be presented in range format. It should be understood that any description in range format is merely for convenience and brevity and not meant to be limiting. Accordingly, the description of a range should be considered to have specifically disclosed all possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6, etc., as well as individual numbers within that range, for example 1, 2, 2.1, 2.2, 2.5, 3, 4, 4.75, 4.8, 4.85, 4.95, 5, 5.5, 5.75, 5.9, 5.00, and 6. This applies to a range of any breadth.

EXAMPLE 1

[0411] This example describes a comparison of design and expression of mRNA and self-replicating RNA (STARR™) platforms.

[0412] Both mRNA and STARR™ vaccine constructs were designed to encode the full-length SARS-CoV-2 S protein (1273 aa), with the STARR™ self-replicating RNA additionally encoding for the Venezuelan equine encephalitis virus (VEEV) replicase genes (Figure 1A; STARR™ vaccine construct corresponding to an RNA having a sequence of SEQ ID NO:125, with U in place of T, referred to herein as "STARR™ SARS-CoV-2 RNA"; mRNA corresponding to a sequence of SEQ ID NO:126, with U in place of T and including a tobacco etch virus (TEV) 5' UTR, a Xenopus beta-globin (Xbg) 3' UTR, and a codon-optimized open reading frame encoding the SARS-CoV-2 glycoprotein). The characteristics of these different constructs was studied first. Constructs were encapsulated in the same LNP composition. Briefly, RNA constructs were encapsulated into lipid nanoparticles (LNPs) that included four lipid excipients (an ionizable cationic lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-DMG) dispersed in HEPES buffer (pH 8.0) containing sodium chloride and the cryoprotectants sucrose and glycerol. The ionizable cationic lipid had the following structure:



[0413] Despite differences in RNA lengths of mRNA and the STARR™ SARS-CoV-2 RNA construct, the LNP diameter, polydispersity index and RNA trapping efficiency were similar (Figure 1B). In vitro expression of the mRNA vaccine and the STARR™ SARS-CoV-2 RNA construct were confirmed in cell lysate 24 hours post-transfection through positive western blot detection of the S protein (Figure 1C). It was also observed that both mRNA and STARR™ vaccines expressed a mixture of full-length S protein and cleaved S protein, i.e., S was cleaved into S1 and S2 transmembrane and cytoplasmic membrane domains (Figure 1C).

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In vivo protein expression of the two RNA platforms in BALB/c mice was compared by using mRNA and STARR™ constructs that expressed a luciferase reporter (Figure 1D). Animals injected with the mRNA vaccine construct showed high in vivo luciferase expression at day 1, although the expression levels declined over time. In contrast, luciferase expression in STARR™ injected mice showed sustained or even increased signals, apart from those given the 0.2 μg dose, until day 7 post-inoculation (Figure 1D).

[0414] These data show that dose-for-dose, antigen expression was more prolonged with the STARR™ compared to the mRNA vaccine.

EXAMPLE 2

[0415] This example describes immune gene expression following the STARR™ construct and mRNA vaccination.

[0416] C57BL/6J mice were inoculated with STARR™ SARS-CoV-2 RNA (encoding the SARS-CoV-2 glycoprotein as described above (Example 1)) and mRNA vaccines at 0.2 μg, 2 μg and 10 μg doses or PBS control. No significant mean loss in animal weight occurred over the first 4 days, except for those that received 10 μg of STARR™ SARS-CoV-2 RNA (Figure 2A). However, apart from weight loss, there were few other clinical signs as indicated by the minimal differences in clinical scores. Both weight and clinical scores improved after day 3 post vaccination.

[0417] The innate immune response, such as the type-I interferon (IFN) response, has previously been shown to be associated with vaccine immunogenicity following yellow fever vaccination, for example. Furthermore, reactive oxygen species-driven pro-inflammatory responses have been shown to underpin systemic adverse events in yellow fever vaccination. Therefore, the expression of innate immune and pro-inflammatory genes in whole blood of C57BL/6 mice inoculated was measured with either PBS, mRNA vaccine, or the STARR™ SARS-CoV-2 RNA construct. Genes in the type-I IFN pathway were the most highly expressed in animals inoculated with STARR™ SARS-CoV-2 RNA compared to either mRNA vaccine or PBS (Figure 2B and Figure 8). By contrast, genes associated with pro-inflammatory responses were mostly reduced in abundance following vaccination STARR™ SARS-CoV-2 RNA compared with either mRNA vaccine or PBS (Figure 2B and Figure 8).

[0418] Since adaptive immune responses develop in germinal centers in the draining lymph nodes, the draining lymph nodes were dissected at day 7 post-inoculation (study schematic in Figure 2A). The inguinal lymph nodes of mice inoculated with STARR™ SARS-CoV-2 RNA showed a dose-dependent increase in weight, unlike those from mice inoculated with either mRNA vaccine or PBS; the mean weight of lymph nodes from mice given 10 μg of STARR™ SARS-CoV-2 RNA was significantly higher than those given the equivalent mRNA vaccine (Figure 2C). Principal component analysis (PCA) of immune gene expression showed clustering of responses to each of the 3 doses of STARR™ SARS-CoV-2 RNA away from the PBS control (STARR™ RNA): depicted as lower sphere in Figure 2D, smallest sphere in Figure 2E, and lower sphere in Figure 2F; PBS control: depicted as upper sphere in Figure 2D, lower elongated and narrow sphere in Figure 2E, and upper sphere in Figure 2F) indicating clear differences in immune gene expression between STARR™ SARS-CoV-2 RNA vaccinated and placebo groups. These trends were also dissimilar to those from mice given mRNA vaccine where at all tested doses, the PCA displayed substantial overlap with placebo (mRNA: shown as center sphere in Figure 2D, large upright sphere in Figure 2E, and as flat line with four data points along the bottom of the center square in Figure 2F; placebo (PBS control): shown as upper sphere in Figure 2D, lower elongated and narrow sphere in Figure 2E, and upper sphere in Figure 2F).

[0419] Differentially expressed genes in the lymph nodes of mice given STARR™ SARS-CoV-2 RNA compared to those inoculated with mRNA vaccine were assessed next. Volcano plot analysis identified significant upregulation of several innate, B cell, and T cells genes in STARR™ SARS-CoV-2 RNA immunized animals (Figure 2G-2I). Some of the most highly differentially expressed genes included, for example, GZMB (important for target cell killing by cytotoxic immune cells), S100A8 and S100A9 (factors that regulate immune responses via TLR4), TNFRSF17 (also known as BCMA and regulates humoral immunity), CXCR3 (chemokine receptor involved in T cell trafficking and function) and AICDA (mediates antibody class switching and somatic hypermutation in B cells).

[0420] These findings collectively indicate that the adaptive immune responses in the draining lymph nodes of mice inoculated with STARR™ SARS-CoV-2 RNA appeared to be significantly different compared to immune responses in mice inoculated with a non-replicating mRNA vaccine.

EXAMPLE 3

[0421] This example describes STARR™ SARS-CoV-2 RNA -induced T cell responses.

[0422] The cellular immune response following vaccination of C57BL/6 mice (n=5 per group) with mRNA or the STARR™ SARS-CoV-2 RNA construct encoding the SARS-CoV-2 glycoprotein described above (Example 1) was investigated next. At day 7 post-vaccination, spleens were harvested and assessed for CD8 and CD4 T cells by flow-cytometry. The CD8+ T cell CD44+CD62L- effector/memory subset was significantly expanded in STARR™ SARS-CoV-2 RNA vaccinated mice compared to those given either PBS or mRNA vaccine (Figure 3A-B). There was no statistically significant difference in the proportion of CD4+ T effector cells of these animals (Figure 3C). IFNγ+ CD8+ T cells (with 2 μg and 10 μg doses) and IFNγ+ CD4+ T cells (in 0.2 μg and 10 μg) were proportionately higher, as found using intracellular staining (ICS) with flow cytometry, in STARR™ SARS-CoV-2 RNA as compared to mRNA vaccinated animals (Figure 3D-3F).

[0423] SARS-CoV-2 specific cellular responses were assessed in vaccinated animals by ELISPOT. A set of 15-mer peptides covering the SARS-CoV-2 S protein were divided into 4 pools and tested for IFNγ+ responses in splenocytes of vaccinated and non-vaccinated animals. SARS-CoV-2-specific cellular responses (displayed as IFNγ+ SFU/106 cells) were detected by ELISPOT in both STARR™ SARS-CoV-2 RNA and mRNA vaccine immunized animals compared to PBS control (Figure 3G-3I). These responses were higher across the doses in STARR™ SARS-CoV-2 RNA compared to mRNA vaccinated groups (Figure 3G-3I). Even the highest tested dose (10 μg) of mRNA vaccine produced IFNγ+ ELISPOT responses that were appreciably lower than those by the lowest dose (0.2 μg) of STARR™ SARS-CoV-2 RNA.

[0424] These results show that the STARR™ SARS-CoV-2 RNA construct induced strong T cell responses.

EXAMPLE 4

[0425] This example illustrates humoral responses following vaccination with STARR™ SARS-CoV-2 RNA.

[0426] SARS-CoV-2-specific humoral responses following vaccination were characterized in two different mouse models, BALB/c and C57BL/6. Female mice (n=5 per group) were

vaccinated at day 0 and bled every 10 days, up to day 60 for BALB/c and day 30 for C57BL/6 (Figure 4A). SARS-CoV-2 S-specific IgM responses were tested at 1:2000 serum dilution using an in-house Luminex immuno-assay. All tested doses of mRNA vaccine and STARR™ SARS-CoV-2 RNA (corresponding to SEQ ID NO:125, as described in Example 1 above) produced detectable S-specific IgM responses in both mouse models (Figure 4B-4C). When comparing mRNA to STARR™ SARS-CoV-2 RNA vaccinated BALC/c mice, no difference in IgM responses was observed; IgM levels in C57BL/6 mice were higher in STARR™ SARS-CoV-2 RNA vaccinated C57BL/6 mice at day 10 post vaccination. In contrast, SARS-CoV-2 S-specific IgG (at 1:2000 serum dilution) levels were higher from day 20 onwards in animals inoculated with STARR™ SARS-CoV-2 RNA compared to mRNA vaccine (Figure 4D-4E). Remarkably, the IgG levels continued to show an increasing trend in STARR™ SARS-CoV-2 RNA vaccinated mice, both BALB/c and C57BL/6, until day 50 post-vaccination with a single inoculation across all the doses. This trend contrasted with mice that received the mRNA vaccine where in BALB/c mice antibody levels plateaued after day 10 post-vaccination; increasing S-specific IgG levels were observed in mRNA-vaccinated C57BL/6 mice but these were lower than those seen in mice that received STARR™ SARS-CoV-2 RNA.

[0427] Further characterization of the SARS-CoV-2 specific IgG response in vaccinated animals was conducted at day 30 post-immunization to assess which regions of the S protein are targeted. IgG endpoint titers were estimated to full ectodomain S protein, S1, S2 and receptor binding domain (RBD) regions. For both vaccine candidates the majority of SARS-CoV-2 specific IgG recognized S1, although high IgG endpoint titers were also detected to S2 protein (Figure 4F-4G). However, STARR™ SARS-CoV-2 RNA elicited IgG endpoint titers were significantly higher compared to those produced by mRNA vaccination (Figure 4F-4G). Notably, IgG that bind the receptor binding domain (RBD) of S protein, which is an immunodominant site of neutralizing antibodies, were also higher in STARR™ SARS-CoV-2 RNA compared to mRNA vaccinated animals. Furthermore, at lower doses, mRNA vaccine but not STARR™ SARS-CoV-2 RNA struggled to elicit high SARS-CoV-2 specific IgG titers in the more Th1 dominant C57BL/6 mouse strain (Figure 4G). Taken collectively, a single dose of STARR™ SARS-CoV-2 RNA induced significant differences in immune gene expression and superior cellular immune responses in draining lymph nodes compared to mRNA vaccine and consequently humoral immune responses.

[0428] These data show that STARR™ SARS-CoV-2 RNA vaccination induced elevated humoral responses as compared to mRNA vaccination.

EXAMPLE 5

[0429] This example illustrates reduced risk of immune enhancement upon STARR™ SARS-CoV-2 RNA vaccination.

[0430] A safety consideration for coronavirus vaccine is a risk of vaccine-mediate immune enhancement of respiratory disease. Indeed, SARS-CoV and MERS-CoV vaccine development have highlighted the importance of Th1 skewed responses to avoid vaccine-induced immune enhancement. Therefore, the Th1/ Th2 balance elicited by both mRNA and STARR™ SARS-CoV-2 RNA (self-replicating RNA construct as described in Example 1 above) vaccination was investigated. The IgG subclass fate of plasma cells is influenced by T helper (Th) cells. At day 30 post-vaccination, both mRNA and STARR™ SARS-CoV-2 RNA, except the 0.2 μg dose in C56BL/6J mice, induced comparable amounts of SARS-CoV-2 S-specific IgG1, a Th2-associated IgG subclass in mice (Figure 5A-5B). In contrast, the Th1-associated IgG subclasses - IgG2a in BALB/c and IgG2c in C56BL/6J - were significantly greater in STARR™ SARS-CoV-2 RNA vaccinated animals. The ratios of S protein-specific IgG2a/IgG1 (BALBc) and IgG2c/IgG1 (C57BL/6) were greater than 1 in STARR™ SARS-CoV-2 RNA vaccinated animals (Figure 5A-5B). Except for the 0.2 ug dose, these ratios were all significantly greater with STARR™ SARS-CoV-2 RNA compared to mRNA vaccinated animals.

[0431] ICS was used to investigate the production of IFNγ (Th1 cytokine) and IL4 (Th2 cytokine) by CD4+ T cells in spleens of day 7 vaccinated C56BL/6J mice. As shown above (Example 3), compared to mRNA vaccination, IFNγ levels were significantly greater in STARR™ SARS-CoV-2 RNA vaccinated animals (Figure 3F). IL4 expression in CD4 T cells was slightly higher in mRNA as compared to STARR™ SARS-CoV-2 RNA at 0.2 μg and 2 μg doses (Figure 5C). In comparing the IFNγ and IL4 levels in individual mice, the ratios of IFNγ/IL4 in CD4+ T cells for both STARR™ SARS-CoV-2 RNA and mRNA vaccinated mice were above 1 (Figure 5D). The ratio of IFNγ/IL4 in CD4+ T cells in mice given the 0.2 μg and 2 μg doses were significantly greater with STARR™ SARS-CoV-2 RNA than mRNA vaccination (Figure 5F). However, without being limited by theory, the elevated ratios in these doses appeared to be due to the lowered IL4 expression at levels below background (i.e., PBS control mice), rather than reduced IFNγ and hence Th1 activity.

[0432] Taken collectively, these data show that STARR™ SARS-CoV-2 RNA produced Th1 instead of Th2 skewed adaptive immune responses.

EXAMPLE 6

[0433] This example illustrates the quality of STARR™ SARS-CoV-2 RNA -induced humoral immune responses.

[0434] The binding strength (avidity) and the neutralizing ability of the antibody response elicited by the self-replicating STARR™ SARS-CoV-2 RNA (construct as described in Example 1 above) and mRNA vaccine constructs was assessed next. Serum IgG avidity was measured at day 30 post-vaccination using a modified Luminex immuno-assay with 8M urea washes. STARR™ SARS-CoV-2 RNA elicited higher avidity S protein-specific IgG than mRNA in both mouse models at all tested doses (Figure 6A). These differences were observed, with the exception of 0.2 μg in BALB/c, across all doses (Figure 6A), indicating that STARR™ SARS-CoV-2 RNA elicited better quality antibodies than conventional mRNA.

[0435] Neutralization of live SARS-CoV-2 by serum from vaccinated animals was assessed using the plaque reduction neutralization test (PRNT). At day 30 STARR™ SARS-CoV-2 RNA vaccinated BALB/c showed a clear dose dependent elevation in PRNT50 titers; 4 out of 5 (80%) of mice in the 10 μg STARR™ SARS-CoV-2 RNA group showed PRNT50 titers above the 320 upper limit (Figure 6B). Similar dose-dependent trends in PRNT50 titers were also found in C57BL/6 mice, although in these animals, the PRNT50 titers of several animals exceeded the 320 upper limit even with a low 0.2 μg dose vaccination (Figure 6B). In contrast, PRNT50 titers in animals inoculated with mRNA vaccine construct were, except for one C57BL/6J mouse that received 10 μg dose, all <20 (Figure 6B). Unexpectedly and surprisingly, PRNT50 and PRNT70 titers of STARR™ SARS-CoV-2 RNA vaccinated BALBc mice continued to rise between day 30 and day 60 after a single dose of vaccination (Figure 6C-6D). These titers were also comparable to PRNT70 titers in sera from convalescent COVID-19 patients (Figure 6D).

[0436] S protein IgG titers also positively correlated with PRNT50 titers in both mouse models (Figure 6E). Similar positive correlations were also observed with IgG against S1 and RBD (Figure 9). By contrast, no correlation was found between IgG and PRNT50 titers in mRNA vaccinated mice (Figure 6E). Taken collectively, without being limited by theory, these antibody response analyses indicate that the higher PRNT50 titers following STARR™ SARS-CoV-2 RNA vaccination are not only attributable to the amount of IgG produced but also due to superiority of the quality of the anti-SARS-CoV-2 antibodies.

[0437] In summary, STARR™ SARS-CoV-2 RNA induced qualitatively superior humoral immune response than conventional mRNA.

EXAMPLE 7

[0438] This example illustrates the effect of a second dose of STARR™ SARS-CoV-2 RNA.

[0439] A possible added benefit of a second dose of STARR™ SARS-CoV-2 RNA (self-replicating RNA construct as described in Example 1 above) to the cellular and humoral immune responses to the S protein of SARS-CoV-2 was explored next. The clinical scores after the second dose were higher than after the first dose (Figure 7A). Like the first dose, mice that received 2 μg and 10 μg of STARR™ SARS-CoV-2 RNA experienced weight loss (Figure 7B). The IgG response to a second dose of STARR™ SARS-CoV-2 RNA produced an appreciable boost in S protein-specific IgG levels, but only with 0.2 μg and 2 μg of STARR™ SARS-CoV-2 RNA (Figure 7C). Without being limited by theory, a likely reason for the lack of increase in the anti-S protein specific IgG levels for the 10 μg dose is that the amount of fluorescence is near the saturation point of the detector and sera was not further diluted to observe and increase. However, in a subsequent Balb/c mouse study, the sera from mice vaccinated with a 5 μg RNA dose administered unilaterally in a 0.05 mL injection volume produced a significant increase in neutralizing antibody titers as assayed using a 96 well microneutralization assay format. Mice were bled every 14 days and a second vaccination of 5 μg was administered on day 28. 4 mice were injected with a VEEV replicon RNA expressing luciferase as a negative control and 6 mice were vaccinated with STARR™ SARS-CoV-2 RNA. The results are shown in Table 8 below.

Table 7. Microneutralization Titers (MN50) in Balb/c Mice

		Microneutralization Titers (MN50)				
Mouse No.	Treatment	Wk 0	Wk2	Wk4	Wk6	Wk8
1	Luciferase	<10	<10	<10	<10	<10
2	Luciferase	<10	<10	<10	<10	<10
3	Luciferase	<10	<10	<10	<10	<10
4	Luciferase	<10	<10	<10	<10	<10

5	STARR™ SARS-CoV-2 RNA	<10	1,280	5,120	327,680	81,920
6	STARR™ SARS-CoV-2 RNA	<10	640	20,480	327,680	327,680
7	STARR™ SARS-CoV-2 RNA	<10	1,280	2,560	163,840	163,840
8	STARR™ SARS-CoV-2 RNA	<10	1,280	10,240	327,680	163,840
9	STARR™ SARS-CoV-2 RNA	<10	640	40,960	327,680	327,680
10	STARR™ SARS-CoV-2 RNA	<10	1,280	10,240	327,680	327,680
Avg Geometric Mean			1,016	10,240	29,1930	206,426

[0440] The neutralization titers increased ~ 10 fold between day 14 and day 28 post vaccination. Following the boost on day 28, the neutralization titers increased an additional 20 fold 14 days post boost.

[0441] To determine if there was added benefit in IFNγ+ CD8+ T cell counts from a second dose vaccination, CD8 T cell IFNγ responses in mice given only a prime were compared to responses of mice given a prime and a boost. Fold change in IFNγ+ CD8+ T cells in the vaccinated over PBS control mice was calculated for mice given either a prime only or given a prime and boost. The fold change of IFNγ+ CD8+ T cells was similar following the prime and prime+boost for 2 μg and 10 μg doses of STARR™ SARS-CoV-2 RNA (Figure 7D-7E); the 0.2 μg dose showed higher fold change of IFNγ+ CD8+ T cells between prime (at day 7) and prime+boost (day 50). Vaccination with 0.2 μg of mRNA also showed increased IFNγ+ CD8+ T cells relative to PBS control after two doses of vaccination. Without being limited by theory, these findings suggest that a second 10 μg dose of STARR™ SARS-CoV-2 RNA did not produce superior cellular immunity compared to single dose vaccination. Thus, there was no apparent benefit from a second 10 μg dose of STARR™ SARS-CoV-2 RNA.

[0442] Taken collectively, these data suggest that 10 μgSTARR™ SARS-CoV-2 RNA offers the opportunity of a single dose vaccination to protect against COVID-19.

EXAMPLE 8

[0443] This example illustrates protection from SARS-CoV-2 viral challenge in mice following vaccination with STARR™ SARS-CoV-2 self-replicating RNA.

[0444] A mouse viral challenge study was conducted with human ACE2 transgenic mice. Mice were immunized with 2 μg and 10 μg RNA doses of STARR™ SARS-CoV-2 RNA (RNA construct as described in Example 1 above) or injected with PBS. There were three different cohorts with 5 mice in each treatment group. Cohorts 1 and 3 received a lethal SARS-CoV-2 virus challenge load of 5 X 105 TCID50. Cohort 1 was monitored for survival and Cohort 3 was euthanized 5 days after challenge. Lungs were assayed for viral load and processed for histopathology. Cohorts 2 received a sublethal viral load of 5 X 104 TCID50. Cohort 2 was euthanized 5 days after virus challenge and lungs were assayed for infectious virus and processed for histopathology. All mice were inoculated intratracheally 30 days post-vaccination with a single dose of STARR™ SARS-CoV-2 RNA.

[0445] All mice injected with PBS in cohort 1 were dead by day 7, whereas all vaccinated mice showed no signs of infection 15 days after viral challenge (Figure 10). For Cohort 2 receiving a sublethal viral load, 10 to 3,300 copies of virus was measured by RT-PCR in the lungs with an average of 1,200 copies, whereas no copies of viral RNA were measured in mice vaccinated with ARTC-021 at 2 μg and 10 μg RNA doses (LOD was 0.1 copies; Figure 11, left). Copies of viral RNA were also observed in the brain ranging from 20 to 80 in the PBS treatment group, whereas no viral RNA copies were measured in the brains of mice vaccinated with either 2.0 μg or 10.0 μg RNA doses (Figure 11, right). Lastly, lungs were carefully processed and assayed for lung plaque titers. The average plaque titers for the group injected with PBS was 8 X 103/mL of lung homogenate, whereas no plaques were detected for mice vaccinated with either 2.0 μg or 10.0 μg or STARR™ SARS-CoV-2 RNA (Figure 12). Lung and brain tissues from Cohort 3 are being assayed for viral copy number and infectious virus. Histopathology of lungs for cohorts 2 and 3 is in progress.

[0446] These results show that vaccination with STARR™ SARS-CoV-2 self-replicating RNA protected mice from a lethal SARS-CoV-2 infection and protected against lung and brain infection upon challenge with a sublethal dose of SARS-CoV-2.

EXAMPLE 9

[0447] The COVID-19 pandemic is caused by infection with the SARS-CoV-2 virus. A major mutation detected to date in the SARS-CoV-2 viral envelope spike protein, which is responsible for virus attachment to the host and is also the main target for host antibodies, is a mutation of an aspartate (D) at position 614 found frequently in Chinese strains to a glycine (G). VEEV Replicon transcripts expressing the D614 and G614 versions of the SARS-CoV-2

spike glycoprotein were formulated with the exact same lipid formulation as studies described in Examples 1-8. Balb/c mice were vaccinated with a single RNA administration of 0.2 μg, 2.0 μg and 10.0 μg of RNA. There were 5 mice per dose. Mice were bled on days, 14, 28 and 42 post vaccination. Sera was diluted 1/2000 and incubated with Luminex beads derivatized with the SARS-CoV-2 spike glycoprotein containing the D614 amino acid sequence. A secondary mouse antibody derivatized with a fluorophore was used to assay for bound antibody to the beads and adjusted mean fluorescence intensity (MFI) was measured as a function of RNA dose, shown in Figure 13. The results showed that MFI increased as a function of RNA dose with slightly higher MFI observed for the serum from mice immunized with the G614 spike glycoprotein. This slight elevation is attributed to a lower percentage of full length RNA with the D614 amino acid sequence. An important conclusion is that the serum from mice immunized with the G614 spike glycoprotein RNA construct was able to bind to spike glycoprotein with the D614 amino acid sequence, indicative of cross reactivity.

[0448] These results show that immunization with a G614 spike glycoprotein expressed from self-replicating RNA results in production of antibodies that are able to bind to a D614 spike glycoprotein.

DISCUSSION OF EXAMPLES 1-9

[0449] The pandemic of COVID-19 has necessitated rapid development of vaccines, as physical distancing to prevent SARS-CoV-2 transmission is not a sustainable long-term solution. Several COVID-19 vaccine candidates are now in clinical trials and more are entering first-in-human trials. However, a majority of vaccine candidates being developed require two doses for sufficient adaptive immunity. A single dose vaccine that generates both cellular and humoral immunity, without elevating the risk of vaccine-mediated immune enhancement, remains an unmet need. Without being limited by theory, deployment of a single dose vaccine would enable greater level of compliance and enable distribution of finite production of vaccines to more susceptible people globally.

[0450] Among licensed vaccines, live attenuated vaccines can offer durable protection against viral diseases. Live vaccines infect and replicate at sites of inoculation and some even in draining lymph nodes. Replication enables endogenous expression of viral antigens that enables antigen presentation to stimulate cytotoxic CD8+ T cells. Expressed antigens would also be taken up by antigen presenting cells to trigger CD4+ T cell help that drive affinity

maturation in B cells. Studies on the live attenuated yellow fever vaccine have shown that a longer period of stimulation of the adaptive immune response results in superior adaptive immune responses. Without being limited by theory, simulating the processes of live vaccination could offer a chance of durable immunity against COVID-19.

[0451] In a crisis such as COVID-19, a nucleic acid vaccine platform offers opportunities for accelerated development. In studies described herein, a side-by-side comparison of the immunogenicity elicited by two SARS-CoV-2 vaccines candidates was conducted, a non-replicative mRNA construct and STARR™ SARS-CoV-2 RNA. Compared to an mRNA vaccine, STARR™ SARS-CoV-2 RNA produced higher and longer protein expression in vivo and upregulated gene expression of several innate, B cell, and T cell response genes in the blood and draining lymph nodes. These properties translated into significantly greater CD8+ T cell responses, IFNγ+ ELISPOT responses, and SARS-CoV-2 specific IgG and Th1 skewed responses. Interestingly, despite the highest tested dose of mRNA eliciting comparable S protein-specific antibodies as the lowest tested dose of STARR™ SARS-CoV-2 RNA, mRNA-elicited IgG did not show similar avidity or neutralization activity as those from STARR™ SARS-CoV-2 RNA vaccination. These findings thus highlight the immunological advantages of self-replicating RNA over mRNA platforms. In addition, mouse challenge studies with SARS-CoV-2 virus showed that vaccination with a single high dose (10μg) or a single low dose (2μg) of STARR™ SARS-CoV-2 self-replicating RNA protected mice from a lethal SARS-CoV-2 infection and protected from lung and brain infection upon challenge with a sublethal SARS-CoV-2 dose.

[0452] The extent to which STARR™ vaccines reproduce the features of live vaccines remain to be experimentally defined. Without being limited by theory, the superior quality of immune responses elicited by STARR™ SARS-CoV-2 RNA over the mRNA vaccine construct could be attributable to multiple factors, all of which have been found to be associated with live vaccination. For example, higher and longer expression of immunogens produce better immunity, likely through better engagement of T follicular helper cells and thereby leading to more diverse antibody targets and more neutralizing antibody responses. Replication of STARR™ SARS-CoV-2 RNA would result in the formation of a negative-strand template for production of more positive-strand mRNA and sub-genomic mRNA expressing the S transgene. Interaction between the negative- and positive-strands would form double stranded RNA (dsRNA), which would interact with TLR3 and RIG-I-like receptors to stimulate

interferon responses, which has been shown to correlate with superior adaptive immune responses. Production of IFNγ can then stimulate development of cytotoxic CD8+ T cells. Importantly, the S protein does contain human CD8+ T cell epitopes. Without being limited by theory, the development of T cell memory could be important for long-term immunity, as suggested by recent findings on T cell responses to SARS-CoV-2 and other coronavirus infections.

[0453] It is unclear whether the VEEV nsP1-4 forming the replication complex contains any immunogenic properties, although mutations in the nsP proteins have been shown to affect induction of type I IFN. VEEV replicons have also been shown to adjuvant immune responses at mucosal sites, further illustrating the advantages of using the STARR™ platform to develop a COVID-19 vaccine. Without being limited by theory, there does not appear to be an immune response to replicon non-structural proteins, as indicated by an increase in antigen-specific IgG production upon a second administration of replicon to animals. In the presence of an immune response to non-structural proteins, a limited or no increase in antigen-specific IgG production may have resulted following a second administration. The RNA is encapsulated in lipid nanoparticles (LNP), which together can form potent adjuvants leading to robust immune responses. In addition, using the genetic sequence of an antigen, including a viral antigen such as the spike protein from SARS-CoV-2, for example, STARR™ vaccines can be rapidly generated and manufactured using cell-free and rapidly scalable techniques.

[0454] In conclusion, a STARR™ vaccine as exemplified by STARR™ SARS-CoV-2 RNA offers an approach to simulate several of the properties of live vaccination and offers a potential for single-dose vaccination against COVID-19.

SEQUENCES

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SEQ ID NO:77

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SEQ ID NO:78

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SEQ ID NO:124

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GCCAGTCTAAGAGAGTGGACTTTTGTGGCAAGGGCTATCACCTGATGTCCTTCCC
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GAGAAGAACTTCACCACAGCCCCTGCCATCTGCCACGATGGCAAGGCCCACTTTC
CAAGGGAGGGCGTGTTCGTGTCCAACGGCACCCACTGGTTTGTGACACAGCGCA
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SEQ ID NO:79

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SEQ ID NO:80

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SEQ ID NO:81

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SEQ ID NO:126

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SEQ ID NO:82

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SEQ ID NO:83

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SEQ ID NO:1

GAGGAAACTT AAGAUGGG

SEQ ID NO:2

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SEQ ID NO:3

GGAUAGG

SEQ ID NO:4

GGAGAGG

SEQ ID NO:58

GGGAUGGG

SEQ ID NO:59

GAGAGG

SEQ ID NO:60

GAGGG

SEQ ID NO:61

GAGAUGGG

SEQ ID NO:62

GAGUGG

SEQ ID NO:63

GAGGGG

SEQ ID NO:64

GAGUAGG

SEQ ID NO:65

GAGUGGG

SEQ ID NO:127 (RNA sequence for a construct with two subgenomic promoters, Luc, and E3L)

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SEQ ID NO:129 (RNA sequence for STARR Fluc IRES-E3L (short 3' UTR))

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Table 8.

SEQ ID NO	Description
SEQ ID NO:72	nsP1-4 ORF, codon-optimized
SEQ ID NO:73	5' UTR
SEQ ID NO:74	5' UTR
SEQ ID NO:75	5' UTR
SEQ ID NO:76	3' UTR
SEQ ID NO:121	SARS-CoV-2 spike glycoprotein (non-codon optimized nucleic acid)
SEQ ID NO:122	SARS-CoV-2 spike glycoprotein (codon-optimized nucleic acid)
SEQ ID NO:123	SARS-CoV-2 spike glycoprotein (wild-type protein)
SEQ ID NO:77	Intergenic region between nsP1-4 ORF and antigenic protein ORF
SEQ ID NO:78	Replicon sequence comprising SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:76, and SEQ ID NO:77
SEQ ID NO:124	Replicon sequence comprising SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:76, SEQ ID NO:121, and SEQ ID NO:77
SEQ ID NO:125	Replicon sequence comprising SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:76, SEQ ID NO:122, and SEQ ID NO:77 (ARCT-021; aka "STARR™ SARS-CoV-2 RNA)
SEQ ID NO:79	nsP1-4 protein sequence
SEQ ID NO:80	nsP1-4 protein sequence
SEQ ID NO:81	nsP1-4 protein sequence
SEQ ID NO:126	mRNA encoding SARS-CoV-2 glycoprotein
SEQ ID NO:82	5' UTR (TEV)
SEQ ID NO:83	3' UTR (Xbg)

EXAMPLE 10

[0455] This example describes characterization of self-replicating (STARR™) technology using firefly luciferase transgene expression.

[0456] In vitro transcripts were formulated with lipid nanoparticles (LNP) at a concentration of 0.1 mg/ml, and injected intramuscularly in both legs of female BALB/C mice (n=3) at a dose of 5 ug per leg. Expression of firefly luciferase (FLuc) was measured by IVIS Lumina LT Series III (PerkinElmer) by administering 100 ul of 1.5 mg Xenolight D-luciferin (PerkinElmer) in PBS via intraperitoneal injection ~10 min prior to the measurement. Six data points per group of mice were obtained at each time point (Figures 18A-18D).

[0457] Firefly luciferase (FLuc) expression was monitored from STARR™ Fluc, SINV FLuc, and mRNA FLuc up to day 28 by In Vivo Imaging System (IVIS). Enhanced levels and durations of transgene expression from STARR™ were observed. The expression from STARR™ Fluc peaked around day 3 to 7 and declined until day 22. Fluc expression from SINV FLuc also peaked on day 10, however, the expression was reduced at a significantly faster rate than STARR™ FLuc. Additionally, the expression on day 3 was significantly lower than STARR™ FLuc. FLuc expression from the conventional mRNA backbone was highest at day 1, the earliest time point in this study, and declined at a slightly faster rate than that of STARR™ –Fluc (Figure 18A). Figure 18B shows that at 14 days post dosing, FLuc expression from STARR™ FLuc was higher than the other groups by about two orders of magnitude. Figure 18D shows that the effect of the STARR™ backbone remained minimal throughout the experimental period (up to day 28), while prior administration of SINV replicon backbone resulted in a reduction of FLuc transgene expression by ~2 orders of magnitude.

[0458] A cancer vaccine substrate, TA STARR™, was constructed next with the STARR™ backbone that encodes AH1A5 epitope from gp70, an envelope glycoprotein of endogenous Murine leukemia virus. AH1 (SPSYVYHQF) (SEQ ID NO:110) is an H-2Ld-restricted antigen of gp70423–431, which is expressed in tumor cells such as the CT26 colorectal cancer cell line, but not expressed in most of the normal tissues. AH1-A5 is a mutated sequence with SPSYAYHQF (SEQ ID NO:111) (the mutation underlined) with enhanced affinity to the T cell receptor (Slansky, et al., 2000, Immunity 13: 529-538). The open reading frame of the TA STARR™ subgenomic RNA contains a cassette with a signal peptide from the HLA class I antigen, gp70 sequence containing AH1A5 epitope, ovalbumin epitope (OVA323-339), and MHC class I trafficking signal (Kreiter, et al. 2008, J Immunol 180: 309-318). Three female

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BALB/c mice were intramuscularly injected with 10 ug of LNP formulated STARR™ transcripts, STARR™ FLuc or TA STARR™, on day 0 and day 7. On day 16, the spleens were harvested and the splenocytes were isolated. Splenocytes (2.5x105 cells) were incubated with or without AH1A5 (SPSYAYHQF) (SEQ ID NO:111), beta-gal peptide (TPHPARIGL) (SEQ ID NO:112) at 1 ug/ml, and 1x Concanavalin A (Life Technologies). ELISpot detecting murine IFN-gamma (ImmunoSpot) was performed according to the manufacturer's instructions. As can be seen in Figure 19, TA STARR™ elicited antigen-specific IFN-gamma responses.

[0459] BALB/c mice, 10 week-old female, were subcutaneously implanted in the right flank with 5x105 cells of CT26 cells in PBS. A day later, LNP-formulated STARR™ RNA was injected intramuscularly in the left leg at a dose of 10 ug in 100 ul. The mice were administered another booster shot on day 8 with the same dose. For a group with combination treatment of anti-mouse PD1 (RMP1-14, BioXCell) and anti-mouse PDL1 (10F.9G2, BioXcell), the combined checkpoint inhibitor (100 ug each) was administered via intraperitoneal injection in the right quadrant twice weekly for two weeks starting on day 3. For a group with the treatment of anti-mouse CTLA4 (9H10, BioxCell), 200 ug of the checkpoint inhibitor was administered in the same manner but starting on day 7. Five mice of the group with the combo treatment of TA STARR™ vaccine and the checkpoint inhibitors remained tumor-free on day 25, and were further challenged by subcutaneous implantation of CT26 (5x105 cells) in the right flank where the implantation site was slightly above the first implantation site. Naïve mice were used as a control group. The tumor growth was monitored for another 17 days (i.e. up to day 42 since the first CT26 implantation) before euthanization. Figures 20A-20F illustrates reduced tumor growth resulting from TA STARR™ vaccination and Figure 21 shows prolonged protection resulting from treatment with the TA STARR™ vaccine in combination with checkpoint inhibitors.

Splenocytes from the combination treatment group with TA STARR™ and anti-PD1/PDL1 were harvested for tetramer staining with AH1 peptide. Splenocytes from the control group with the LNP formulation buffer with the same dosing schedule were used as a negative control. The splenocytes (2x106 cells) were incubated with AH1 (H-2Ld)-tetramer (MBL) followed by appropriate fluorescent-labeled antibodies (Alexa Fluor 488 anti-CD8a (53-6.7), Pacific Orange anti-CD4 (RM4-5), and Pacific Blue anti-mouse CD3ε (145-2C11), eBioscience) and DRAQ7 (Invitrogen) by following the manufacture's recommendation, and 500K events were analyzed by ZE5 Cell Analyzer (Bio-Rad). Results are shown in Figures 22A-22C.

Table 9.

Transgene ORF nucleotide sequence			
mARM #	RNA backbone	Transgene	Sequence
2809 (SEQ ID NO:84)	STARR™	Fluc	AUGGAAGAUGCCAAAAACAUUAAGAAGGGCCCAGCGCCAUUCUACC CACUCGAAGACGGGACCGCCGGCGAGCAGCUGCACAAAGCCAUGAA GCGCUACGCCCUGGUGCCCGGCACCAUCGCCUUUACCGACGCACAU AUCGAGGUGGACAUUACCUACGCCGAGUACUUCGAGAUGAGCGUUC GGCUGGCAGAAGCUAUGAAGCGCUAUGGGCUGAAUACAAACCAUCG GAUCGUGGUGUGCAGCGAGAAUAGCUUGCAGUUCUUCAUGCCCGUG UUGGGUGCCCUGUUCAUCGGUGUGGCUGUGGCCCCAGCUAACGACA UCUACAACGAGCGCGAGCUGCUGAACAGCAUGGGCAUCAGCCAGCC CACCGUCGUAUUCGUGAGCAAGAAAGGGCUGCAAAAGAUCCUCAAC GUGCAAAAGAAGCUACCGAUCAUACAAAAGAUCAUCAUCAUGGAUA GCAAGACCGACUACCAGGGCUUCCAAAGCAUGUACACCUUCGUGAC UUCCCAUUUGCCACCCGGCUUCAACGAGUACGACUUCGUGCCCGAG AGCUUCGACCGGGACAAAACCAUCGCCCUGAUCAUGAACAGUAGUG GCAGUACCGGAUUGCCCAAGGGCGUAGCCCUACCGCACCGCACCGC UUGUGUCCGAUUCAGUCAUGCCCGCGACCCCAUCUUCGGCAACCAG AUCAUCCCCGACACCGCUAUCCUCAGCGUGGUGCCAUUUCACCACG GCUUCGGCAUGUUCACCACGCUGGGCUACUUGAUCUGCGGCUUUCG GGUCGUGCUCAUGUACCGCUUCGAGGAGGAGCUAUUCUUGCGCAGC UUGCAAGACUAUAAGAUUCAAUCUGCCCUGCUGGUGCCCACACUAU UUAGCUUCUUCGCUAAGAGCACUCUCAUCGACAAGUACGACCUAAG CAACUUGCACGAGAUCGCCAGCGGCGGGGCGCCGCUCAGCAAGGAG GUAGGUGAGGCCGUGGCCAAACGCUUCCACCUACCAGGCAUCCGAC AGGGCUACGGCCUGACAGAAACAACCAGCGCCAUUCUGAUCACCCC CGAAGGGGACGACAAGCCUGGCGCAGUAGGCAAGGUGGUGCCCUUC UUCGAGGCUAAGGUGGUGGACUUGGACACCGGUAAGACACUGGGUG UGAACCAGCGCGGCGAGCUGUGCGUCCGUGGCCCCAUGAUCAUGAG CGGCUACGUUAACAACCCCGAGGCUACAAACGCUCUCAUCGACAAG GACGGCUGGCUGCACAGCGGCGACAUCGCCUACUGGGACGAGGACG AGCACUUCUUCAUCGUGGACCGGCUGAAGUCCCUGAUCAAAUACAA GGGCUACCAGGUAGCCCCAGCCGAACUGGAGAGCAUCCUGCUGCAA CACCCCAACAUCUUCGACGCCGGGGUCGCCGGCCUGCCCGACGACG AUGCCGGCGAGCUGCCCGCCGCAGUCGUCGUGCUGGAACACGGUAA AACCAUGACCGAGAAGGAGAUCGUGGACUAUGUGGCCAGCCAGGUU ACAACCGCCAAGAAGCUGCGCGGUGGUGUUGUGUUCGUGGACGAGG UGCCUAAAGGACUGACCGGCAAGUUGGACGCCCGCAAGAUCCGCGA GAUUCUCAUUAAGGCCAAGAAGGGCGGCAAGAUCGCCGUGUAA
2842 (SEQ ID NO:85)	SINV replicon	Fluc	AUGGAAGAUGCCAAAAACAUUAAGAAGGGCCCAGCGCCAUUCUACC CACUCGAAGACGGGACCGCCGGCGAGCAGCUGCACAAAGCCAUGAA GCGCUACGCCCUGGUGCCCGGCACCAUCGCCUUUACCGACGCACAU AUCGAGGUGGACAUUACCUACGCCGAGUACUUCGAGAUGAGCGUUC GGCUGGCAGAAGCUAUGAAGCGCUAUGGGCUGAAUACAAACCAUCG GAUCGUGGUGUGCAGCGAGAAUAGCUUGCAGUUCUUCAUGCCCGUG UUGGGUGCCCUGUUCAUCGGUGUGGCUGUGGCCCCAGCUAACGACA UCUACAACGAGCGCGAGCUGCUGAACAGCAUGGGCAUCAGCCAGCC CACCGUCGUAUUCGUGAGCAAGAAAGGGCUGCAAAAGAUCCUCAAC GUGCAAAAGAAGCUACCGAUCAUACAAAAGAUCAUCAUCAUGGAUA GCAAGACCGACUACCAGGGCUUCCAAAGCAUGUACACCUUCGUGAC

			UUCCCAUUUGCCACCCGGCUUCAACGAGUACGACUUCGUGCCCGAG AGCUUCGACCGGGACAAAACCAUCGCCCUGAUCAUGAACAGUAGUG GCAGUACCGGAUUGCCCAAGGGCGUAGCCCUACCGCACCGCACCGC UUGUGUCCGAUUCAGUCAUGCCCGCGACCCCAUCUUCGGCAACCAG AUCAUCCCCGACACCGCUAUCCUCAGCGUGGUGCCAUUUCACCACG GCUUCGGCAUGUUCACCACGCUGGGCUACUUGAUCUGCGGCUUUCG GGUCGUGCUCAUGUACCGCUUCGAGGAGGAGCUAUUCUUGCGCAGC UUGCAAGACUAUAAGAUUCAAUCUGCCCUGCUGGUGCCCACACUAU UUAGCUUCUUCGCUAAGAGCACUCUCAUCGACAAGUACGACCUAAG CAACUUGCACGAGAUCGCCAGCGGCGGGGGCGCCGCUCAGCAAGGAG GUAGGUGAGGCCGUGGCCAAACGCUUCCACCUACCAGGCAUCCGAC AGGGCUACGGCCUGACAGAAACAACCAGCGCCAUUCUGAUCACCCC CGAAGGGGACGACAAGCCUGGCGCAGUAGGCAAGGUGGUGCCCUUC UUCGAGGCUAAGGUGGUGGACUUGGACACCGGUAAGACACUGGGUG UGAACCAGCGCGGCGAGCUGUGCGUCCGUGGCCCCAUGAUCAUGAG CGGCUACGUUAACAACCCCGAGGCUACAAACGCUCUCAUCGACAAG GACGGCUGGCUGCACAGCGGCGACAUCGCCUACUGGGACGAGGACG AGCACUUCUUCAUCGUGGACCGGCUGAAGUCCCUGAUCAAAUACAA GGGCUACCAGGUAGCCCCAGCCGAACUGGAGAGCAUCCUGCUGCAA CACCCCAACAUCUUCGACGCCGGGGUCGCCGGCCUGCCCGACGACG AUGCCGGCGAGCUGCCCGCCGCAGUCGUCGUGCUGGAACACGGUAA AACCAUGACCGAGAAGGAGAUCGUGGACUAUGUGGCCAGCCAGGUU ACAACCGCCAAGAAGCUGCGCGGUGGUGUUGUGUUCGUGGACGAGG UGCCUAAAGGACUGACCGGCAAGUUGGACGCCCGCAAGAUCCGCGA GAUUCUCAUUAAGGCCAAGAAGGGCGGCAAGAUCGCCGUGUAA
1782 (SEQ ID NO:86)	mRNA (TEV-XbG)	Fluc	AUGGAAGAUGCCAAAAACAUUAAGAAGGGCCCAGCGCCAUUCUACC CACUCGAAGACGGGACCGCCGGCGAGCAGCUGCACAAAGCCAUGAA GCGCUACGCCCUGGUGCCCGGCACCAUCGCCUUUACCGACGCACAU AUCGAGGUGGACAUUACCUACGCCGAGUACUUCGAGAUGAGCGUUC GGCUGGCAGAAGCUAUGAAGCGCUAUGGGCUGAAUACAAACCAUCG GAUCGUGGUGUGCAGCGAGAAUAGCUUGCAGUUCUUCAUGCCCGUG UUGGGUGCCCUGUUCAUCGGUGUGGCUGUGGCCCCAGCUAACGACA UCUACAACGAGCGCGAGCUGCUGAACAGCAUGGGCAUCAGCCAGCC CACCGUCGUAUUCGUGAGCAAGAAAGGGCUGCAAAAGAUCCUCAAC GUGCAAAAGAAGCUACCGAUCAUACAAAAGAUCAUCAUCAUGGAUA GCAAGACCGACUACCAGGGCUUCCAAAGCAUGUACACCUUCGUGAC UUCCCAUUUGCCACCCGGCUUCAACGAGUACGACUUCGUGCCCGAG AGCUUCGACCGGGACAAAACCAUCGCCCUGAUCAUGAACAGUAGUG GCAGUACCGGAUUGCCCAAGGGCGUAGCCCUACCGCACCGCACCGC UUGUGUCCGAUUCAGUCAUGCCCGCGACCCCAUCUUCGGCAACCAG AUCAUCCCCGACACCGCUAUCCUCAGCGUGGUGCCAUUUCACCACG GCUUCGGCAUGUUCACCACGCUGGGCUACUUGAUCUGCGGCUUUCG GGUCGUGCUCAUGUACCGCUUCGAGGAGGAGCUAUUCUUGCGCAGC UUGCAAGACUAUAAGAUUCAAUCUGCCCUGCUGGUGCCCACACUAU UUAGCUUCUUCGCUAAGAGCACUCUCAUCGACAAGUACGACCUAAG CAACUUGCACGAGAUCGCCAGCGGCGGGGGCGCCGCUCAGCAAGGAG GUAGGUGAGGCCGUGGCCAAACGCUUCCACCUACCAGGCAUCCGAC AGGGCUACGGCCUGACAGAAACAACCAGCGCCAUUCUGAUCACCCC CGAAGGGGACGACAAGCCUGGCGCAGUAGGCAAGGUGGUGCCCUUC UUCGAGGCUAAGGUGGUGGACUUGGACACCGGUAAGACACUGGGUG UGAACCAGCGCGGCGAGCUGUGCGUCCGUGGCCCCAUGAUCAUGAG CGGCUACGUUAACAACCCCGAGGCUACAAACGCUCUCAUCGACAAG GACGGCUGGCUGCACAGCGGCGACAUCGCCUACUGGGACGAGGACG AGCACUUCUUCAUCGUGGACCGGCUGAAGUCCCUGAUCAAAUACAA GGGCUACCAGGUAGCCCCAGCCGAACUGGAGAGCAUCCUGCUGCAA

			CACCCCAACAUCUUCGACGCCGGGGUCGCCGGCCUGCCCGACGACG AUGCCGGCGAGCUGCCCGCCGCAGUCGUCGUGCUGGAACACGGUAA AACCAUGACCGAGAAGGAGAUCGUGGACUAUGUGGCCAGCCAGGUU ACAACCGCCAAGAAGCUGCGCGGUGGUGUUGUGUUCGUGGACGAGG UGCCUAAAGGACUGACCGGCAAGUUGGACGCCCGCAAGAUCCGCGA GAUUCUCAUUAAGGCCAAGAAGGGCGGCAAGAUCGCCGUGUAA
2847 (SEQ ID NO:87)	STARRT M	KRAS epitope wt	AUGAAGUUGGUGGUUGUGGGGGCCGGGGGUGUUGGCAAAAGCGCCC UUACAAUUUGA
2862 (SEQ ID NO:88)	SINV replicon	Empty	AUGGAUCCUAGACGCUACGCCCCAAUGAUCCGACCAGCAAAACUCG AUGUACUUCCGAGGAACUGA
3060 (SEQ ID NO:89)	STARRT M	Signal peptide-gp70 with AH1A5-MITD	AUGAGAGUGACAGCCCCUAGAACCUUACUGCUUCUGCUUUGGGGAG CUGUUGCUCUGACAGAGACAUGGGCUGGAUCUCUGAGCGAGGUGAC CGGCCAGGGCCUGUGCAUCGGCGCCGUGCCCAAGACCCACCAGGUG CUGUGCAACACCACCCAGAAGACCAGCGACGGCAGCUACUACCUGG CCGCUCCCACCGGCACCACCUGGGCCUGCAGCACCGGCCUGACCCC UUGCAUCAGCACCACCAUCCUGAACCUGACCACCGACUACUGCGUG CUGGUGGAGCUGUGGCCCAGGGUGACCUACCACAGCCCCAGCUACG CCUACCACCAGUUCGAGAGGAGGGCCAAGUACAAGAGGGAGCCCGU GAGCCUGACCCUGGCCCUGCUGCUGGGCGGCCUGACAAUGGGCGGC AUCGCCGCCGGCGUGGGCACCGGCACCACCGCCCUGGUGGCCACCC AGCAGUUCCAGCAGCUGCAGGCCGCCAUGCACGACGACCUGAAGGA GGUGGAGAAGUCCAUCACCAACCUGGAGAAGUCCCUGACCAGCCUG AGCGAGGUGGUGCUGCAGAACAGGAGGGGCCUGGACCUGCUGUUCC UGAAGGAGGGCGGCCUGUGCGCCGCCCUGAAGGAGGAGUGCUGCCU GUACGCCGACCACACCGGCCUGGUGAUCGUGGGCAUUGUCGCUGGC CUGGCCGUCCUCGCCGUGGUGGUGAUUGGAGCUGUGGUCGCAGCUG UUAUGUGCAGAAGAAAGUCAUCCGGCGGAAAGGGAGGCUCCUACUC UCAGGCUGCUUCUGCUACAGUGCCUAGAGCUCUUAUGUGUUUAUCU CAGCUGUAA
3061 (SEQ ID NO:90)	STARRT M	Signal peptide-AH1A5 OVA-MITD	AUGAGAGUGACAGCCCCUAGAACCUUACUGCUUCUGCUUUGGGGAG CUGUUGCUCUGACAGAGACAUGGGCUGGAUCUUACCACAGCCCCAG CUACGCCUACCACCAGUUCGAGAGGGGGGGAGGAGGCUCCGGGGGA GGAGGCUCCCUGAAGAUCAGCCAGGCCGUGCACGCCGCCCACGCCG AGAUCAACGAGGCCGGCCGGGAGGUGAUCGUGGGCAUUGUCGCUGG CCUGGCCGUCCUCGCCGUGGUGGUGAUUGGAGCUGUGGUCGCAGCU GUUAUGUGCAGAAGAAAGUCAUCCGGCGGAAAGGGAGGCUCCUACU CUCAGGCUGCUUCUGCUACAGUGCCUAGAGCUCUUAUGUGUUUAUC UCAGCUGUAA
3076	STARRT M	Signal peptide-gp70 with	AUGAGAGUGACAGCCCCUAGAACCUUACUGCUUCUGCUUUGGGGAG CUGUUGCUCUGACAGAGACAUGGGCUGGAUCUCUGAGCGAGGUGAC CGGCCAGGGCCUGUGCAUCGGCGCCGUGCCCAAGACCCACCAGGUG CUGUGCAACACCACCCAGAAGACCAGCGACGGCAGCUACUACCUGG CCGCUCCCACCGGCACCACCUGGGCCUGCAGCACCGGCCUGACCCC UUGCAUCAGCACCACCAUCCUGAACCUGACCACCGACUACUGCGUG

(SEQ ID NO:91)		AH1A5-MITD-FLAG	CUGGUGGAGCUGUGGCCCAGGGUGACCUACCACAGCCCCAGCUACG CCUACCACCAGUUCGAGAGGAGGGCCAAGUACAAGAGGGAGCCCGU GAGCCUGACCCUGGCCCUGCUGCUGGGCGGCCUGACAAUGGGCGGC AUCGCCGCCGGCGUGGGCACCGGCACCACCGCCCUGGUGGCCACCC AGCAGUUCCAGCAGCUGCAGGCCGCCAUGCACGACGACCUGAAGGA GGUGGAGAAGUCCAUCACCAACCUGGAGAAGUCCCUGACCAGCCUG AGCGAGGUGGUGCUGCAGAACAGGAGGGGCCUGGACCUGCUGUUCC UGAAGGAGGGCGGCCUGUGCGCCGCCCUGAAGGAGGAGUGCUGCCU GUACGCCGACCACACCGGCCUGGUGAUCGUGGGCAUUGUCGCUGGC CUGGCCGUCCUCGCCGUGGUGGUGAUUGGAGCUGUGGUCGCAGCUG UUAUGUGCAGAAGAAAGUCAUCCGGCGGAAAGGGAGGCUCCUACUC UCAGGCUGCUUCUGCUACAGUGCCUAGAGCUCUUAUGUGUUUAUCU CAGCUGGGCGGCGGAGGCAGCGACUACAAGGACGACGAUGACAAGU AA
3068 (SEQ ID NO:92)	STAR R	Signal peptide-AH1A5 OVA-MITD-FLAG	AUGAGAGUGACAGCCCCUAGAACCUUACUGCUUCUGCUUUGGGGAG CUGUUGCUCUGACAGAGACAUGGGCUGGAUCUUACCACAGCCCCAG CUACGCCUACCACCAGUUCGAGAGGGGGGGAGGAGGCUCCGGGGGA GGAGGCUCCCUGAAGAUCAGCCAGGCCGUGCACGCCGCCCACGCCG AGAUCAACGAGGCCGGCCGGGAGGUGAUCGUGGGCAUUGUCGCUGG CCUGGCCGUCCUCGCCGUGGUGGUGAUUGGAGCUGUGGUCGCAGCU GUUAUGUGCAGAAGAAAGUCAUCCGGCGGAAAGGGAGGCUCCUACU CUCAGGCUGCUUCUGCUACAGUGCCUAGAGCUCUUAUGUGUUUAUC UCAGCUGGGCGGCGGAGGCAGCGACUACAAGGACGACGAUGACAAG UAA
Transgene ORF amino acid sequence			
mARM #		transgene description	Sequence
2809, 2842, 1782 (SEQ ID NO:93)		Fluc	MEDAKNIKKGPAPFYPLEDGTAGEQLHKAMKRYALVPGTIAFTDAH IEVDITYAEYFEMSVRLAEAMKRYGLNTNHRIVVCSENSLQFFMPV LGALFIGVAVAPANDIYNERELLNSMGISQPTVVFVSKKGLQKILN VQKKLPIIQKIIIMDSKTDYQGFQSMYTFVTSHLPPGFNEYDFVPE SFDRDKTIALIMNSSGSTGLPKGVALPHRTACVRFSHARDPIFGNQ IIPDTAILSVVPFHHGFGMFTTLGYLICGFRVVLMYRFEEELFLRS LQDYKIQSALLVPTLFSFFAKSTLIDKYDLSNLHEIASGGAPLSKE VGEAVAKRFHLPGIRQGYGLTETTSAILITPEGDDKPGAVGKVVPF FEAKVVDLDTGKTLGVNQRGELCVRGPMIMSGYVNNPEATNALIDK DGWLHSGDIAYWDEDEHFFIVDRLKSLIKYKGYQVAPAELESILLQ HPNIFDAGVAGLPDDDAGELPAAVVVLEHGKTMTEKEIVDYVASQV TTAKKLRGGVVFVDEVPKGLTGKLDARKIREILIKAKKGGKIAV*
2847 (SEQ ID NO:94)		KRAS epitope wt	MKLVVVGAGGVGKSALTI*
2862		Empty	MDPRRYAPMIRPAKLDVLPRN*

(SEQ ID NO:95)			
3060 (SEQ ID NO:96)		Signal peptide-gp70 with AH1A5-MITD	MRVTAPRTLLLLLWGAVALTETWAGSLSEVTGQGLCIGAVPKTHQV LCNTTQKTSDGSYYLAAPTGTTWACSTGLTPCISTTILNLTTDYCV LVELWPRVTYHSPSYAYHQFERRAKYKREPVSLTLALLLGGLTMGG IAAGVGTGTTALVATQQFQQLQAAMHDDLKEVEKSITNLEKSLTSL SEVVLQNRRGLDLLFLKEGGLCAALKEECCLYADHTGLVIVGIVAG LAVLAVVVIGAVVAAVMCRRKSSGGKGGSYSQAASATVPRALMCLS QL*
3061 (SEQ ID NO:97)		Signal peptide-AH1A5 OVA-MITD	MRVTAPRTLLLLLWGAVALTETWAGSYHSPSYAYHQFERGGGGSGG GGSLKISQAVHAAHAEINEAGREVIVGIVAGLAVLAVVVIGAVVAA VMCRRKSSGGKGGSYSQAASATVPRALMCLSQL*
3076 (SEQ ID NO:98)		Signal peptide-gp70 with AH1A5-MITD-FLAG	MRVTAPRTLLLLLWGAVALTETWAGSLSEVTGQGLCIGAVPKTHQV LCNTTQKTSDGSYYLAAPTGTTWACSTGLTPCISTTILNLTTDYCV LVELWPRVTYHSPSYAYHQFERRAKYKREPVSLTLALLLGGLTMGG IAAGVGTGTTALVATQQFQQLQAAMHDDLKEVEKSITNLEKSLTSL SEVVLQNRRGLDLLFLKEGGLCAALKEECCLYADHTGLVIVGIVAG LAVLAVVVIGAVVAAVMCRRKSSGGKGGSYSQAASATVPRALMCLS QLGGGGSDYKDDDDK*
3068 (SEQ ID NO:99)		Signal peptide-AH1A5 OVA-MITD-FLAG	MRVTAPRTLLLLLWGAVALTETWAGSYHSPSYAYHQFERGGGGSGG GGSLKISQAVHAAHAEINEAGREVIVGIVAGLAVLAVVVIGAVVAA VMCRRKSSGGKGGSYSQAASATVPRALMCLSQLGGGGSDYKDDDDK *
whole RNA sequence			
mARM #	brief name		Sequence
2809 (SEQ ID	STARR^{TM} Fluc	2809	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAU GGAGAAAGUUCACGUUGACAUCGAGGAAGACAGCCCAUUCCUCAGA GCUUUGCAGCGGAGCUUCCCGCAGUUUGAGGUAGAAGCCAAGCAGG UCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGC UUCAAAACUGAUCGAAACGGAGGUGGACCCAUCCGACACGAUCCUU GACAUUGGAAGUGCGCCCGCCCGCAGAAUGUAUUCUAAGCACAAGU AUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUU GUAUAAGUAUGCAACUAAGCUGAAGAAAAACUGUAAGGAAAUAACU

NO:100)			GAUAAGGAAUUGGACAAGAAAAUGAAGGAGCUGGCCGCCGUCAUGA GCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGACGA GUCGUGUCGCUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUAC GCCGUCGACGGCCCCACCAGCCUGUACCACCAGGCCAACAAGGGCG UGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCCUUCAUGUU CAAGAACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCC GACGAGACCGUGCUGACCGCCAGGAACAUCGGCCUGUGCAGCAGCG ACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAUCCUGAGGAAGAA AUACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACC AUCUACCACGAGAAGAGGGACCUGCUCAGGAGCUGGCACCUGCCCA GCGUGUUCCACCUGAGGGGCAAGCAGAACUACACCUGCAGGUGCGA GACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUC AGCCCCGGCCUGUACGGCAAGCCCAGCGGCUACGCCGCUACAAUGC ACAGGGAGGGCUUCCUGUGCUGCAAGGUGACCGACACCCUGAACGG CGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUG UGCGACCAGAUGACCGGCAUCCUGGCCACCGACGUGAGCGCCGACG ACGCCCAGAAGCUGCUCGUGGGCCUGAACCAGAGGAUCGUGGUCAA CGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUGCUG CCCGUGGUGGCCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGG AGGACCAGGAAGACGAGAGGCCCCUGGGCCUGAGGGACAGGCAGCU GGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAUCACCAGC AUCUACAAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCG ACUUCCACAGCUUCGUGCUGCCCAGGAUCGGCAGCAACACCCUGGA GAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGGAGGAACACAAG GAGCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGU GCGCUGCCGACGAGGCCAAGGAGGUGAGGGAGGCCGAGGAACUGAG GGCCGCCCUGCCACCCCUGGCUGCCGACGUGGAGGAACCCACCCUG GAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCG UGGAGACACCCAGGGGCCUGAUCAAGGUGACCAGCUACGACGGCGA GGACAAGAUCGGCAGCUACGCCGUGCUGAGCCCACAGGCCGUGCUG AAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGA UCGUGAUCACCCACAGCGGCAGGAAGGGCAGGUACGCCGUGGAGCC CUACCACGGCAAGGUGGUCGUGCCCGAGGGCCACGCCAUCCCCGUG CAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAACG AGAGGGAGUUCGUGAACAGGUACCUGCACCAUAUCGCCACCCACGG CGGAGCCCUGAACACCGACGAGGAAUACUACAAGACCGUGAAGCCC AGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGAAGCAGU GCGUGAAGAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCU GGUGGACCCACCCUUCCACGAGUUCGCCUACGAGAGCCUGAGGACC AGACCCGCCGCUCCCUACCAGGUGCCCACCAUCGGCGUGUACGGCG UGCCCGGCAGCGGAAAGAGCGGCAUCAUCAAGAGCGCCGUGACCAA GAAAGACCUGGUGGUCAGCGCCAAGAAAGAGAACUGCGCCGAGAUC AUCAGGGACGUGAAGAAGAUGAAAGGCCUGGACGUGAACGCGCGCA CCGUGGACAGCGUGCUGCUGAACGGCUGCAAGCACCCCGUGGAGAC CCUGUACAUCGACGAGGCCUUCGCUUGCCACGCCGGCACCCUGAGG GCCCUGAUCGCCAUCAUCAGGCCCAAGAAAGCCGUGCUGUGCGGCG ACCCCAAGCAGUGCGGCUUCUUCAACAUGAUGUGCCUGAAGGUGCA CUUCAACCACGAGAUCUGCACCCAGGUGUUCCACAAGAGCAUCAGC AGGCGGUGCACCAAGAGCGUGACCAGCGUCGUGAGCACCCUGUUCU ACGACAAGAAAAUGAGGACCACCAACCCCAAGGAGACCAAAAUCGU GAUCGACACCACAGGCAGCACCAAGCCCAAGCAGGACGACCUGAUC CUGACCUGCUUCAGGGGCUGGGUGAAGCAGCUGCAGAUCGACUACA AGGGCAACGAGAUCAUGACCGCCGCUGCCAGCCAGGGCCUGACCAG GAAGGGCGUGUACGCCGUGAGGUACAAGGUGAACGAGAACCCACUG UACGCUCCCACCAGCGAGCACGUGAACGUGCUGCUGACCAGGACCG

			AGGACAGGAUCGUGUGGAAGACCCUGGCCGGCGACCCCUGGAUCAA GACCCUGACCGCCAAGUACCCCGGCAACUUCACCGCCACCAUCGAA GAGUGGCAGGCCGAGCACGACGCCAUCAUGAGGCACAUCCUGGAGA GGCCCGACCCCACCGACGUGUUCCAGAACAAGGCCAACGUGUGCUG GGCCAAGGCCCUGGUGCCCGUGCUGAAGACCGCCGGCAUCGACAUG ACCACAGAGCAGUGGAACACCGUGGACUACUUCGAGACCGACAAGG CCCACAGCGCCGAGAUCGUGCUGAACCAGCUGUGCGUGAGGUUCUU CGGCCUGGACCUGGACAGCGGCCUGUUCAGCGCCCCCACCGUGCCA CUGAGCAUCAGGAACAACCACUGGGACAACAGCCCCAGCCCAAACA UGUACGGCCUGAACAAGGAGGUGGUCAGGCAGCUGAGCAGGCGGUA CCCACAGCUGCCCAGGGCCGUGGCCACCGGCAGGGUGUACGACAUG AACACCGGCACCCUGAGGAACUACGACCCCAGGAUCAACCUGGUGC CCGUGAACAGGCGGCUGCCCCACGCCCUGGUGCUGCACCACAACGA GCACCCACAGAGCGACUUCAGCUCCUUCGUGAGCAAGCUGAAAGGC AGGACCGUGCUGGUCGUGGGCGAGAAGCUGAGCGUGCCCGGCAAGA UGGUGGACUGGCUGAGCGACAGGCCCGAGGCCACCUUCCGGGCCAG GCUGGACCUCGGCAUCCCCGGCGACGUGCCCAAGUACGACAUCAUC UUCGUGAACGUCAGGACCCCAUACAAGUACCACCAUUACCAGCAGU GCGAGGACCACGCCAUCAAGCUGAGCAUGCUGACCAAGAAGGCCUG CCUGCACCUGAACCCCGGAGGCACCUGCGUGAGCAUCGGCUACGGC UACGCCGACAGGGCCAGCGAGAGCAUCAUUGGCGCCAUCGCCAGGC UGUUCAAGUUCAGCAGGGUGUGCAAACCCAAGAGCAGCCUGGAGGA AACCGAGGUGCUGUUCGUGUUCAUCGGCUACGACCGGAAGGCCAGG ACCCACAACCCCUACAAGCUGAGCAGCACCCUGACAAACAUCUACA CCGGCAGCAGGCUGCACGAGGCCGGCUGCGCCCCCAGCUACCACGU GGUCAGGGGCGAUAUCGCCACCGCCACCGAGGGCGUGAUCAUCAAC GCUGCCAACAGCAAGGGCCAGCCCGGAGGCGGAGUGUGCGGCGCCC UGUACAAGAAGUUCCCCGAGAGCUUCGACCUGCAGCCCAUCGAGGU GGGCAAGGCCAGGCUGGUGAAGGGCGCCGCUAAGCACAUCAUCCAC GCCGUGGGCCCCAACUUCAACAAGGUGAGCGAGGUGGAAGGCGACA AGCAGCUGGCCGAAGCCUACGAGAGCAUCGCCAAGAUCGUGAACGA CAAUAACUACAAGAGCGUGGCCAUCCCACUGCUCAGCACCGGCAUC UUCAGCGGCAACAAGGACAGGCUGACCCAGAGCCUGAACCACCUGC UCACCGCCCUGGACACCACCGAUGCCGACGUGGCCAUCUACUGCAG GGACAAGAAGUGGGAGAUGACCCUGAAGGAGGCCGUGGCCAGGCGG GAGGCCGUGGAAGAGAUCUGCAUCAGCGACGACUCCAGCGUGACCG AGCCCGACGCCGAGCUGGUGAGGGUGCACCCCAAGAGCUCCCUGGC CGGCAGGAAGGGCUACAGCACCAGCGACGGCAAGACCUUCAGCUAC CUGGAGGGCACCAAGUUCCACCAGGCCGCUAAGGACAUCGCCGAGA UCAACGCUAUGUGGCCCGUGGCCACCGAGGCCAACGAGCAGGUGUG CAUGUACAUCCUGGGCGAGAGCAUGUCCAGCAUCAGGAGCAAGUGC CCCGUGGAGGAAAGCGAGGCCAGCACACCACCCAGCACCCUGCCCU GCCUGUGCAUCCACGCUAUGACACCCGAGAGGGUGCAGCGGCUGAA GGCCAGCAGGCCCGAGCAGAUCACCGUGUGCAGCUCCUUCCCACUG CCCAAGUACAGGAUCACCGGCGUGCAGAAGAUCCAGUGCAGCCAGC CCAUCCUGUUCAGCCCAAAGGUGCCCGCCUACAUCCACCCCAGGAA GUACCUGGUGGAGACCCCACCCGUGGACGAGACACCCGAGCCAAGC GCCGAGAACCAGAGCACCGAGGGCACACCCGAGCAGCCACCCCUGA UCACCGAGGACGAGACAAGGACCCGGACCCCAGAGCCCAUCAUUAU CGAGGAAGAGGAAGAGGACAGCAUCAGCCUGCUGAGCGACGGCCCC ACCCACCAGGUGCUGCAGGUGGAGGCCGACAUCCACGGCCCACCCA GCGUGUCCAGCUCCAGCUGGAGCAUCCCACACGCCAGCGACUUCGA CGUGGACAGCCUGAGCAUCCUGGACACCCUGGAGGGCGCCAGCGUG ACCUCCGGCGCCACCAGCGCCGAGACCAACAGCUACUUCGCCAAGA GCAUGGAGUUCCUGGCCAGGCCCGUGCCAGCUCCCAGGACCGUGUU

			CAGGAACCCACCCCACCCAGCUCCCAGGACCAGGACCCCAAGCCUG GCUCCCAGCAGGGCCUGCAGCAGGACCAGCCUGGUGAGCACCCCAC CCGGCGUGAACAGGGUGAUCACCAGGGAGGAACUGGAGGCCCUGAC ACCCAGCAGGACCCCCAGCAGGUCCGUGAGCAGGACUAGUCUGGUG UCCAACCCACCCGGCGUGAACAGGGUGAUCACCAGGGAGGAAUUCG AGGCCUUCGUGGCCCAGCAACAGAGACGGUUCGACGCCGGCGCCUA CAUCUUCAGCAGCGACACCGGCCAGGGACACCUGCAGCAAAAGAGC GUGAGGCAGACCGUGCUGAGCGAGGUGGUGCUGGAGAGGACCGAGC UGGAAAUCAGCUACGCCCCCAGGCUGGACCAGGAGAAGGAGGAACU GCUCAGGAAGAAACUGCAGCUGAACCCCACCCCAGCCAACAGGAGC AGGUACCAGAGCAGGAAGGUGGAGAACAUGAAGGCCAUCACCGCCA GGCGGAUCCUGCAGGGCCUGGGACACUACCUGAAGGCCGAGGGCAA GGUGGAGUGCUACAGGACCCUGCACCCCGUGCCACUGUACAGCUCC AGCGUGAACAGGGCCUUCUCCAGCCCCAAGGUGGCCGUGGAGGCCU GCAACGCUAUGCUGAAGGAGAACUUCCCCCACCGUGGCCAGCUACUG CAUCAUCCCCGAGUACGACGCCUACCUGGACAUGGUGGACGGCGCC AGCUGCUGCCUGGACACCGCCAGCUUCUGCCCCGCCAAGCUGAGGA GCUUCCCCAAGAAACACAGCUACCUGGAGCCCACCAUCAGGAGCGC CGUGCCCAGCGCCAUCCAGAACACCCUGCAGAACGUGCUGGCCGCU GCCACCAAGAGGAACUGCAACGUGACCCAGAUGAGGGAGCUGCCCG UGCUGGACAGCGCUGCCUUCAACGUGGAGUGCUUCAAGAAAUACGC CUGCAACAACGAGUACUGGGAGACCUUCAAGGAGAACCCCAUCAGG CUGACCGAAGAGAACGUGGUGAACUACAUCACCAAGCUGAAGGGCC CCAAGGCCGCUGCCCUGUUCGCUAAGACCCACAACCUGAACAUGCU GCAGGACAUCCCAAUGGACAGGUUCGUGAUGGACCUGAAGAGGGAC GUGAAGGUGACACCCGGCACCAAGCACACCGAGGAGAGGCCCAAGG UGCAGGUGAUCCAGGCCGCUGACCCACUGGCCACCGCCUACCUGUG CGGCAUCCACAGGGAGCUGGUGAGGCGGCUGAACGCCGUGCUGCUG CCCAACAUCCACACCCUGUUCGACAUGAGCGCCGAGGACUUCGACG CCAUCAUCGCCGAGCACUUCCAGCCCGGCGACUGCGUGCUGGAGAC CGACAUCGCCAGCUUCGACAAGAGCGAGGAUGACGCUAUGGCCCUG ACCGCUCUGAUGAUCCUGGAGGACCUGGGCGUGGACGCCGAGCUGC UCACCCUGAUCGAGGCUGCCUUCGGCGAGAUCAGCUCCAUCCACCU GCCCACCAAGACCAAGUUCAAGUUCGGCGCUAUGAUGAAAAGCGGA AUGUUCCUGACCCUGUUCGUGAACACCGUGAUCAACAUUGUGAUCG CCAGCAGGGUGCUGCGGGAGAGGCUGACCGGCAGCCCCUGCGCUGC CUUCAUCGGCGACGACAACAUCGUGAAGGGCGUGAAAAGCGACAAG CUGAUGGCCGACAGGUGCGCCACCUGGCUGAACAUGGAGGUGAAGA UCAUCGACGCCGUGGUGGGCGAGAAGGCCCCCUACUUCUGCGGCGG AUUCAUCCUGUGCGACAGCGUGACCGGCACCGCCUGCAGGGUGGCC GACCCCCUGAAGAGGCUGUUCAAGCUGGGCAAGCCACUGGCCGCUG ACGAUGAGCACGACGAUGACAGGCGGAGGGCCCUGCACGAGGAAAG CACCAGGUGGAACAGGGUGGGCAUCCUGAGCGAGCUGUGCAAGGCC GUGGAGAGCAGGUACGAGACCGUGGGCACCAGCAUCAUCGUGAUGG CUAUGACCACACUGGCCAGCUCCGUCAAGAGCUUCUCCUACCUGAG GGGGGCCCCUAUAACUCUCUACGGCUAACCUGAAUGGACUACGACA UAGUCUAGUCCGCCAAGGCCGCCACCAUGGAAGAUGCCAAAAACAU UAAGAAGGGCCCAGCGCCAUUCUACCCACUCGAAGACGGGACCGCC GGCGAGCAGCUGCACAAAGCCAUGAAGCGCUACGCCCUGGUGCCCG GCACCAUCGCCUUUACCGACGCACAUAUCGAGGUGGACAUUACCUA CGCCGAGUACUUCGAGAUGAGCGUUCGGCUGGCAGAAGCUAUGAAG CGCUAUGGGCUGAAUACAAACCAUCGGAUCGUGGUGUGCAGCGAGA AUAGCUUGCAGUUCUUCAUGCCCGUGUUGGGUGCCCUGUUCAUCGG UGUGGCUGUGGCCCCAGCUAACGACAUCUACAACGAGCGCGAGCUG CUGAACAGCAUGGGCAUCAGCCAGCCCACCGUCGUAUUCGUGAGCA

			AGAAAGGGCUGCAAAAGAUCCUCAACGUGCAAAAGAAGCUACCGAU CAUACAAAAGAUCAUCAUCAUGGAUAGCAAGACCGACUACCAGGGC UUCCAAAGCAUGUACACCUUCGUGACUUCCCAUUUGCCACCCGGCU UCAACGAGUACGACUUCGUGCCCGAGAGCUUCGACCGGGACAAAAC CAUCGCCCUGAUCAUGAACAGUAGUGGCAGUACCGGAUUGCCCAAG GGCGUAGCCCUACCGCACCGCACCGCUUGUGUCCGAUUCAGUCAUG CCCGCGACCCCAUCUUCGGCAACCAGAUCAUCCCCGACACCGCUAU CCUCAGCGUGGUGCCAUUUCACCACGGCUUCGGCAUGUUCACCACG CUGGGCUACUUGAUCUGCGGCUUUCGGGUCGUGCUCAUGUACCGCU UCGAGGAGGAGCUAUUCUUGCGCAGCUUGCAAGACUAUAAGAUUCA AUCUGCCCUGCUGGUGCCCACACUAUUUAGCUUCUUCGCUAAGAGC ACUCUCAUCGACAAGUACGACCUAAGCAACUUGCACGAGAUCGCCA GCGGCGGGGCGCCGCUCAGCAAGGAGGUAGGUGAGGCCGUGGCCAA ACGCUUCCACCUACCAGGCAUCCGACAGGGCUACGGCCUGACAGAA ACAACCAGCGCCAUUCUGAUCACCCCCGAAGGGGACGACAAGCCUG GCGCAGUAGGCAAGGUGGUGCCCUUCUUCGAGGCUAAGGUGGUGGA CUUGGACACCGGUAAGACACUGGGUGUGAACCAGCGCGGCGAGCUG UGCGUCCGUGGCCCCAUGAUCAUGAGCGGCUACGUUAACAACCCCG AGGCUACAAACGCUCUCAUCGACAAGGACGGCUGGCUGCACAGCGG CGACAUCGCCUACUGGGACGAGGACGAGCACUUCUUCAUCGUGGAC CGGCUGAAGUCCCUGAUCAAAUACAAGGGCUACCAGGUAGCCCCAG CCGAACUGGAGAGCAUCCUGCUGCAACACCCCAACAUCUUCGACGC CGGGGUCGCCGGCCUGCCCGACGACGAUGCCGGCGAGCUGCCCGCC GCAGUCGUCGUGCUGGAACACGGUAAAACCAUGACCGAGAAGGAGA UCGUGGACUAUGUGGCCAGCCAGGUUACAACCGCCAAGAAGCUGCG CGGUGGUGUUGUGUUCGUGGACGAGGUGCCUAAAGGACUGACCGGC AAGUUGGACGCCCGCAAGAUCCGCGAGAUUCUCAUUAAGGCCAAGA AGGGCGGCAAGAUCGCCGUGUAACUCGAGUAUGUUACGUGCAAAGG UGAUUGUCACCCCCCGAAAGACCAUAUUGUGACACACCCUCAGUAU CACGCCCAAACAUUUACAGCCGCGGUGUCAAAAACCGCGUGGACGU GGUUAACAUCCCUGCUGGGAGGAUCAGCCGUAAUUAUUAUAAUUGG CUUGGUGCUGGCUACUAUUGUGGCCAUGUACGUGCUGACCAACCAG AAACAUAAUUGAAUACAGCAGCAAUUGGCAAGCUGCUUACAUAGAA CUCGCGGCGAUUGGCAUGCCGCCUUAAAAUUUUUAUUUUAUUUUUU CUUUUCUUUUCCGAAUCGGAUUUUGUUUUUAAUAUUUCAAAAAAAA AAAAAAAAAAAAAAAAAAUCUAGAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAA
2842 (SEQ ID NO:101)	SINV Fluc	2842	AUUGACGGCGUAGUACACACUAUUGAAUCAAACAGCCGACCAAUUG CACUACCAUCACAAUGGAGAAGCCAGUAGUAAACGUAGACGUAGAC CCCCAGAGUCCGUUUGUCGUGCAACUGCAAAAAAGCUUCCCGCAAU UUGAGGUAGUAGCACAGCAGGUCACUCCAAAUGACCAUGCUAAUGC CAGAGCAUUUUCGCAUCUGGCCAGUAAACUAAUCGAGCUGGAGGUU CCUACCACAGCGACGAUCUUGGACAUAGGCAGCGCACCGGCUCGUA GAAUGUUUUCCGAGCACCAGUAUCAUUGUGUCUGCCCCAUGCGUAG UCCAGAAGACCCGGACCGCAUGAUGAAAUAUGCCAGUAAACUGGCG GAAAAAGCGUGCAAGAUUACAAACAAGAACUUGCAUGAGAAGAUUA AGGAUCUCCGGACCGUACUUGAUACGCCGGAUGCUGAAACACCAUC GCUCUGCUUUCACAACGAUGUUACCUGCAACAUGCGUGCCGAAUAU UCCGUCAUGCAGGACGUGUAUAUCAACGCUCCCGGAACUAUCUAUC AUCAGGCUAUGAAAGGCGUGCGGACCCUGUACUGGAUUGGCUUCGA CACCACCCAGUUCAUGUUCUCGGCUAUGGCAGGUUCGUACCCUGCG UACAACACCAACUGGGCCGACGAGAAAGUCCUUGAAGCGCGUAACA UCGGACUUUGCAGCACAAAGCUGAGUGAAGGUAGGACAGGAAAAUU GUCGAUAAUGAGGAAGAAGGAGUUGAAGCCCGGGUCGCGGGUUUAU

			UUCUCCGUAGGAUCGACACUUUAUCCAGAACACAGAGCCAGCUUGC AGAGCUGGCAUCUUCCAUCGGUGUUCCACUUGAAUGGAAAGCAGUC GUACACUUGCCGCUGUGAUACAGUGGUGAGUUGCGAAGGCUACGUA GUGAAGAAAAUCACCAUCAGUCCCGGGAUCACGGGAGAAACCGUGG GAUACGCGGUUACACACAAUAGCGAGGGCUUCUUGCUAUGCAAAGU UACUGACACAGUAAAAGGAGAACGGGUAUCGUUCCCUGUGUGCACG UACAUCCCGGCCACCAUAUGCGAUCAGAUGACUGGUAUAAUGGCCA CGGAUAUAUCACCUGACGAUGCACAAAAACUUCUGGUUGGGCUCAA CCAGCGAAUUGUCAUUAACGGUAGGACUAACAGGAACACCAACACC AUGCAAAAUUACCUUCUGCCGAUCAUAGCACAAGGGUUCAGCAAAU GGGCUAAGGAGCGCAAGGAUGAUCUUGAUAACGAGAAAAUGCUGGG UACUAGAGAACGCAAGCUUACGUAUGGCUGCUUGUGGGCGUUUCGC ACUAAGAAAGUACAUUCGUUUUAUCGCCCACCUGGAACGCAGACCU GCGUAAAAGUCCCAGCCUCUUUUAGCGCUUUUCCCAUGUCGUCCGU AUGGACGACCUCUUUGCCCAUGUCGCUGAGGCAGAAAUUGAAACUG GCAUUGCAACCAAAGAAGGAGGAAAAACUGCUGCAGGUCUCGGAGG AAUUAGUCAUGGAGGCCAAGGCUGCUUUUGAGGAUGCUCAGGAGGA AGCCAGAGCGGAGAAGCUCCGAGAAGCACUUCCACCAUUAGUGGCA GACAAAGGCAUCGAGGCAGCCGCAGAAGUUGUCUGCGAAGUGGAGG GGCUCCAGGCGGACAUCGGAGCAGCAUUAGUUGAAACCCCGCGCGG UCACGUAAGGAUAAUACCUCAAGCAAAUGACCGUAUGAUCGGACAG UAUAUCGUUGUCUCGCCAAACUCUGUGCUGAAGAAUGCCAAACUCG CACCAGCGCACCCGCUAGCAGAUCAGGUUAAGAUCAUAACACACUC CGGAAGAUCAGGAAGGUACGCGGUCGAACCAUACGACGCUAAAGUA CUGAUGCCAGCAGGAGGUGCCGUACCAUGGCCAGAAUUCCUAGCAC UGAGUGAGAGCGCCACGUUAGUGUACAACGAAAGAGAGUUUGUGAA CCGCAAACUAUACCACAUUGCCAUGCAUGGCCCCGCCAAGAAUACA GAAGAGGAGCAGUACAAGGUUACAAAGGCAGAGCUUGCAGAAACAG AGUACGUGUUUGACGUGGACAAGAAGCGUUGCGUUAAGAAGGAAGA AGCCUCAGGUCUGGUCCUCUCGGGAGAACUGACCAACCCUCCCUAU CAUGAGCUAGCUCUGGAGGGACUGAAGACCCGACCUGCGGUCCCGU ACAAGGUCGAAACAAUAGGAGUGAUAGGCACACCGGGGUCGGGCAA GUCAGCUAUUAUCAAGUCAACUGUCACGGCACGAGAUCUUGUUACC AGCGGAAAGAAAGAAAAUUGUCGCGAAAUUGAGGCCGACGUGCUAA GACUGAGGGGUAUGCAGAUUACGUCGAAGACAGUAGAUUCGGUUAU GCUCAACGGAUGCCACAAAGCCGUAGAAGUGCUGUACGUUGACGAA GCGUUCGCGUGCCACGCAGGAGCACUACUUGCCUUGAUUGCUAUCG UCAGGCCCCGCAAGAAGGUAGUACUAUGCGGAGACCCCAUGCAAUG CGGAUUCUUCAACAUGAUGCAACUAAAGGUACAUUUCAAUCACCCU GAAAAAGACAUAUGCACCAAGACAUUCUACAAGUAUAUCUCCCGGC GUUGCACACAGCCAGUUACAGCUAUUGUAUCGACACUGCAUUACGA UGGAAAGAUGAAAACCACGAACCCGUGCAAGAAGAACAUUGAAAUC GAUAUUACAGGGGCCACAAAGCCGAAGCCAGGGGAUAUCAUCCUGA CAUGUUUCCGCGGGUGGGUUAAGCAAUUGCAAAUCGACUAUCCCGG ACAUGAAGUAAUGACAGCCGCGGCCUCACAAGGGCUAACCAGAAAA GGAGUGUAUGCCGUCCGGCAAAAAGUCAAUGAAAACCCACUGUACG CGAUCACAUCAGAGCAUGUGAACGUGUUGCUCACCCGCACUGAGGA CAGGCUAGUGUGGAAAACCUUGCAGGGCGACCCAUGGAUUAAGCAG CUCACUAACAUACCUAAAGGAAACUUUCAGGCUACUAUAGAGGACU GGGAAGCUGAACACAAGGGAAUAAUUGCUGCAAUAAACAGCCCCAC UCCCCGUGCCAAUCCGUUCAGCUGCAAGACCAACGUUUGCUGGGCG AAAGCAUUGGAACCGAUACUAGCCACGGCCGGUAUCGUACUUACCG GUUGCCAGUGGAGCGAACUGUUCCCACAGUUUGCGGAUGACAAACC ACAUUCGGCCAUUUACGCCUUAGACGUAAUUUGCAUUAAGUUUUUC GGCAUGGACUUGACAAGCGGACUGUUUUCUAAACAGAGCAUCCCAC

			UAACGUACCAUCCCGCCGAUUCAGCGAGGCCGGUAGCUCAUUGGGA CAACAGCCCAGGAACCCGCAAGUAUGGGUACGAUCACGCCAUUGCC GCCGAACUCUCCCGUAGAUUUCCGGUGUUCCAGCUAGCUGGGAAGG GCACACAACUUGAUUUGCAGACGGGGAGAACCAGAGUUAUCUCUGC ACAGCAUAACCUGGUCCCGGUGAACCGCAAUCUUCCUCACGCCUUA GUCCCCGAGUACAAGGAGAAGCAACCCGGCCCGGUCGAAAAAUUCU UGAACCAGUUCAAACACCACUCAGUACUUGUGGUAUCAGAGGAAAA AAUUGAAGCUCCCCGUAAGAGAAUCGAAUGGAUCGCCCCGAUUGGC AUAGCCGGUGCAGAUAAGAACUACAACCUGGCUUUCGGGUUUCCGC CGCAGGCACGGUACGACCUGGUGUUCAUCAACAUUGGAACUAAAUA CAGAAACCACCACUUUCAGCAGUGCGAAGACCAUGCGGCGACCUUA AAAACCCUUUCGCGUUCGGCCCUGAAUUGCCUUAACCCAGGAGGCA CCCUCGUGGUGAAGUCCUAUGGCUACGCCGACCGCAACAGUGAGGA CGUAGUCACCGCUCUUGCCAGAAAGUUUGUCAGGGUGUCUGCAGCG AGACCAGAUUGUGUCUCAAGCAAUACAGAAAUGUACCUGAUUUUCC GACAACUAGACAACAGCCGUACACGGCAAUUCACCCCGCACCAUCU GAAUUGCGUGAUUUCGUCCGUGUAUGAGGGUACAAGAGAUGGAGUU GGAGCCGCGCCGUCAUACCGCACCAAAAGGGAGAAUAUUGCUGACU GUCAAGAGGAAGCAGUUGUCAACGCAGCCAAUCCGCUGGGUAGACC AGGCGAAGGAGUCUGCCGUGCCAUCUAUAAACGUUGGCCGACCAGU UUUACCGAUUCAGCCACGGAGACAGGCACCGCAAGAAUGACUGUGU GCCUAGGAAAGAAAGUGAUCCACGCGGUCGGCCCUGAUUUCCGGAA GCACCCAGAAGCAGAAGCCUUGAAAUUGCUACAAAACGCCUACCAU GCAGUGGCAGACUUAGUAAAUGAACAUAACAUCAAGUCUGUCGCCA UUCCACUGCUAUCUACAGGCAUUUACGCAGCCGGAAAAGACCGCCU UGAAGUAUCACUUAACUGCUUGACAACCGCGCUAGACAGAACUGAC GCGGACGUAACCAUCUAUUGCCUGGAUAAGAAGUGGAAGGAAAGAA UCGACGCGGCACUCCAACUUAAGGAGUCUGUAACAGAGCUGAAGGA UGAAGAUAUGGAGAUCGACGAUGAGUUAGUAUGGAUCCAUCCAGAC AGUUGCUUGAAGGGAAGAAAGGGAUUCAGUACUACAAAAGGAAAAU UGUAUUCGUACUUCGAAGGCACCAAAUUCCAUCAAGCAGCAAAAGA CAUGGCGGAGAUAAAGGUCCUGUUCCCUAAUGACCAGGAAAGUAAU GAACAACUGUGUGCCUACAUAUUGGGUGAGACCAUGGAAGCAAUCC GCGAAAAGUGCCCGGUCGACCAUAACCCGUCGUCUAGCCCGCCCAA AACGUUGCCGUGCCUUUGCAUGUAUGCCAUGACGCCAGAAAGGGUC CACAGACUUAGAAGCAAUAACGUCAAAGAAGUUACAGUAUGCUCCU CCACCCCCCUUCCUAAGCACAAAAUUAAGAAUGUUCAGAAGGUUCA GUGCACGAAAGUAGUCCUGUUUAAUCCGCACACUCCCGCAUUCGUU CCCGCCCGUAAGUACAUAGAAGUGCCAGAACAGCCUACCGCUCCUC CUGCACAGGCCGAGGAGGCCCCCGAAGUUGUAGCGACACCGUCACC AUCUACAGCUGAUAACACCUCGCUUGAUGUCACAGACAUCUCACUG GAUAUGGAUGACAGUAGCGAAGGCUCACUUUUUUCGAGCUUUAGCG GAUCGGACAACUCUAUUACUAGUAUGGACAGUUGGUCGUCAGGACC UAGUUCACUAGAGAUAGUAGACCGAAGGCAGGUGGUGGUGGCUGAC GUUCAUGCCGUCCAAGAGCCUGCCCCUAUUCCACCGCCAAGGCUAA AGAAGAUGGCCCGCCUGGCAGCGGCAAGAAAAGAGCCCACUCCACC GGCAAGCAAUAGCUCUGAGUCCCUCCACCUCUCUUUUGGUGGGGUA UCCAUGUCCCUCGGAUCAAUUUUCGACGGAGAGACGGCCCGCCAGG CAGCGGUACAACCCCUGGCAACAGGCCCCACGGAUGUGCCUAUGUC UUUCGGAUCGUUUUCCGACGGAGAGAUUGAUGAGCUGAGCCGCAGA GUAACUGAGUCCGAACCCGUCCUGUUUGGAUCAUUUGAACCGGGCG AAGUGAACUCAAUUAUAUCGUCCCGAUCAGCCGUAUCUUUUCCUCU ACGCAAGCAGAGACGUAGACGCAGGAGCAGGAGGACUGAAUACUGA CUAACCGGGGUAGGUGGGUACAUAUUUUCGACGGACACAGGCCCUG GGCACUUGCAAAAGAAGUCCGUUCUGCAGAACCAGCUUACAGAACC

			GACCUUGGAGCGCAAUGUCCUGGAAAGAAUUCAUGCCCCGGUGCUC GACACGUCGAAAGAGGAACAACUCAAACUCAGGUACCAGAUGAUGC CCACCGAAGCCAACAAAAGUAGGUACCAGUCUCGUAAAGUAGAAAA UCAGAAAGCCAUAACCACUGAGCGACUACUGUCAGGACUACGACUG UAUAACUCUGCCACAGAUCAGCCAGAAUGCUAUAAGAUCACCUAUC CGAAACCAUUGUACUCCAGUAGCGUACCGGCGAACUACUCCGAUCC ACAGUUCGCUGUAGCUGUCUGUAACAACUAUCUGCAUGAGAACUAU CCGACAGUAGCAUCUUAUCAGAUUACUGACGAGUACGAUGCUUACU UGGAUAUGGUAGACGGGACAGUCGCCUGCCUGGACACUGCAACCUU CUGCCCCGCUAAGCUUAGAAGUUACCCGAAAAAACAUGAGUAUAGA GCCCCGAAUAUCCGCAGUGCGGUUCCAUCAGCGAUGCAGAACACGC UACAAAAUGUGCUCAUUGCCGCAACUAAAAGAAAUUGCAACGUCAC GCAGAUGCGUGAACUGCCAACACUGGACUCAGCGACAUUCAAUGUC GAAUGCUUUCGAAAAUAUGCAUGUAAUGACGAGUAUUGGGAGGAGU UCGCUCGGAAGCCAAUUAGGAUUACCACUGAGUUUGUCACCGCAUA UGUAGCUAGACUGAAAGGCCCUAAGGCCGCCGCACUAUUUGCAAAG ACGUAUAAUUUGGUCCCAUUGCAAGAAGUGCCUAUGGAUAGAUUCG UCAUGGACAUGAAAAGAGACGUGAAAGUUACACCAGGCACGAAACA CACAGAAGAAAGACCGAAAGUACAAGUGAUACAAGCCGCAGAACCC CUGGCGACUGCUUACUUAUGCGGGAUUCACCGGGAAUUAGUGCGUA GGCUUACGGCCGUCUUGCUUCCAAACAUUCACACGCUUUUUGACAU GUCGGCGGAGGAUUUUGAUGCAAUCAUAGCAGAACACUUCAAGCAA GGCGACCCGGUACUGGAGACGGAUAUCGCAUCAUUCGACAAAAGCC AAGACGACGCUAUGGCGUUAACCGGUCUGAUGAUCUUGGAGGACCU GGGUGUGGAUCAACCACUACUCGACUUGAUCGAGUGCGCCUUUGGA GAAAUAUCAUCCACCCAUCUACCUACGGGUACUCGUUUUAAAUUCG GGGCGAUGAUGAAAUCCGGAAUGUUCCUCACACUUUUUGUCAACAC AGUUUUGAAUGUCGUUAUCGCCAGCAGAGUACUAGAGGAGCGGCUU AAAACGUCCAGAUGUGCAGCGUUCAUUGGCGACGACAACAUCAUAC AUGGAGUAGUAUCUGACAAAGAAAUGGCUGAGAGGUGCGCCACCUG GCUCAACAUGGAGGUUAAGAUCAUCGACGCAGUCAUCGGUGAGAGA CCACCUUACUUCUGCGGCGGAUUUAUCUUGCAAGAUUCGGUUACUU CCACAGCGUGCCGCGUGGCGGAUCCCCUGAAAAGGCUGUUUAAGUU GGGUAAACCGCUCCCAGCCGACGACGAGCAAGACGAAGACAGAAGA CGCGCUCUGCUAGAUGAAACAAAGGCGUGGUUUAGAGUAGGUAUAA CAGGCACUUUAGCAGUGGCCGUGACGACCCGGUAUGAGGUAGACAA UAUUACACCUGUCCUACUGGCAUUGAGAACUUUUGCCCAGAGCAAA AGAGCAUUCCAAGCCAUCAGAGGGGAAAUAAAGCAUCUCUACGGUG GUCCUAAAUAGUCAGCAUAGUACAUUUCAUCUGACUAAUACUACAA CACCACCACCAUGGAAGAUGCCAAAAACAUUAAGAAGGGCCCAGCG CCAUUCUACCCACUCGAAGACGGGACCGCCGGCGAGCAGCUGCACA AAGCCAUGAAGCGCUACGCCCUGGUGCCCGGCACCAUCGCCUUUAC CGACGCACAUAUCGAGGUGGACAUUACCUACGCCGAGUACUUCGAG AUGAGCGUUCGGCUGGCAGAAGCUAUGAAGCGCUAUGGGCUGAAUA CAAACCAUCGGAUCGUGGUGUGCAGCGAGAAUAGCUUGCAGUUCUU CAUGCCCGUGUUGGGUGCCCUGUUCAUCGGUGUGGCUGUGGCCCCA GCUAACGACAUCUACAACGAGCGCGAGCUGCUGAACAGCAUGGGCA UCAGCCAGCCCACCGUCGUAUUCGUGAGCAAGAAAGGGCUGCAAAA GAUCCUCAACGUGCAAAAGAAGCUACCGAUCAUACAAAAGAUCAUC AUCAUGGAUAGCAAGACCGACUACCAGGGCUUCCAAAGCAUGUACA CCUUCGUGACUUCCCAUUUGCCACCCGGCUUCAACGAGUACGACUU CGUGCCCGAGAGCUUCGACCGGGACAAAACCAUCGCCCUGAUCAUG AACAGUAGUGGCAGUACCGGAUUGCCCAAGGGCGUAGCCCUACCGC ACCGCACCGCUUGUGUCCGAUUCAGUCAUGCCCGCGACCCCAUCUU CGGCAACCAGAUCAUCCCCGACACCGCUAUCCUCAGCGUGGUGCCA

			UUUCACCACGGCUUCGGCAUGUUCACCACGCUGGGCUACUUGAUCU GCGGCUUUCGGGUCGUGCUCAUGUACCGCUUCGAGGAGGAGCUAUU CUUGCGCAGCUUGCAAGACUAUAAGAUUCAAUCUGCCCUGCUGGUG CCCACACUAUUUAGCUUCUUCGCUAAGAGCACUCUCAUCGACAAGU ACGACCUAAGCAACUUGCACGAGAUCGCCAGCGGCGGGGCGCCGCU CAGCAAGGAGGUAGGUGAGGCCGUGGCCAAACGCUUCCACCUACCA GGCAUCCGACAGGGCUACGGCCUGACAGAAACAACCAGCGCCAUUC UGAUCACCCCCGAAGGGGACGACAAGCCUGGCGCAGUAGGCAAGGU GGUGCCCUUCUUCGAGGCUAAGGUGGUGGACUUGGACACCGGUAAG ACACUGGGUGUGAACCAGCGCGGCGAGCUGUGCGUCCGUGGCCCCA UGAUCAUGAGCGGCUACGUUAACAACCCCGAGGCUACAAACGCUCU CAUCGACAAGGACGGCUGGCUGCACAGCGGCGACAUCGCCUACUGG GACGAGGACGAGCACUUCUUCAUCGUGGACCGGCUGAAGUCCCUGA UCAAAUACAAGGGCUACCAGGUAGCCCCAGCCGAACUGGAGAGCAU CCUGCUGCAACACCCCAACAUCUUCGACGCCGGGGUCGCCGGCCUG CCCGACGACGAUGCCGGCGAGCUGCCCGCCGCAGUCGUCGUGCUGG AACACGGUAAAACCAUGACCGAGAAGGAGAUCGUGGACUAUGUGGC CAGCCAGGUUACAACCGCCAAGAAGCUGCGCGGUGGUGUUGUGUUC GUGGACGAGGUGCCUAAAGGACUGACCGGCAAGUUGGACGCCCGCA AGAUCCGCGAGAUUCUCAUUAAGGCCAAGAAGGGCGGCAAGAUCGC CGUGUAAACGCGUGCUAGACCAUGGAUCCUAGACGCUACGCCCCAA UGAUCCGACCAGCAAAACUCGAUGUACUUCCGAGGAACUGAUGUGC AUAAUGCAUCAGGCUGGUACAUUAGAUCCCCGCUUACCGCGGGCAA UAUAGCAACACUAAAAACUCGAUGUACUUCCGAGGAAGCGCAGUGC AUAAUGCUGCGCAGUGUUGCCACAUAACCACUAUAUUAACCAUUUA UCUAGCGGACGCCAAAAACUCAAUGUAUUUCUGAGGAAGCGUGGUG CAUAAUGCCACGCAGCGUCUGCAUAACUUUUAUUAUUUCUUUUAUU AAUCAACAAAAUUUUGUUUUUAACAUUUCAAAAAAAAAAAAAAAAA AAAAAAAAUCUAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAA
1782 (SEQ ID NO:102)	mRNA Fluc	1782	AGGAAACUUAAGUCAACACAACAUAUACAAAACAAACGAAUCUCAA GCAAUCAAGCAUUCUACUUCUAUUGCAGCAAUUUAAAUCAUUUCUU UUAAAGCAAAAGCAAUUUUCUGAAAAUUUUCACCAUUUACGAACGA UAGCCAUGGAAGAUGCCAAAAACAUUAAGAAGGGCCCAGCGCCAUU CUACCCACUCGAAGACGGGACCGCCGGCGAGCAGCUGCACAAAGCC AUGAAGCGCUACGCCCUGGUGCCCGGCACCAUCGCCUUUACCGACG CACAUAUCGAGGUGGACAUUACCUACGCCGAGUACUUCGAGAUGAG CGUUCGGCUGGCAGAAGCUAUGAAGCGCUAUGGGCUGAAUACAAAC CAUCGGAUCGUGGUGUGCAGCGAGAAUAGCUUGCAGUUCUUCAUGC CCGUGUUGGGUGCCCUGUUCAUCGGUGUGGCUGUGGCCCCAGCUAA CGACAUCUACAACGAGCGCGAGCUGCUGAACAGCAUGGGCAUCAGC CAGCCCACCGUCGUAUUCGUGAGCAAGAAAGGGCUGCAAAAGAUCC UCAACGUGCAAAAGAAGCUACCGAUCAUACAAAAGAUCAUCAUCAU GGAUAGCAAGACCGACUACCAGGGCUUCCAAAGCAUGUACACCUUC GUGACUUCCCAUUUGCCACCCGGCUUCAACGAGUACGACUUCGUGC CCGAGAGCUUCGACCGGGACAAAACCAUCGCCCUGAUCAUGAACAG UAGUGGCAGUACCGGAUUGCCCAAGGGCGUAGCCCUACCGCACCGC ACCGCUUGUGUCCGAUUCAGUCAUGCCCGCGACCCCAUCUUCGGCA ACCAGAUCAUCCCCGACACCGCUAUCCUCAGCGUGGUGCCAUUUCA CCACGGCUUCGGCAUGUUCACCACGCUGGGCUACUUGAUCUGCGGC UUUCGGGUCGUGCUCAUGUACCGCUUCGAGGAGGAGCUAUUCUUGC GCAGCUUGCAAGACUAUAAGAUUCAAUCUGCCCUGCUGGUGCCCAC ACUAUUUAGCUUCUUCGCUAAGAGCACUCUCAUCGACAAGUACGAC CUAAGCAACUUGCACGAGAUCGCCAGCGGCGGGGCGCCGCUCAGCA

			AGGAGGUAGGUGAGGCCGUGGCCAAACGCUUCCACCUACCAGGCAU CCGACAGGGCUACGGCCUGACAGAAACAACCAGCGCCAUUCUGAUC ACCCCCGAAGGGGACGACAAGCCUGGCGCAGUAGGCAAGGUGGUGC CCUUCUUCGAGGCUAAGGUGGUGGACUUGGACACCGGUAAGACACU GGGUGUGAACCAGCGCGGCGAGCUGUGCGUCCGUGGCCCCAUGAUC AUGAGCGGCUACGUUAACAACCCCGAGGCUACAAACGCUCUCAUCG ACAAGGACGGCUGGCUGCACAGCGGCGACAUCGCCUACUGGGACGA GGACGAGCACUUCUUCAUCGUGGACCGGCUGAAGUCCCUGAUCAAA UACAAGGGCUACCAGGUAGCCCCAGCCGAACUGGAGAGCAUCCUGC UGCAACACCCCAACAUCUUCGACGCCGGGGUCGCCGGCCUGCCCGA CGACGAUGCCGGCGAGCUGCCCGCCGCAGUCGUCGUGCUGGAACAC GGUAAAACCAUGACCGAGAAGGAGAUCGUGGACUAUGUGGCCAGCC AGGUUACAACCGCCAAGAAGCUGCGCGGUGGUGUUGUGUUCGUGGA CGAGGUGCCUAAAGGACUGACCGGCAAGUUGGACGCCCGCAAGAUC CGCGAGAUUCUCAUUAAGGCCAAGAAGGGCGGCAAGAUCGCCGUGU AACUCGAGCUAGUGACUGACUAGGAUCUGGUUACCACUAAACCAGC CUCAAGAACACCCGAAUGGAGUCUCUAAGCUACAUAAUACCAACUU ACACUUACAAAAUGUUGUCCCCCAAAAUGUAGCCAUUCGUAUCUGC UCCUAAUAAAAAGAAAGUUUCUUCACAUUCUAGAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAA
2847 (SEQ ID NO:103)	STARR™ KRAS wt	2847	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAU GGAGAAAGUUCACGUUGACAUCGAGGAAGACAGCCCAUUCCUCAGA GCUUUGCAGCGGAGCUUCCCGCAGUUUGAGGUAGAAGCCAAGCAGG UCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGC UUCAAAACUGAUCGAAACGGAGGUGGACCCAUCCGACACGAUCCUU GACAUUGGAAGUGCGCCCGCCCGCAGAAUGUAUUCUAAGCACAAGU AUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUU GUAUAAGUAUGCAACUAAGCUGAAGAAAAACUGUAAGGAAAUAACU GAUAAGGAAUUGGACAAGAAAAUGAAGGAGCUGGCCGCCGUCAUGA GCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGACGA GUCGUGUCGCUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUAC GCCGUCGACGGCCCCACCAGCCUGUACCACCAGGCCAACAAGGGCG UGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCCUUCAUGUU CAAGAACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCC GACGAGACCGUGCUGACCGCCAGGAACAUCGGCCUGUGCAGCAGCG ACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAUCCUGAGGAAGAA AUACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACC AUCUACCACGAGAAGAGGGACCUGCUCAGGAGCUGGCACCUGCCCA GCGUGUUCCACCUGAGGGGCAAGCAGAACUACACCUGCAGGUGCGA GACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUC AGCCCCGGCCUGUACGGCAAGCCCAGCGGCUACGCCGCUACAAUGC ACAGGGAGGGCUUCCUGUGCUGCAAGGUGACCGACACCCUGAACGG CGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUG UGCGACCAGAUGACCGGCAUCCUGGCCACCGACGUGAGCGCCGACG ACGCCCAGAAGCUGCUCGUGGGCCUGAACCAGAGGAUCGUGGUCAA CGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUGCUG CCCGUGGUGGCCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGG AGGACCAGGAAGACGAGAGGCCCCUGGGCCUGAGGGACAGGCAGCU GGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAUCACCAGC AUCUACAAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCG ACUUCCACAGCUUCGUGCUGCCCAGGAUCGGCAGCAACACCCUGGA GAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGGAGGAACACAAG GAGCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGU

			GCGCUGCCGACGAGGCCAAGGAGGUGAGGGAGGCCGAGGAACUGAG GGCCGCCCUGCCACCCCUGGCUGCCGACGUGGAGGAACCCACCCUG GAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCG UGGAGACACCCAGGGGCCUGAUCAAGGUGACCAGCUACGACGGCGA GGACAAGAUCGGCAGCUACGCCGUGCUGAGCCCACAGGCCGUGCUG AAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGA UCGUGAUCACCCACAGCGGCAGGAAGGGCAGGUACGCCGUGGAGCC CUACCACGGCAAGGUGGUCGUGCCCGAGGGCCACGCCAUCCCCGUG CAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAACG AGAGGGAGUUCGUGAACAGGUACCUGCACCAUAUCGCCACCCACGG CGGAGCCCUGAACACCGACGAGGAAUACUACAAGACCGUGAAGCCC AGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGAAGCAGU GCGUGAAGAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCU GGUGGACCCACCCUUCCACGAGUUCGCCUACGAGAGCCUGAGGACC AGACCCGCCGCUCCCUACCAGGUGCCCACCAUCGGCGUGUACGGCG UGCCCGGCAGCGGAAAGAGCGGCAUCAUCAAGAGCGCCGUGACCAA GAAAGACCUGGUGGUCAGCGCCAAGAAAGAGAACUGCGCCGAGAUC AUCAGGGACGUGAAGAAGAUGAAAGGCCUGGACGUGAACGCGCGCA CCGUGGACAGCGUGCUGCUGAACGGCUGCAAGCACCCCGUGGAGAC CCUGUACAUCGACGAGGCCUUCGCUUGCCACGCCGGCACCCUGAGG GCCCUGAUCGCCAUCAUCAGGCCCAAGAAAGCCGUGCUGUGCGGCG ACCCCAAGCAGUGCGGCUUCUUCAACAUGAUGUGCCUGAAGGUGCA CUUCAACCACGAGAUCUGCACCCAGGUGUUCCACAAGAGCAUCAGC AGGCGGUGCACCAAGAGCGUGACCAGCGUCGUGAGCACCCUGUUCU ACGACAAGAAAAUGAGGACCACCAACCCCAAGGAGACCAAAAUCGU GAUCGACACCACAGGCAGCACCAAGCCCAAGCAGGACGACCUGAUC CUGACCUGCUUCAGGGGCUGGGUGAAGCAGCUGCAGAUCGACUACA AGGGCAACGAGAUCAUGACCGCCGCUGCCAGCCAGGGCCUGACCAG GAAGGGCGUGUACGCCGUGAGGUACAAGGUGAACGAGAACCCACUG UACGCUCCCACCAGCGAGCACGUGAACGUGCUGCUGACCAGGACCG AGGACAGGAUCGUGUGGAAGACCCUGGCCGGCGACCCCUGGAUCAA GACCCUGACCGCCAAGUACCCCGGCAACUUCACCGCCACCAUCGAA GAGUGGCAGGCCGAGCACGACGCCAUCAUGAGGCACAUCCUGGAGA GGCCCGACCCCACCGACGUGUUCCAGAACAAGGCCAACGUGUGCUG GGCCAAGGCCCUGGUGCCCGUGCUGAAGACCGCCGGCAUCGACAUG ACCACAGAGCAGUGGAACACCGUGGACUACUUCGAGACCGACAAGG CCCACAGCGCCGAGAUCGUGCUGAACCAGCUGUGCGUGAGGUUCUU CGGCCUGGACCUGGACAGCGGCCUGUUCAGCGCCCCCACCGUGCCA CUGAGCAUCAGGAACAACCACUGGGACAACAGCCCCAGCCCAAACA UGUACGGCCUGAACAAGGAGGUGGUCAGGCAGCUGAGCAGGCGGUA CCCACAGCUGCCCAGGGCCGUGGCCACCGGCAGGGUGUACGACAUG AACACCGGCACCCUGAGGAACUACGACCCCAGGAUCAACCUGGUGC CCGUGAACAGGCGGCUGCCCCACGCCCUGGUGCUGCACCACAACGA GCACCCACAGAGCGACUUCAGCUCCUUCGUGAGCAAGCUGAAAGGC AGGACCGUGCUGGUCGUGGGCGAGAAGCUGAGCGUGCCCGGCAAGA UGGUGGACUGGCUGAGCGACAGGCCCGAGGCCACCUUCCGGGCCAG GCUGGACCUCGGCAUCCCCGGCGACGUGCCCAAGUACGACAUCAUC UUCGUGAACGUCAGGACCCCAUACAAGUACCACCAUUACCAGCAGU GCGAGGACCACGCCAUCAAGCUGAGCAUGCUGACCAAGAAGGCCUG CCUGCACCUGAACCCCGGAGGCACCUGCGUGAGCAUCGGCUACGGC UACGCCGACAGGGCCAGCGAGAGCAUCAUUGGCGCCAUCGCCAGGC UGUUCAAGUUCAGCAGGGUGUGCAAACCCAAGAGCAGCCUGGAGGA AACCGAGGUGCUGUUCGUGUUCAUCGGCUACGACCGGAAGGCCAGG ACCCACAACCCCUACAAGCUGAGCAGCACCCUGACAAACAUCUACA CCGGCAGCAGGCUGCACGAGGCCGGCUGCGCCCCCAGCUACCACGU

			GGUCAGGGGCGAUAUCGCCACCGCCACCGAGGGCGUGAUCAUCAAC GCUGCCAACAGCAAGGGCCAGCCCGGAGGCGGAGUGUGCGGCGCCC UGUACAAGAAGUUCCCCGAGAGCUUCGACCUGCAGCCCAUCGAGGU GGGCAAGGCCAGGCUGGUGAAGGGCGCCGCUAAGCACAUCAUCCAC GCCGUGGGCCCCAACUUCAACAAGGUGAGCGAGGUGGAAGGCGACA AGCAGCUGGCCGAAGCCUACGAGAGCAUCGCCAAGAUCGUGAACGA CAAUAACUACAAGAGCGUGGCCAUCCCACUGCUCAGCACCGGCAUC UUCAGCGGCAACAAGGACAGGCUGACCCAGAGCCUGAACCACCUGC UCACCGCCCUGGACACCACCGAUGCCGACGUGGCCAUCUACUGCAG GGACAAGAAGUGGGAGAUGACCCUGAAGGAGGCCGUGGCCAGGCGG GAGGCCGUGGAAGAGAUCUGCAUCAGCGACGACUCCAGCGUGACCG AGCCCGACGCCGAGCUGGUGAGGGUGCACCCCAAGAGCUCCCUGGC CGGCAGGAAGGGCUACAGCACCAGCGACGGCAAGACCUUCAGCUAC CUGGAGGGCACCAAGUUCCACCAGGCCGCUAAGGACAUCGCCGAGA UCAACGCUAUGUGGCCCGUGGCCACCGAGGCCAACGAGCAGGUGUG CAUGUACAUCCUGGGCGAGAGCAUGUCCAGCAUCAGGAGCAAGUGC CCCGUGGAGGAAAGCGAGGCCAGCACACCACCCAGCACCCUGCCCU GCCUGUGCAUCCACGCUAUGACACCCGAGAGGGUGCAGCGGCUGAA GGCCAGCAGGCCCGAGCAGAUCACCGUGUGCAGCUCCUUCCCACUG CCCAAGUACAGGAUCACCGGCGUGCAGAAGAUCCAGUGCAGCCAGC CCAUCCUGUUCAGCCCAAAGGUGCCCGCCUACAUCCACCCCAGGAA GUACCUGGUGGAGACCCCACCCGUGGACGAGACACCCGAGCCAAGC GCCGAGAACCAGAGCACCGAGGGCACACCCGAGCAGCCACCCCUGA UCACCGAGGACGAGACAAGGACCCGGACCCCAGAGCCCAUCAUUAU CGAGGAAGAGGAAGAGGACAGCAUCAGCCUGCUGAGCGACGGCCCC ACCCACCAGGUGCUGCAGGUGGAGGCCGACAUCCACGGCCCACCCA GCGUGUCCAGCUCCAGCUGGAGCAUCCCACACGCCAGCGACUUCGA CGUGGACAGCCUGAGCAUCCUGGACACCCUGGAGGGCGCCAGCGUG ACCUCCGGCGCCACCAGCGCCGAGACCAACAGCUACUUCGCCAAGA GCAUGGAGUUCCUGGCCAGGCCCGUGCCAGCUCCCAGGACCGUGUU CAGGAACCCACCCCACCCAGCUCCCAGGACCAGGACCCCAAGCCUG GCUCCCAGCAGGGCCUGCAGCAGGACCAGCCUGGUGAGCACCCCAC CCGGCGUGAACAGGGUGAUCACCAGGGAGGAACUGGAGGCCCUGAC ACCCAGCAGGACCCCCAGCAGGUCCGUGAGCAGGACUAGUCUGGUG UCCAACCCACCCGGCGUGAACAGGGUGAUCACCAGGGAGGAAUUCG AGGCCUUCGUGGCCCAGCAACAGAGACGGUUCGACGCCGGCGCCUA CAUCUUCAGCAGCGACACCGGCCAGGGACACCUGCAGCAAAAGAGC GUGAGGCAGACCGUGCUGAGCGAGGUGGUGCUGGAGAGGACCGAGC UGGAAAUCAGCUACGCCCCCAGGCUGGACCAGGAGAAGGAGGAACU GCUCAGGAAGAAACUGCAGCUGAACCCCACCCCAGCCAACAGGAGC AGGUACCAGAGCAGGAAGGUGGAGAACAUGAAGGCCAUCACCGCCA GGCGGAUCCUGCAGGGCCUGGGACACUACCUGAAGGCCGAGGGCAA GGUGGAGUGCUACAGGACCCUGCACCCCGUGCCACUGUACAGCUCC AGCGUGAACAGGGCCUUCUCCAGCCCCAAGGUGGCCGUGGAGGCCU GCAACGCUAUGCUGAAGGAGAACUUCCCCACCGUGGCCAGCUACUG CAUCAUCCCCGAGUACGACGCCUACCUGGACAUGGUGGACGGCGCC AGCUGCUGCCUGGACACCGCCAGCUUCUGCCCCGCCAAGCUGAGGA GCUUCCCCAAGAAACACAGCUACCUGGAGCCCACCAUCAGGAGCGC CGUGCCCAGCGCCAUCCAGAACACCCUGCAGAACGUGCUGGCCGCU GCCACCAAGAGGAACUGCAACGUGACCCAGAUGAGGGAGCUGCCCG UGCUGGACAGCGCUGCCUUCAACGUGGAGUGCUUCAAGAAAUACGC CUGCAACAACGAGUACUGGGAGACCUUCAAGGAGAACCCCAUCAGG CUGACCGAAGAGAACGUGGUGAACUACAUCACCAAGCUGAAGGGCC CCAAGGCCGCUGCCCUGUUCGCUAAGACCCACAACCUGAACAUGCU GCAGGACAUCCCAAUGGACAGGUUCGUGAUGGACCUGAAGAGGGAC

			GUGAAGGUGACACCCGGCACCAAGCACACCGAGGAGAGGCCCAAGG UGCAGGUGAUCCAGGCCGCUGACCCACUGGCCACCGCCUACCUGUG CGGCAUCCACAGGGAGCUGGUGAGGCGGCUGAACGCCGUGCUGCUG CCCAACAUCCACACCCUGUUCGACAUGAGCGCCGAGGACUUCGACG CCAUCAUCGCCGAGCACUUCCAGCCCGGCGACUGCGUGCUGGAGAC CGACAUCGCCAGCUUCGACAAGAGCGAGGAUGACGCUAUGGCCCUG ACCGCUCUGAUGAUCCUGGAGGACCUGGGCGUGGACGCCGAGCUGC UCACCCUGAUCGAGGCUGCCUUCGGCGAGAUCAGCUCCAUCCACCU GCCCACCAAGACCAAGUUCAAGUUCGGCGCUAUGAUGAAAAGCGGA AUGUUCCUGACCCUGUUCGUGAACACCGUGAUCAACAUUGUGAUCG CCAGCAGGGUGCUGCGGGAGAGGCUGACCGGCAGCCCCUGCGCUGC CUUCAUCGGCGACGACAACAUCGUGAAGGGCGUGAAAAGCGACAAG CUGAUGGCCGACAGGUGCGCCACCUGGCUGAACAUGGAGGUGAAGA UCAUCGACGCCGUGGUGGGCGAGAAGGCCCCCUACUUCUGCGGCGG AUUCAUCCUGUGCGACAGCGUGACCGGCACCGCCUGCAGGGUGGCC GACCCCCUGAAGAGGCUGUUCAAGCUGGGCAAGCCACUGGCCGCUG ACGAUGAGCACGACGAUGACAGGCGGAGGGCCCUGCACGAGGAAAG CACCAGGUGGAACAGGGUGGGCAUCCUGAGCGAGCUGUGCAAGGCC GUGGAGAGCAGGUACGAGACCGUGGGCACCAGCAUCAUCGUGAUGG CUAUGACCACACUGGCCAGCUCCGUCAAGAGCUUCUCCUACCUGAG GGGGGCCCCUAUAACUCUCUACGGCUAACCUGAAUGGACUACGACA UAGUCUAGUCCGCCAAGGCCGCCACCCAUGAAGUUGGUGGUUGUGG GGGCCGGGGGUGUUGGCAAAAGCGCCCUUACAAUUUGACUCGAGUA UGUUACGUGCAAAGGUGAUUGUCACCCCCCGAAAGACCAUAUUGUG ACACACCCUCAGUAUCACGCCCAAACAUUUACAGCCGCGGUGUCAA AAACCGCGUGGACGUGGUUAACAUCCCUGCUGGGAGGAUCAGCCGU AAUUAUUAUAAUUGGCUUGGUGCUGGCUACUAUUGUGGCCAUGUAC GUGCUGACCAACCAGAAACAUAAUUGAAUACAGCAGCAAUUGGCAA GCUGCUUACAUAGAACUCGCGGCGAUUGGCAUGCCGCCUUAAAAUU UUUAUUUUAUUUUUUCUUUUCUUUUCCGAAUCGGAUUUUGUUUUUA AUAUUUCAAAAAAAAAAAAAAAAAAAAAAAAAAUCUAGAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
2862 (SEQ ID NO:104)	SINV empty	2862	AUUGACGGCGUAGUACACACUAUUGAAUCAAACAGCCGACCAAUUG CACUACCAUCACAAUGGAGAAGCCAGUAGUAAACGUAGACGUAGAC CCCCAGAGUCCGUUUGUCGUGCAACUGCAAAAAAGCUUCCCGCAAU UUGAGGUAGUAGCACAGCAGGUCACUCCAAAUGACCAUGCUAAUGC CAGAGCAUUUUCGCAUCUGGCCAGUAAACUAAUCGAGCUGGAGGUU CCUACCACAGCGACGAUCUUGGACAUAGGCAGCGCACCGGCUCGUA GAAUGUUUUCCGAGCACCAGUAUCAUUGUGUCUGCCCCAUGCGUAG UCCAGAAGACCCGGACCGCAUGAUGAAAUAUGCCAGUAAACUGGCG GAAAAAGCGUGCAAGAUUACAAACAAGAACUUGCAUGAGAAGAUUA AGGAUCUCCGGACCGUACUUGAUACGCCGGAUGCUGAAACACCAUC GCUCUGCUUUCACAACGAUGUUACCUGCAACAUGCGUGCCGAAUAU UCCGUCAUGCAGGACGUGUAUAUCAACGCUCCCGGAACUAUCUAUC AUCAGGCUAUGAAAGGCGUGCGGACCCUGUACUGGAUUGGCUUCGA CACCACCCAGUUCAUGUUCUCGGCUAUGGCAGGUUCGUACCCUGCG UACAACACCAACUGGGCCGACGAGAAAGUCCUUGAAGCGCGUAACA UCGGACUUUGCAGCACAAAGCUGAGUGAAGGUAGGACAGGAAAAUU GUCGAUAAUGAGGAAGAAGGAGUUGAAGCCCGGGUCGCGGGUUUAU UUCUCCGUAGGAUCGACACUUUAUCCAGAACACAGAGCCAGCUUGC AGAGCUGGCAUCUUCCAUCGGUGUUCCACUUGAAUGGAAAGCAGUC GUACACUUGCCGCUGUGAUACAGUGGUGAGUUGCGAAGGCUACGUA GUGAAGAAAAUCACCAUCAGUCCCGGGAUCACGGGAGAAACCGUGG GAUACGCGGUUACACACAAUAGCGAGGGCUUCUUGCUAUGCAAAGU

			UACUGACACAGUAAAAGGAGAACGGGUAUCGUUCCCUGUGUGCACG
			UACAUCCCGGCCACCAUAUGCGAUCAGAUGACUGGUAUAAUGGCCA
			CGGAUAUAUCACCUGACGAUGCACAAAAACUUCUGGUUGGGCUCAA
			CCAGCGAAUUGUCAUUAACGGUAGGACUAACAGGAACACCAACACC
			AUGCAAAAUUACCUUCUGCCGAUCAUAGCACAAGGGUUCAGCAAAU
			GGGCUAAGGAGCGCAAGGAUGAUCUUGAUAACGAGAAAAUGCUGGG
			UACUAGAGAACGCAAGCUUACGUAUGGCUGCUUGUGGGCGUUUCGC
			ACUAAGAAAGUACAUUCGUUUUAUCGCCCACCUGGAACGCAGACCU
			GCGUAAAAGUCCCAGCCUCUUUUAGCGCUUUUCCCAUGUCGUCCGU
			AUGGACGACCUCUUUGCCCAUGUCGCUGAGGCAGAAAUUGAAACUG
			GCAUUGCAACCAAAGAAGGAGGAAAAACUGCUGCAGGUCUCGGAGG
			AAUUAGUCAUGGAGGCCAAGGCUGCUUUUGAGGAUGCUCAGGAGGA
			AGCCAGAGCGGAGAAGCUCCGAGAAGCACUUCCACCAUUAGUGGCA
			GACAAAGGCAUCGAGGCAGCCGCAGAAGUUGUCUGCGAAGUGGAGG
			GGCUCCAGGCGGACAUCGGAGCAGCAUUAGUUGAAACCCCGCGCGG
			UCACGUAAGGAUAAUACCUCAAGCAAAUGACCGUAUGAUCGGACAG
			UAUAUCGUUGUCUCGCCAAACUCUGUGCUGAAGAAUGCCAAACUCG
			CACCAGCGCACCCGCUAGCAGAUCAGGUUAAGAUCAUAACACACUC
			CGGAAGAUCAGGAAGGUACGCGGUCGAACCAUACGACGCUAAAGUA
			CUGAUGCCAGCAGGAGGUGCCGUACCAUGGCCAGAAUUCCUAGCAC
			UGAGUGAGAGCGCCACGUUAGUGUACAACGAAAGAGAGUUUGUGAA
			CCGCAAACUAUACCACAUUGCCAUGCAUGGCCCCGCCAAGAAUACA
			GAAGAGGAGCAGUACAAGGUUACAAAGGCAGAGCUUGCAGAAACAG
			AGUACGUGUUUGACGUGGACAAGAAGCGUUGCGUUAAGAAGGAAGA
			AGCCUCAGGUCUGGUCCUCUCGGGAGAACUGACCAACCCUCCCUAU
			CAUGAGCUAGCUCUGGAGGGACUGAAGACCCGACCUGCGGUCCCGU
			ACAAGGUCGAAACAAUAGGAGUGAUAGGCACACCGGGGUCGGGCAA
			GUCAGCUAUUAUCAAGUCAACUGUCACGGCACGAGAUCUUGUUACC
			AGCGGAAAGAAAGAAAAUUGUCGCGAAAUUGAGGCCGACGUGCUAA
			GACUGAGGGGUAUGCAGAUUACGUCGAAGACAGUAGAUUCGGUUAU
			GCUCAACGGAUGCCACAAAGCCGUAGAAGUGCUGUACGUUGACGAA
			GCGUUCGCGUGCCACGCAGGAGCACUACUUGCCUUGAUUGCUAUCG
			UCAGGCCCCGCAAGAAGGUAGUACUAUGCGGAGACCCCAUGCAAUG
			CGGAUUCUUCAACAUGAUGCAACUAAAGGUACAUUUCAAUCACCCU
			GAAAAAGACAUAUGCACCAAGACAUUCUACAAGUAUAUCUCCCGGC
			GUUGCACACAGCCAGUUACAGCUAUUGUAUCGACACUGCAUUACGA
			UGGAAAGAUGAAAACCACGAACCCGUGCAAGAAGAACAUUGAAAUC
			GAUAUUACAGGGGCCACAAAGCCGAAGCCAGGGGAUAUCAUCCUGA
			CAUGUUUCCGCGGGUGGGUUAAGCAAUUGCAAAUCGACUAUCCCGG
			ACAUGAAGUAAUGACAGCCGCGGCCUCACAAGGGCUAACCAGAAAA
			GGAGUGUAUGCCGUCCGGCAAAAAGUCAAUGAAAACCCACUGUACG
			CGAUCACAUCAGAGCAUGUGAACGUGUUGCUCACCCGCACUGAGGA
			CAGGCUAGUGUGGAAAACCUUGCAGGGCGACCCAUGGAUUAAGCAG
			CUCACUAACAUACCUAAAGGAAACUUUCAGGCUACUAUAGAGGACU
			GGGAAGCUGAACACAAGGGAAUAAUUGCUGCAAUAAACAGCCCCAC
			UCCCCGUGCCAAUCCGUUCAGCUGCAAGACCAACGUUUGCUGGGCG
			AAAGCAUUGGAACCGAUACUAGCCACGGCCGGUAUCGUACUUACCG
			GUUGCCAGUGGAGCGAACUGUUCCCACAGUUUGCGGAUGACAAACC
			ACAUUCGGCCAUUUACGCCUUAGACGUAAUUUGCAUUAAGUUUUUC
			GGCAUGGACUUGACAAGCGGACUGUUUUCUAAACAGAGCAUCCCAC
			UAACGUACCAUCCCGCCGAUUCAGCGAGGCCGGUAGCUCAUUGGGA
			CAACAGCCCAGGAACCCGCAAGUAUGGGUACGAUCACGCCAUUGCC
			GCCGAACUCUCCCGUAGAUUUCCGGUGUUCCAGCUAGCUGGGAAGG
			GCACACAACUUGAUUUGCAGACGGGGAGAACCAGAGUUAUCUCUGC
			ACAGCAUAACCUGGUCCCGGUGAACCGCAAUCUUCCUCACGCCUUA

			GUCCCCGAGUACAAGGAGAAGCAACCCGGCCCGGUCGAAAAAUUCU UGAACCAGUUCAAACACCACUCAGUACUUGUGGUAUCAGAGGAAAA AAUUGAAGCUCCCCGUAAGAGAAUCGAAUGGAUCGCCCCGAUUGGC AUAGCCGGUGCAGAUAAGAACUACAACCUGGCUUUCGGGUUUCCGC CGCAGGCACGGUACGACCUGGUGUUCAUCAACAUUGGAACUAAAUA CAGAAACCACCACUUUCAGCAGUGCGAAGACCAUGCGGCGACCUUA AAAACCCUUUCGCGUUCGGCCCUGAAUUGCCUUAACCCAGGAGGCA CCCUCGUGGUGAAGUCCUAUGGCUACGCCGACCGCAACAGUGAGGA CGUAGUCACCGCUCUUGCCAGAAAGUUUGUCAGGGUGUCUGCAGCG AGACCAGAUUGUGUCUCAAGCAAUACAGAAAUGUACCUGAUUUUCC GACAACUAGACAACAGCCGUACACGGCAAUUCACCCCGCACCAUCU GAAUUGCGUGAUUUCGUCCGUGUAUGAGGGUACAAGAGAUGGAGUU GGAGCCGCGCCGUCAUACCGCACCAAAAGGGAGAAUAUUGCUGACU GUCAAGAGGAAGCAGUUGUCAACGCAGCCAAUCCGCUGGGUAGACC AGGCGAAGGAGUCUGCCGUGCCAUCUAUAAACGUUGGCCGACCAGU UUUACCGAUUCAGCCACGGAGACAGGCACCGCAAGAAUGACUGUGU GCCUAGGAAAGAAAGUGAUCCACGCGGUCGGCCCUGAUUUCCGGAA GCACCCAGAAGCAGAAGCCUUGAAAUUGCUACAAAACGCCUACCAU GCAGUGGCAGACUUAGUAAAUGAACAUAACAUCAAGUCUGUCGCCA UUCCACUGCUAUCUACAGGCAUUUACGCAGCCGGAAAAGACCGCCU UGAAGUAUCACUUAACUGCUUGACAACCGCGCUAGACAGAACUGAC GCGGACGUAACCAUCUAUUGCCUGGAUAAGAAGUGGAAGGAAAGAA UCGACGCGGCACUCCAACUUAAGGAGUCUGUAACAGAGCUGAAGGA UGAAGAUAUGGAGAUCGACGAUGAGUUAGUAUGGAUCCAUCCAGAC AGUUGCUUGAAGGGAAGAAAGGGAUUCAGUACUACAAAAGGAAAAU UGUAUUCGUACUUCGAAGGCACCAAAUUCCAUCAAGCAGCAAAAGA CAUGGCGGAGAUAAAGGUCCUGUUCCCUAAUGACCAGGAAAGUAAU GAACAACUGUGUGCCUACAUAUUGGGUGAGACCAUGGAAGCAAUCC GCGAAAAGUGCCCGGUCGACCAUAACCCGUCGUCUAGCCCGCCCAA AACGUUGCCGUGCCUUUGCAUGUAUGCCAUGACGCCAGAAAGGGUC CACAGACUUAGAAGCAAUAACGUCAAAGAAGUUACAGUAUGCUCCU CCACCCCCCUUCCUAAGCACAAAAUUAAGAAUGUUCAGAAGGUUCA GUGCACGAAAGUAGUCCUGUUUAAUCCGCACACUCCCGCAUUCGUU CCCGCCCGUAAGUACAUAGAAGUGCCAGAACAGCCUACCGCUCCUC CUGCACAGGCCGAGGAGGCCCCCGAAGUUGUAGCGACACCGUCACC AUCUACAGCUGAUAACACCUCGCUUGAUGUCACAGACAUCUCACUG GAUAUGGAUGACAGUAGCGAAGGCUCACUUUUUUCGAGCUUUAGCG GAUCGGACAACUCUAUUACUAGUAUGGACAGUUGGUCGUCAGGACC UAGUUCACUAGAGAUAGUAGACCGAAGGCAGGUGGUGGUGGCUGAC GUUCAUGCCGUCCAAGAGCCUGCCCCUAUUCCACCGCCAAGGCUAA AGAAGAUGGCCCGCCUGGCAGCGGCAAGAAAAGAGCCCACUCCACC GGCAAGCAAUAGCUCUGAGUCCCUCCACCUCUCUUUUGGUGGGGUA UCCAUGUCCCUCGGAUCAAUUUUCGACGGAGAGACGGCCCGCCAGG CAGCGGUACAACCCCUGGCAACAGGCCCCACGGAUGUGCCUAUGUC UUUCGGAUCGUUUUCCGACGGAGAGAUUGAUGAGCUGAGCCGCAGA GUAACUGAGUCCGAACCCGUCCUGUUUGGAUCAUUUGAACCGGGCG AAGUGAACUCAAUUAUAUCGUCCCGAUCAGCCGUAUCUUUUCCUCU ACGCAAGCAGAGACGUAGACGCAGGAGCAGGAGGACUGAAUACUGA CUAACCGGGGUAGGUGGGUACAUAUUUUCGACGGACACAGGCCCUG GGCACUUGCAAAAGAAGUCCGUUCUGCAGAACCAGCUUACAGAACC GACCUUGGAGCGCAAUGUCCUGGAAAGAAUUCAUGCCCCGGUGCUC GACACGUCGAAAGAGGAACAACUCAAACUCAGGUACCAGAUGAUGC CCACCGAAGCCAACAAAAGUAGGUACCAGUCUCGUAAAGUAGAAAA UCAGAAAGCCAUAACCACUGAGCGACUACUGUCAGGACUACGACUG UAUAACUCUGCCACAGAUCAGCCAGAAUGCUAUAAGAUCACCUAUC

			CGAAACCAUUGUACUCCAGUAGCGUACCGGCGAACUACUCCGAUCC ACAGUUCGCUGUAGCUGUCUGUAACAACUAUCUGCAUGAGAACUAU CCGACAGUAGCAUCUUAUCAGAUUACUGACGAGUACGAUGCUUACU UGGAUAUGGUAGACGGGACAGUCGCCUGCCUGGACACUGCAACCUU CUGCCCCGCUAAGCUUAGAAGUUACCCGAAAAAACAUGAGUAUAGA GCCCCGAAUAUCCGCAGUGCGGUUCCAUCAGCGAUGCAGAACACGC UACAAAAUGUGCUCAUUGCCGCAACUAAAAGAAAUUGCAACGUCAC GCAGAUGCGUGAACUGCCAACACUGGACUCAGCGACAUUCAAUGUC GAAUGCUUUCGAAAAUAUGCAUGUAAUGACGAGUAUUGGGAGGAGU UCGCUCGGAAGCCAAUUAGGAUUACCACUGAGUUUGUCACCGCAUA UGUAGCUAGACUGAAAGGCCCUAAGGCCGCCGCACUAUUUGCAAAG ACGUAUAAUUUGGUCCCAUUGCAAGAAGUGCCUAUGGAUAGAUUCG UCAUGGACAUGAAAAGAGACGUGAAAGUUACACCAGGCACGAAACA CACAGAAGAAAGACCGAAAGUACAAGUGAUACAAGCCGCAGAACCC CUGGCGACUGCUUACUUAUGCGGGAUUCACCGGGAAUUAGUGCGUA GGCUUACGGCCGUCUUGCUUCCAAACAUUCACACGCUUUUUGACAU GUCGGCGGAGGAUUUUGAUGCAAUCAUAGCAGAACACUUCAAGCAA GGCGACCCGGUACUGGAGACGGAUAUCGCAUCAUUCGACAAAAGCC AAGACGACGCUAUGGCGUUAACCGGUCUGAUGAUCUUGGAGGACCU GGGUGUGGAUCAACCACUACUCGACUUGAUCGAGUGCGCCUUUGGA GAAAUAUCAUCCACCCAUCUACCUACGGGUACUCGUUUUAAAUUCG GGGCGAUGAUGAAAUCCGGAAUGUUCCUCACACUUUUUGUCAACAC AGUUUUGAAUGUCGUUAUCGCCAGCAGAGUACUAGAGGAGCGGCUU AAAACGUCCAGAUGUGCAGCGUUCAUUGGCGACGACAACAUCAUAC AUGGAGUAGUAUCUGACAAAGAAAUGGCUGAGAGGUGCGCCACCUG GCUCAACAUGGAGGUUAAGAUCAUCGACGCAGUCAUCGGUGAGAGA CCACCUUACUUCUGCGGCGGAUUUAUCUUGCAAGAUUCGGUUACUU CCACAGCGUGCCGCGUGGCGGAUCCCCUGAAAAGGCUGUUUAAGUU GGGUAAACCGCUCCCAGCCGACGACGAGCAAGACGAAGACAGAAGA CGCGCUCUGCUAGAUGAAACAAAGGCGUGGUUUAGAGUAGGUAUAA CAGGCACUUUAGCAGUGGCCGUGACGACCCGGUAUGAGGUAGACAA UAUUACACCUGUCCUACUGGCAUUGAGAACUUUUGCCCAGAGCAAA AGAGCAUUCCAAGCCAUCAGAGGGGAAAUAAAGCAUCUCUACGGUG GUCCUAAAUAGUCAGCAUAGUACAUUUCAUCUGACUAAUACUACAA CACCACCACCACGCGUGCUAGACCAUGGAUCCUAGACGCUACGCCC CAAUGAUCCGACCAGCAAAACUCGAUGUACUUCCGAGGAACUGAUG UGCAUAAUGCAUCAGGCUGGUACAUUAGAUCCCCGCUUACCGCGGG CAAUAUAGCAACACUAAAAACUCGAUGUACUUCCGAGGAAGCGCAG UGCAUAAUGCUGCGCAGUGUUGCCACAUAACCACUAUAUUAACCAU UUAUCUAGCGGACGCCAAAAACUCAAUGUAUUUCUGAGGAAGCGUG GUGCAUAAUGCCACGCAGCGUCUGCAUAACUUUUAUUAUUUCUUUU AUUAAUCAACAAAAUUUUGUUUUUAACAUUUCAAAAAAAAAAAAAA AAAAAAAAAAAUCUAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAA
3060 (SEQ ID NO:105)	STARR™ gp70	3060	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAU GGAGAAAGUUCACGUUGACAUCGAGGAAGACAGCCCAUUCCUCAGA GCUUUGCAGCGGAGCUUCCCGCAGUUUGAGGUAGAAGCCAAGCAGG UCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGC UUCAAAACUGAUCGAAACGGAGGUGGACCCAUCCGACACGAUCCUU GACAUUGGAAGUGCGCCCGCCCGCAGAAUGUAUUCUAAGCACAAGU AUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUU GUAUAAGUAUGCAACUAAGCUGAAGAAAAACUGUAAGGAAAUAACU GAUAAGGAAUUGGACAAGAAAAUGAAGGAGCUGGCCGCCGUCAUGA GCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGACGA

			GUCGUGUCGCUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUAC
			GCCGUCGACGGCCCCACCAGCCUGUACCACCAGGCCAACAAGGGCG
			UGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCCUUCAUGUU
			CAAGAACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCC
			GACGAGACCGUGCUGACCGCCAGGAACAUCGGCCUGUGCAGCAGCG
			ACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAUCCUGAGGAAGAA
			AUACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACC
			AUCUACCACGAGAAGAGGGACCUGCUCAGGAGCUGGCACCUGCCCA
			GCGUGUUCCACCUGAGGGGCAAGCAGAACUACACCUGCAGGUGCGA
			GACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUC
			AGCCCCGGCCUGUACGGCAAGCCCAGCGGCUACGCCGCUACAAUGC
			ACAGGGAGGGCUUCCUGUGCUGCAAGGUGACCGACACCCUGAACGG
			CGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUG
			UGCGACCAGAUGACCGGCAUCCUGGCCACCGACGUGAGCGCCGACG
			ACGCCCAGAAGCUGCUCGUGGGCCUGAACCAGAGGAUCGUGGUCAA
			CGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUGCUG
			CCCGUGGUGGCCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGG
			AGGACCAGGAAGACGAGAGGCCCCUGGGCCUGAGGGACAGGCAGCU
			GGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAUCACCAGC
			AUCUACAAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCG
			ACUUCCACAGCUUCGUGCUGCCCAGGAUCGGCAGCAACACCCUGGA
			GAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGGAGGAACACAAG
			GAGCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGU
			GCGCUGCCGACGAGGCCAAGGAGGUGAGGGAGGCCGAGGAACUGAG
			GGCCGCCCUGCCACCCCUGGCUGCCGACGUGGAGGAACCCACCCUG
			GAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCG
			UGGAGACACCCAGGGGCCUGAUCAAGGUGACCAGCUACGACGGCGA
			GGACAAGAUCGGCAGCUACGCCGUGCUGAGCCCACAGGCCGUGCUG
			AAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGA
			UCGUGAUCACCCACAGCGGCAGGAAGGGCAGGUACGCCGUGGAGCC
			CUACCACGGCAAGGUGGUCGUGCCCGAGGGCCACGCCAUCCCCGUG
			CAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAACG
			AGAGGGAGUUCGUGAACAGGUACCUGCACCAUAUCGCCACCCACGG
			CGGAGCCCUGAACACCGACGAGGAAUACUACAAGACCGUGAAGCCC
			AGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGAAGCAGU
			GCGUGAAGAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCU
			GGUGGACCCACCCUUCCACGAGUUCGCCUACGAGAGCCUGAGGACC
			AGACCCGCCGCUCCCUACCAGGUGCCCACCAUCGGCGUGUACGGCG
			UGCCCGGCAGCGGAAAGAGCGGCAUCAUCAAGAGCGCCGUGACCAA
			GAAAGACCUGGUGGUCAGCGCCAAGAAAGAGAACUGCGCCGAGAUC
			AUCAGGGACGUGAAGAAGAUGAAAGGCCUGGACGUGAACGCGCGCA
			CCGUGGACAGCGUGCUGCUGAACGGCUGCAAGCACCCCGUGGAGAC
			CCUGUACAUCGACGAGGCCUUCGCUUGCCACGCCGGCACCCUGAGG
			GCCCUGAUCGCCAUCAUCAGGCCCAAGAAAGCCGUGCUGUGCGGCG
			ACCCCAAGCAGUGCGGCUUCUUCAACAUGAUGUGCCUGAAGGUGCA
			CUUCAACCACGAGAUCUGCACCCAGGUGUUCCACAAGAGCAUCAGC
			AGGCGGUGCACCAAGAGCGUGACCAGCGUCGUGAGCACCCUGUUCU
			ACGACAAGAAAAUGAGGACCACCAACCCCAAGGAGACCAAAAUCGU
			GAUCGACACCACAGGCAGCACCAAGCCCAAGCAGGACGACCUGAUC
			CUGACCUGCUUCAGGGGCUGGGUGAAGCAGCUGCAGAUCGACUACA
			AGGGCAACGAGAUCAUGACCGCCGCUGCCAGCCAGGGCCUGACCAG
			GAAGGGCGUGUACGCCGUGAGGUACAAGGUGAACGAGAACCCACUG
			UACGCUCCCACCAGCGAGCACGUGAACGUGCUGCUGACCAGGACCG
			AGGACAGGAUCGUGUGGAAGACCCUGGCCGGCGACCCCUGGAUCAA
			GACCCUGACCGCCAAGUACCCCGGCAACUUCACCGCCACCAUCGAA

			GAGUGGCAGGCCGAGCACGACGCCAUCAUGAGGCACAUCCUGGAGA GGCCCGACCCCACCGACGUGUUCCAGAACAAGGCCAACGUGUGCUG GGCCAAGGCCCUGGUGCCCGUGCUGAAGACCGCCGGCAUCGACAUG ACCACAGAGCAGUGGAACACCGUGGACUACUUCGAGACCGACAAGG CCCACAGCGCCGAGAUCGUGCUGAACCAGCUGUGCGUGAGGUUCUU CGGCCUGGACCUGGACAGCGGCCUGUUCAGCGCCCCCACCGUGCCA CUGAGCAUCAGGAACAACCACUGGGACAACAGCCCCAGCCCAAACA UGUACGGCCUGAACAAGGAGGUGGUCAGGCAGCUGAGCAGGCGGUA CCCACAGCUGCCCAGGGCCGUGGCCACCGGCAGGGUGUACGACAUG AACACCGGCACCCUGAGGAACUACGACCCCAGGAUCAACCUGGUGC CCGUGAACAGGCGGCUGCCCCACGCCCUGGUGCUGCACCACAACGA GCACCCACAGAGCGACUUCAGCUCCUUCGUGAGCAAGCUGAAAGGC AGGACCGUGCUGGUCGUGGGCGAGAAGCUGAGCGUGCCCGGCAAGA UGGUGGACUGGCUGAGCGACAGGCCCGAGGCCACCUUCCGGGCCAG GCUGGACCUCGGCAUCCCCGGCGACGUGCCCAAGUACGACAUCAUC UUCGUGAACGUCAGGACCCCAUACAAGUACCACCAUUACCAGCAGU GCGAGGACCACGCCAUCAAGCUGAGCAUGCUGACCAAGAAGGCCUG CCUGCACCUGAACCCCGGAGGCACCUGCGUGAGCAUCGGCUACGGC UACGCCGACAGGGCCAGCGAGAGCAUCAUUGGCGCCAUCGCCAGGC UGUUCAAGUUCAGCAGGGUGUGCAAACCCAAGAGCAGCCUGGAGGA AACCGAGGUGCUGUUCGUGUUCAUCGGCUACGACCGGAAGGCCAGG ACCCACAACCCCUACAAGCUGAGCAGCACCCUGACAAACAUCUACA CCGGCAGCAGGCUGCACGAGGCCGGCUGCGCCCCCAGCUACCACGU GGUCAGGGGCGAUAUCGCCACCGCCACCGAGGGCGUGAUCAUCAAC GCUGCCAACAGCAAGGGCCAGCCCGGAGGCGGAGUGUGCGGCGCCC UGUACAAGAAGUUCCCCGAGAGCUUCGACCUGCAGCCCAUCGAGGU GGGCAAGGCCAGGCUGGUGAAGGGCGCCGCUAAGCACAUCAUCCAC GCCGUGGGCCCCAACUUCAACAAGGUGAGCGAGGUGGAAGGCGACA AGCAGCUGGCCGAAGCCUACGAGAGCAUCGCCAAGAUCGUGAACGA CAAUAACUACAAGAGCGUGGCCAUCCCACUGCUCAGCACCGGCAUC UUCAGCGGCAACAAGGACAGGCUGACCCAGAGCCUGAACCACCUGC UCACCGCCCUGGACACCACCGAUGCCGACGUGGCCAUCUACUGCAG GGACAAGAAGUGGGAGAUGACCCUGAAGGAGGCCGUGGCCAGGCGG GAGGCCGUGGAAGAGAUCUGCAUCAGCGACGACUCCAGCGUGACCG AGCCCGACGCCGAGCUGGUGAGGGUGCACCCCAAGAGCUCCCUGGC CGGCAGGAAGGGCUACAGCACCAGCGACGGCAAGACCUUCAGCUAC CUGGAGGGCACCAAGUUCCACCAGGCCGCUAAGGACAUCGCCGAGA UCAACGCUAUGUGGCCCGUGGCCACCGAGGCCAACGAGCAGGUGUG CAUGUACAUCCUGGGCGAGAGCAUGUCCAGCAUCAGGAGCAAGUGC CCCGUGGAGGAAAGCGAGGCCAGCACACCACCCAGCACCCUGCCCU GCCUGUGCAUCCACGCUAUGACACCCGAGAGGGUGCAGCGGCUGAA GGCCAGCAGGCCCGAGCAGAUCACCGUGUGCAGCUCCUUCCCACUG CCCAAGUACAGGAUCACCGGCGUGCAGAAGAUCCAGUGCAGCCAGC CCAUCCUGUUCAGCCCAAAGGUGCCCGCCUACAUCCACCCCAGGAA GUACCUGGUGGAGACCCCACCCGUGGACGAGACACCCGAGCCAAGC GCCGAGAACCAGAGCACCGAGGGCACACCCGAGCAGCCACCCCUGA UCACCGAGGACGAGACAAGGACCCGGACCCCAGAGCCCAUCAUUAU CGAGGAAGAGGAAGAGGACAGCAUCAGCCUGCUGAGCGACGGCCCC ACCCACCAGGUGCUGCAGGUGGAGGCCGACAUCCACGGCCCACCCA GCGUGUCCAGCUCCAGCUGGAGCAUCCCACACGCCAGCGACUUCGA CGUGGACAGCCUGAGCAUCCUGGACACCCUGGAGGGCGCCAGCGUG ACCUCCGGCGCCACCAGCGCCGAGACCAACAGCUACUUCGCCAAGA GCAUGGAGUUCCUGGCCAGGCCCGUGCCAGCUCCCAGGACCGUGUU CAGGAACCCACCCCACCCAGCUCCCAGGACCAGGACCCCAAGCCUG GCUCCCAGCAGGGCCUGCAGCAGGACCAGCCUGGUGAGCACCCCAC

			CCGGCGUGAACAGGGUGAUCACCAGGGAGGAACUGGAGGCCCUGAC ACCCAGCAGGACCCCCAGCAGGUCCGUGAGCAGGACUAGUCUGGUG UCCAACCCACCCGGCGUGAACAGGGUGAUCACCAGGGAGGAAUUCG AGGCCUUCGUGGCCCAGCAACAGAGACGGUUCGACGCCGGCGCCUA CAUCUUCAGCAGCGACACCGGCCAGGGACACCUGCAGCAAAAGAGC GUGAGGCAGACCGUGCUGAGCGAGGUGGUGCUGGAGAGGACCGAGC UGGAAAUCAGCUACGCCCCCAGGCUGGACCAGGAGAAGGAGGAACU GCUCAGGAAGAAACUGCAGCUGAACCCCACCCCAGCCAACAGGAGC AGGUACCAGAGCAGGAAGGUGGAGAACAUGAAGGCCAUCACCGCCA GGCGGAUCCUGCAGGGCCUGGGACACUACCUGAAGGCCGAGGGCAA GGUGGAGUGCUACAGGACCCUGCACCCCGUGCCACUGUACAGCUCC AGCGUGAACAGGGCCUUCUCCAGCCCCAAGGUGGCCGUGGAGGCCU GCAACGCUAUGCUGAAGGAGAACUUCCCCACCGUGGCCAGCUACUG CAUCAUCCCCGAGUACGACGCCUACCUGGACAUGGUGGACGGCGCC AGCUGCUGCCUGGACACCGCCAGCUUCUGCCCCGCCAAGCUGAGGA GCUUCCCCAAGAAACACAGCUACCUGGAGCCCACCAUCAGGAGCGC CGUGCCCAGCGCCAUCCAGAACACCCUGCAGAACGUGCUGGCCGCU GCCACCAAGAGGAACUGCAACGUGACCCAGAUGAGGGAGCUGCCCG UGCUGGACAGCGCUGCCUUCAACGUGGAGUGCUUCAAGAAAUACGC CUGCAACAACGAGUACUGGGAGACCUUCAAGGAGAACCCCAUCAGG CUGACCGAAGAGAACGUGGUGAACUACAUCACCAAGCUGAAGGGCC CCAAGGCCGCUGCCCUGUUCGCUAAGACCCACAACCUGAACAUGCU GCAGGACAUCCCAAUGGACAGGUUCGUGAUGGACCUGAAGAGGGAC GUGAAGGUGACACCCGGCACCAAGCACACCGAGGAGAGGCCCAAGG UGCAGGUGAUCCAGGCCGCUGACCCACUGGCCACCGCCUACCUGUG CGGCAUCCACAGGGAGCUGGUGAGGCGGCUGAACGCCGUGCUGCUG CCCAACAUCCACACCCUGUUCGACAUGAGCGCCGAGGACUUCGACG CCAUCAUCGCCGAGCACUUCCAGCCCGGCGACUGCGUGCUGGAGAC CGACAUCGCCAGCUUCGACAAGAGCGAGGAUGACGCUAUGGCCCUG ACCGCUCUGAUGAUCCUGGAGGACCUGGGCGUGGACGCCGAGCUGC UCACCCUGAUCGAGGCUGCCUUCGGCGAGAUCAGCUCCAUCCACCU GCCCACCAAGACCAAGUUCAAGUUCGGCGCUAUGAUGAAAAGCGGA AUGUUCCUGACCCUGUUCGUGAACACCGUGAUCAACAUUGUGAUCG CCAGCAGGGUGCUGCGGGAGAGGCUGACCGGCAGCCCCUGCGCUGC CUUCAUCGGCGACGACAACAUCGUGAAGGGCGUGAAAAGCGACAAG CUGAUGGCCGACAGGUGCGCCACCUGGCUGAACAUGGAGGUGAAGA UCAUCGACGCCGUGGUGGGCGAGAAGGCCCCCUACUUCUGCGGCGG AUUCAUCCUGUGCGACAGCGUGACCGGCACCGCCUGCAGGGUGGCC GACCCCCUGAAGAGGCUGUUCAAGCUGGGCAAGCCACUGGCCGCUG ACGAUGAGCACGACGAUGACAGGCGGAGGGCCCUGCACGAGGAAAG CACCAGGUGGAACAGGGUGGGCAUCCUGAGCGAGCUGUGCAAGGCC GUGGAGAGCAGGUACGAGACCGUGGGCACCAGCAUCAUCGUGAUGG CUAUGACCACACUGGCCAGCUCCGUCAAGAGCUUCUCCUACCUGAG GGGGGCCCCUAUAACUCUCUACGGCUAACCUGAAUGGACUACGACA UAGUCUAGUCCGCCAAGGCCGCCACCAUGAGAGUGACAGCCCCUAG AACCUUACUGCUUCUGCUUUGGGGAGCUGUUGCUCUGACAGAGACA UGGGCUGGAUCUCUGAGCGAGGUGACCGGCCAGGGCCUGUGCAUCG GCGCCGUGCCCAAGACCCACCAGGUGCUGUGCAACACCACCCAGAA GACCAGCGACGGCAGCUACUACCUGGCCGCUCCCACCGGCACCACC UGGGCCUGCAGCACCGGCCUGACCCCUUGCAUCAGCACCACCAUCC UGAACCUGACCACCGACUACUGCGUGCUGGUGGAGCUGUGGCCCAG GGUGACCUACCACAGCCCCAGCUACGCCUACCACCAGUUCGAGAGG AGGGCCAAGUACAAGAGGGAGCCCGUGAGCCUGACCCUGGCCCUGC UGCUGGGCGGCCUGACAAUGGGCGGCAUCGCCGCCGGCGUGGGCAC CGGCACCACCGCCCUGGUGGCCACCCAGCAGUUCCAGCAGCUGCAG

			GCCGCCAUGCACGACGACCUGAAGGAGGUGGAGAAGUCCAUCACCA ACCUGGAGAAGUCCCUGACCAGCCUGAGCGAGGUGGUGCUGCAGAA CAGGAGGGGCCUGGACCUGCUGUUCCUGAAGGAGGGCGGCCUGUGC GCCGCCCUGAAGGAGGAGUGCUGCCUGUACGCCGACCACACCGGCC UGGUGAUCGUGGGCAUUGUCGCUGGCCUGGCCGUCCUCGCCGUGGU GGUGAUUGGAGCUGUGGUCGCAGCUGUUAUGUGCAGAAGAAAGUCA UCCGGCGGAAAGGGAGGCUCCUACUCUCAGGCUGCUUCUGCUACAG UGCCUAGAGCUCUUAUGUGUUUAUCUCAGCUGUAAACUCGAGUAUG UUACGUGCAAAGGUGAUUGUCACCCCCCGAAAGACCAUAUUGUGAC ACACCCUCAGUAUCACGCCCAAACAUUUACAGCCGCGGUGUCAAAA ACCGCGUGGACGUGGUUAACAUCCCUGCUGGGAGGAUCAGCCGUAA UUAUUAUAAUUGGCUUGGUGCUGGCUACUAUUGUGGCCAUGUACGU GCUGACCAACCAGAAACAUAAUUGAAUACAGCAGCAAUUGGCAAGC UGCUUACAUAGAACUCGCGGCGAUUGGCAUGCCGCCUUAAAAUUUU UAUUUUAUUUUUUCUUUUCUUUUCCGAAUCGGAUUUUGUUUUUAAU AUUUCAAAAAAAAAAAAAAAAAAAAAAAAUCUAGAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
3061 (SEQ ID NO:106)	STARR™ AH1A5	3061	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAUGGAGAAAGU CGAGGAAGACAGCCCAUUCCUCAGAGCUUUGCAGCGGAGCUUCCCGCAGUUUGAC CAGGUCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGCUUCAU CGGAGGUGGACCCAUCCGACACGAUCCUUGACAUUGGAAGUGCGCCCGCCCGCAC GCACAAGUAUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUUC ACUAAGCUGAAGAAAAACUGUAAGGAAAUAACUGAUAAGGAAUUGGACAAGAAA CCGCCGUCAUGAGCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGA CUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUACGCCGUCGACGGCCCCAC CAGGCCAACAAGGGCGUGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCC ACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCCGACGAGACCGUGC CAUCGGCCUGUGCAGCAGCGACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAU UACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACCAUCUACCAC UGCUCAGGAGCUGGCACCUGCCCAGCGUGUUCCACCUGAGGGGCAAGCAGAACU CGAGACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUCAGCCC AAGCCCAGCGGCUACGCCGCUACAAUGCACAGGGAGGGCUUCCUGUGCUGCAAG UGAACGGCGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUGU CGGCAUCCUGGCCACCGACGUGAGCGCCGACGACGCCCAGAAGCUGCUCGUGGG AUCGUGGUCAACGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUG CCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGGAGGACCAGGAAGACGAGA GAGGGACAGGCAGCUGGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAU AAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCGACUUCCACAGCUUC UCGGCAGCAACACCCUGGAGAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGG GCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGUGCGCUGCCGA GUGAGGGAGGCCGAGGAACUGAGGGCCGCCCUGCCACCCCUGGCUGCCGACGUG UGGAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCGUGGAGA GAUCAAGGUGACCAGCUACGACGGCGAGGACAAGAUCGGCAGCUACGCCGUGCU GUGCUGAAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGAUC GCGGCAGGAAGGGCAGGUACGCCGUGGAGCCCUACCACGGCAAGGUGGUCGUGC CAUCCCCGUGCAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAA GUGAACAGGUACCUGCACCAUAUCGCCACCCACGGCGGAGCCCUGAACACCGAC AGACCGUGAAGCCCAGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGA GAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCUGGUGGACCCACCCUU UACGAGAGCCUGAGGACCAGACCCGCCGCUCCCUACCAGGUGCCCACCAUCGGC CCGGCAGCGGAAAGAGCGGCAUCAUCAAGAGCGCCGUGACCAAGAAAGACCUGG GAAAGAGAACUGCGCCGAGAUCAUCAGGGACGUGAAGAAGAUGAAAGGCCUGGA ACCGUGGACAGCGUGCUGCUGAACGGCUGCAAGCACCCCGUGGAGACCCUGUAC UCGCUUGCCACGCCGGCACCCUGAGGGCCCUGAUCGCCAUCAUCAGGCCCAAGA

			CGGCGACCCCAAGCAGUGCGGCUUCUUCAACAUGAUGUGCCUGAAGGUGCACUU UGCACCCAGGUGUUCCACAAGAGCAUCAGCAGGCGGUGCACCAAGAGCGUGACC CCCUGUUCUACGACAAGAAAAUGAGGACCACCAACCCCAAGGAGACCAAAAUCG AGGCAGCACCAAGCCCAAGCAGGACGACCUGAUCCUGACCUGCUUCAGGGGCUG CAGAUCGACUACAAGGGCAACGAGAUCAUGACCGCCGCUGCCAGCCAGGGCCUG UGUACGCCGUGAGGUACAAGGUGAACGAGAACCCACUGUACGCUCCCACCAGCG GCUGCUGACCAGGACCGAGGACAGGAUCGUGUGGAAGACCCUGGCCGGCGACCC CUGACCGCCAAGUACCCCGGCAACUUCACCGCCACCAUCGAAGAGUGGCAGGCC UCAUGAGGCACAUCCUGGAGAGGCCCGACCCCACCGACGUGUUCCAGAACAAGG GGCCAAGGCCCUGGUGCCCGUGCUGAAGACCGCCGGCAUCGACAUGACCACAGA GUGGACUACUUCGAGACCGACAAGGCCCACAGCGCCGAGAUCGUGCUGAACCAG UCUUCGGCCUGGACCUGGACAGCGGCCUGUUCAGCGCCCCCACCGUGCCACUGA CCACUGGGACAACAGCCCCAGCCCAAACAUGUACGGCCUGAACAAGGAGGUGGU AGGCGGUACCCACAGCUGCCCAGGGCCGUGGCCACCGGCAGGGUGUACGACAUG UGAGGAACUACGACCCCAGGAUCAACCUGGUGCCCGUGAACAGGCGGCUGCCCC GCACCACAACGAGCACCCACAGAGCGACUUCAGCUCCUUCGUGAGCAAGCUGAA CUGGUCGUGGGCGAGAAGCUGAGCGUGCCCGGCAAGAUGGUGGACUGGCUGAGC CCACCUUCCGGGCCAGGCUGGACCUCGGCAUCCCCGGCGACGUGCCCAAGUACG GAACGUCAGGACCCCAUACAAGUACCACCAUUACCAGCAGUGCGAGGACCACGC AUGCUGACCAAGAAGGCCUGCCUGCACCUGAACCCCGGAGGCACCUGCGUGAGC ACGCCGACAGGGCCAGCGAGAGCAUCAUUGGCGCCAUCGCCAGGCUGUUCAAGU CAAACCCAAGAGCAGCCUGGAGGAAACCGAGGUGCUGUUCGUGUUCAUCGGCUA AGGACCCACAACCCCUACAAGCUGAGCAGCACCCUGACAAACAUCUACACCGGC AGGCCGGCUGCGCCCCCAGCUACCACGUGGUCAGGGGCGAUAUCGCCACCGCCA CAUCAACGCUGCCAACAGCAAGGGCCAGCCCGGAGGCGGAGUGUGCGGCGCCCU CCCGAGAGCUUCGACCUGCAGCCCAUCGAGGUGGGCAAGGCCAGGCUGGUGAAG ACAUCAUCCACGCCGUGGGCCCCAACUUCAACAAGGUGAGCGAGGUGGAAGGCG CGAAGCCUACGAGAGCAUCGCCAAGAUCGUGAACGACAAUAACUACAAGAGCGU CUCAGCACCGGCAUCUUCAGCGGCAACAAGGACAGGCUGACCCAGAGCCUGAAC CCCUGGACACCACCGAUGCCGACGUGGCCAUCUACUGCAGGGACAAGAAGUGGG GGAGGCCGUGGCCAGGCGGGAGGCCGUGGAAGAGAUCUGCAUCAGCGACGACUC CCCGACGCCGAGCUGGUGAGGGUGCACCCCAAGAGCUCCCUGGCCGGCAGGAAG GCGACGGCAAGACCUUCAGCUACCUGGAGGGCACCAAGUUCCACCAGGCCGCUA GAUCAACGCUAUGUGGCCCGUGGCCACCGAGGCCAACGAGCAGGUGUGCAUGUA AGCAUGUCCAGCAUCAGGAGCAAGUGCCCCGUGGAGGAAAGCGAGGCCAGCACA UGCCCUGCCUGUGCAUCCACGCUAUGACACCCGAGAGGGUGCAGCGGCUGAAGG GCAGAUCACCGUGUGCAGCUCCUUCCCACUGCCCAAGUACAGGAUCACCGGCGU UGCAGCCAGCCCAUCCUGUUCAGCCCAAAGGUGCCCGCCUACAUCCACCCCAGG AGACCCCACCCGUGGACGAGACACCCGAGCCAAGCGCCGAGAACCAGAGCACCG GCAGCCACCCCUGAUCACCGAGGACGAGACAAGGACCCGGACCCCAGAGCCCAU GAGGAAGAGGACAGCAUCAGCCUGCUGAGCGACGGCCCCACCCACCAGGUGCUG ACAUCCACGGCCCACCCAGCGUGUCCAGCUCCAGCUGGAGCAUCCCACACGCCA GGACAGCCUGAGCAUCCUGGACACCCUGGAGGGCGCCAGCGUGACCUCCGGCGC ACCAACAGCUACUUCGCCAAGAGCAUGGAGUUCCUGGCCAGGCCCGUGCCAGCU UCAGGAACCCACCCCACCCAGCUCCCAGGACCAGGACCCCAAGCCUGGCUCCCA CAGGACCAGCCUGGUGAGCACCCCACCCGGCGUGAACAGGGUGAUCACCAGGGA CUGACACCCAGCAGGACCCCCAGCAGGUCCGUGAGCAGGACUAGUCUGGUGUCC UGAACAGGGUGAUCACCAGGGAGGAAUUCGAGGCCUUCGUGGCCCAGCAACAGA CGGCGCCUACAUCUUCAGCAGCGACACCGGCCAGGGACACCUGCAGCAAAAGAG GUGCUGAGCGAGGUGGUGCUGGAGAGGACCGAGCUGGAAAUCAGCUACGCCCCC AGAAGGAGGAACUGCUCAGGAAGAAACUGCAGCUGAACCCCACCCCAGCCAACA GAGCAGGAAGGUGGAGAACAUGAAGGCCAUCACCGCCAGGCGGAUCCUGCAGGG CUGAAGGCCGAGGGCAAGGUGGAGUGCUACAGGACCCUGCACCCCGUGCCACUG UGAACAGGGCCUUCUCCAGCCCCAAGGUGGCCGUGGAGGCCUGCAACGCUAUGC CCCCACCGUGGCCAGCUACUGCAUCAUCCCCGAGUACGACGCCUACCUGGACAU

			AGCUGCUGCCUGGACACCGCCAGCUUCUGCCCCGCCAAGCUGAGGAGCUUCCCC ACCUGGAGCCCACCAUCAGGAGCGCCGUGCCCAGCGCCAUCCAGAACACCCUGC CGCUGCCACCAAGAGGAACUGCAACGUGACCCAGAUGAGGGAGCUGCCCGUGCU UUCAACGUGGAGUGCUUCAAGAAAUACGCCUGCAACAACGAGUACUGGGAGACC CCAUCAGGCUGACCGAAGAGAACGUGGUGAACUACAUCACCAAGCUGAAGGGCC CCUGUUCGCUAAGACCCACAACCUGAACAUGCUGCAGGACAUCCCAAUGGACAG CUGAAGAGGGACGUGAAGGUGACACCCGGCACCAAGCACACCGAGGAGAGGCCC UCCAGGCCGCUGACCCACUGGCCACCGCCUACCUGUGCGGCAUCCACAGGGAGC GAACGCCGUGCUGCUGCCCAACAUCCCACACCCUGUUCGACAUGAGCGCCGAGGA AUCGCCGAGCACUUCCAGCCCGGCGACUGCGUGCUGGAGACCGACAUCGCCAGC AGGAUGACGCUAUGGCCCUGACCGCUCUGAUGAUCCUGGAGGACCUGGGCGUGG CACCCUGAUCGAGGCUGCCUUCGGCGAGAUCAGCUCCAUCCACCUGCCCACCAA UUCGGCGCUAUGAUGAAAAGCGGAAUGUUCCUGACCCUGUUCGUGAACACCGUG UCGCCAGCAGGGUGCUGCGGGAGAGGCUGACCGGCAGCCCCUGCGCUGCCUUCA CAUCGUGAAGGGCGUGAAAAGCGACAAGCUGAUGGCCGACAGGUGCGCCACCUG GUGAAGAUCAUCGACGCCGUGGUGGGCGAGAAGGCCCCCUACUUCUGCGGCGGA ACAGCGUGACCGGCACCGCCUGCAGGGUGGCCGACCCCCUGAAGAGGCUGUUCA ACUGGCCGCUGACGAUGAGCACGACGAUGACAGGCGGAGGGCCCUGCACGAGGA AACAGGGUGGGCAUCCUGAGCGAGCUGUGCAAGGCCGUGGAGAGCAGGUACGAG GCAUCAUCGUGAUGGCUAUGACCACACUGGCCAGCUCCGUCAAGAGCUUCUCCU CCCUAUAACUCUCUACGGCUAACCUGAAUGGACUACGACAUAGUCUAGUCCGCC UGAGAGUGACAGCCCCUAGAACCUUACUGCUUCUGCUUUGGGGAGCUGUUGCUC GGCUGGAUCUUACCACAGCCCCAGCUACGCCUACCACCAGUUCGAGAGGGGGGG GGAGGAGGCUCCCUGAAGAUCAGCCAGGCCGUGCACGCCGCCCACGCCGAGAUC GGGAGGUGAUCGUGGGCAUUGUCGCUGGCCUGGCCGUCCUCGCCGUGGUGGUGA CGCAGCUGUUAUGUGCAGAAGAAAGUCAUCCGGCGGAAAGGGAGGCUCCUACUC GCUACAGUGCCUAGAGCUCUUAUGUGUUUAUCUCAGCUGUAAACUCGAGUAUGU GAUUGUCACCCCCCGAAAGACCAUAUUGUGACACACCCUCAGUAUCACGCCCAA CGGUGUCAAAAACCGCGUGGACGUGGUUAACAUCCCUGCUGGGAGGAUCAGCCG UGGCUUGGUGCUGGCUACUAUUGUGGCCAUGUACGUGCUGACCAACCAGAAACA CAGCAAUUGGCAAGCUGCUUACAUAGAACUCGCGGCGAUUGGCAUGCCGCCUUA AUUUUUUCUUUUCUUUUCCGAAUCGGAUUUUGUUUUUAAUAUUUCAAAAAAAAA AAAUCUAGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
3067 (SEQ ID NO:107)	STARR™ gp70-FLAG	3067	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAU GGAGAAAGUUCACGUUGACAUCGAGGAAGACAGCCCAUUCCUCAGA GCUUUGCAGCGGAGCUUCCCGCAGUUUGAGGUAGAAGCCAAGCAGG UCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGC UUCAAAACUGAUCGAAACGGAGGUGGACCCAUCCGACACGAUCCUU GACAUUGGAAGUGCGCCCGCCCGCAGAAUGUAUUCUAAGCACAAGU AUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUU GUAUAAGUAUGCAACUAAGCUGAAGAAAAACUGUAAGGAAAUAACU GAUAAGGAAUUGGACAAGAAAAUGAAGGAGCUGGCCGCCGUCAUGA GCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGACGA GUCGUGUCGCUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUAC GCCGUCGACGGCCCCACCAGCCUGUACCACCAGGCCAACAAGGGCG UGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCCUUCAUGUU CAAGAACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCC GACGAGACCGUGCUGACCGCCAGGAACAUCGGCCUGUGCAGCAGCG ACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAUCCUGAGGAAGAA AUACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACC AUCUACCACGAGAAGAGGGACCUGCUCAGGAGCUGGCACCUGCCCA GCGUGUUCCACCUGAGGGGCAAGCAGAACUACACCUGCAGGUGCGA GACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUC AGCCCCGGCCUGUACGGCAAGCCCAGCGGCUACGCCGCUACAAUGC

			ACAGGGAGGGCUUCCUGUGCUGCAAGGUGACCGACACCCUGAACGG CGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUG UGCGACCAGAUGACCGGCAUCCUGGCCACCGACGUGAGCGCCGACG ACGCCCAGAAGCUGCUCGUGGGCCUGAACCAGAGGAUCGUGGUCAA CGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUGCUG CCCGUGGUGGCCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGG AGGACCAGGAAGACGAGAGGCCCCUGGGCCUGAGGGACAGGCAGCU GGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAUCACCAGC AUCUACAAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCG ACUUCCACAGCUUCGUGCUGCCCAGGAUCGGCAGCAACACCCUGGA GAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGGAGGAACACAAG GAGCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGU GCGCUGCCGACGAGGCCAAGGAGGUGAGGGAGGCCGAGGAACUGAG GGCCGCCCUGCCACCCCUGGCUGCCGACGUGGAGGAACCCACCCUG GAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCG UGGAGACACCCAGGGGCCUGAUCAAGGUGACCAGCUACGACGGCGA GGACAAGAUCGGCAGCUACGCCGUGCUGAGCCCACAGGCCGUGCUG AAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGA UCGUGAUCACCCACAGCGGCAGGAAGGGCAGGUACGCCGUGGAGCC CUACCACGGCAAGGUGGUCGUGCCCGAGGGCCACGCCAUCCCCGUG CAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAACG AGAGGGAGUUCGUGAACAGGUACCUGCACCAUAUCGCCACCCACGG CGGAGCCCUGAACACCGACGAGGAAUACUACAAGACCGUGAAGCCC AGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGAAGCAGU GCGUGAAGAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCU GGUGGACCCACCCUUCCACGAGUUCGCCUACGAGAGCCUGAGGACC AGACCCGCCGCUCCCUACCAGGUGCCCACCAUCGGCGUGUACGGCG UGCCCGGCAGCGGAAAGAGCGGCAUCAUCAAGAGCGCCGUGACCAA GAAAGACCUGGUGGUCAGCGCCAAGAAAGAGAACUGCGCCGAGAUC AUCAGGGACGUGAAGAAGAUGAAAGGCCUGGACGUGAACGCGCGCA CCGUGGACAGCGUGCUGCUGAACGGCUGCAAGCACCCCGUGGAGAC CCUGUACAUCGACGAGGCCUUCGCUUGCCACGCCGGCACCCUGAGG GCCCUGAUCGCCAUCAUCAGGCCCAAGAAAGCCGUGCUGUGCGGCG ACCCCAAGCAGUGCGGCUUCUUCAACAUGAUGUGCCUGAAGGUGCA CUUCAACCACGAGAUCUGCACCCAGGUGUUCCACAAGAGCAUCAGC AGGCGGUGCACCAAGAGCGUGACCAGCGUCGUGAGCACCCUGUUCU ACGACAAGAAAAUGAGGACCACCAACCCCAAGGAGACCAAAAUCGU GAUCGACACCACAGGCAGCACCAAGCCCAAGCAGGACGACCUGAUC CUGACCUGCUUCAGGGGCUGGGUGAAGCAGCUGCAGAUCGACUACA AGGGCAACGAGAUCAUGACCGCCGCUGCCAGCCAGGGCCUGACCAG GAAGGGCGUGUACGCCGUGAGGUACAAGGUGAACGAGAACCCACUG UACGCUCCCACCAGCGAGCACGUGAACGUGCUGCUGACCAGGACCG AGGACAGGAUCGUGUGGAAGACCCUGGCCGGCGACCCCUGGAUCAA GACCCUGACCGCCAAGUACCCCGGCAACUUCACCGCCACCAUCGAA GAGUGGCAGGCCGAGCACGACGCCAUCAUGAGGCACAUCCUGGAGA GGCCCGACCCCACCGACGUGUUCCAGAACAAGGCCAACGUGUGCUG GGCCAAGGCCCUGGUGCCCGUGCUGAAGACCGCCGGCAUCGACAUG ACCACAGAGCAGUGGAACACCGUGGACUACUUCGAGACCGACAAGG CCCACAGCGCCGAGAUCGUGCUGAACCAGCUGUGCGUGAGGUUCUU CGGCCUGGACCUGGACAGCGGCCUGUUCAGCGCCCCCACCGUGCCA CUGAGCAUCAGGAACAACCACUGGGACAACAGCCCCAGCCCAAACA UGUACGGCCUGAACAAGGAGGUGGUCAGGCAGCUGAGCAGGCGGUA CCCACAGCUGCCCAGGGCCGUGGCCACCGGCAGGGUGUACGACAUG AACACCGGCACCCUGAGGAACUACGACCCCAGGAUCAACCUGGUGC CCGUGAACAGGCGGCUGCCCCACGCCCUGGUGCUGCACCACAACGA

			GCACCCACAGAGCGACUUCAGCUCCUUCGUGAGCAAGCUGAAAGGC AGGACCGUGCUGGUCGUGGGCGAGAAGCUGAGCGUGCCCGGCAAGA UGGUGGACUGGCUGAGCGACAGGCCCGAGGCCACCUUCCGGGCCAG GCUGGACCUCGGCAUCCCCGGCGACGUGCCCAAGUACGACAUCAUC UUCGUGAACGUCAGGACCCCAUACAAGUACCACCAUUACCAGCAGU GCGAGGACCACGCCAUCAAGCUGAGCAUGCUGACCAAGAAGGCCUG CCUGCACCUGAACCCCGGAGGCACCUGCGUGAGCAUCGGCUACGGC UACGCCGACAGGGCCAGCGAGAGCAUCAUUGGCGCCAUCGCCAGGC UGUUCAAGUUCAGCAGGGUGUGCAAACCCAAGAGCAGCCUGGAGGA AACCGAGGUGCUGUUCGUGUUCAUCGGCUACGACCGGAAGGCCAGG ACCCACAACCCCUACAAGCUGAGCAGCACCCUGACAAACAUCUACA CCGGCAGCAGGCUGCACGAGGCCGGCUGCGCCCCCAGCUACCACGU GGUCAGGGGCGAUAUCGCCACCGCCACCGAGGGCGUGAUCAUCAAC GCUGCCAACAGCAAGGGCCAGCCCGGAGGCGGAGUGUGCGGCGCCC UGUACAAGAAGUUCCCCGAGAGCUUCGACCUGCAGCCCAUCGAGGU GGGCAAGGCCAGGCUGGUGAAGGGCGCCGCUAAGCACAUCAUCCAC GCCGUGGGCCCCAACUUCAACAAGGUGAGCGAGGUGGAAGGCGACA AGCAGCUGGCCGAAGCCUACGAGAGCAUCGCCAAGAUCGUGAACGA CAAUAACUACAAGAGCGUGGCCAUCCCACUGCUCAGCACCGGCAUC UUCAGCGGCAACAAGGACAGGCUGACCCAGAGCCUGAACCACCUGC UCACCGCCCUGGACACCACCGAUGCCGACGUGGCCAUCUACUGCAG GGACAAGAAGUGGGAGAUGACCCUGAAGGAGGCCGUGGCCAGGCGG GAGGCCGUGGAAGAGAUCUGCAUCAGCGACGACUCCAGCGUGACCG AGCCCGACGCCGAGCUGGUGAGGGUGCACCCCAAGAGCUCCCUGGC CGGCAGGAAGGGCUACAGCACCAGCGACGGCAAGACCUUCAGCUAC CUGGAGGGCACCAAGUUCCACCAGGCCGCUAAGGACAUCGCCGAGA UCAACGCUAUGUGGCCCGUGGCCACCGAGGCCAACGAGCAGGUGUG CAUGUACAUCCUGGGCGAGAGCAUGUCCAGCAUCAGGAGCAAGUGC CCCGUGGAGGAAAGCGAGGCCAGCACACCACCCAGCACCCUGCCCU GCCUGUGCAUCCACGCUAUGACACCCGAGAGGGUGCAGCGGCUGAA GGCCAGCAGGCCCGAGCAGAUCACCGUGUGCAGCUCCUUCCCACUG CCCAAGUACAGGAUCACCGGCGUGCAGAAGAUCCAGUGCAGCCAGC CCAUCCUGUUCAGCCCAAAGGUGCCCGCCUACAUCCACCCCAGGAA GUACCUGGUGGAGACCCCACCCGUGGACGAGACACCCGAGCCAAGC GCCGAGAACCAGAGCACCGAGGGCACACCCGAGCAGCCACCCCUGA UCACCGAGGACGAGACAAGGACCCGGACCCCAGAGCCCAUCAUUAU CGAGGAAGAGGAAGAGGACAGCAUCAGCCUGCUGAGCGACGGCCCC ACCCACCAGGUGCUGCAGGUGGAGGCCGACAUCCACGGCCCACCCA GCGUGUCCAGCUCCAGCUGGAGCAUCCCACACGCCAGCGACUUCGA CGUGGACAGCCUGAGCAUCCUGGACACCCUGGAGGGCGCCAGCGUG ACCUCCGGCGCCACCAGCGCCGAGACCAACAGCUACUUCGCCAAGA GCAUGGAGUUCCUGGCCAGGCCCGUGCCAGCUCCCAGGACCGUGUU CAGGAACCCACCCCACCCAGCUCCCAGGACCAGGACCCCAAGCCUG GCUCCCAGCAGGGCCUGCAGCAGGACCAGCCUGGUGAGCACCCCAC CCGGCGUGAACAGGGUGAUCACCAGGGAGGAACUGGAGGCCCUGAC ACCCAGCAGGACCCCCAGCAGGUCCGUGAGCAGGACUAGUCUGGUG UCCAACCCACCCGGCGUGAACAGGGUGAUCACCAGGGAGGAAUUCG AGGCCUUCGUGGCCCAGCAACAGAGACGGUUCGACGCCGGCGCCUA CAUCUUCAGCAGCGACACCGGCCAGGGACACCUGCAGCAAAAGAGC GUGAGGCAGACCGUGCUGAGCGAGGUGGUGCUGGAGAGGACCGAGC UGGAAAUCAGCUACGCCCCCAGGCUGGACCAGGAGAAGGAGGAACU GCUCAGGAAGAAACUGCAGCUGAACCCCACCCCAGCCAACAGGAGC AGGUACCAGAGCAGGAAGGUGGAGAACAUGAAGGCCAUCACCGCCA GGCGGAUCCUGCAGGGCCUGGGACACUACCUGAAGGCCGAGGGCAA GGUGGAGUGCUACAGGACCCUGCACCCCGUGCCACUGUACAGCUCC

			AGCGUGAACAGGGCCUUCUCCAGCCCCAAGGUGGCCGUGGAGGCCU
			GCAACGCUAUGCUGAAGGAGAACUUCCCCACCGUGGCCAGCUACUG
			CAUCAUCCCCGAGUACGACGCCUACCUGGACAUGGUGGACGGCGCC
			AGCUGCUGCCUGGACACCGCCAGCUUCUGCCCCGCCAAGCUGAGGA
			GCUUCCCCAAGAAACACAGCUACCUGGAGCCCACCAUCAGGAGCGC
			CGUGCCCAGCGCCAUCCAGAACACCCUGCAGAACGUGCUGGCCGCU
			GCCACCAAGAGGAACUGCAACGUGACCCAGAUGAGGGAGCUGCCCG
			UGCUGGACAGCGCUGCCUUCAACGUGGAGUGCUUCAAGAAAUACGC
			CUGCAACAACGAGUACUGGGAGACCUUCAAGGAGAACCCCAUCAGG
			CUGACCGAAGAGAACGUGGUGAACUACAUCACCAAGCUGAAGGGCC
			CCAAGGCCGCUGCCCUGUUCGCUAAGACCCACAACCUGAACAUGCU
			GCAGGACAUCCCAAUGGACAGGUUCGUGAUGGACCUGAAGAGGGAC
			GUGAAGGUGACACCCGGCACCAAGCACACCGAGGAGAGGCCCAAGG
			UGCAGGUGAUCCAGGCCGCUGACCCACUGGCCACCGCCUACCUGUG
			CGGCAUCCACAGGGAGCUGGUGAGGCGGCUGAACGCCGUGCUGCUG
			CCCAACAUCCACACCCUGUUCGACAUGAGCGCCGAGGACUUCGACG
			CCAUCAUCGCCGAGCACUUCCAGCCCGGCGACUGCGUGCUGGAGAC
			CGACAUCGCCAGCUUCGACAAGAGCGAGGAUGACGCUAUGGCCCUG
			ACCGCUCUGAUGAUCCUGGAGGACCUGGGCGUGGACGCCGAGCUGC
			UCACCCUGAUCGAGGCUGCCUUCGGCGAGAUCAGCUCCAUCCACCU
			GCCCACCAAGACCAAGUUCAAGUUCGGCGCUAUGAUGAAAAGCGGA
			AUGUUCCUGACCCUGUUCGUGAACACCGUGAUCAACAUUGUGAUCG
			CCAGCAGGGUGCUGCGGGAGAGGCUGACCGGCAGCCCCUGCGCUGC
			CUUCAUCGGCGACGACAACAUCGUGAAGGGCGUGAAAAGCGACAAG
			CUGAUGGCCGACAGGUGCGCCACCUGGCUGAACAUGGAGGUGAAGA
			UCAUCGACGCCGUGGUGGGCGAGAAGGCCCCCUACUUCUGCGGCGG
			AUUCAUCCUGUGCGACAGCGUGACCGGCACCGCCUGCAGGGUGGCC
			GACCCCCUGAAGAGGCUGUUCAAGCUGGGCAAGCCACUGGCCGCUG
			ACGAUGAGCACGACGAUGACAGGCGGAGGGCCCUGCACGAGGAAAG
			CACCAGGUGGAACAGGGUGGGCAUCCUGAGCGAGCUGUGCAAGGCC
			GUGGAGAGCAGGUACGAGACCGUGGGCACCAGCAUCAUCGUGAUGG
			CUAUGACCACACUGGCCAGCUCCGUCAAGAGCUUCUCCUACCUGAG
			GGGGGCCCCUAUAACUCUCUACGGCUAACCUGAAUGGACUACGACA
			UAGUCUAGUCCGCCAAGGCCGCCACCAUGAGAGUGACAGCCCCUAG
			AACCUUACUGCUUCUGCUUUGGGGAGCUGUUGCUCUGACAGAGACA
			UGGGCUGGAUCUCUGAGCGAGGUGACCGGCCAGGGCCUGUGCAUCG
			GCGCCGUGCCCAAGACCCACCAGGUGCUGUGCAACACCACCCAGAA
			GACCAGCGACGGCAGCUACUACCUGGCCGCUCCCACCGGCACCACC
			UGGGCCUGCAGCACCGGCCUGACCCCUUGCAUCAGCACCACCAUCC
			UGAACCUGACCACCGACUACUGCGUGCUGGUGGAGCUGUGGCCCAG
			GGUGACCUACCACAGCCCCAGCUACGCCUACCACCAGUUCGAGAGG
			AGGGCCAAGUACAAGAGGGAGCCCGUGAGCCUGACCCUGGCCCUGC
			UGCUGGGCGGCCUGACAAUGGGCGGCAUCGCCGCCGGCGUGGGCAC
			CGGCACCACCGCCCUGGUGGCCACCCAGCAGUUCCAGCAGCUGCAG
			GCCGCCAUGCACGACGACCUGAAGGAGGUGGAGAAGUCCAUCACCA
			ACCUGGAGAAGUCCCUGACCAGCCUGAGCGAGGUGGUGCUGCAGAA
			CAGGAGGGGCCUGGACCUGCUGUUCCUGAAGGAGGGCGGCCUGUGC
			GCCGCCCUGAAGGAGGAGUGCUGCCUGUACGCCGACCACACCGGCC
			UGGUGAUCGUGGGCAUUGUCGCUGGCCUGGCCGUCCUCGCCGUGGU
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			UCCGGCGGAAAGGGAGGCUCCUACUCUCAGGCUGCUUCUGCUACAG
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3068 (SEQ ID NO:108)	STARR™ AH1A5-FLAG	3068	AUGGGCGGCGCAUGAGAGAAGCCCAGACCAAUUACCUACCCAAAAU GGAGAAAGUUCACGUUGACAUCGAGGAAGACAGCCCAUUCCUCAGA GCUUUGCAGCGGAGCUUCCCGCAGUUUGAGGUAGAAGCCAAGCAGG UCACUGAUAAUGACCAUGCUAAUGCCAGAGCGUUUUCGCAUCUGGC UUCAAAACUGAUCGAAACGGAGGUGGACCCAUCCGACACGAUCCUU GACAUUGGAAGUGCGCCCGCCCGCAGAAUGUAUUCUAAGCACAAGU AUCAUUGUAUCUGUCCGAUGAGAUGUGCGGAAGAUCCGGACAGAUU GUAUAAGUAUGCAACUAAGCUGAAGAAAAACUGUAAGGAAAUAACU GAUAAGGAAUUGGACAAGAAAAUGAAGGAGCUGGCCGCCGUCAUGA GCGACCCUGACCUGGAAACUGAGACUAUGUGCCUCCACGACGACGA GUCGUGUCGCUACGAAGGGCAAGUCGCUGUUUACCAGGAUGUAUAC GCCGUCGACGGCCCCACCAGCCUGUACCACCAGGCCAACAAGGGCG UGAGGGUGGCCUACUGGAUCGGCUUCGACACCACACCCUUCAUGUU CAAGAACCUGGCCGGCGCCUACCCCAGCUACAGCACCAACUGGGCC GACGAGACCGUGCUGACCGCCAGGAACAUCGGCCUGUGCAGCAGCG ACGUGAUGGAGAGGAGCCGGAGAGGCAUGAGCAUCCUGAGGAAGAA AUACCUGAAGCCCAGCAACAACGUGCUGUUCAGCGUGGGCAGCACC AUCUACCACGAGAAGAGGGACCUGCUCAGGAGCUGGCACCUGCCCA GCGUGUUCCACCUGAGGGGCAAGCAGAACUACACCUGCAGGUGCGA GACCAUCGUGAGCUGCGACGGCUACGUGGUGAAGAGGAUCGCCAUC AGCCCCGGCCUGUACGGCAAGCCCAGCGGCUACGCCGCUACAAUGC ACAGGGAGGGCUUCCUGUGCUGCAAGGUGACCGACACCCUGAACGG CGAGAGGGUGAGCUUCCCCGUGUGCACCUACGUGCCCGCCACCCUG UGCGACCAGAUGACCGGCAUCCUGGCCACCGACGUGAGCGCCGACG ACGCCCAGAAGCUGCUCGUGGGCCUGAACCAGAGGAUCGUGGUCAA CGGCAGGACCCAGAGGAACACCAACACAAUGAAGAACUACCUGCUG CCCGUGGUGGCCCAGGCUUUCGCCAGGUGGGCCAAGGAGUACAAGG AGGACCAGGAAGACGAGAGGCCCCUGGGCCUGAGGGACAGGCAGCU GGUGAUGGGCUGCUGCUGGGCCUUCAGGCGGCACAAGAUCACCAGC AUCUACAAGAGGCCCGACACCCAGACCAUCAUCAAGGUGAACAGCG ACUUCCACAGCUUCGUGCUGCCCAGGAUCGGCAGCAACACCCUGGA GAUCGGCCUGAGGACCCGGAUCAGGAAGAUGCUGGAGGAACACAAG GAGCCCAGCCCACUGAUCACCGCCGAGGACGUGCAGGAGGCCAAGU GCGCUGCCGACGAGGCCAAGGAGGUGAGGGAGGCCGAGGAACUGAG GGCCGCCCUGCCACCCCUGGCUGCCGACGUGGAGGAACCCACCCUG GAAGCCGACGUGGACCUGAUGCUGCAGGAGGCCGGCGCCGGAAGCG UGGAGACACCCAGGGGCCUGAUCAAGGUGACCAGCUACGACGGCGA GGACAAGAUCGGCAGCUACGCCGUGCUGAGCCCACAGGCCGUGCUG AAGUCCGAGAAGCUGAGCUGCAUCCACCCACUGGCCGAGCAGGUGA UCGUGAUCACCCACAGCGGCAGGAAGGGCAGGUACGCCGUGGAGCC CUACCACGGCAAGGUGGUCGUGCCCGAGGGCCACGCCAUCCCCGUG CAGGACUUCCAGGCCCUGAGCGAGAGCGCCACCAUCGUGUACAACG AGAGGGAGUUCGUGAACAGGUACCUGCACCAUAUCGCCACCCACGG CGGAGCCCUGAACACCGACGAGGAAUACUACAAGACCGUGAAGCCC AGCGAGCACGACGGCGAGUACCUGUACGACAUCGACAGGAAGCAGU GCGUGAAGAAAGAGCUGGUGACCGGCCUGGGACUGACCGGCGAGCU GGUGGACCCACCCUUCCACGAGUUCGCCUACGAGAGCCUGAGGACC

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non structural protein of SINV			
mARM #			
2842 and 2862 (SEQ ID NO:109)	SINV nsP1-4 AA		MEKPVVNVDVDPQSPFVVQLQKSFPQFEVVAQQVTPNDHANARAFS HLASKLIELEVPTTATILDIGSAPARRMFSEHQYHCVCPMRSPEDP DRMMKYASKLAEKACKITNKNLHEKIKDLRTVLDTPDAETPSLCFH NDVTCNMRAEYSVMQDVYINAPGTIYHQAMKGVRTLYWIGFDTTQF MFSAMAGSYPAYNTNWADEKVLEARNIGLCSTKLSEGRTGKLSIMR KKELKPGSRVYFSVGSTLYPEHRASLQSWHLPSVFHLNGKQSYTCR CDTVVSCEGYVVKKITISPGITGETVGYAVTHNSEGFLLCKVTDTV KGERVSFPVCTYIPATICDQMTGIMATDISPDDAQKLLVGLNQRIV INGRTNRNTNTMQNYLLPIIAQGFSKWAKERKDDLDNEKMLGTRER KLTYGCLWAFRTKKVHSFYRPPGTQTCVKVPASFSAFPMSSVWTTS LPMSLRQKLKLALQPKKEEKLLQVSEELVMEAKAAFEDAQEEARAE KLREALPPLVADKGIEAAAEVVCEVEGLQADIGAALVETPRGHVRI IPQANDRMIGQYIVVSPNSVLKNAKLAPAHPLADQVKIITHSGRSG RYAVEPYDAKVLMPAGGAVPWPEFLALSESATLVYNEREFVNRKLY HIAMHGPAKNTEEEQYKVTKAELAETEYVFDVDKKRCVKKEEASGL VLSGELTNPPYHELALEGLKTRPAVPYKVETIGVIGTPGSGKSAII KSTVTARDLVTSGKKENCREIEADVLRLRGMQITSKTVDSVMLNGC HKAVEVLYVDEAFACHAGALLALIAIVRPRKKVVLCGDPMQCGFFN MMQLKVHFNHPEKDICTKTFYKYISRRCTQPVTAIVSTLHYDGKMK TTNPCKKNIEIDITGATKPKPGDIILTCFRGWVKQLQIDYPGHEVM

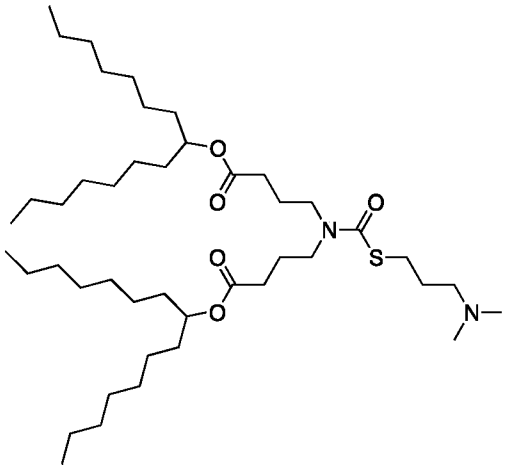
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EXAMPLE 11

[0460] This example describes analysis of the immunogenicity of influenza hemagglutinin (HA) expressed from self-replicating RNA or mRNA.

[0461] Self-replicating RNA and mRNA vaccine constructs were designed to encode the full-length hemagglutinin (HA) protein from influenza virus A/California/07/2009 (H1N1) (SEQ ID NO:113 and 114). As described above for Example 1, the mRNA vaccine construct encoding HA included a tobacco etch virus (TEV) 5' UTR and a Xenopus beta-globin (Xbg) 3' UTR. Both self-replicating RNA (SEQ ID NO:56; entire RNA mARM3039) and mRNA vaccine constructs (SEQ ID NO:116; entire RNA sequence mARM3038) were encapsulated in the same lipid nanoparticle (LNP) composition that included four lipid excipients (an ionizable

cationic lipid, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and PEG2000-DMG) dispersed in HEPES buffer (pH 8.0) containing sodium chloride and the cryoprotectants sucrose and glycerol. The N:P ratio of complexing lipid and RNA was approximately 9:1. The ionizable cationic lipid had the following structure:



[0462] Five female, 8-10 week old Balb/c mice were injected intramuscularly with 2mg of mRNA or self-replicating RNA encoding HA. Mice were bled on days 14, 28, 42, and 56, followed by hemagglutination inhibition (HAI) assay using serially diluted sera. The reciprocal of the highest dilution of serum that caused inhibition of hemagglutination was considered the HAI titer, with a titer of 1/40 being protective against influenza virus infection and four-fold higher titers than baseline indicating seroconversion.

[0463] Results in Figure 23 show that greater HAI titers were obtained with self-replicating RNA encoding HA as compared to mRNA encoding HA. HAI titers for the self-replicating RNA construct encoding HA were greater than HAI titers for the mRNA encoding HA at all time points beginning at day 28. In addition, protective HAI titers were seen for the self-replicating RNA construct encoding HA beginning at day 28 that were maintained for at least 56 days. By contrast, mRNA encoding HA showed protective HAI titers only at day 56 that were lower than HAI titers seen for the self-replicating RNA HA construct. At all other time points, HAI titers for the mRNA construct encoding HA were below the protective titer threshold, with an HAI titer that was comparable to injection with PBS control at day 28.

[0464] These results show that the self-replicating RNA construct encoding HA elicited protective HA antibody titers, with greater HAI titers as compared to the mRNA construct encoding HA.

EXAMPLE 12

[0465] This example describes dsRNA production and luciferase expression for self-replicating RNA.

[0466] Several self-replicating RNA systems from different alphaviruses were tested for expression in vitro using either green fluorescent protein (GFP) or firefly luciferase (Luc) as reporter genes. Initial transfection of cells with increasing amounts of self-replicating RNA resulted in expression of reporter genes at a lower dose compared to mRNA. However, as the amount of input self-replicating RNA increased, detectable expression of the reporter gene decreased.

[0467] Self-replicating RNA produces double stranded RNA (dsRNA) as an intermediate in the amplification process. Overproduction of dsRNA can suppress translation. To evaluate the effect of dsRNA production on transgene expression, dsRNA and the expression of reporter gene luciferase were measured simultaneouosly. HEK293 cells were transfected with 2 μg of replicon A (SEQ ID NO:115; entire RNA sequence mARM2826) or replicon B (SEQ ID NO:100, entire RNA sequence mARM2809) self-replicating RNA, or mRNA expressing Luc (SEQ ID NO:102, entire mRNA sequence mARM1782) using a commercial RNA transfection reagent. Untransfected cells (UTC) served as a control. dsRNA production (Figure 24A) was quantified using immunohistochemical staining for dsRNA, followed by fluorescence quantification using a fluorescence scanner 24 hours after transfection. Luciferase expression (Figure 24B) was assayed by measuring bioluminescence in parallel.

[0468] Replicon A produced a 3-fold higher level of dsRNA than replicon B 24 hrs after transfection (Figure 24A). However, replicon B produced a 2.4-fold higher expression level of luciferase compared to replicon A. Furthermore, the level of luciferase expression from replicon A was equivalent to that observed for mRNA. Thus, even though replicon A had the ability to amplify the amount of replicon RNA and transcribed mRNA encoding luciferase, translation of the amplified mRNA was inhibited, consistent with overproduction of dsRNA inhibiting translation. Furthermore, higher levels of luciferase gene expression were seen for replicon RNA as compared to mRNA at 24, 48, and 72 hours after transfection of HEK293 cells (Figure 15A). Self-replicating RNA with an expression cassette that included a luciferase reporter gene followed by an IRES and E3L also showed robust luciferase expression (Figures 15B, 15C; SEQ ID NOs: 128 and 129). Luciferase expression was also seen for a self-

replicating RNA that expressed E3L from a first subgenomic promoter and a luciferase reporter gene from a second subgenomic promoter located 3' of the E3L open reading frame (not shown). Thus, not only did replicon RNA produce higher levels of luciferase gene expression compared to mRNA, but replicon RNA also showed increased duration of expression over a 72-hr period.

EXAMPLE 13

[0469] This example describes immunogenicity of liquid and lyophilized self-replicating RNA formulations. Immunogenicity of self-replicating RNA (SEQ ID NO:125) formulated as a lyophilized lipid nanoparticle (LYO-LNP) was tested in BALB/c mice in two separate preclinical studies and compared with the liquid (frozen) LNP formulation (Liquid-LNP). Each study included the use of a PBS dosing group as a negative control and a Liquid dosing group (Liquid-LNP) as a positive control. Both LYO-LNP and Liquid-LNP formulations were dosed at 0.2 and 2 μg. There were n=5 animals per dose group in each study. Test formulations were administered intramuscularly (IM) and serum was collected at various timepoints (Days 10, 19, 31 for the first study and Days 10, 20, 30 for the second study) post-immunization to measure the production of anti-SARS-CoV-2 spike protein IgG using a Luminex bead fluorescent assay.

[0470] In both studies, anti-SARS-CoV-2 spike protein IgGs were detected in serum in a time- and dose-dependent manner for both Liquid-LNP and LYO-LNP formulations, whereas PBS injection did not elicit an immunogenic response (Figure 16A-16D). There was no statistical difference in immunogenicity seen between Liquid-LNP and LYO-LNP dose groups in the first study, whereas LYO-LNP produced statistically different and greater IgG than Liquid-LNP in the second study. Without being limited by theory, under-powering (n=5/group) of these two separate studies may have contributed to the statistical differences in immunogenicity results observed in the two studies. In combining the results of both studies, no statistically significant differences were observed between Liquid-LNP and LYO-LNP formulations at the 0.2 and 2 μg dose levels (Figure 17A, 17B). Taken together, the results of these studies demonstrate that the immunogenicity of the liquid and lyophilized formulations were comparable.

[0471] In summary, the liquid and lyophilized formulations of the self-replicating RNA vaccine (SEQ ID NO:125) showed comparable immunogenicity. The vaccine can induce

effective, adaptive humoral (neutralizing antibodies) and cellular (CD8+) immune responses targeting the SARS-CoV-2 S glycoprotein. The vaccine also elicits induction of anti-spike glycoprotein antibodies (IgG) levels that are higher than a conventional mRNA vaccine and also induces production of IgG antibodies at a faster rate than a conventional mRNA vaccine. It continues to produce increasing levels of IgG up to 50 days post vaccination whereas the conventional mRNA vaccine plateaus by day 10 post vaccination. It produces an RNA dose-dependent increase in CD8+ T lymphocytes and a balanced, Th1 dominant CD4+ T helper cell immune response with no skew towards a Th2 response.

[0472] Any and all references and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, that have been made throughout this disclosure are hereby incorporated herein in their entirety for all purposes.

[0473] Although the invention has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the invention. Accordingly, the invention is limited only by the following claims.

EXAMPLE 14

Lyophilization of Self-Replicating RNA-Lipid Nanoparticle Formulation Materials and Methods Generally

[0474] The processes conducted in this example were conducted using lipid nanoparticle compositions that were manufactured according to well-known processes, for example, those described in U.S. App. No. 16/823,212, the contents of which are incorporated by reference for the specific purpose of teaching lipid nanoparticle manufacturing processes. The lipid nanoparticle compositions and the lyophilized products were characterized for several properties. The materials and methods for these characterization processes as well as a general method of manufacturing the lipid nanoparticle compositions that were used for lyophilization experiments are provided in this example.

Lipid Nanoparticle Manufacture

[0475] Lipid nanoparticle formulations used in this example were manufactured by mixing lipids (ionizable cationic lipid (ATX-126): helper lipid: cholesterol: PEG-lipid) in ethanol with RNA dissolved in citrate buffer. The mixed material was instantaneously diluted with Phosphate Buffer. Ethanol was removed by dialysis against phosphate buffer using regenerated cellulose membrane (100 kD MWCO) or by tangential flow filtration (TFF) using modified

polyethersulfone (mPES) hollow fiber membranes (100 kD MWCO). Once the ethanol was completely removed, the buffer was exchanged with HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) buffer containing 10-300 (for example, 40-60) mM NaCl and 5-15% sucrose, pH 7.3. The formulation was concentrated followed by 0.2 μm filtration using PES filters. The RNA concentration in the formulation was then measured by RiboGreen fluorimetric assay, and the concentration was adjusted to a final desired concentration by diluting with HEPES buffer containing 10-100 (for example 40-60) mM NaCl, 0-15% sucrose, pH 7.2-8.5 containing glycerol. If not used immediately for further studies, the final formulation was then filtered through a 0.2 μm filter and filled into glass vials, stoppered, capped and placed at -70 ± 5 °C. The lipid nanoparticles formulations were characterized for their pH and osmolality. Lipid Content and RNA content were measured by high performance liquid chromatography (HPLC), and mRNA integrity by was measured by fragment analyzer.

Dynamic Light Scattering (DLS)

[0476] The average particle size (z) and polydispersity index (PDI) of lipid nanoparticle formulations used in the Examples was measured by dynamic light scattering on a Malvern Zetasizer Nano ZS (United Kingdom).

RiboGreen Assay

[0477] The encapsulation efficiency of the lipid nanoparticle formulations was characterized using the RiboGreen fluorometric assay. RiboGreen is a proprietary fluorescent dye (Molecular Probes/Invitrogen a division of Life Technologies, now part of Thermo Fisher Scientific of Eugene, Oregon, United States) that is used in the detection and quantification of nucleic acids, including both RNA and DNA. In its free form, RiboGreen exhibits little fluorescence and possesses a negligible absorbance signature. When bound to nucleic acids, the dye fluoresces with an intensity that is several orders of magnitude greater than the unbound form. The fluorescence can be then be detected by a sensor (fluorimeter) and the nucleic acid can be quantified.

Lyophilization Process

[0478] Self-Replicating RNAs (aka Replicon RNA) are typically larger than the average mRNA, and tests were designed to determine whether self-replicating RNA lipid nanoparticle formulations could be successfully lyophilized. The quality of lyophilized lipid nanoparticle formulations was assessed by analyzing the formulations post-lyophilization and comparing

this to the lipid nanoparticle formulation prior to lyophilization as well as after a conventional freeze/thaw cycle (i.e., frozen at ~ -70 °C then allowed to thaw at room temperature).

[0479] The analysis of the lipid nanoparticle formulations included the analysis of particle size and polydispersity (PDI) and encapsulation efficiency (%Encap). The particle size post-lyophilization was compared to the particle size pre-lyophilization and the difference can be reported as a delta (δ). The various compositions tested were screened as to whether a threshold of properties was met including minimal particle size increase (δ < 10 nm), the maintenance of PDI (< 0.2), and maintenance of high encapsulation efficiency (> 85%).

[0480] The lipid nanoparticle formulations were prepared as described above, with self-replicating RNA (SEQ ID NO: 125). The resulting lipid nanoparticle formulation was then processed with a buffer exchange to form a prelyophilization suspension having a concentration of 0.05 to 2.0 mg/mL self-replicating RNA, 0.01 to 0.05 M potassium sorbate, 0.01 to 0.10 % w/v Poloxamer 188 (Kolliphor®), 14 to 18% w/v sucrose, 25 to 75 mM NaCl, and 15 to 25 mM pH 8.0 Tris buffer. The prelyophilization formulation was then lyophilized in a Millrock Revo Freeze Dryer (Model No. RV85S4), using aliquots of 2.0 mL of suspension and the lyophilization cycle provided in Table 10 below. The lyophilized formulations of this example were then applied to the studies of Example 13 above as "LYO-LNP".

TABLE 10: Lyophilization Cycle for Self-Replicating RNA-Lipid Nanoparticle Formulation

Freeze drying cycle			
Step	***shelf temperature***	***step duration***	***chamber vacuum***
	(°C, ±2°C)	***(h:min)***	**(mbar)**
Initial Freezing	- 50	4:00	atmosphere
Evacuation	-50	00:30 - 01:45	*from atmosph. pressure to 0.05*
Primary drying (ramp down)	- 50 → 0	63:00	0.05
Secondary drying (ramp up)	0 → +25	39:30	0.05
Backfill with N_2 and stoppering	25	00:10 - 00:20	700 ± 50
Aeration with air	5	00:10 - 00:20	atmosphere

[0481] The lyophilized particles prepared following the methods described above were reconstituted in 2 mL of water and characterized using DLS and RiboGreen. The results provided in Table 11 below show that the lyophilized compositions were found to produce

lyophilized lipid nanoparticle formulations with adequate size, polydispersity, and delta values (~5.3 nm) upon reconstitution.

TABLE 11: Self-Replicating RNA-Lipid Nanoparticle Characteristics Pre- and Post-LYO

	Average Particle Size (nm)	PDI	encap (%)
Pre-LYO	76.3	0.129	97
Post-LYO	81.6	0.152	93

CLAIMS

What is claimed is:

1. A nucleic acid molecule comprising:

(i) a first polynucleotide encoding one or more viral replication proteins, wherein the first polynucleotide is codon-optimized as compared to a wild-type polynucleotide encoding the one or more viral replication proteins; and

(ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof, wherein the first antigenic protein is a coronavirus protein.

2. The nucleic acid molecule of claim 1, wherein the one or more viral replication proteins are alphavirus proteins or rubivirus proteins.

3. The nucleic acid molecule of claim 2, wherein the alphavirus proteins are from Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), Buggy Creek Virus (BCRV), or any combination thereof.

4. The nucleic acid molecule of any one of claims 1-3, wherein the first polynucleotide encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, an alphavirus nsP4 protein, or any combination thereof.

5. The nucleic acid molecule of any one of claims 1-3, wherein the first polynucleotide encodes a polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and an alphavirus nsP4 protein.

6. The nucleic acid molecule of claim 5, further comprising a first intergenic region between a sequence encoding the polyprotein comprising an alphavirus nsP1 protein, an alphavirus nsP2 protein, an alphavirus nsP3 protein, or any combination thereof, and a sequence encoding an alphavirus nsP4 protein.

7. The nucleic acid molecule of claim 6, wherein the first intergenic region comprises an alphavirus sequence.

8. The nucleic acid molecule of claim 1, wherein the first polynucleotide comprises a sequence having at least 80% identity to a sequence of SEQ ID NO:72.

9. The nucleic acid molecule of any one of claims 1-8, further comprising a 5' untranslated region (UTR).

10. The nucleic acid molecule of claim 9, wherein the 5' UTR comprises a viral 5' UTR, a non-viral 5' UTR, or a combination of viral and non-viral 5' UTR sequences.

11. The nucleic acid molecule of claim 10, wherein the 5' UTR comprises an alphavirus 5' UTR.

12. The nucleic acid molecule of claim 11, wherein the alphavirus 5' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 5' UTR sequence.

13. The nucleic acid molecule of claim 9, wherein the 5' UTR comprises a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75.

14. The nucleic acid molecule of any one of claims 1-13, further comprising a 3' untranslated region (UTR).

15. The nucleic acid molecule of claim 14, wherein the 3' UTR comprises a viral 3' UTR, a non-viral 3' UTR, or a combination of viral and non-viral 3' UTR sequences.

16. The nucleic acid molecule of claim 15, wherein the 3' UTR comprises an alphavirus 3' UTR.

17. The nucleic acid molecule of claim 16, wherein the alphavirus 3' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV),

Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 3' UTR sequence.

18. The nucleic acid molecule of claim 17, wherein the 3' UTR comprises a poly-A sequence.

19. The nucleic acid molecule of claim 14, wherein the 3' UTR comprises a sequence of SEQ ID NO:76.

20. The nucleic acid molecule of any of claims 1-19, wherein the antigenic protein is a SARS-CoV-2 protein.

21. The nucleic acid molecule of claim 20, wherein the antigenic protein is a SARS-CoV-2 spike glycoprotein.

22. The nucleic acid molecule of claim 21, wherein the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein having an amino acid sequence of SEQ ID NO:123.

23. The nucleic acid molecule of any one of claims 1-22, wherein the second polynucleotide comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

24. The nucleic acid molecule of any one of claims 1-23, wherein the second polynucleotide comprises at least two transgenes.

25. The nucleic acid molecule of claim 24, wherein a second transgene encodes a second antigenic protein or a fragment thereof or an immunomodulatory protein.

26. The nucleic acid molecule of claim 24 or claim 25, wherein the second polynucleotide further comprises a sequence encoding a 2A peptide, an internal ribosomal entry site (IRES), or a combination thereof, located between transgenes.

27. The nucleic acid molecule of claim 25 or claim 26, wherein the immunomodulatory protein is a cytokine, a chemokine, or an interleukin.

28. The nucleic acid molecule of any one of claims 25-27, wherein the second transgene encodes a second coronavirus protein.

29. The nucleic acid molecule of any one of claims 1-28, wherein the first polynucleotide is located 5' of the second polynucleotide.

30. The nucleic acid molecule of claim 29, further comprising a second intergenic region located between the first polynucleotide and the second polynucleotide.

31. The nucleic acid molecule of claim 30, wherein the second intergenic region comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:77.

32. The nucleic acid molecule of any one of claims 1-31, wherein the nucleic acid molecule is

(c) a DNA molecule; or

(d) an RNA molecule, wherein T is substituted with U.

33. The nucleic acid molecule of claim 32, wherein the DNA molecule further comprises a promoter.

34. The nucleic acid molecule of claim 33, wherein the promoter is located 5' of the 5'UTR.

35. The nucleic acid molecule of claim 34, wherein the promoter is a T7 promoter, a T3 promoter, or an SP6 promoter.

36. The nucleic acid molecule of claim 32, wherein the RNA molecule is a self-replicating RNA molecule.

37. The nucleic acid molecule of claim 32 or claim 36, wherein the RNA molecule further comprises a 5' cap.

38. The nucleic acid molecule of claim 37, wherein the 5' cap has a Cap 1 structure, a Cap 1 (^{m6}A) structure, a Cap 2 structure, a Cap 0 structure, or any combination thereof.

39. A nucleic acid molecule comprising

(a) a sequence of SEQ ID NO:124;

(b) a sequence of SEQ ID NO:124, wherein T is substituted with U;

(c) a sequence of SEQ ID NO:125; or

(d) a sequence of SEQ ID NO:125, wherein T is substituted with U.

40. The nucleic acid molecule of claim 39, wherein the nucleic acid molecule is an RNA molecule.

41. The nucleic acid molecule of claim 40, further comprising a 5' cap having a Cap 1 structure.

42. A nucleic acid molecule comprising:

(i) a first polynucleotide comprising a sequence having at least 80% identity to a sequence of SEQ ID NO:72; and

(ii) a second polynucleotide comprising a first transgene encoding a first antigenic protein or a fragment thereof, wherein the first antigenic protein is a coronavirus protein.

43. The nucleic acid molecule of claim 42, further comprising a 5' untranslated region (UTR).

44. The nucleic acid molecule of claim 43, wherein the 5' UTR comprises a viral 5' UTR, a non-viral 5' UTR, or a combination of viral and non-viral 5' UTR sequences.

45. The nucleic acid molecule of claim 44, wherein the 5' UTR comprises an alphavirus 5' UTR.

46. The nucleic acid molecule of claim 45, wherein the alphavirus 5' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 5' UTR sequence.

47. The nucleic acid molecule of claim 43, wherein the 5' UTR comprises a sequence of SEQ ID NO:73, SEQ ID NO:74, or SEQ ID NO:75.

48. The nucleic acid molecule of any one of claims 42-47, further comprising a 3' untranslated region (UTR).

49. The nucleic acid molecule of claim 48, wherein the 3' UTR comprises a viral 3' UTR, a non-viral 3' UTR, or a combination of viral and non-viral 3' UTR sequences.

50. The nucleic acid molecule of claim 49, wherein the 3' UTR comprises an alphavirus 3' UTR.

51. The nucleic acid molecule of claim 50, wherein the alphavirus 3' UTR comprises a Venezuelan Equine Encephalitis Virus (VEEV), Eastern Equine Encephalitis Virus (EEEV), Everglades Virus (EVEV), Mucambo Virus (MUCV), Semliki Forest Virus (SFV), Pixuna Virus (PIXV), Middleburg Virus (MIDV), Chikungunya Virus (CHIKV), O'Nyong-Nyong Virus (ONNV), Ross River Virus (RRV), Barmah Forest Virus (BFV), Getah Virus (GETV), Sagiyama Virus (SAGV), Bebaru Virus (BEBV), Mayaro Virus (MAYV), Una Virus (UNAV), Sindbis Virus (SINV), Aura Virus (AURAV), Whataroa Virus (WHAV), Babanki Virus (BABV), Kyzylagach Virus (KYZV), Western Equine Encephalitis Virus (WEEV), Highland J Virus (HJV), Fort Morgan Virus (FMV), Ndumu Virus (NDUV), Salmonid Alphavirus (SAV), or Buggy Creek Virus (BCRV) 3' UTR sequence.

52. The nucleic acid molecule of claim 48, wherein the 3' UTR comprises a poly-A sequence.

53. The nucleic acid molecule of claim 48, wherein the 3' UTR comprises a sequence of SEQ ID NO:76.

54. The nucleic acid molecule of any one of claims claim 42-53, wherein the antigenic protein is a SARS-CoV-2 protein.

55. The nucleic acid molecule of claim 54, wherein the antigenic protein is a SARS-CoV-2 spike glycoprotein.

56. The nucleic acid molecule of claim 55, wherein the SARS-CoV-2 spike glycoprotein is a wild-type SARS-CoV-2 spike glycoprotein having an amino acid sequence of SEQ ID NO:123.

57. The nucleic acid molecule of any one of claims 42-56, wherein the second polynucleotide comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:121 or SEQ ID NO:122.

58. The nucleic acid molecule of any one of claims 42-57, wherein the second polynucleotide comprises at least two transgenes.

59. The nucleic acid molecule of claim 58, wherein a second transgene encodes a second antigenic protein or a fragment thereof or an immunomodulatory protein.

60. The nucleic acid molecule of claim 58 or claim 59, wherein the second polynucleotide further comprises a sequence encoding a 2A peptide, an internal ribosomal entry site (IRES), or a combination thereof, located between transgenes.

61. The nucleic acid molecule of claim 59 or claim 60, wherein the immunomodulatory protein is a cytokine, a chemokine, or an interleukin.

62. The nucleic acid molecule of any one of claims 59-61, wherein the second transgene encodes a second coronavirus protein.

63. The nucleic acid molecule of any one of claims 42-62, wherein the first polynucleotide is located 5' of the second polynucleotide.

64. The nucleic acid molecule of any one of claims 42-63, further comprising a second intergenic region located between the first polynucleotide and the second polynucleotide.

65. The nucleic acid molecule of claim 64, wherein the second intergenic region comprises a sequence having at least 85% identity to a sequence of SEQ ID NO:77.

66. The nucleic acid molecule of any one of claims 42-65, wherein the nucleic acid molecule is

(c) a DNA molecule; or

(d) an RNA molecule, wherein T is substituted with U.

67. The nucleic acid molecule of claim 66, wherein the DNA molecule further comprises a promoter.

68. The nucleic acid molecule of claim 67, wherein the promoter is located 5' of the 5'UTR.

69. The nucleic acid molecule of claim 68, wherein the promoter is a T7 promoter, a T3 promoter, or an SP6 promoter.

70. The nucleic acid molecule of claim 66, wherein the RNA molecule is a self-replicating RNA molecule.

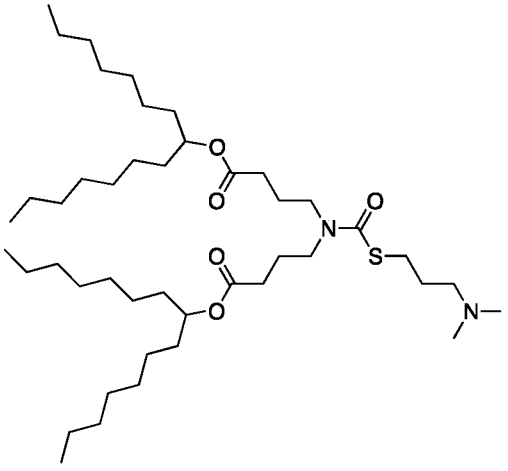
71. The nucleic acid molecule of claim 66 or claim 70, wherein the RNA molecule further comprises a 5' cap.

72. The nucleic acid molecule of claim 71, wherein the 5' cap has a Cap 1 structure, a Cap 1 (^{m6}A) structure, a Cap 2 structure, a Cap 0 structure, or any combination thereof.

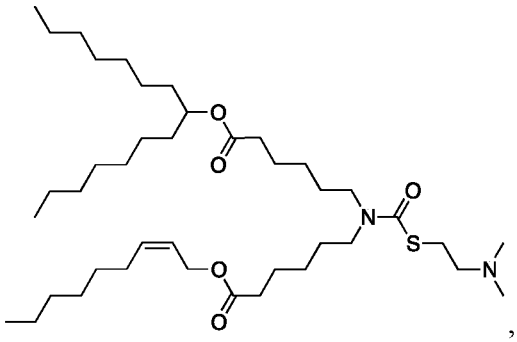
73. A composition comprising the nucleic acid molecule of any one of claims 1-72 and a lipid.

74. The composition of claim 73, wherein the lipid comprises an ionizable cationic lipid.

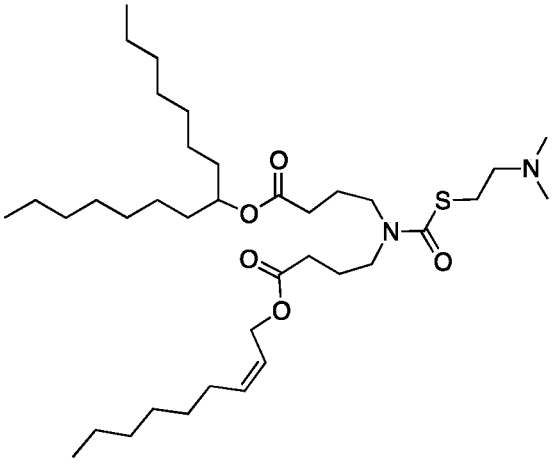
75. The composition of claim 74, wherein the ionizable cationic lipid has a structure of



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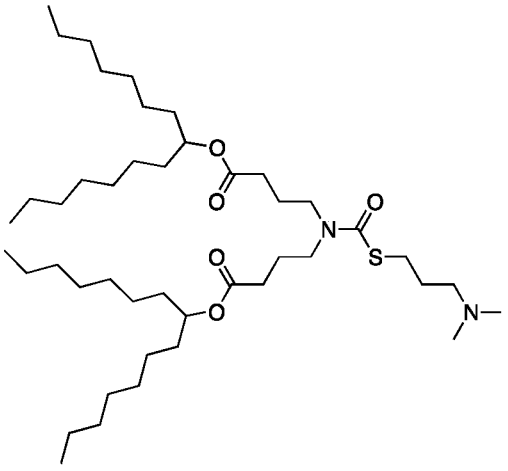


, or a pharmaceutically acceptable salt thereof.

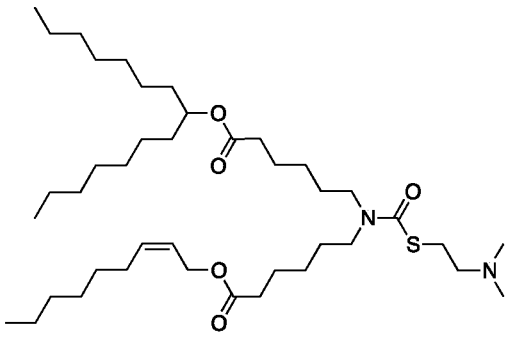
76. A composition comprising the nucleic acid molecule of any one of claims 1-72 and a lipid formulation.

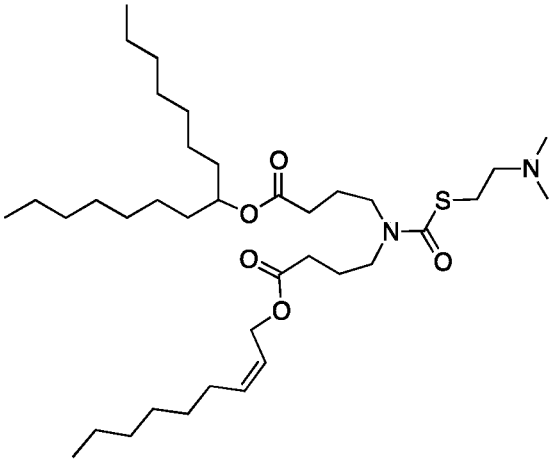
77. The composition of claim 76, wherein the lipid formulation comprises an ionizable cationic lipid.

78. The composition of claim 77, wherein the ionizable cationic lipid has a structure of



,





, or a pharmaceutically acceptable salt thereof.

79. The composition of claim 76, wherein the lipid formulation is selected from a lipoplex, a liposome, a lipid nanoparticle, a polymer-based carrier, an exosome, a lamellar body, a micelle, and an emulsion.

80. The composition of claim 79, wherein the lipid formulation is a liposome selected from a cationic liposome, a nanoliposome, a proteoliposome, a unilamellar liposome, a multilamellar liposome, a ceramide-containing nanoliposome, and a multivesicular liposome.

81. The composition of claim 79, wherein the lipid formulation is a lipid nanoparticle.

82. The composition of claim 81, wherein the lipid nanoparticle has a size of less than about 200 nm.

83. The composition of claim 81, wherein the lipid nanoparticle has a size of less than about 150 nm.

84. The composition of claim 81, wherein the lipid nanoparticle has a size of less than about 100 nm.

85. The lipid composition of claim 81, wherein the lipid nanoparticle has a size of about 55 nm to about 90 nm.

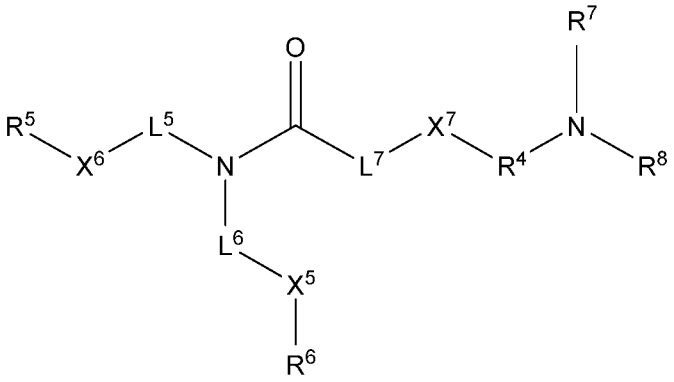
86. The lipid composition of any one of claims 76 to 85, wherein the lipid formulation comprises one or more cationic lipids.

87. The lipid composition of claim 86, wherein the one or more cationic lipids is selected from 5-carboxyspermylglycinedioctadecylamide (DOGS), 2,3-dioleyloxy-N-[2(spermine-carboxamido)ethyl]-N,N-dimethyl-1-propanaminium (DOSPA), 1,2-Dioleoyl-3-Dimethylammonium-Propane (DODAP), 1,2-Dioleoyl-3-Trimethylammonium-Propane (DOTAP), 1,2-distearyloxy-N,N-dimethyl-3-aminopropane (DSDMA), 1,2-dioleyloxy-N,N-dimethyl-3-aminopropane (DODMA), 1,2-dilinoleyloxy-N,N-dimethyl-3-aminopropane (DLinDMA), 1,2-dilinolenyloxy-N,N-dimethyl-3-aminopropane (DLenDMA), N-dioleyl-

N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide (DMRIE), 3-dimethylamino-2-(cholest-5-en-3-beta-oxybutan-4-oxy)-1-(cis,cis-9,12-oc-tadecadienoxy)propane (CLinDMA), 2-[5′-(cholest-5-en-3-beta-oxy)-3′-oxapentoxy)-3-dimethy 1-1-(cis,cis-9′,1-2′-octadecadienoxy)propane (CpLinDMA), N,N-dimethyl-3,4-dioleyloxybenzylamine (DMOBA), 1,2-N,N′-dioleylcarbamyl-3-dimethylaminopropane (DOcarbDAP), 2,3-Dilinoleoyloxy-N,N-dimethylpropylamine (DLinDAP), 1,2-N,N′-Dilinoleylcarbamyl-3-dimethylaminopropane (DLincarbDAP), 1,2-Dilinoleoylcarbamyl-3-dimethylaminopropane (DLinCDAP), 2,2-dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA), and 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane or (DLin-K-XTC2-DMA).

88. The composition of any one of claims 76 to 85, wherein the lipid formulation comprises an ionizable cationic lipid.

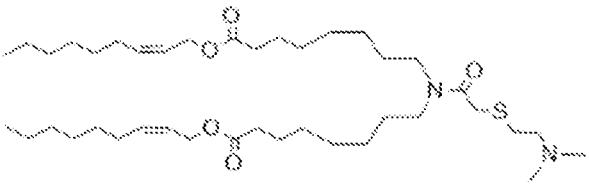
89. The composition of claim 88, wherein the ionizable cationic lipid has a structure of Formula I:



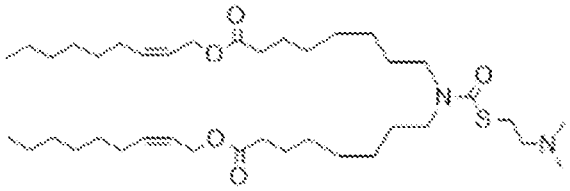
(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 and R^6 are each independently selected from the group consisting of a linear or branched C_1-C_{31} alkyl, C_2-C_{31} alkenyl or C_2-C_{31} alkynyl and cholesteryl; L^5 and L^6 are each independently selected from the group consisting of a linear C_1-C_{20} alkyl and C_2-C_{20} alkenyl; X^5 is -C(O)O-, whereby -C(O)O-R^6 is formed or -OC(O)- whereby -OC(O)-R^6 is formed; X^6 is -C(O)O- whereby -C(O)O-R^5 is formed or -OC(O)- whereby -OC(O)-R^5 is formed; X^7 is S or O; L^7 is absent or lower alkyl; R^4 is a linear or branched C_1-C_6 alkyl; and R^7 and R^8 are each independently selected from the group consisting of a hydrogen and a linear or branched C_1-C_6 alkyl.

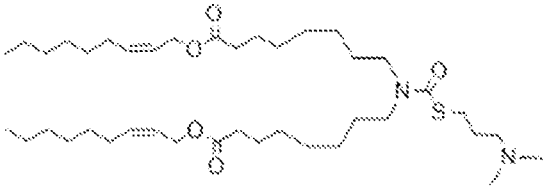
90. The composition of claim 88, wherein the ionizable cationic lipid is selected from



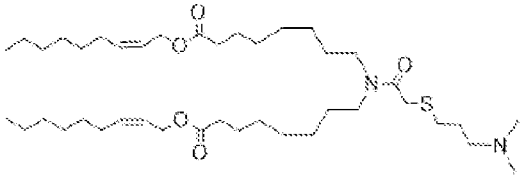
ATX-001



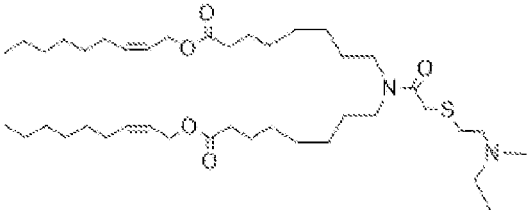
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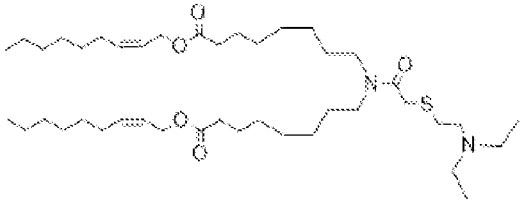
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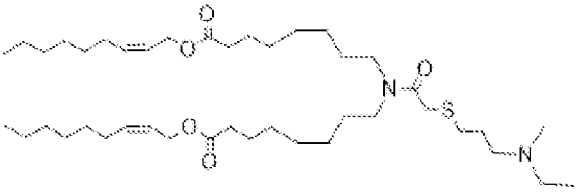
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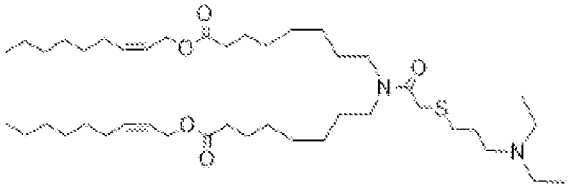
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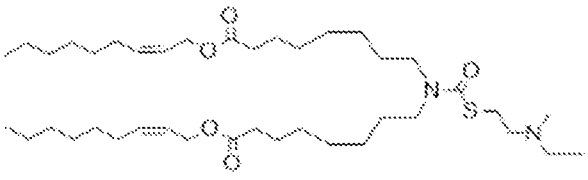
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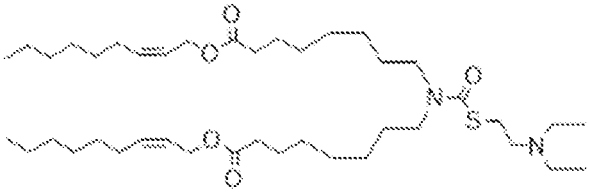
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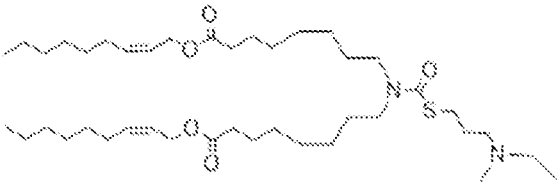
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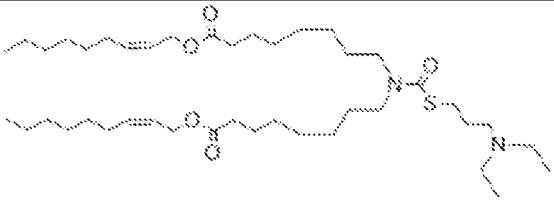
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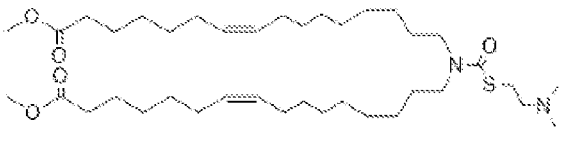
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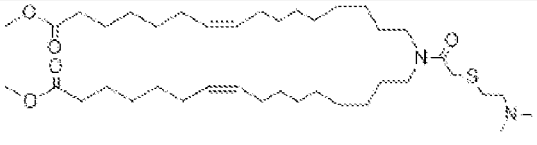
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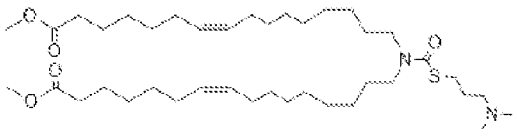
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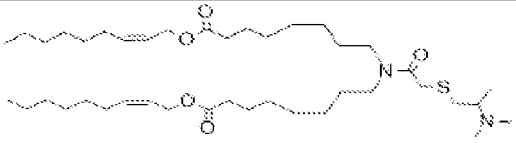
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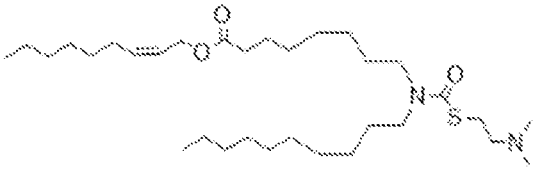
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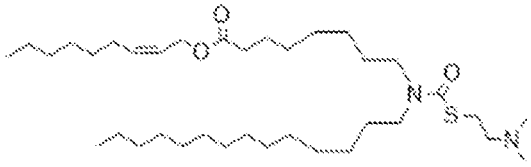
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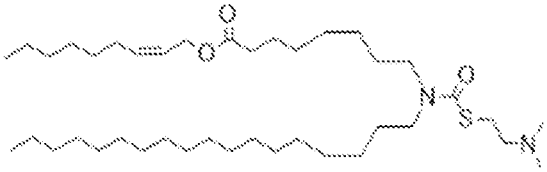
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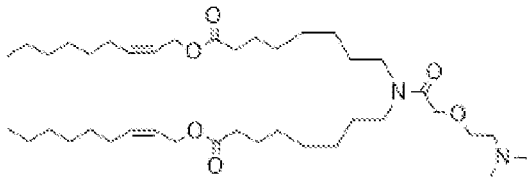
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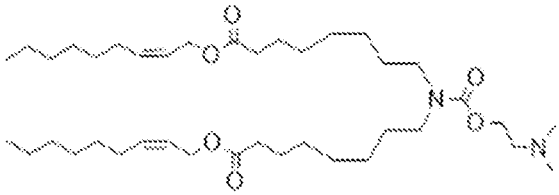
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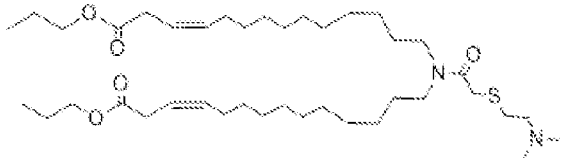
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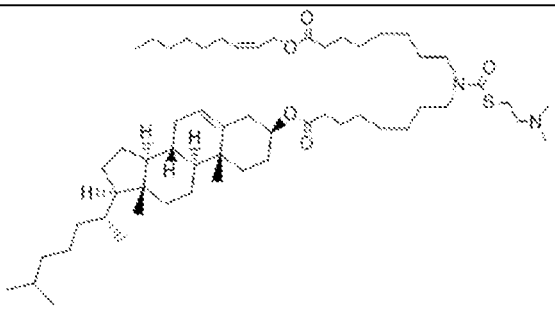
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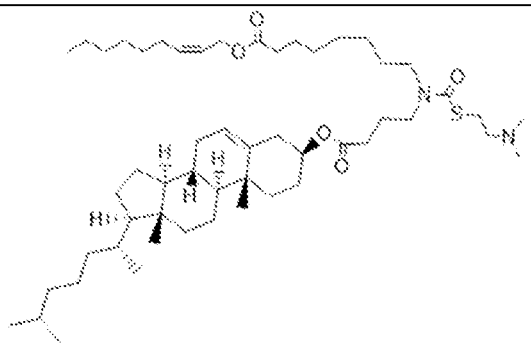
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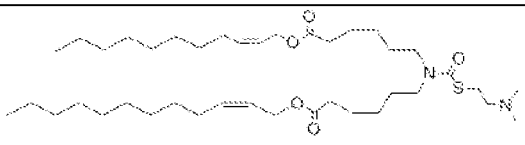
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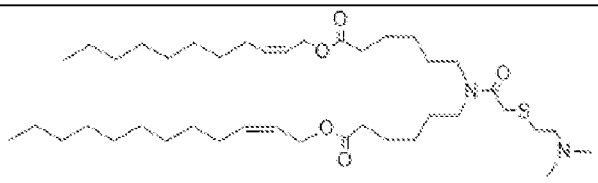
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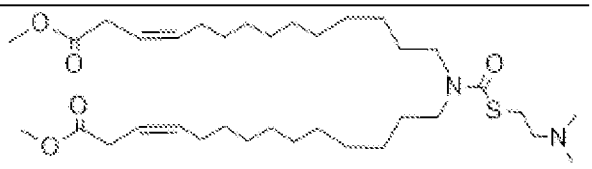
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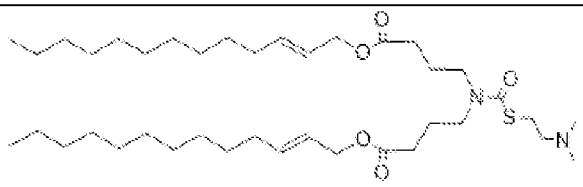
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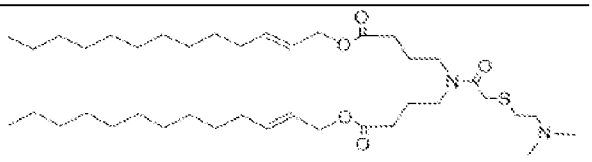
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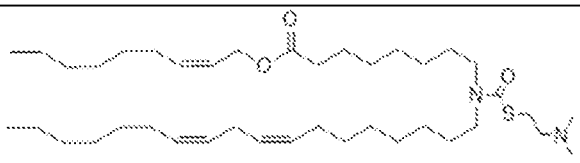
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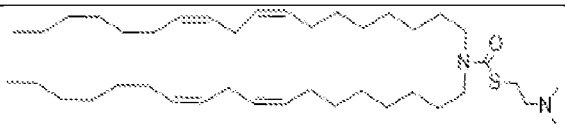
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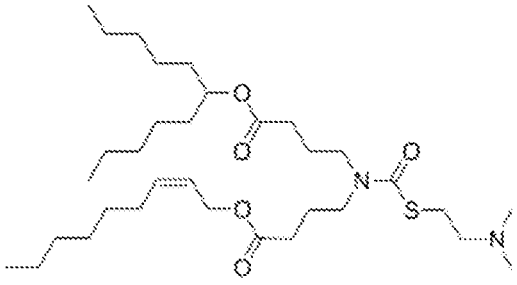
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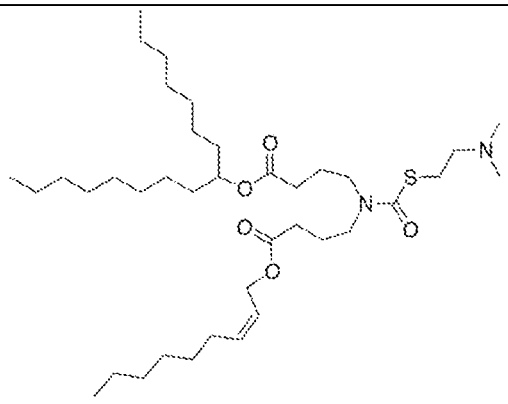
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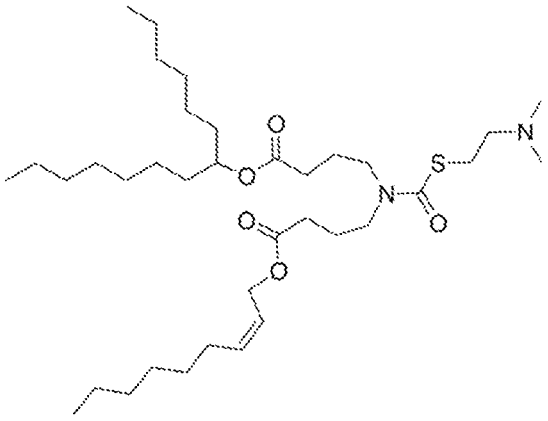
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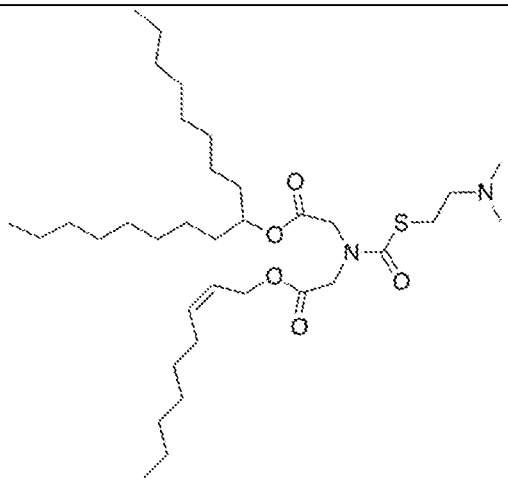
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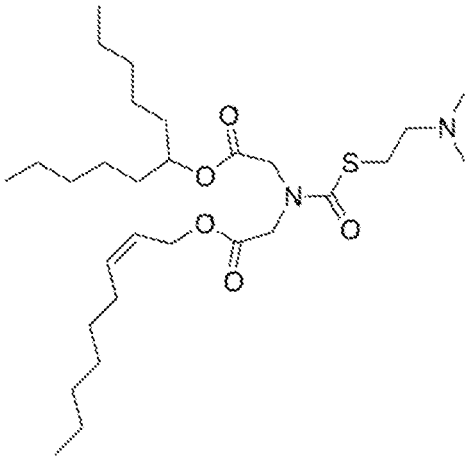
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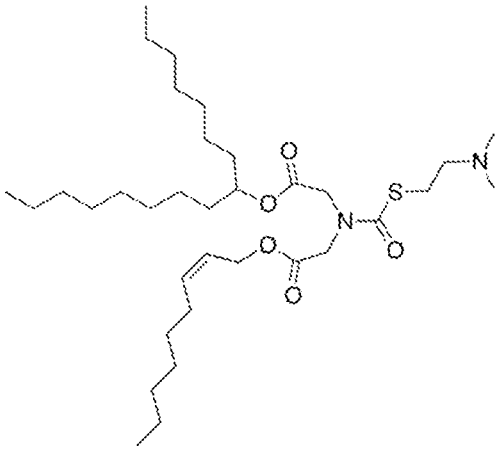
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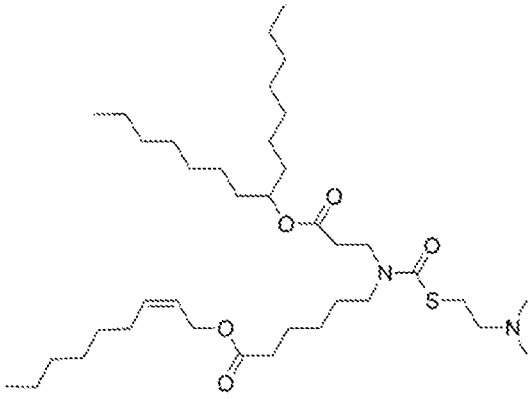
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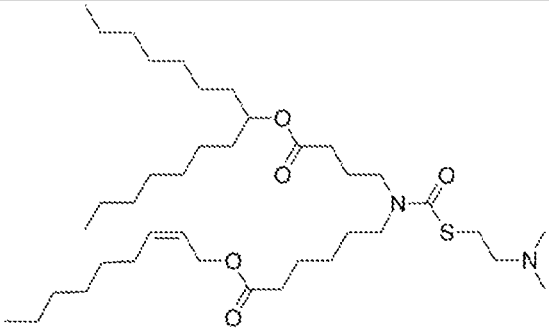
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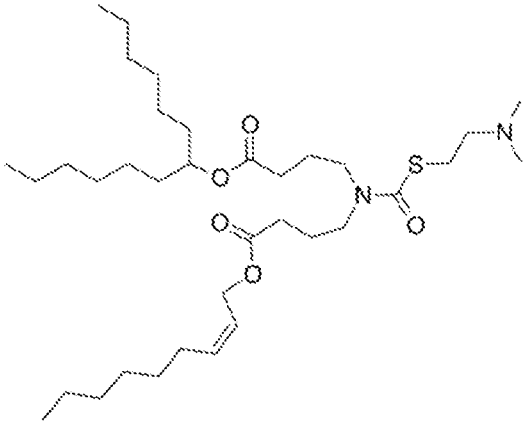
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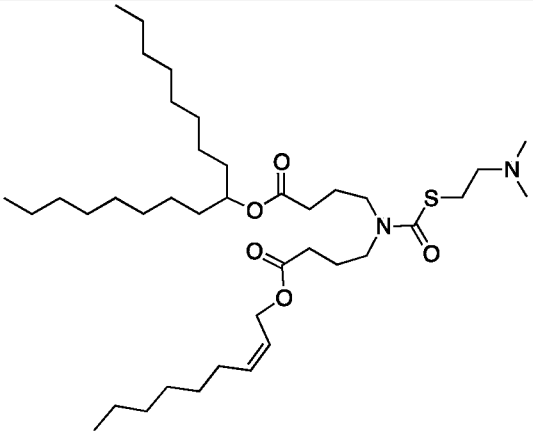
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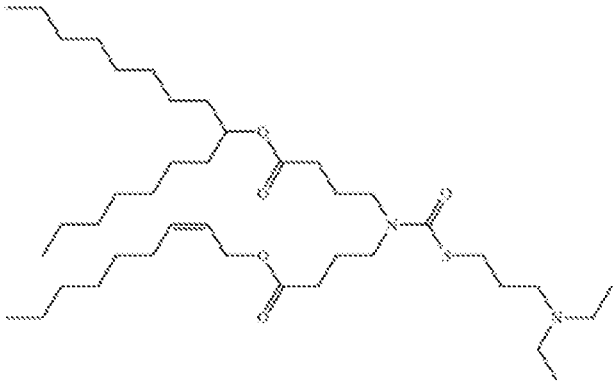
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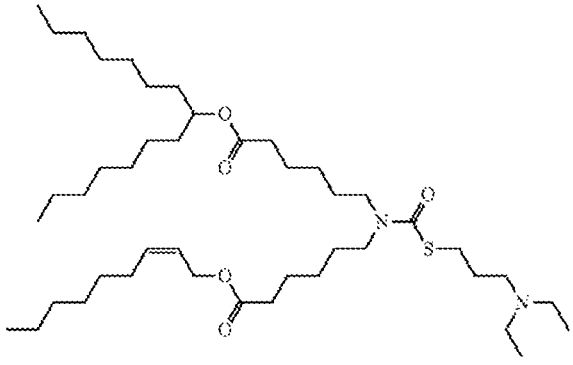
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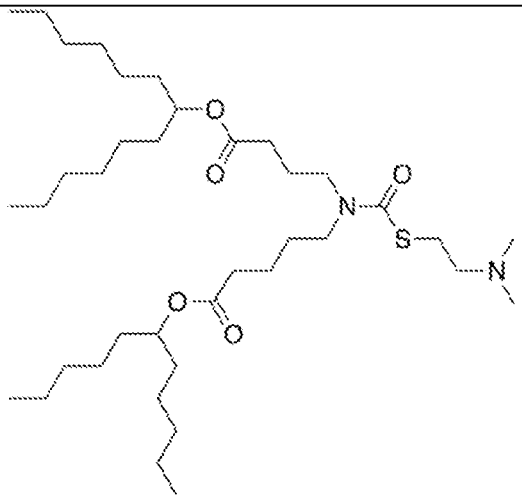
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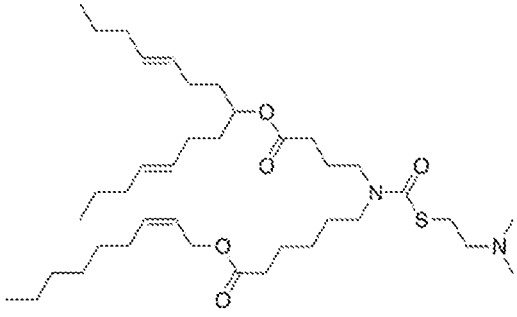
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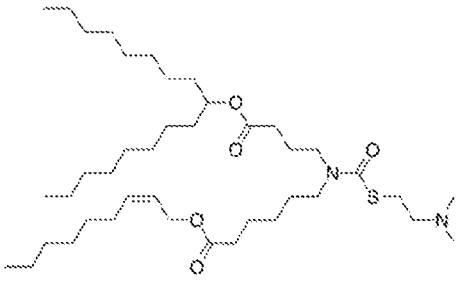
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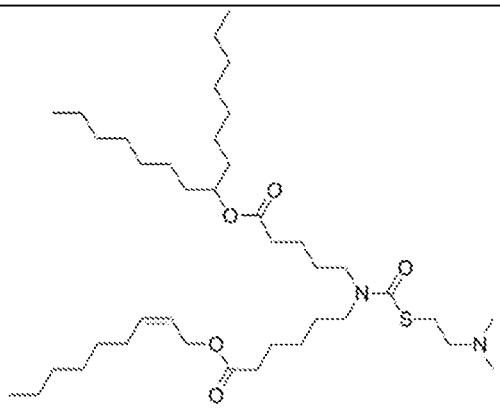
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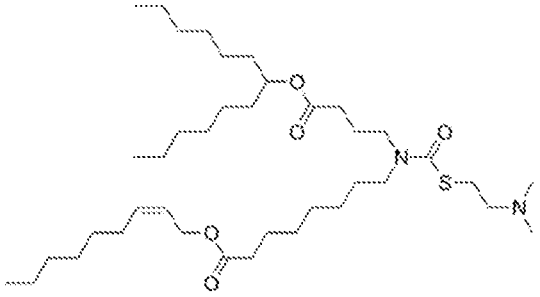
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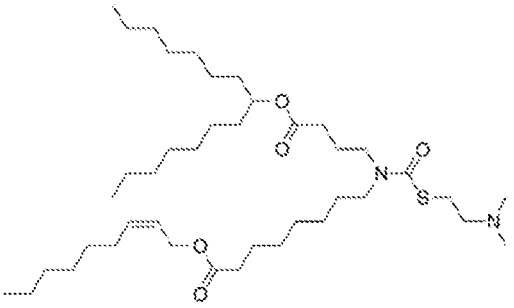
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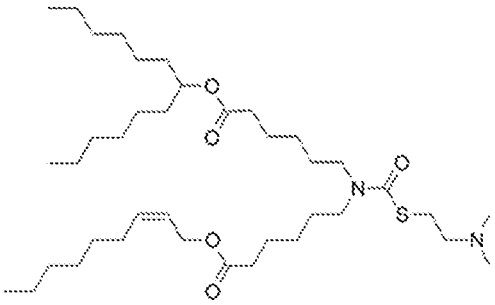
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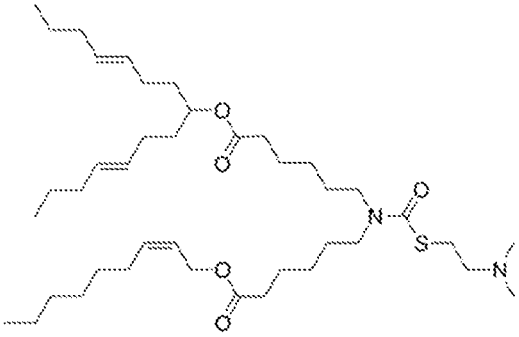
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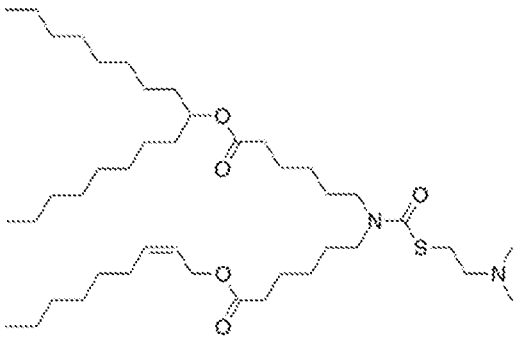
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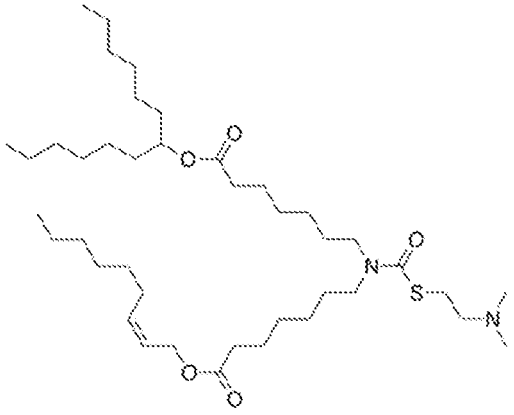
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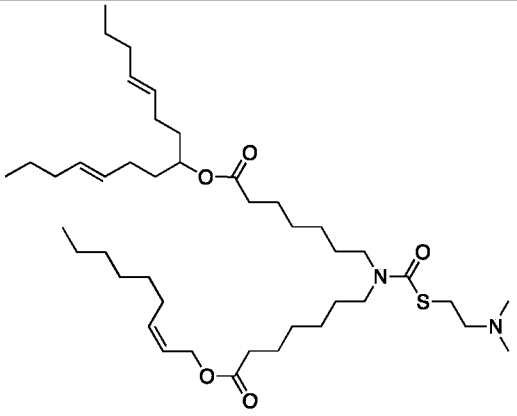
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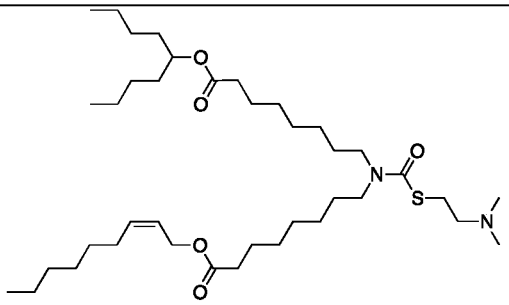
ATX-094



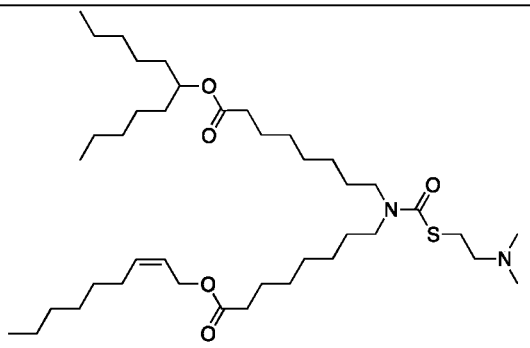
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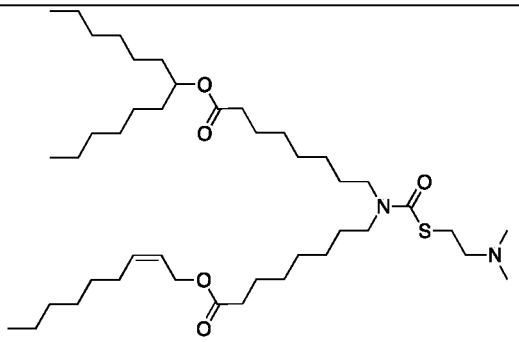
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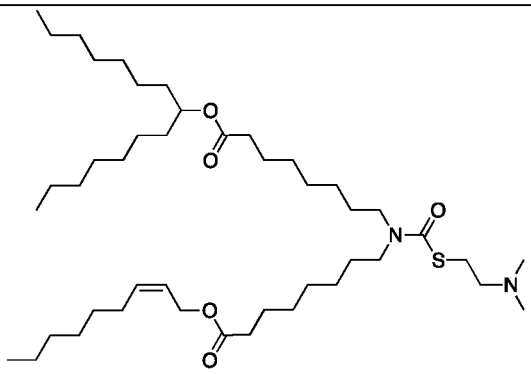
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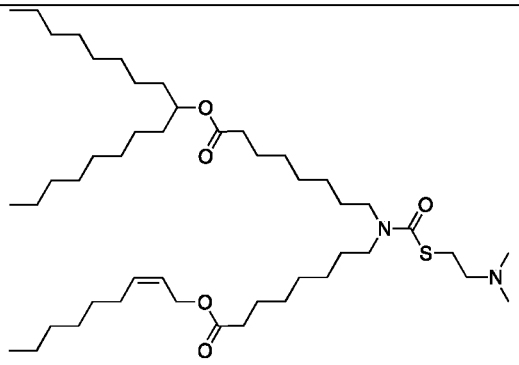
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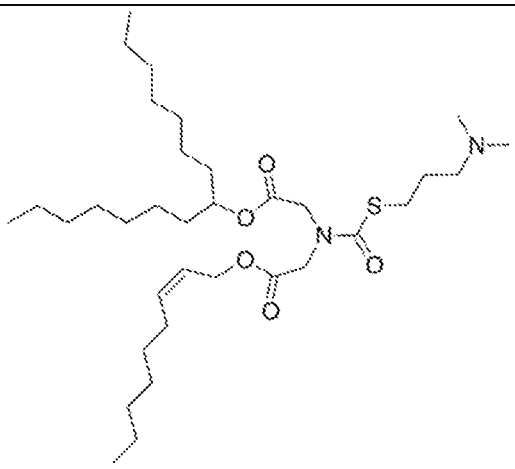
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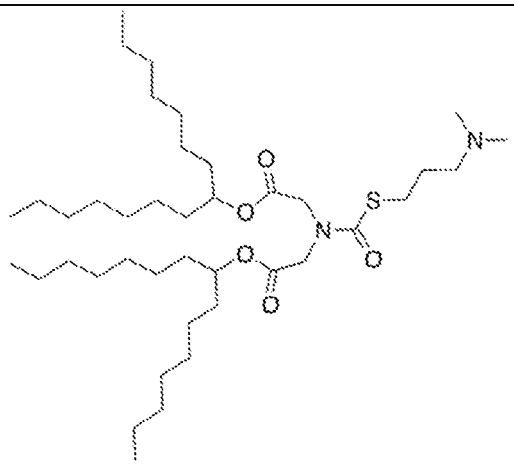
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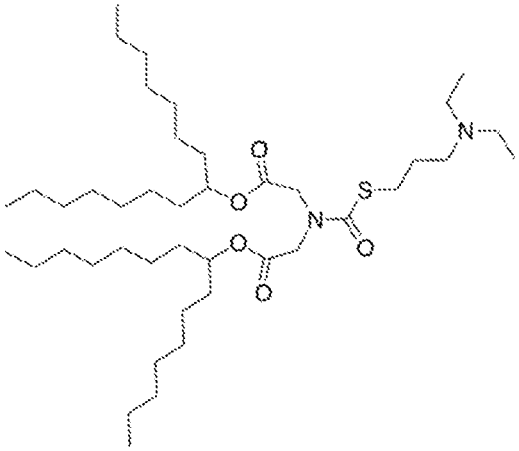
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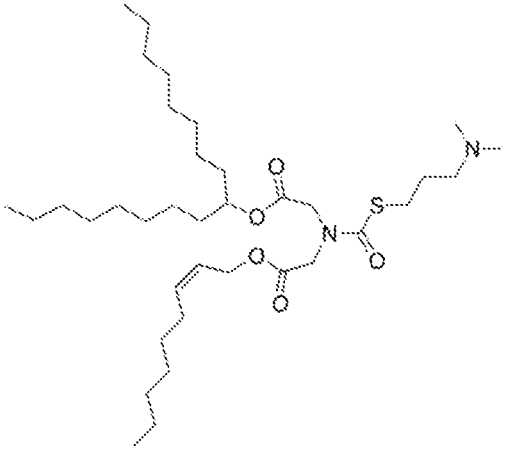
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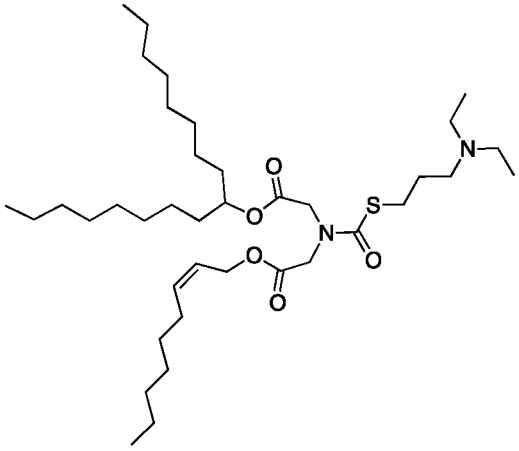
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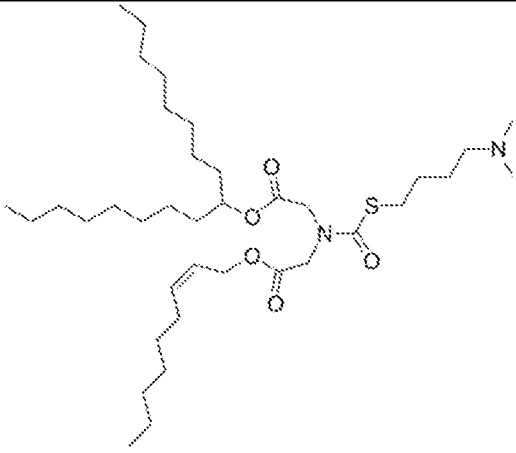
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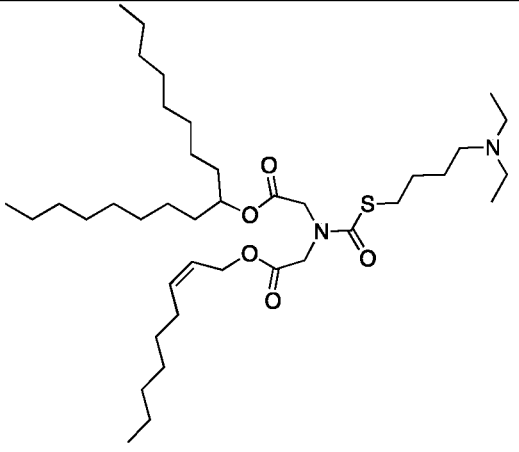
ATX-0100



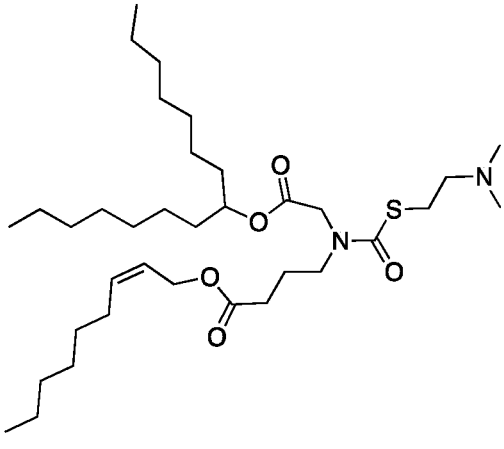
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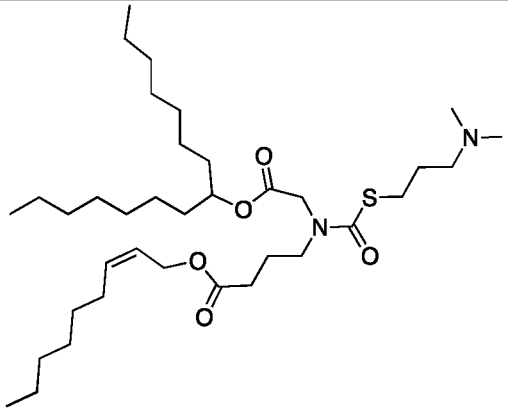
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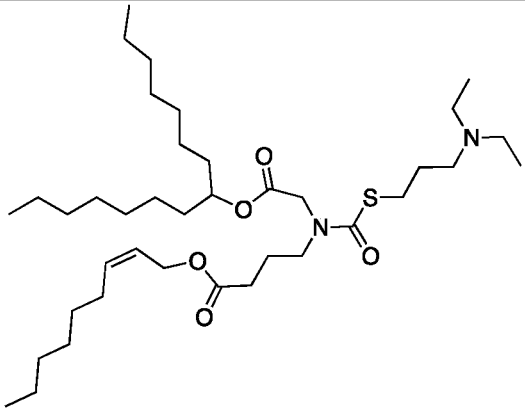
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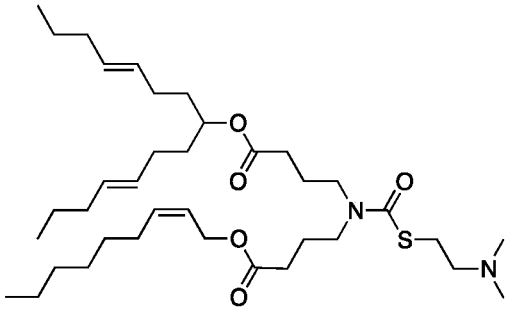
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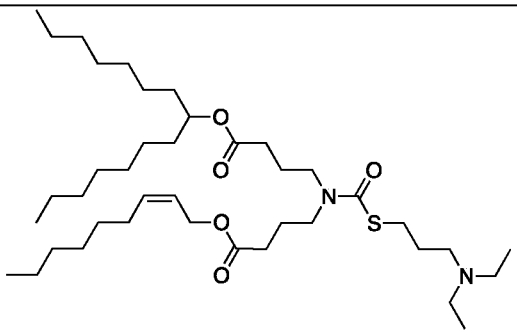
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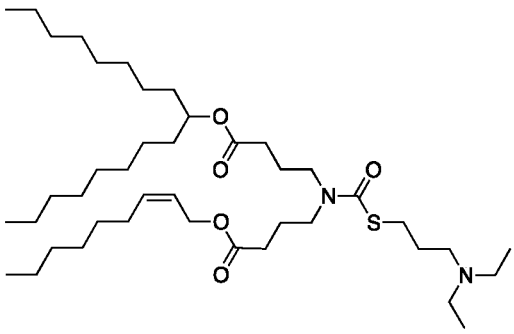
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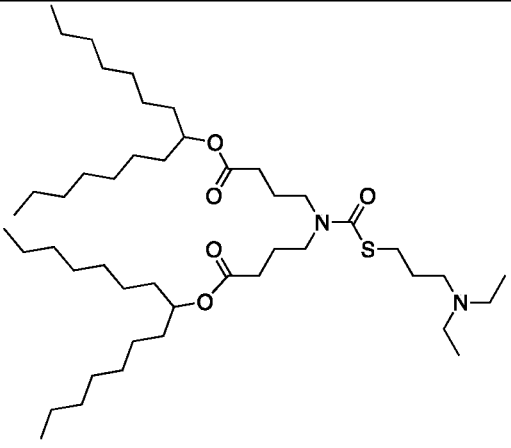
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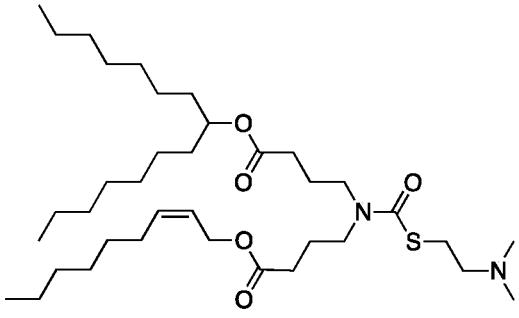
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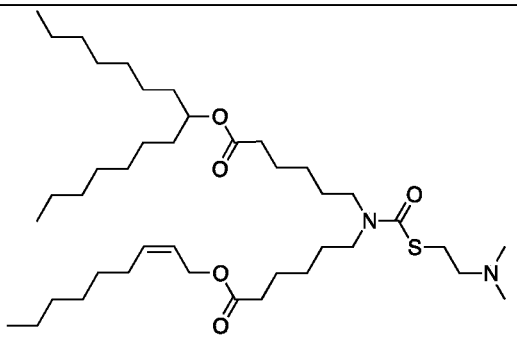
ATX-0124



ATX-0129

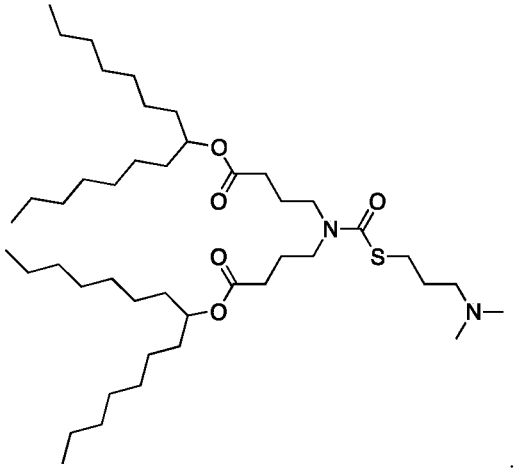


ATX-081



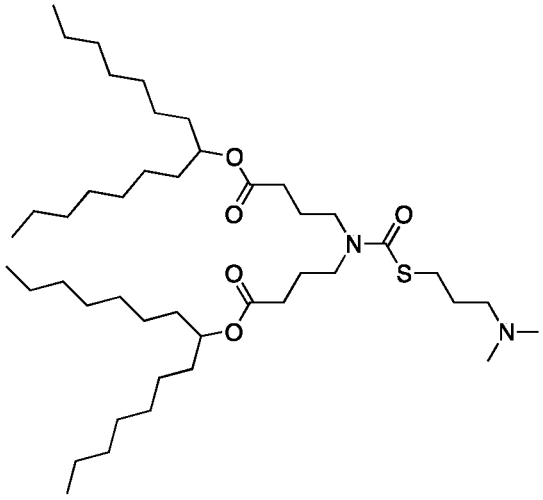
ATX-095

and



ATX-0126

91. The composition of claim 88, wherein the ionizable cationic lipid is ATX-126:



ATX-126.

92. The composition of any one of claims 76 to 91, wherein the lipid formulation encapsulates the nucleic acid molecule.

93. The composition of any one of claims 76 to 92, wherein the lipid formulation is complexed to the nucleic acid molecule.

94. The composition of any one of claims 76 to 93, wherein the lipid formulation further comprises a helper lipid.

95. The composition of claim 94, wherein the helper lipid is a phospholipid.

96. The composition of claim 94, wherein the helper lipid is selected from dioleoylphosphatidyl ethanolamine (DOPE), dimyristoylphosphatidyl choline (DMPC), distearoylphosphatidyl choline (DSPC), dimyristoylphosphatidyl glycerol (DMPG), dipalmitoyl phosphatidylcholine (DPPC), and phosphatidylcholine (PC).

97. The composition of claim 96, wherein the helper lipid is distearoylphosphatidylcholine (DSPC).

98. The composition of any one of claims 76 to 97, wherein the lipid formulation further comprises cholesterol.

99. The composition of any one of claims 76 to 98, wherein the lipid formulation further comprises a polyethylene glycol (PEG)-lipid conjugate.

100. The composition of claim 99, wherein the PEG-lipid conjugate is PEG-DMG.

101. The composition of claim 100, wherein the PEG-DMG is PEG2000-DMG.

102. The composition of any one of claims 76 to 98, wherein the lipid portion of the lipid formulation comprises about 40 mol% to about 60 mol% of the ionizable cationic lipid, about 4 mol% to about 16 mol% DSPC, about 30 mol% to about 47 mol% cholesterol, and about 0.5 mol% to about 3 mol% PEG2000-DMG.

103. The composition of claim 102, wherein the lipid portion of the lipid formulation comprises about 42 mol% to about 58 mol% of the ionizable cationic lipid, about 6 mol% to about 14 mol% DSPC, about 32 mol% to about 44 mol% cholesterol, and about 1 mol% to about 2 mol% PEG2000-DMG.

104. The composition of claim 103, wherein the lipid portion of the lipid formulation comprises about 45 mol% to about 55 mol% of the ionizable cationic lipid, about 8 mol% to about 12 mol% DSPC, about 35 mol% to about 42 mol% cholesterol, and about 1.25 mol% to about 1.75 mol% PEG2000-DMG.

105. The composition of any one of claims 76 to 104, wherein the composition has a total lipid:nucleic acid molecule weight ratio of about 50:1 to about 10:1.

106. The composition of claim 105, wherein the composition has a total lipid:nucleic acid molecule weight ratio of about 44:1 to about 24:1.

107. The composition of claim 106, wherein the composition has a total lipid: nucleic acid molecule weight ratio of about 40:1 to about 28:1.

108. The composition of claim 76, wherein the composition has a total lipid: nucleic acid molecule weight ratio of about 38:1 to about 30:1.

109. The composition of claim 108, wherein the composition has a total lipid: nucleic acid molecule weight ratio of about 37:1 to about 33:1.

110. The composition of any one of claims 76 to 109, wherein the composition comprises a HEPES or TRIS buffer at a pH of about 7.0 to about 8.5.

111. The composition of claim 110, wherein the HEPES or TRIS buffer is at a concentration of about 7 mg/mL to about 15 mg/mL.

112. The composition of claim 110 or 111, wherein the composition further comprises about 2.0 mg/mL to about 4.0 mg/mL of NaCl.

113. The composition of any one of claims 76 to 112, wherein the composition further comprises one or more cryoprotectants.

114. The composition of claim 113, wherein the one or more cryoprotectants are selected from sucrose, glycerol, or a combination of sucrose and glycerol.

115. The composition of claim 114, wherein the composition comprises a combination of sucrose at a concentration of about 70 mg/mL to about 110 mg/mL of sucrose and glycerol at a concentration of about 50 mg/mL to about 70 mg/mL.

116. The composition of any one of claims 76 to 112, wherein the composition is a lyophilized composition.

117. The composition of claim 116, wherein the lyophilized composition comprises one or more lyoprotectants.

118. The composition of claim 116, wherein the lyophilized composition comprises a poloxamer, potassium sorbate, sucrose, or any combination thereof.

119. The composition of claim 118, wherein the poloxamer is poloxamer 188.

120. The composition of any one of claims 116 to 119, wherein the lyophilized composition comprises about 0.01 to about 1.0 % w/w of the nucleic acid molecule.

121. The composition of any one of claims 116 to 119, wherein the lyophilized composition comprises about 1.0 to about 5.0 % w/w lipids.

122. The composition of any one of claims 116 to 121, wherein the lyophilized composition comprises about 0.5 to about 2.5 % w/w of TRIS buffer.

123. The composition of any one of claims 116 to 122, wherein the lyophilized composition comprises about 0.75 to about 2.75 % w/w of NaCl.

124. The composition of any one of claims 116 to 123, wherein the lyophilized composition comprises about 85 to about 95 % w/w of a sugar.

125. The composition of claim 124, wherein the sugar is sucrose.

126. The composition of any one of claims 116 to 125, wherein the lyophilized composition comprises about 0.01 to about 1.0 % w/w of a poloxamer.

127. The composition of claim 126, wherein the poloxamer is poloxamer 188.

128. The composition of any one of claims 116 to 127, wherein the lyophilized composition comprises about 1.0 to about 5.0 % w/w of potassium sorbate.

129. The composition of any of the preceding claims, wherein the nucleic acid molecule comprises

(a) a sequence of SEQ ID NO:124;

(b) a sequence of SEQ ID NO:124, wherein T is substituted with U;

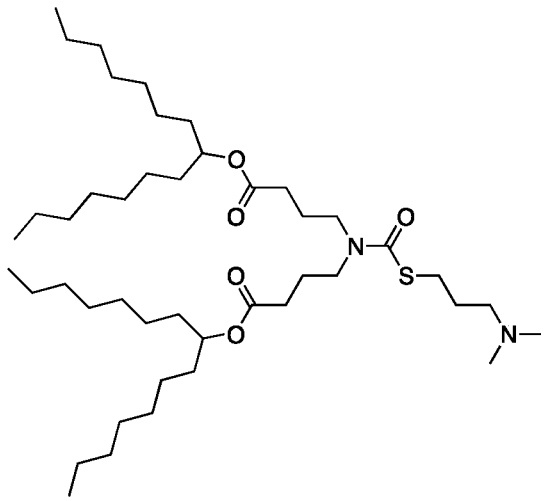
(c) a sequence of SEQ ID NO:125; or

(d) a sequence of SEQ ID NO:125, wherein T is substituted with U.

130. A lipid nanoparticle composition comprising

a. a lipid formulation comprising

i. about 45 mol% to about 55 mol% of an ionizable cationic lipid having the structure of ATX-126:



ATX-126;

ii. about 8 mol% to about 12 mol% DSPC;

iii. about 35 mol% to about 42 mol% cholesterol; and

iv. about 1.25 mol% to about 1.75 mol% PEG2000-DMG; and

b. a nucleic acid molecule having at least 85% sequence identity to SEQ ID NO:125;

wherein the lipid formulation encapsulates the nucleic acid molecule and the lipid nanoparticle has a size of about 60 to about 90 nm.

131. A method for administering the composition of any of claims 76-129 to a subject in need thereof, wherein the composition is administered intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route.

132. The method of claim 131, wherein the composition is administered intramuscularly.

133. A method of administering the composition of any of claims 76-129 to a subject in need thereof, wherein the composition is lyophilized and is reconstituted prior to administration.

134. A method of preventing or ameliorating COVID-19, comprising administering the composition of any of claims 76-129 to a subject in need thereof.

135. The method of claim 134, wherein the composition is administered one time.

136. The method of claim 134, wherein the composition is administered two times.

137. A method of administering a booster dose to a vaccinated subject, comprising administering the composition of claims 76-129 to a subject who was previously vaccinated against coronavirus.

138. The method of claim 131-137, wherein the composition is administered at a dosage of about 0.01 μg to about 1,000 μg of nucleic acid.

139. The method of claim 138, wherein the composition is administered at a dosage of about 1, 2, 5, 7.5, or 10 μg of nucleic acid.

140. A method of inducing an immune response in a subject comprising:

administering to the subject an effective amount of a nucleic acid molecule of any one of claims 1-75.

141. The method of claim 140, comprising administering the nucleic acid molecule intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route.

142. A method of inducing an immune response in a subject comprising:

administering to the subject an effective amount of a composition of any one of claims 76-129.

143. The method of claim 142, comprising administering the composition intramuscularly, subcutaneously, intradermally, transdermally, intranasally, orally, sublingually, intravenously, intraperitoneally, topically, by aerosol, or by a pulmonary route.

144. The nucleic acid molecule of any one of claims 1-75 for use in inducing an immune response to the first antigenic protein or fragment thereof.

145. Use of the nucleic acid molecule of any one of claims 1-75 in the manufacture of a medicament for inducing an immune response to the first antigenic protein or fragment thereof.

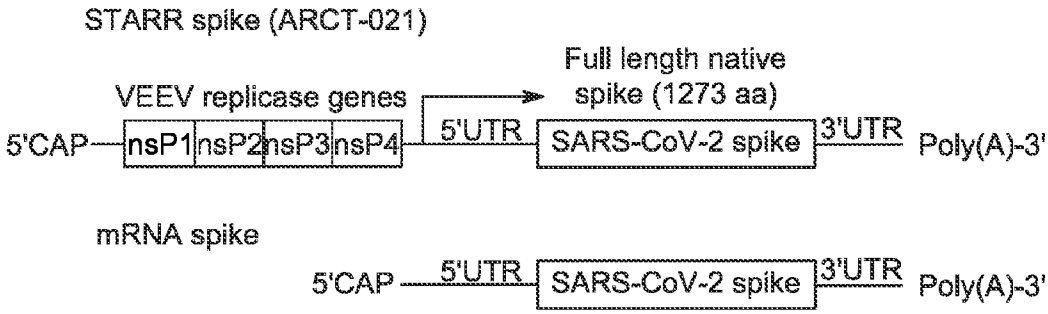


FIG. 1A

Lipid nano particle (LNP) formulations

	Particle diameter	Polydispersity index (PDI)	RNA trapping efficiency
mRNA	67 nm	0.09	92%
ARCT-021	69 nm	0.09	91%

FIG. 1B

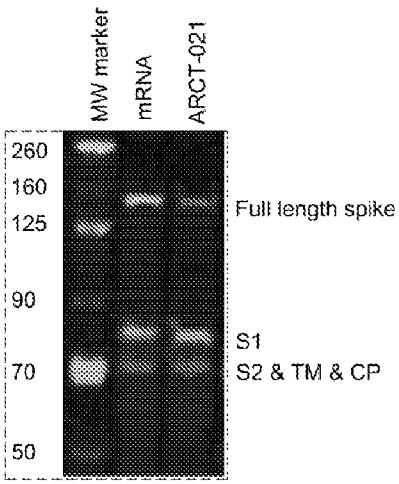

MW marker
mRNA
ARCT-021
260
160
125
90
70
50
Full length spike
S1
S2 & TM & CP

FIG. 1C

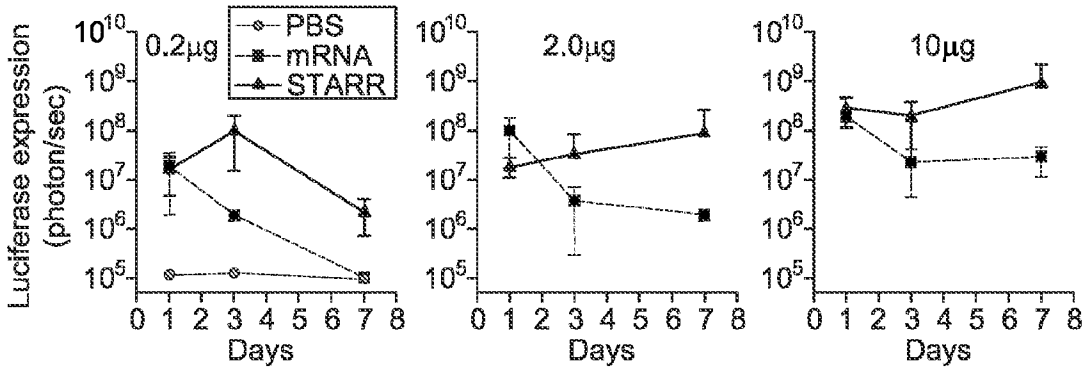

Luciferase expression (photon/sec)
0.2µg
2.0µg
10µg
PBS
mRNA
STARR
Days

FIG. 1D

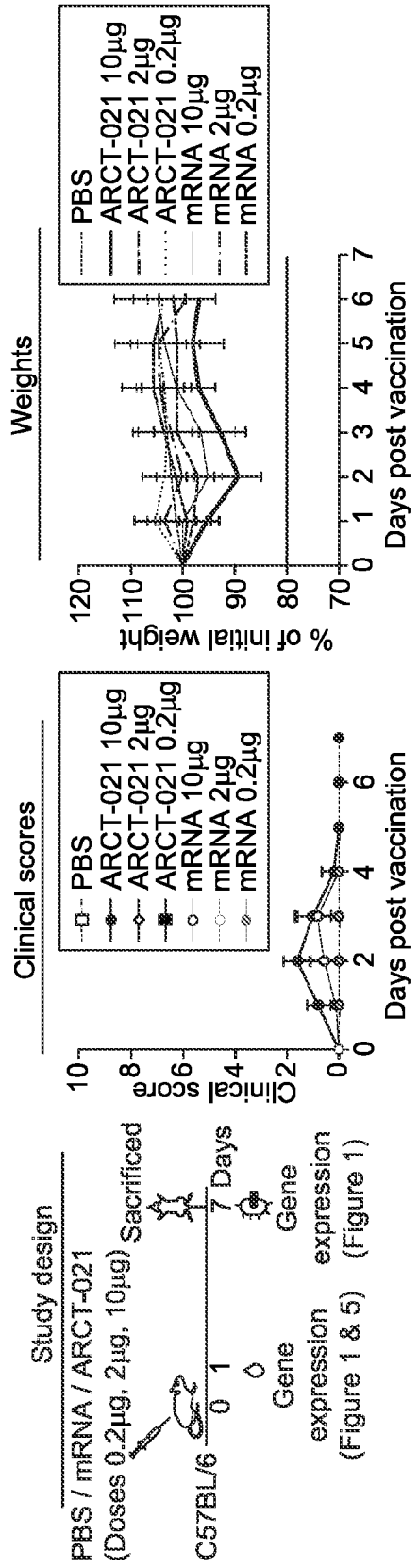

Study design
PBS / mRNA / ARCT-021
(Doses 0.2µg, 2µg, 10µg)
C57BL/6
0
1
7 Days
Sacrificed
Gene expression (Figure 1 & 5)
Gene expression (Figure 1)
Clinical scores
Clinical score
Days post vaccination
PBS
ARCT-021 10µg
ARCT-021 2µg
ARCT-021 0.2µg
mRNA 10µg
mRNA 2µg
mRNA 0.2µg
Weights
% of initial weight
Days post vaccination

FIG. 2A

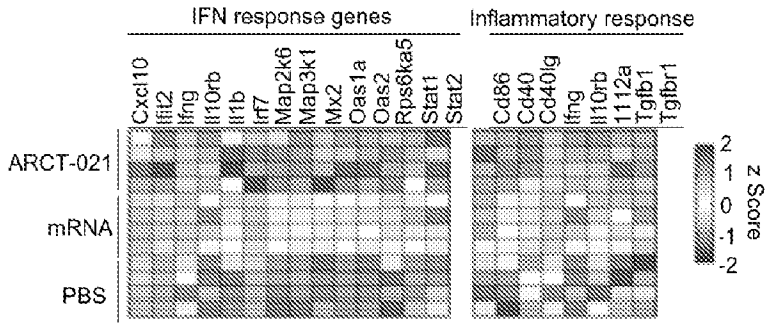

IFN response genes
Inflammatory response
Cxcl10
Ifit2
Ifng
Il10rb
Il1b
Irf7
Map2k6
Map3k1
Mx2
Oas1a
Oas2
Rps6ka5
Stat1
Stat2
Cd86
Cd40
Cd40lg
Ifng
Il10rb
Il12a
Tgfb1
Tgfbr1
ARCT-021
mRNA
PBS
2
1
0
-1
-2
z Score

FIG. 2B

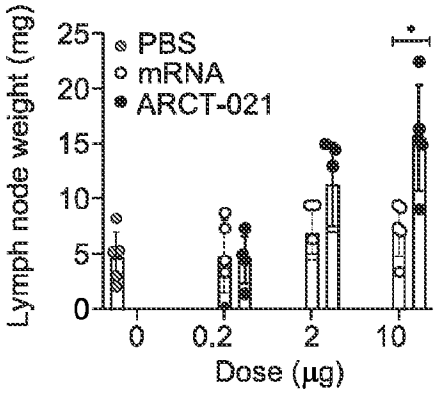

Lymph node weight (mg)
25
20
15
10
5
0
PBS
mRNA
ARCT-021
*
0
0.2
2
10
Dose (µg)

FIG. 2C

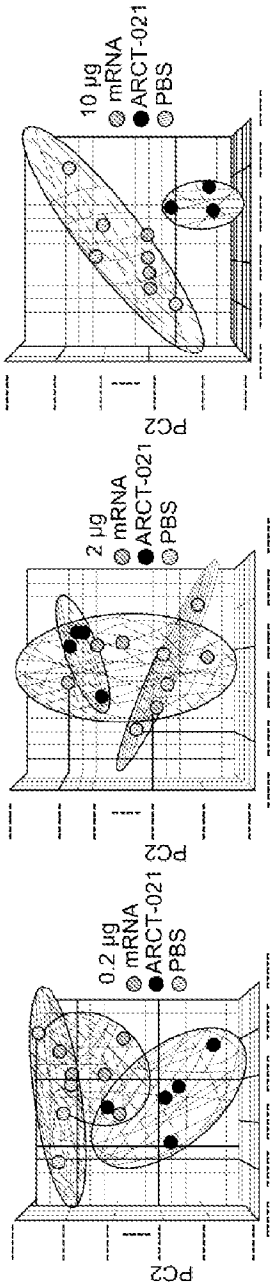


FIG. 2D

FIG. 2E

FIG. 2F



FIG. 2G

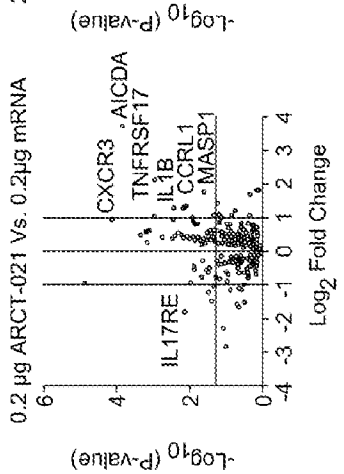


FIG. 2H

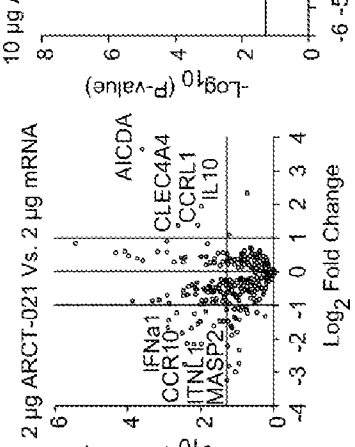


FIG. 2I

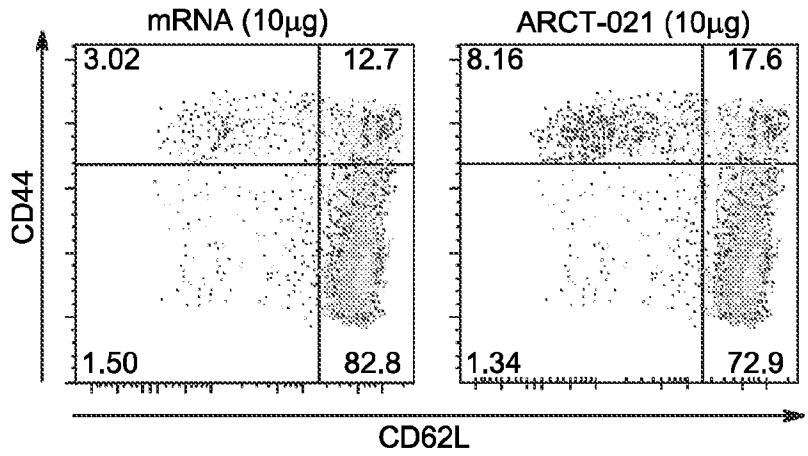


FIG. 3A

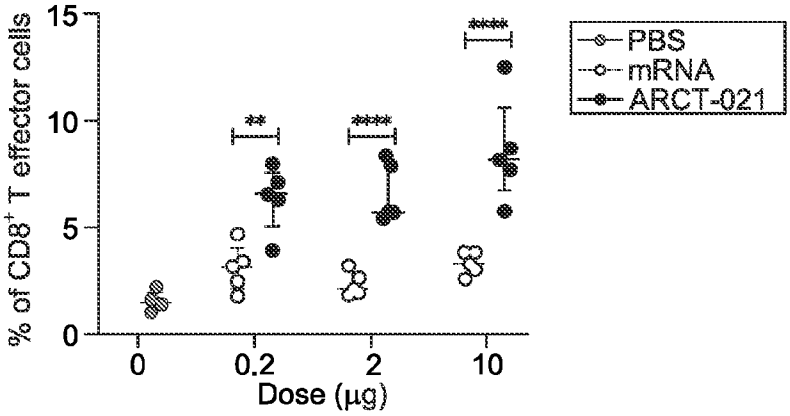


FIG. 3B

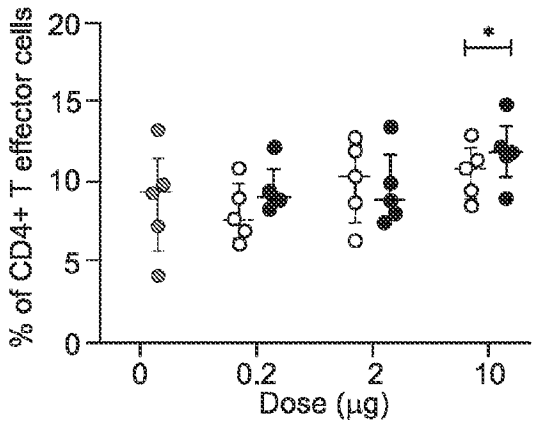


FIG. 3C

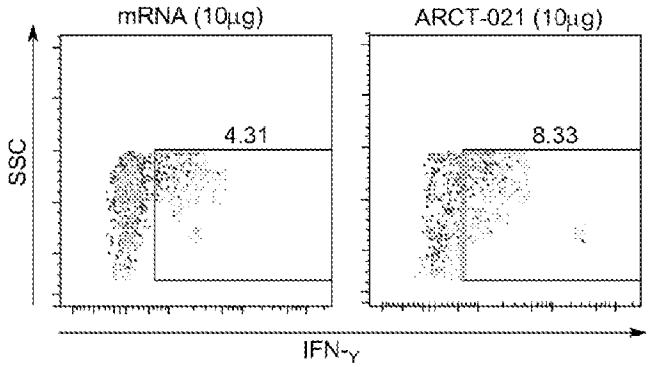


FIG. 3D

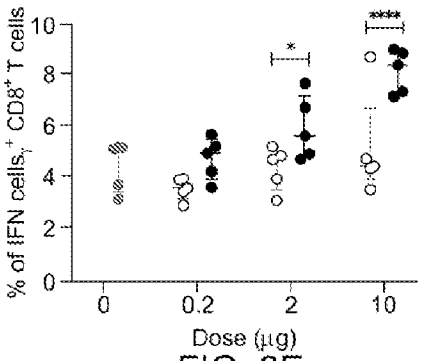


FIG. 3E

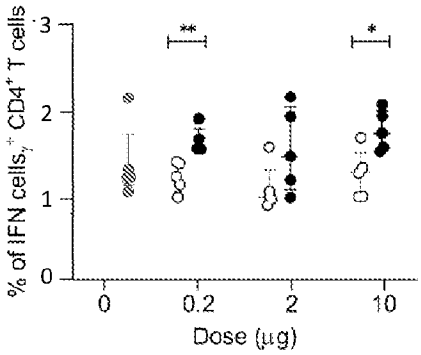


FIG. 3F

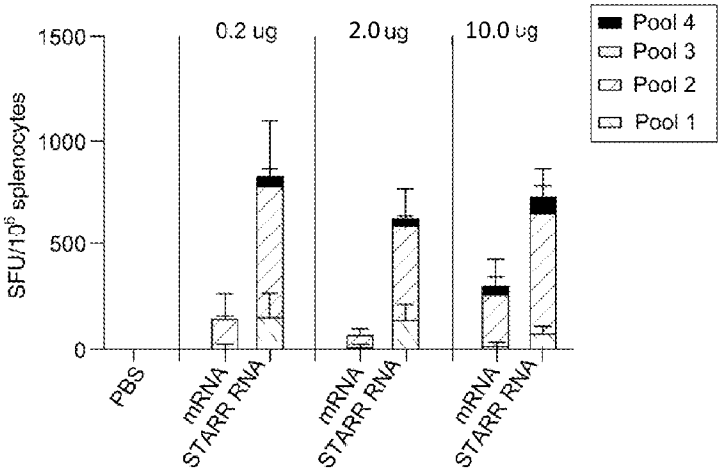

1500
1000
500
0
SFU/10^6 splenocytes
0.2 ug
2.0 ug
10.0 ug
Pool 4
Pool 3
Pool 2
Pool 1
PBS
mRNA
STARR RNA
mRNA
STARR RNA
mRNA
STARR RNA

FIG. 3G

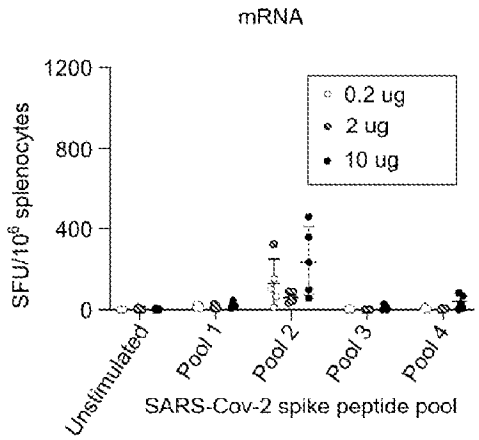

mRNA
1200
800
400
0
SFU/10^6 splenocytes
0.2 ug
2 ug
10 ug
Unstimulated
Pool 1
Pool 2
Pool 3
Pool 4
SARS-Cov-2 spike peptide pool

FIG. 3H

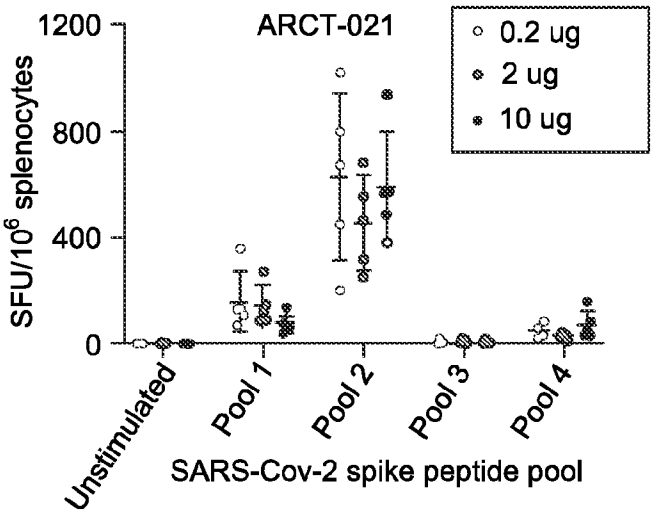

ARCT-021
0.2 ug
2 ug
10 ug
1200
800
400
0
SFU/10^6 splenocytes
Unstimulated
Pool 1
Pool 2
Pool 3
Pool 4
SARS-Cov-2 spike peptide pool

FIG. 3I

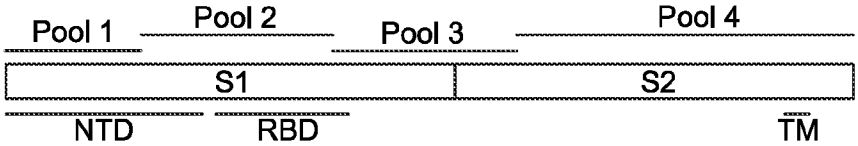

Pool 1
Pool 2
Pool 3
Pool 4
S1
S2
NTD
RBD
TM

FIG. 3J

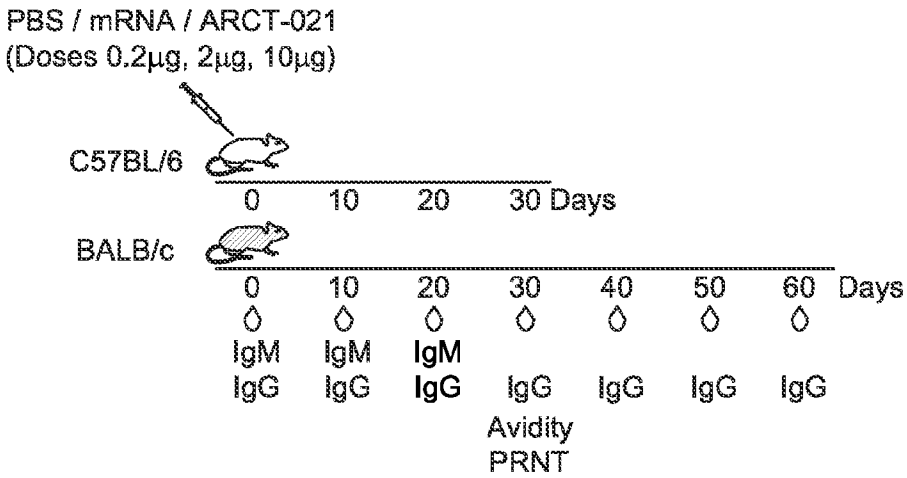


FIG. 4A

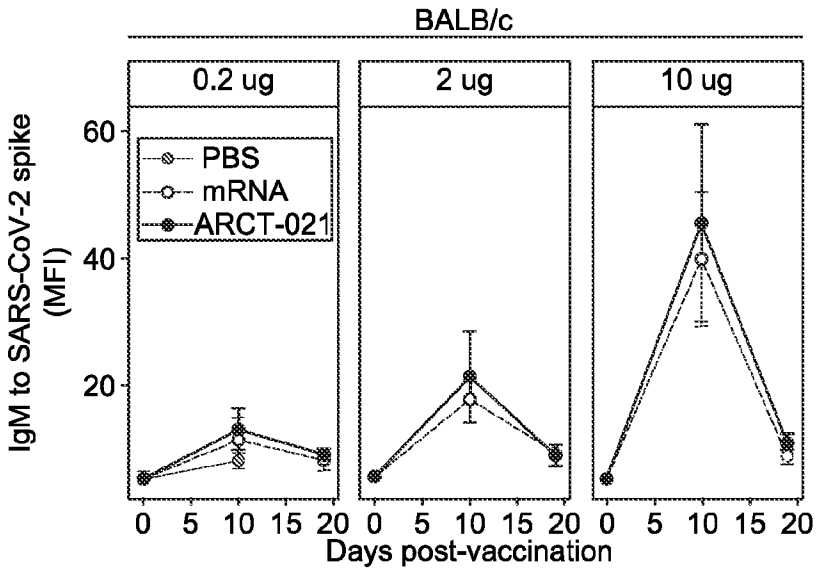


FIG. 4B

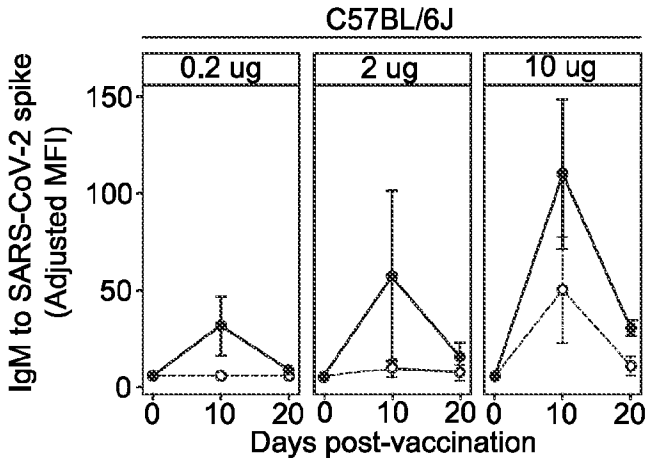


FIG. 4C

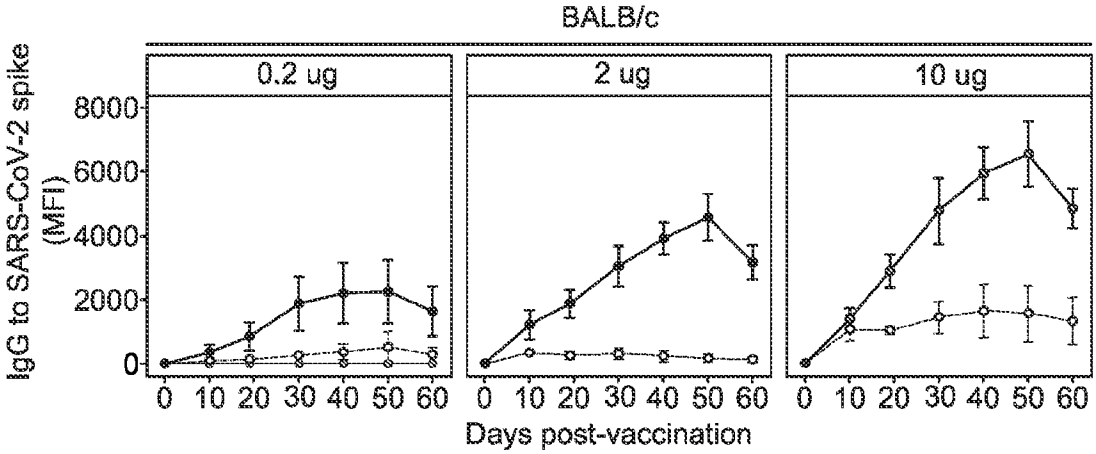

BALB/c
0.2 ug
2 ug
10 ug
IgG to SARS-CoV-2 spike (MFI)
8000
6000
4000
2000
0
0 10 20 30 40 50 60
Days post-vaccination

FIG. 4D

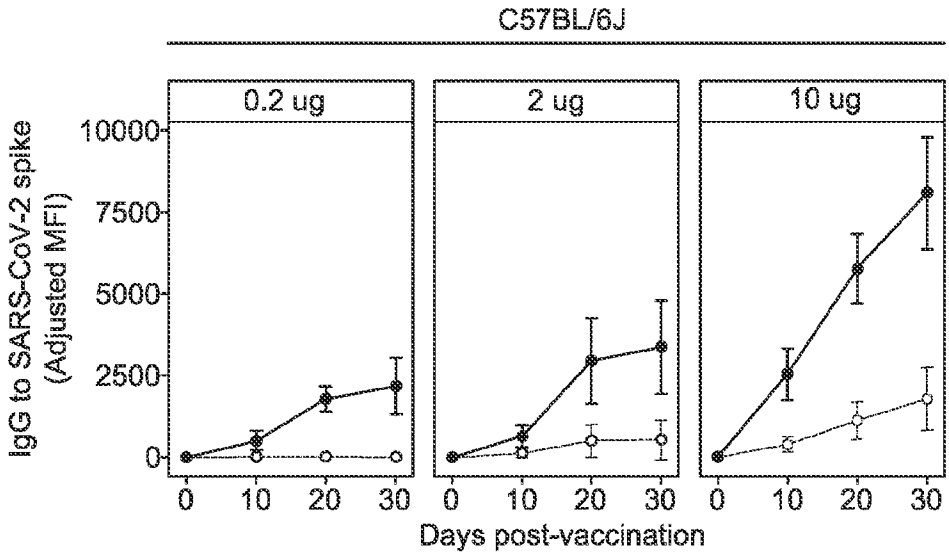

C57BL/6J
0.2 ug
2 ug
10 ug
IgG to SARS-CoV-2 spike (Adjusted MFI)
10000
7500
5000
2500
0
0 10 20 30
Days post-vaccination

FIG. 4E

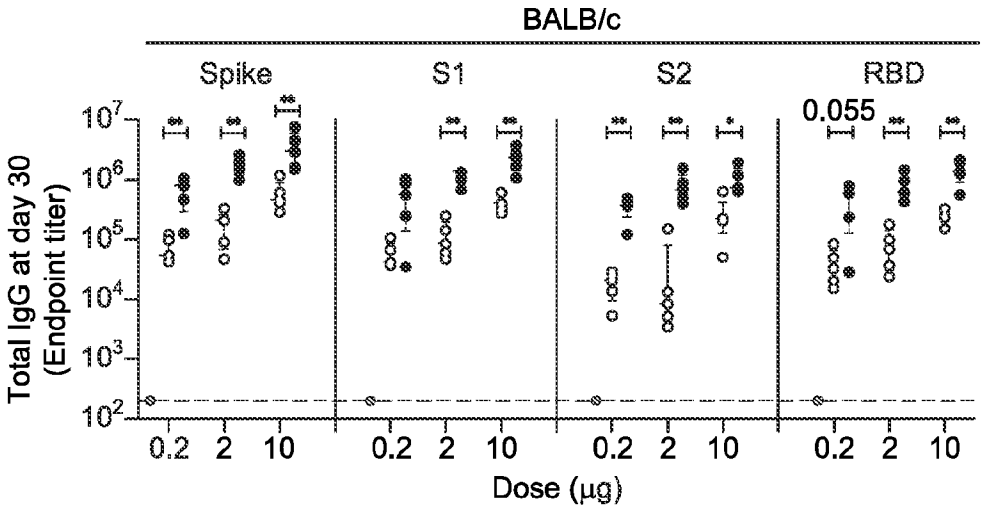

BALB/c
Spike
S1
S2
RBD
0.055
Total IgG at day 30
(Endpoint titer)
10^7
10^6
10^5
10^4
10^3
10^2
0.2
2
10
Dose (µg)

FIG. 4F

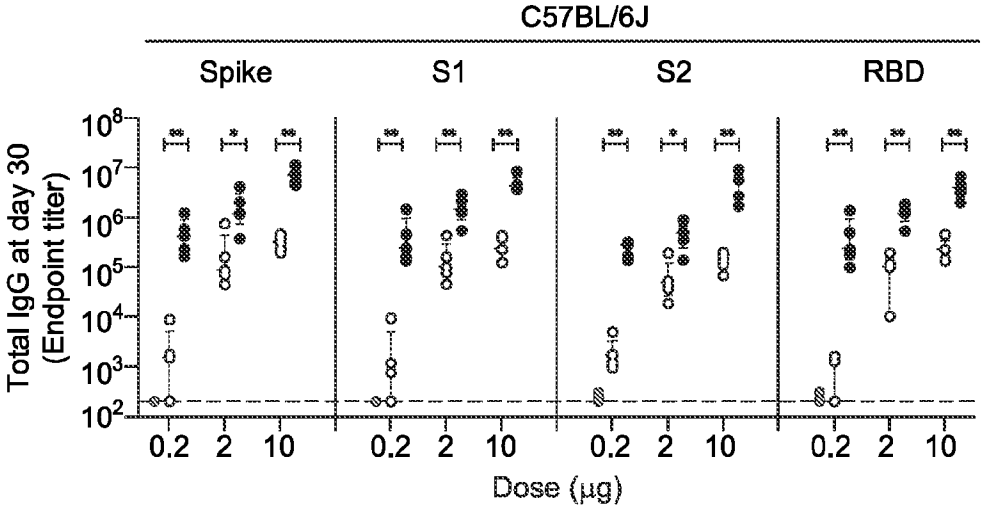

C57BL/6J
Spike
S1
S2
RBD
Total IgG at day 30
(Endpoint titer)
10^8
10^7
10^6
10^5
10^4
10^3
10^2
0.2
2
10
Dose (µg)

FIG. 4G

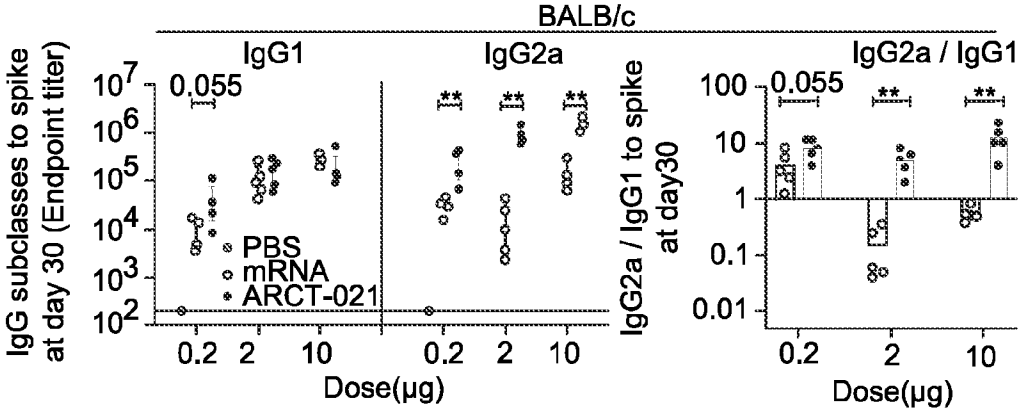


FIG. 5A

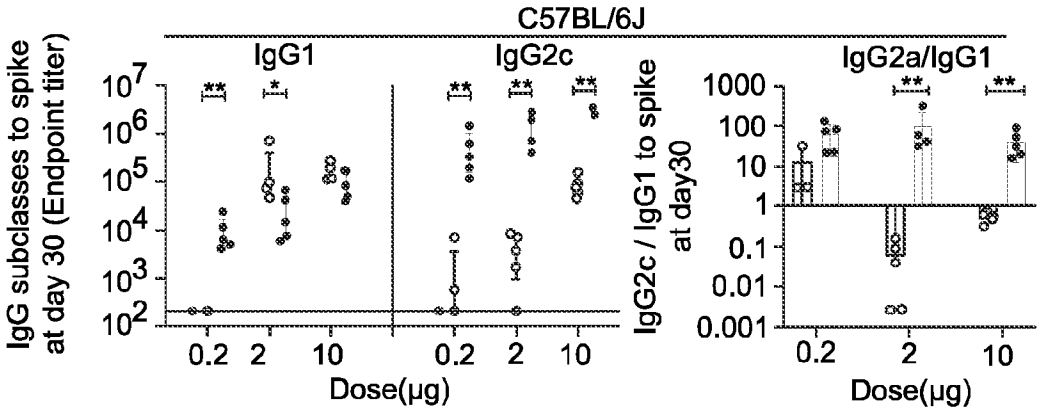


FIG. 5B

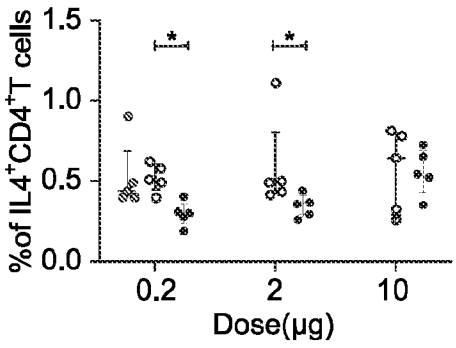


FIG. 5C

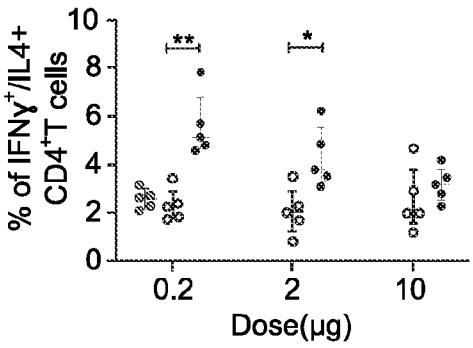


FIG. 5D

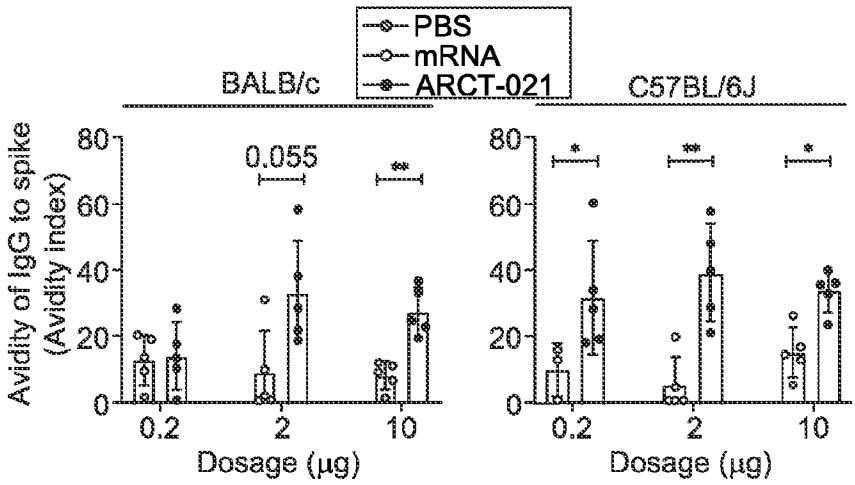


FIG. 6A

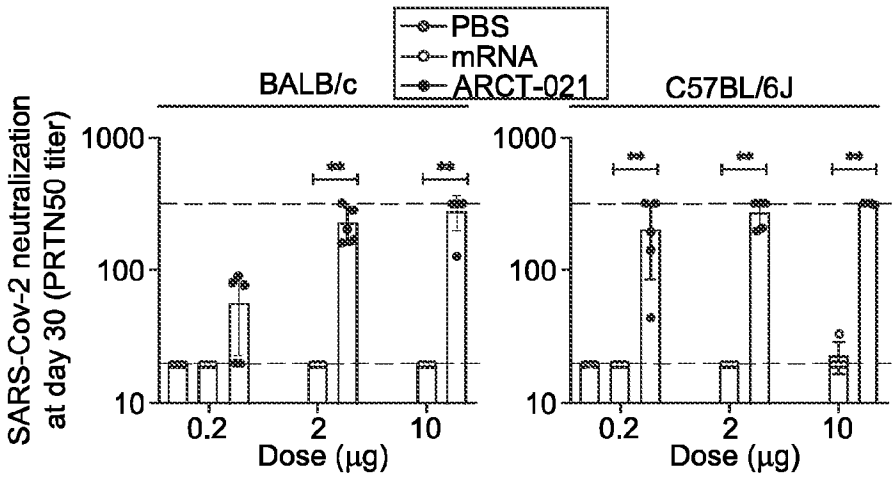


FIG. 6B

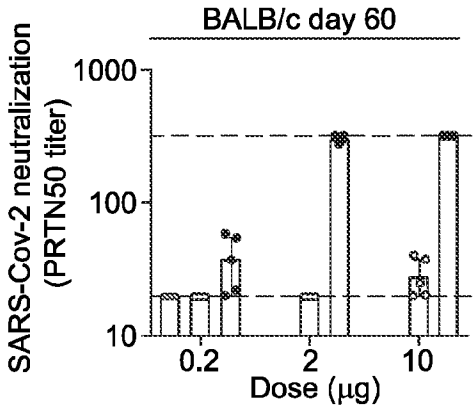


FIG. 6C

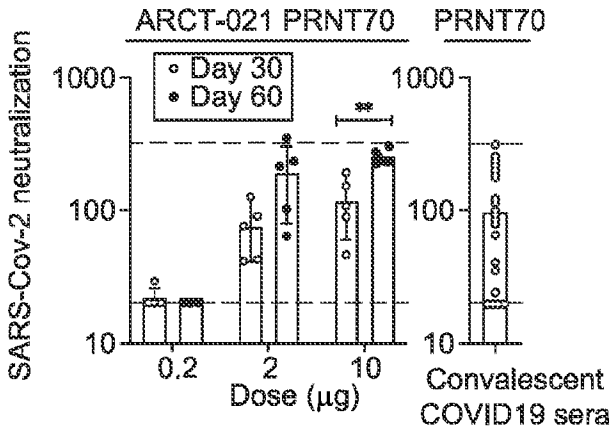

ARCT-021 PRNT70
PRNT70
Day 30
Day 60
SARS-Cov-2 neutralization
1000
100
10
**
0.2
2
10
Dose (µg)
Convalescent
COVID19 sera

FIG. 6D

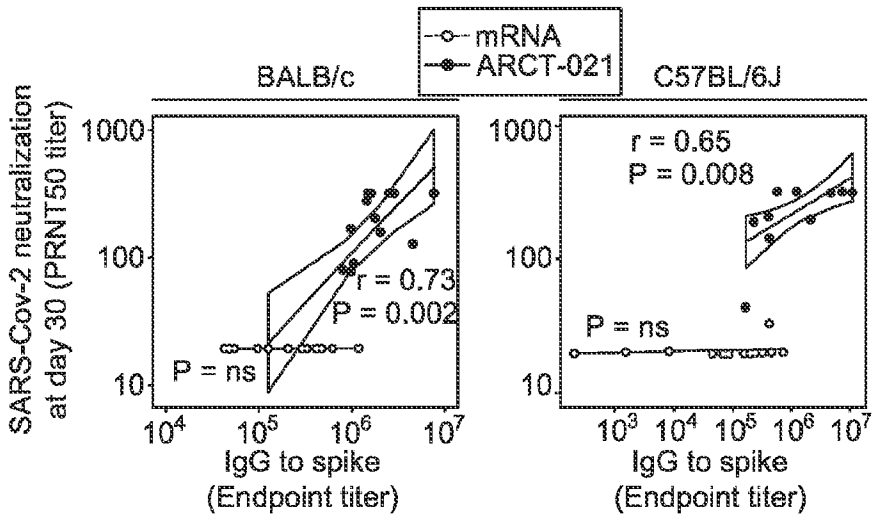

mRNA
ARCT-021
BALB/c
C57BL/6J
SARS-Cov-2 neutralization
at day 30 (PRNT50 titer)
1000
100
10
r = 0.73
P = 0.002
P = ns
r = 0.65
P = 0.008
P = ns
IgG to spike
(Endpoint titer)
IgG to spike
(Endpoint titer)

FIG. 6E

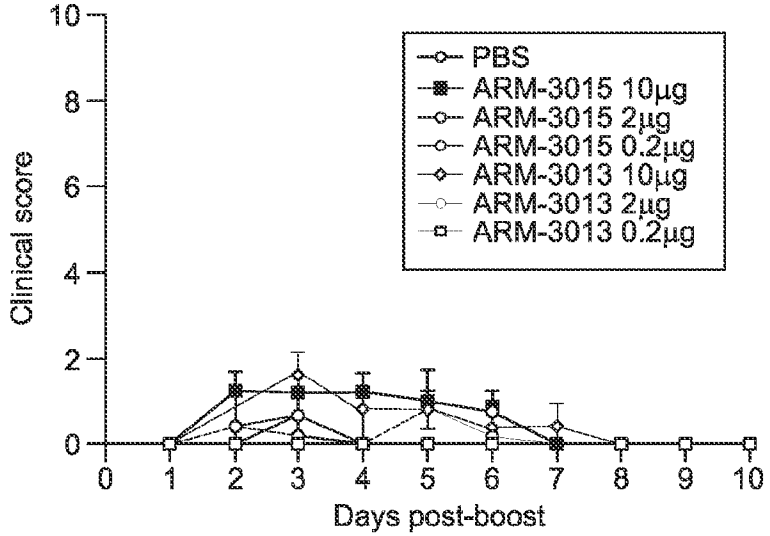

Clinical score
Days post-boost
PBS
ARM-3015 10µg
ARM-3015 2µg
ARM-3015 0.2µg
ARM-3013 10µg
ARM-3013 2µg
ARM-3013 0.2µg

FIG. 7A

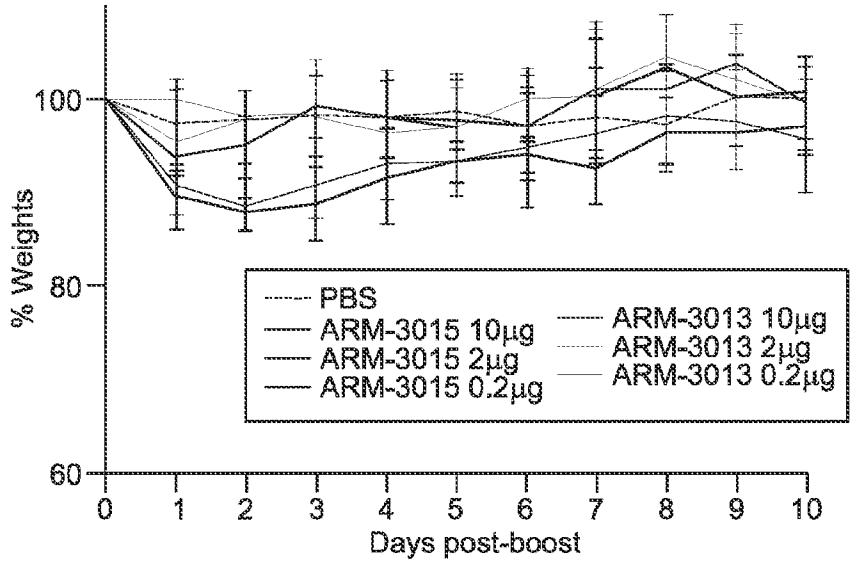

% Weights
Days post-boost
PBS
ARM-3015 10µg
ARM-3015 2µg
ARM-3015 0.2µg
ARM-3013 10µg
ARM-3013 2µg
ARM-3013 0.2µg

FIG. 7B

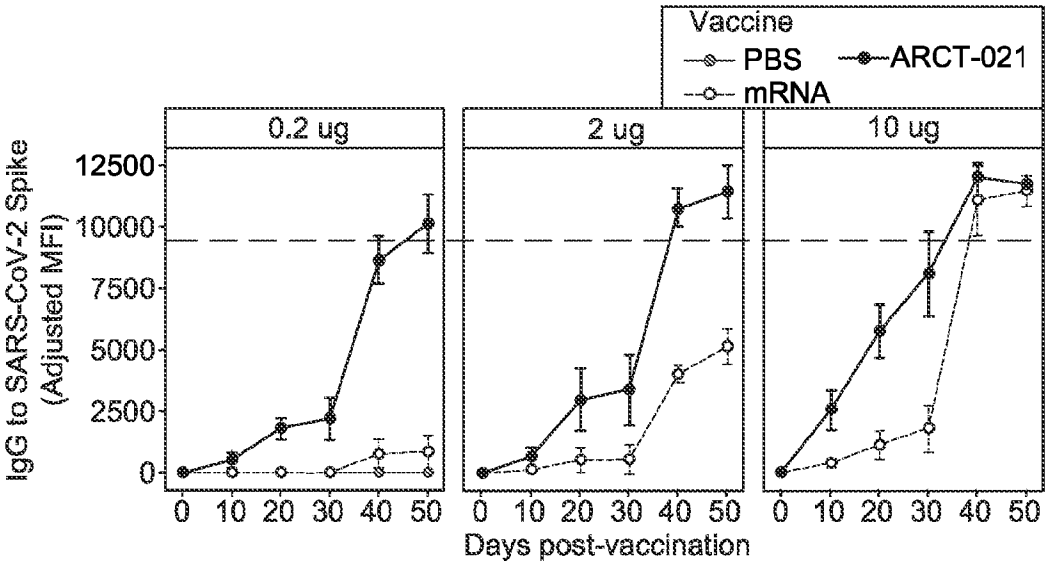


FIG. 7C

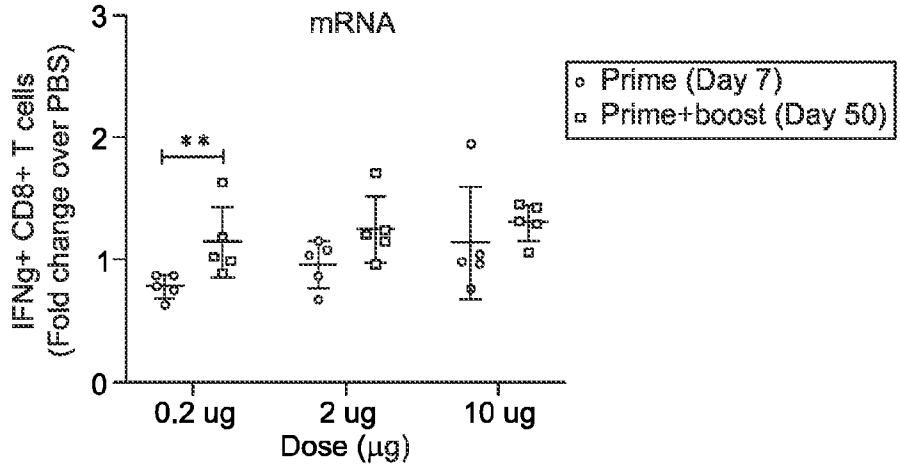


FIG. 7D

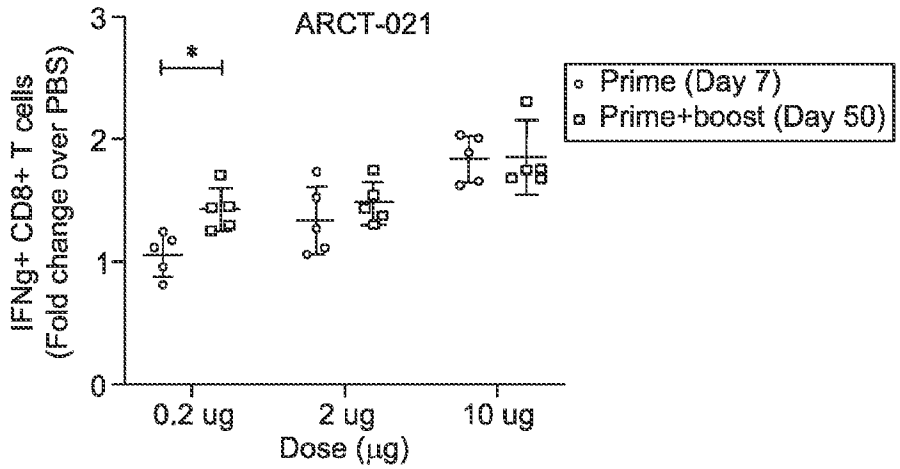


FIG. 7E

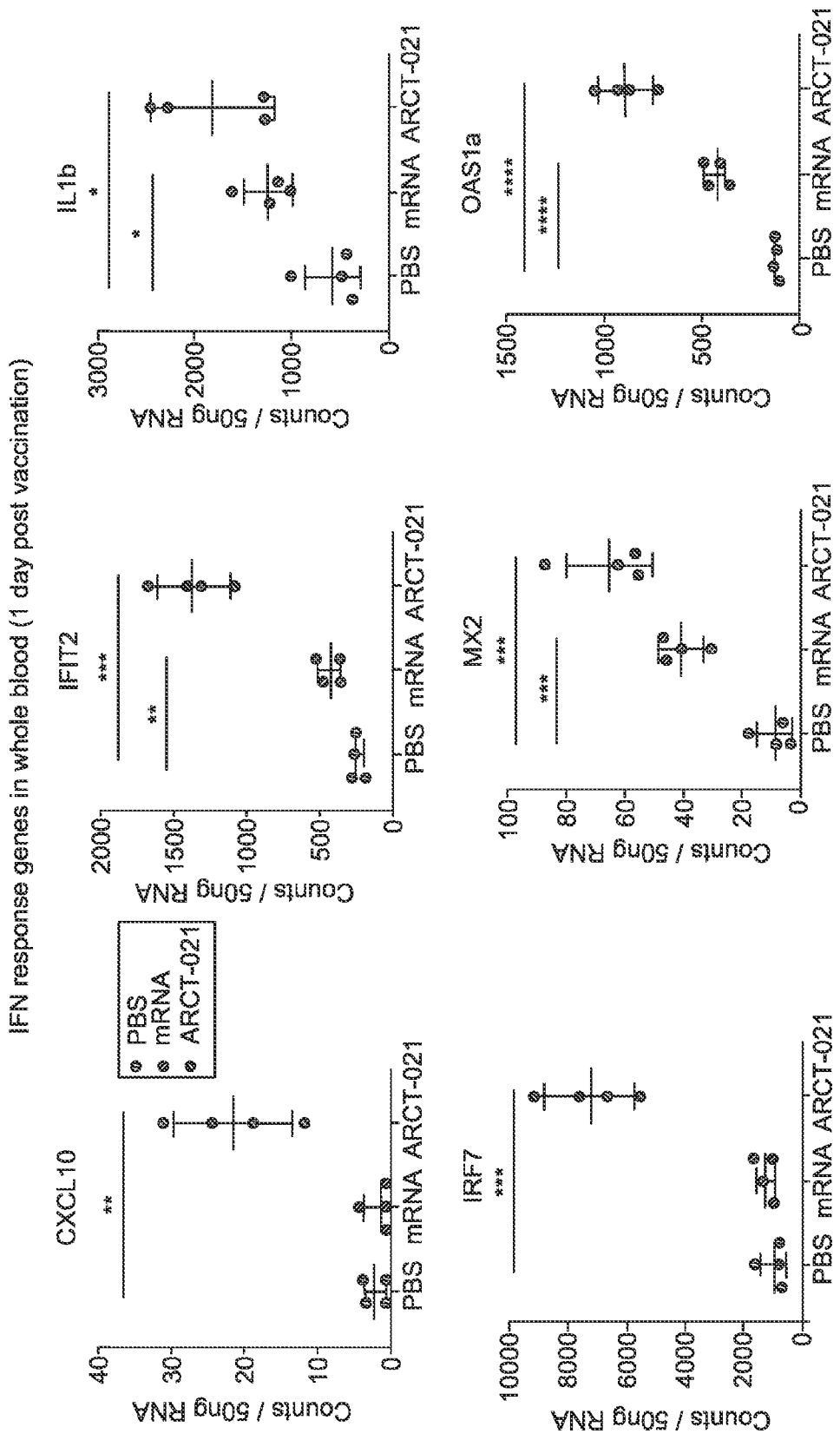

IFN response genes in whole blood (1 day post vaccination)
CXCL10
IFIT2
IL1b
OAS1a
IRF7
MX2
Counts / 50ng RNA
PBS
mRNA ARCT-021
PBS mRNA ARCT-021

FIG. 8A

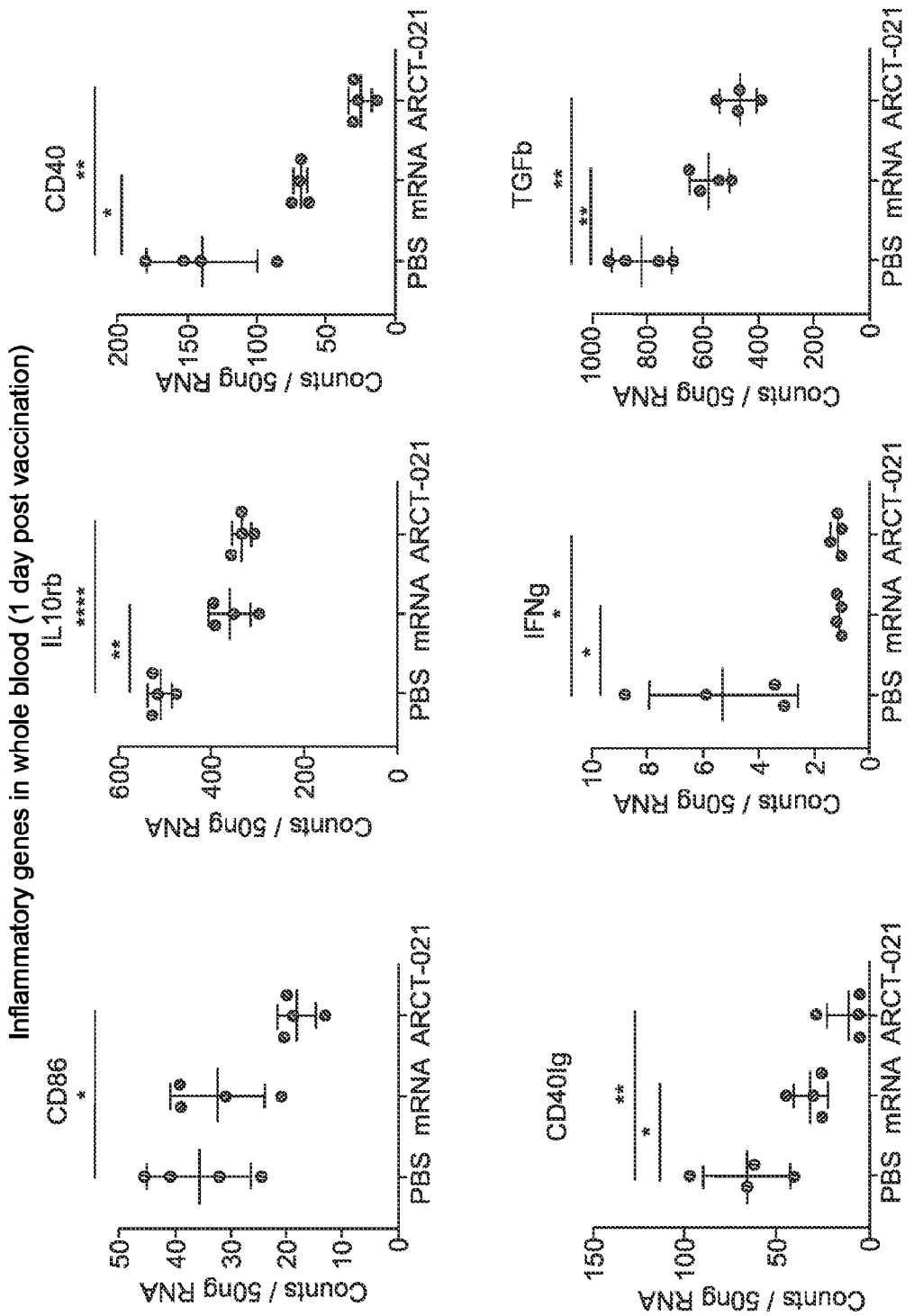

Inflammatory genes in whole blood (1 day post vaccination)
CD86
IL10rb
CD40
IFNg
TGFb
CD40lg
Counts / 50ng RNA
PBS
mRNA ARCT-021

FIG. 8B

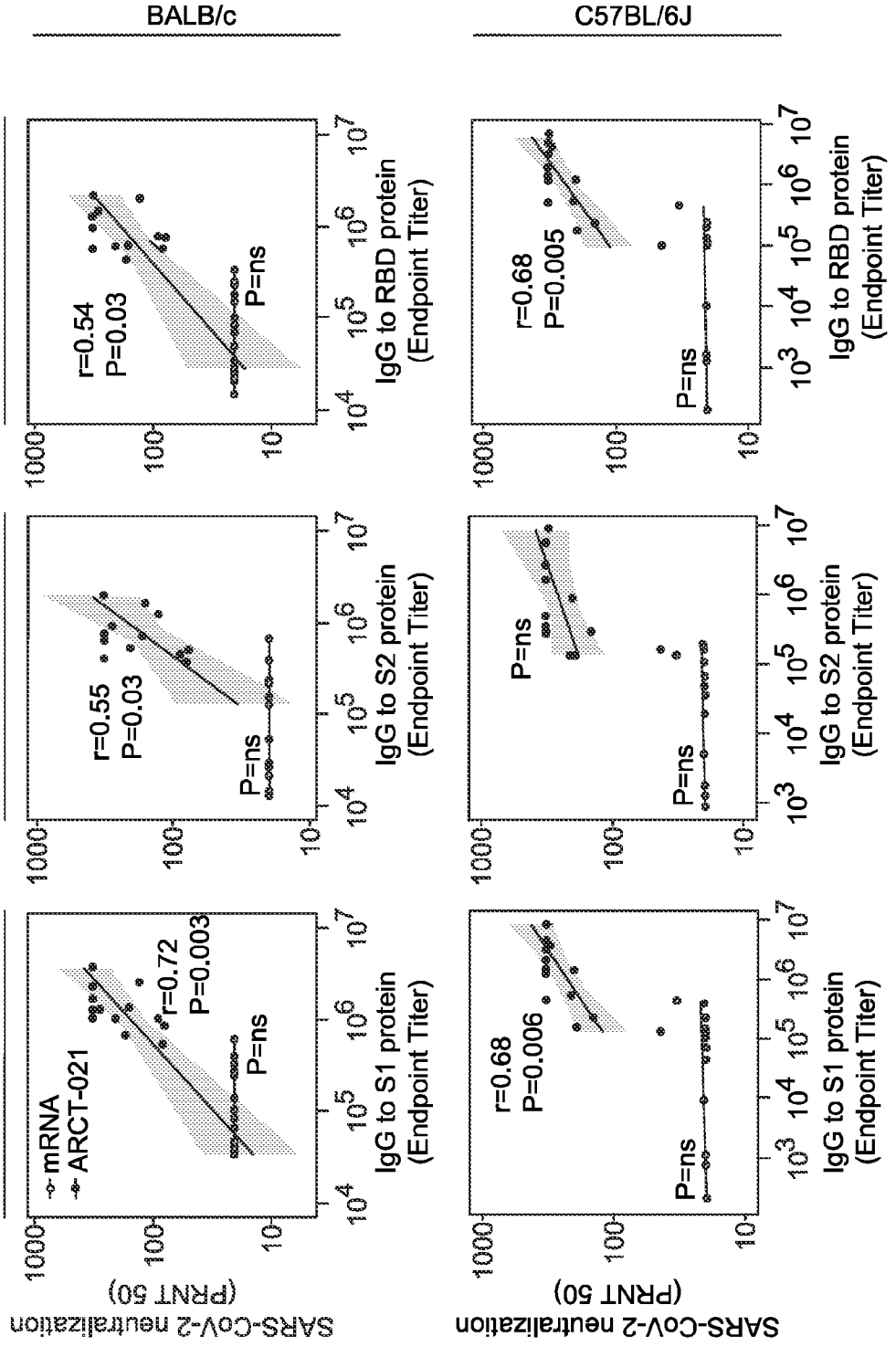

BALB/c
C57BL/6J
S1 Protein
S2 Protein
RBD Protein
mRNA
ARCT-021
r=0.72
P=0.003
P=ns
r=0.68
P=0.006
r=0.55
P=0.03
r=0.54
P=0.03
r=0.68
P=0.005
SARS-CoV-2 neutralization
(PRNT 50)
IgG to S1 protein
(Endpoint Titer)
IgG to S2 protein
(Endpoint Titer)
IgG to RBD protein
(Endpoint Titer)

FIG. 9A

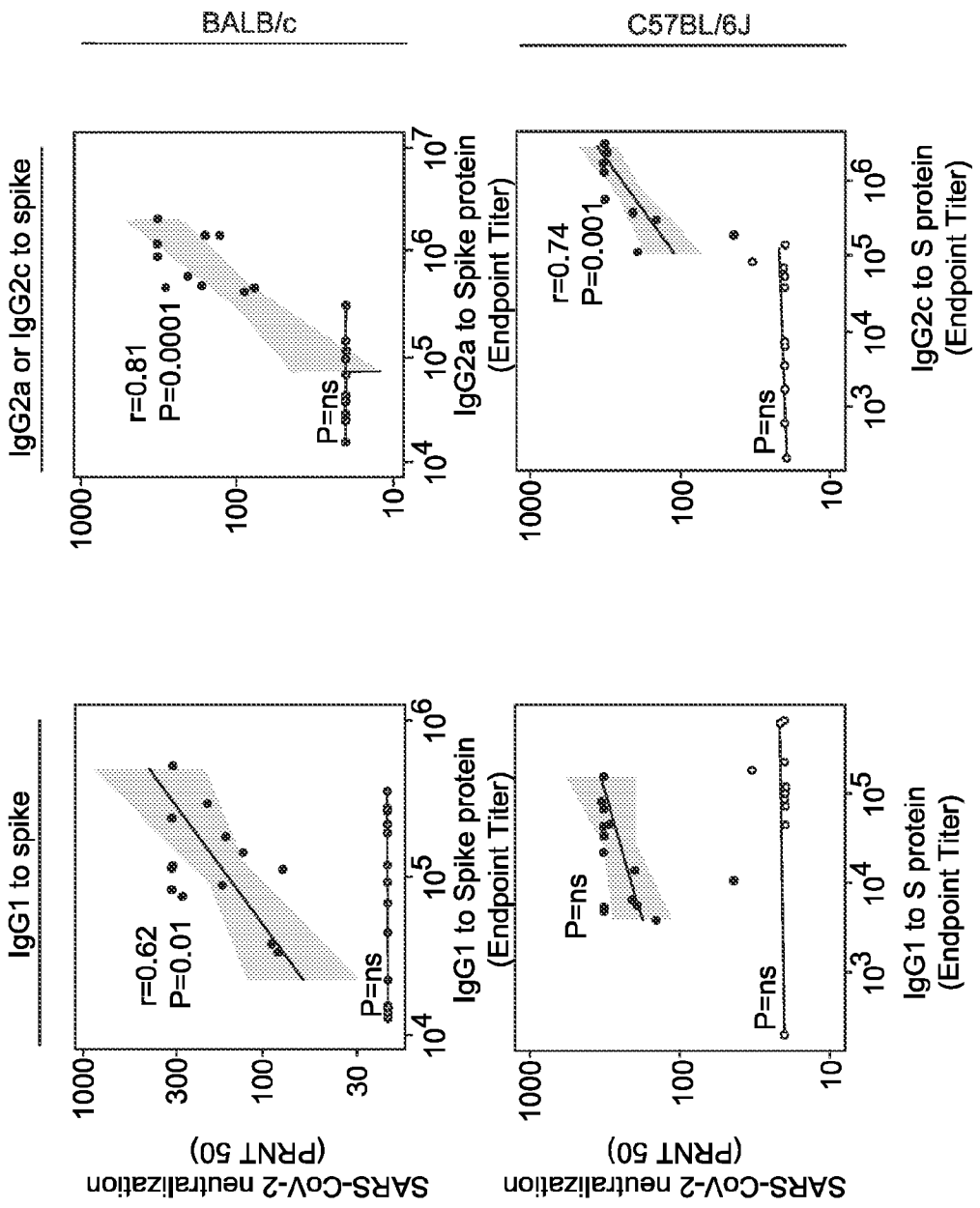

BALB/c
C57BL/6J
IgG1 to spike
IgG2a or IgG2c to spike
SARS-CoV-2 neutralization (PRNT 50)
IgG1 to Spike protein (Endpoint Titer)
IgG2a to Spike protein (Endpoint Titer)
IgG1 to S protein (Endpoint Titer)
IgG2c to S protein (Endpoint Titer)
r=0.62
P=0.01
r=0.81
P=0.0001
r=0.74
P=0.001
P=ns

FIG. 9B

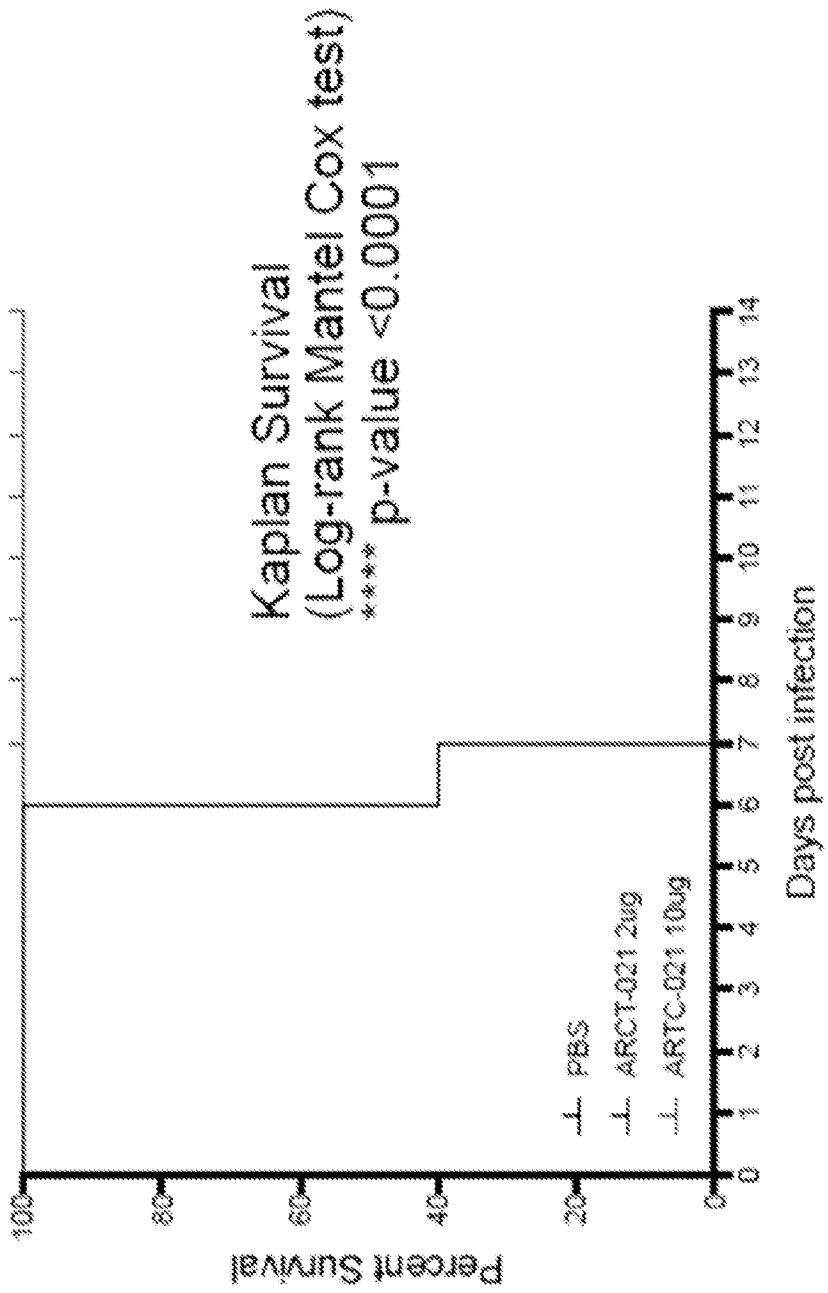

Kaplan Survival
(Log-rank Mantel Cox test)
**** p-value <0.0001
Percent Survival
100
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days post infection
PBS
ARCT-021 2mg
ARTC-021 10mg

FIG. 10

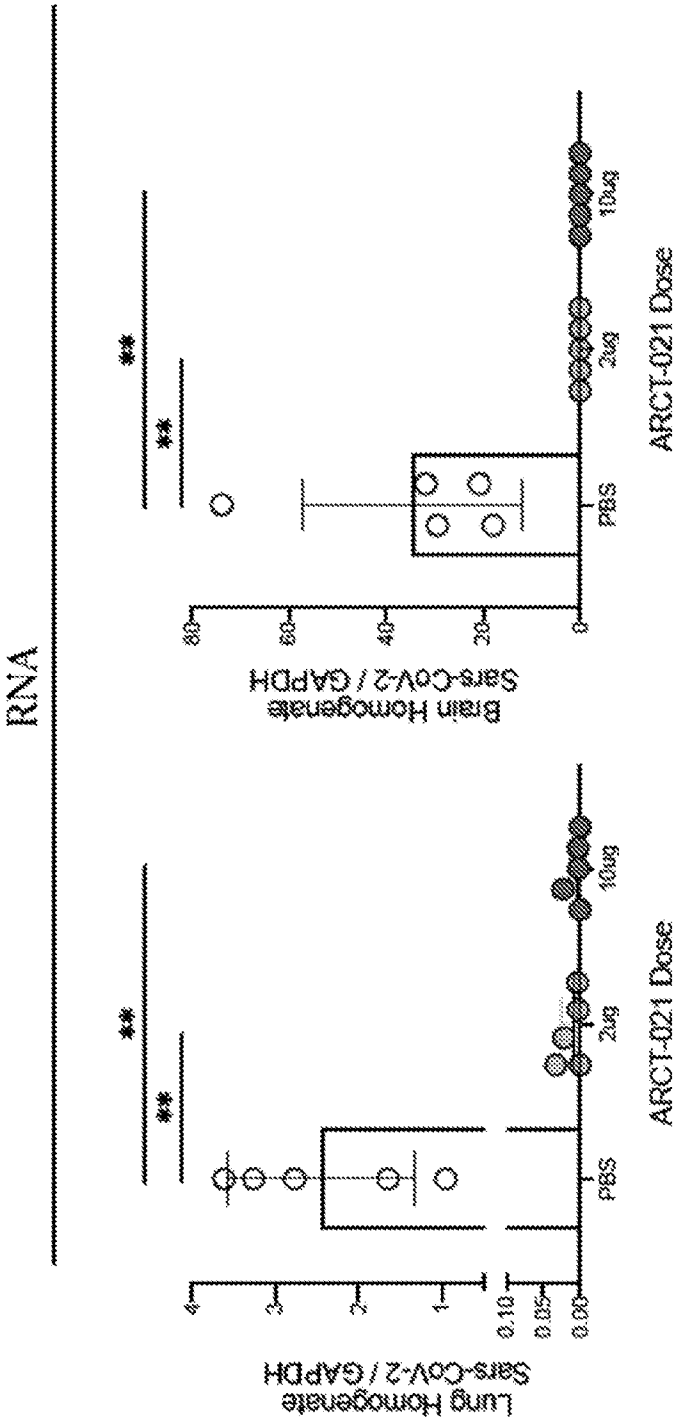

RNA
Lung Homogenate
Sars-CoV-2 / GAPDH
0.00
0.05
0.10
1
2
3
4
PBS
2ug
10ug
ARCT-021 Dose
**
**
Brain Homogenate
Sars-CoV-2 / GAPDH
0
20
40
60
80
PBS
2ug
10ug
ARCT-021 Dose
**
**

FIG. 11

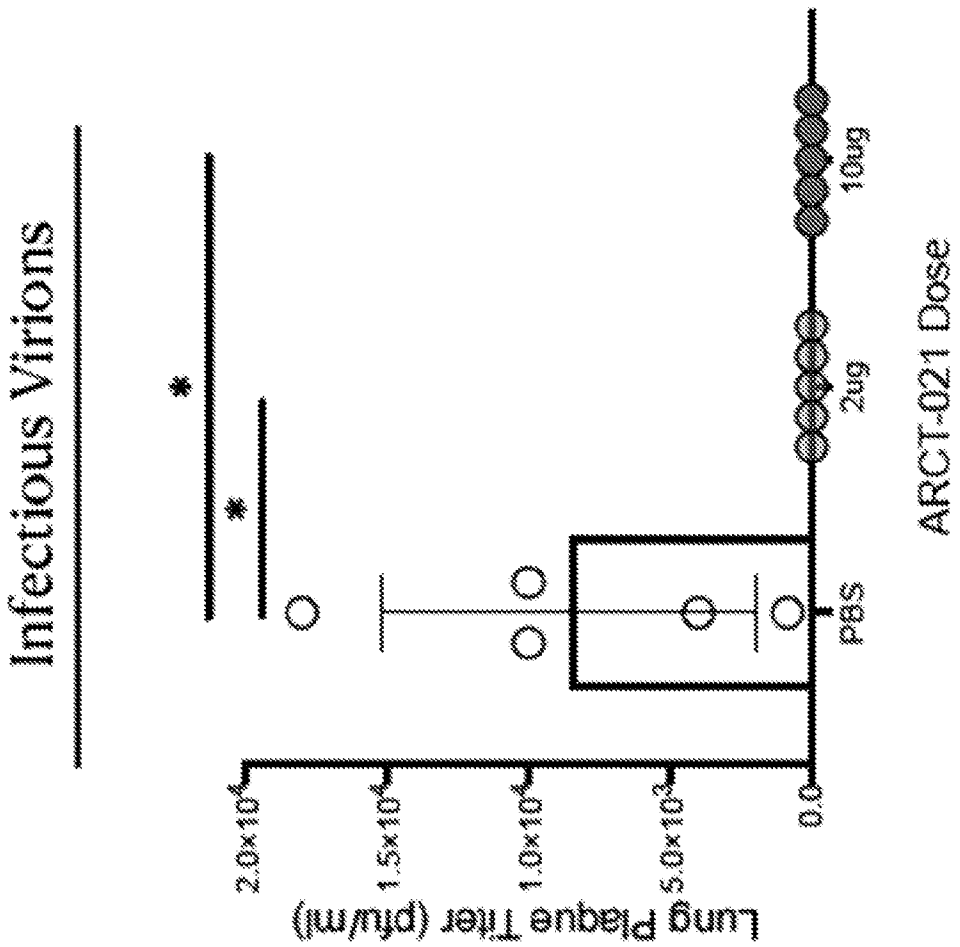

Infectious Virions
Lung Plaque Titer (pfu/ml)
2.0x10^4
1.5x10^4
1.0x10^4
5.0x10^3
0.0
PBS
2ug
10ug
ARCT-021 Dose
*
*

FIG. 12

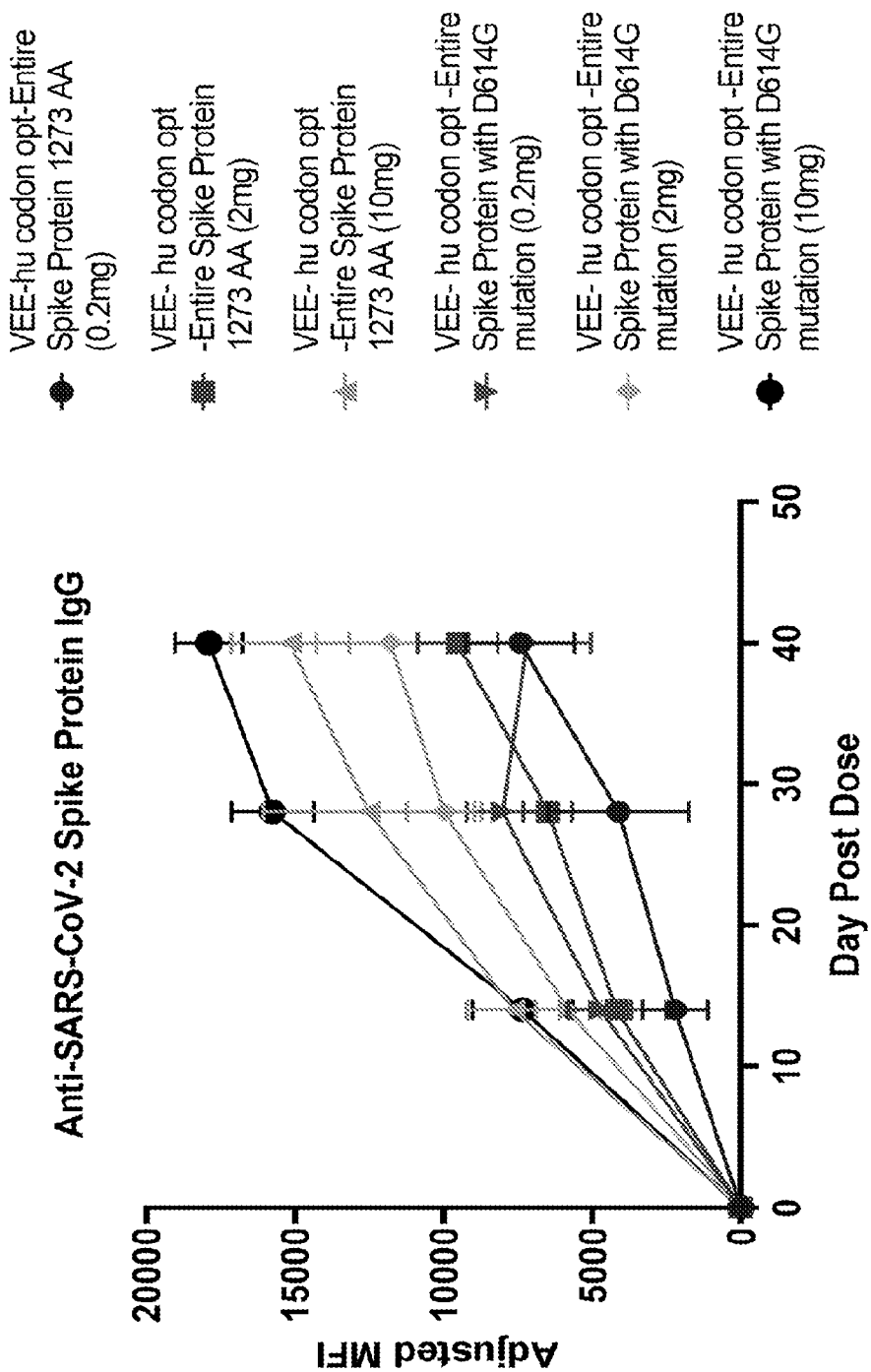

Anti-SARS-CoV-2 Spike Protein IgG
Adjusted MFI
20000
15000
10000
5000
0
0
10
20
30
40
50
Day Post Dose
VEE-hu codon opt-Entire Spike Protein 1273 AA (0.2mg)
VEE- hu codon opt -Entire Spike Protein 1273 AA (2mg)
VEE- hu codon opt -Entire Spike Protein 1273 AA (10mg)
VEE- hu codon opt -Entire Spike Protein with D614G mutation (0.2mg)
VEE- hu codon opt -Entire Spike Protein with D614G mutation (2mg)
VEE- hu codon opt -Entire Spike Protein with D614G mutation (10mg)

FIG. 13

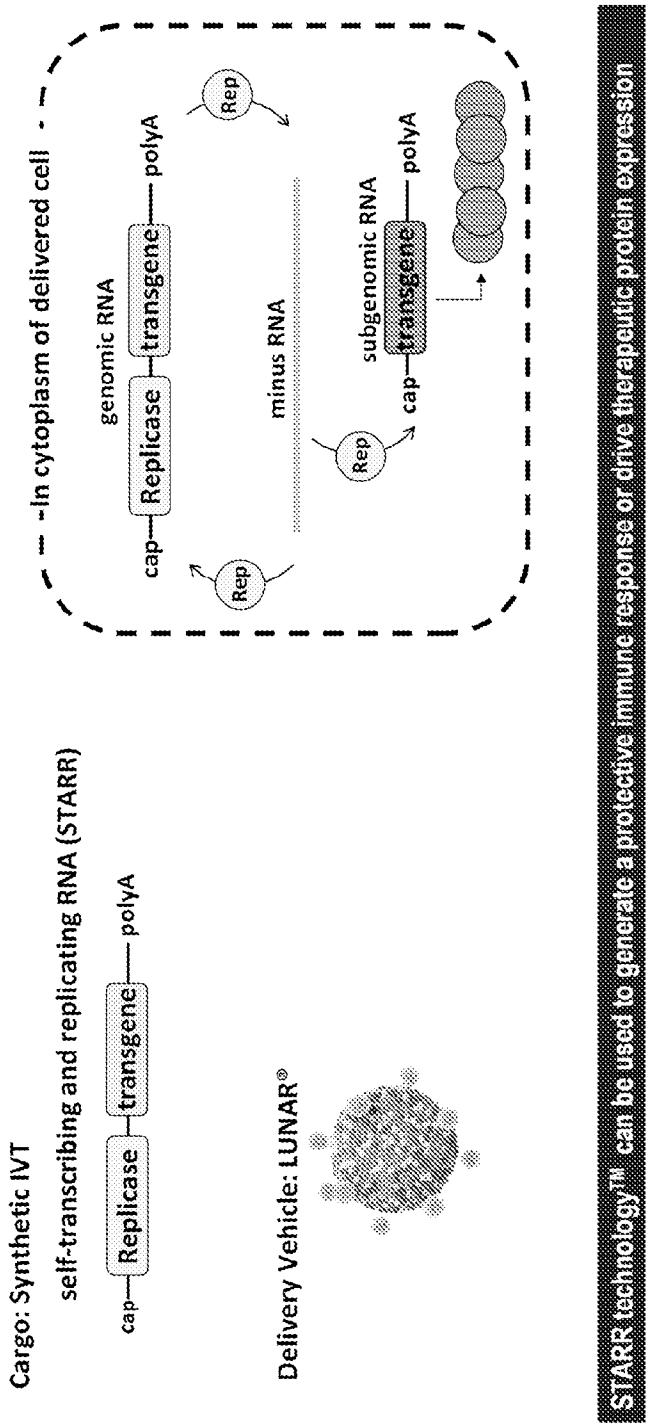

[STARR™] self-replicating RNA
Cargo: Synthetic IVT
self-transcribing and replicating RNA (STARR)
cap
Replicase
transgene
polyA
Delivery Vehicle: LUNAR®
-In cytoplasm of delivered cell -
genomic RNA
cap
Replicase
transgene
polyA
Rep
Rep
minus RNA
Rep
subgenomic RNA
cap
transgene
polyA
STARR technology™ can be used to generate a protective immune response or drive therapeutic protein expression

FIG. 14

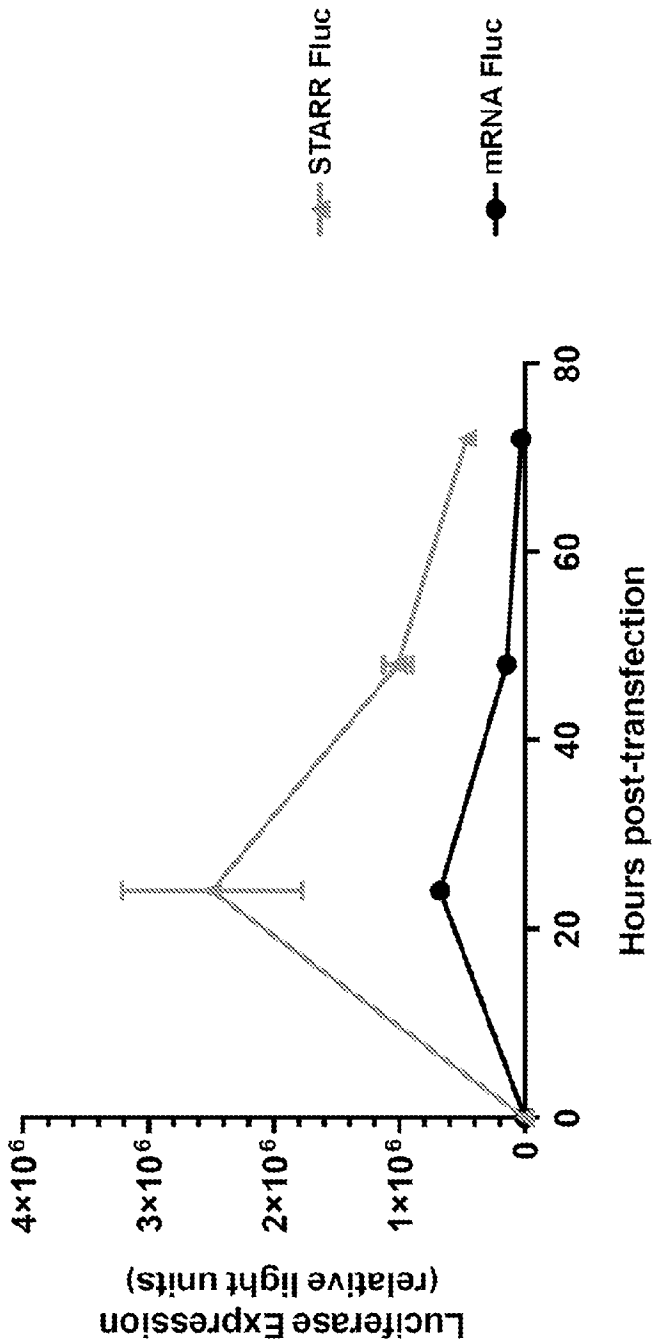

STARR Fluc
mRNA Fluc
Luciferase Expression
(relative light units)
4×10^6
3×10^6
2×10^6
1×10^6
0
0
20
40
60
80
Hours post-transfection

FIG. 15A

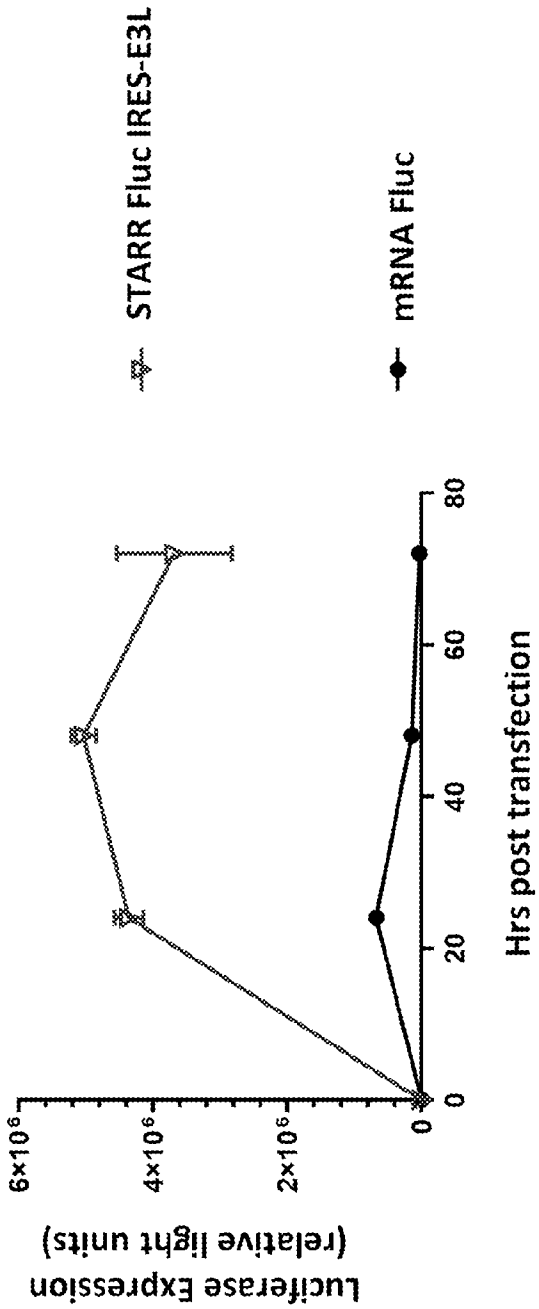

STARR Fluc IRES-E3L
mRNA Fluc
Luciferase Expression
(relative light units)
6×10^6
4×10^6
2×10^6
0
0
20
40
60
80
Hrs post transfection

FIG. 15B

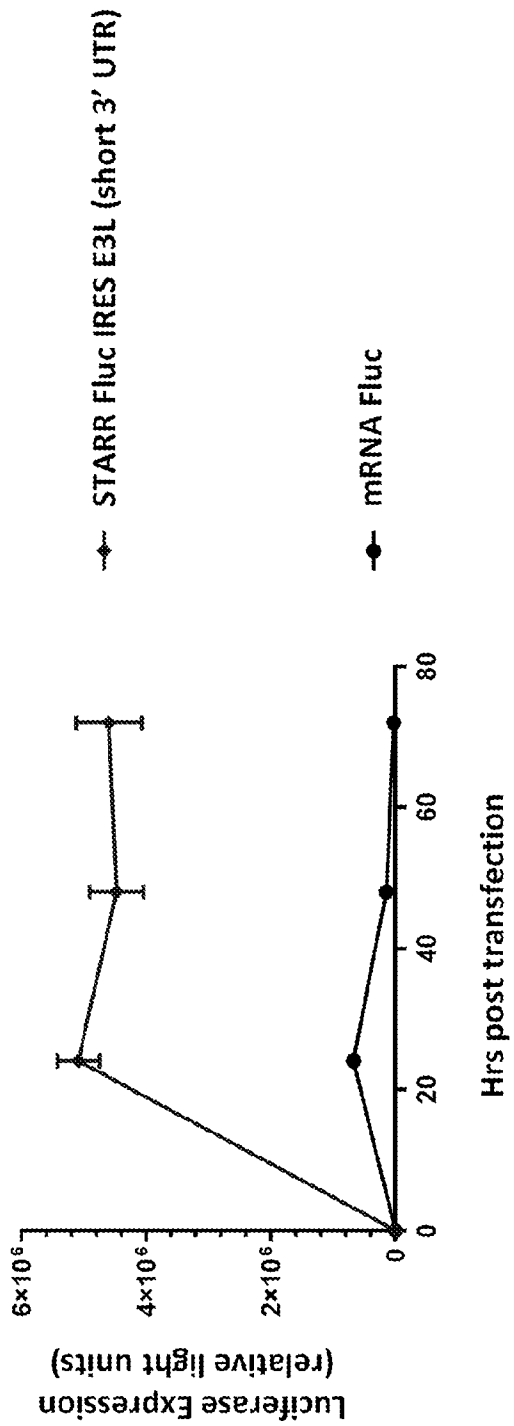

STARR Fluc IRES E3L (short 3' UTR)
mRNA Fluc
Luciferase Expression
(relative light units)
6×10^6
4×10^6
2×10^6
0
0
20
40
60
80
Hrs post transfection

FIG. 15C

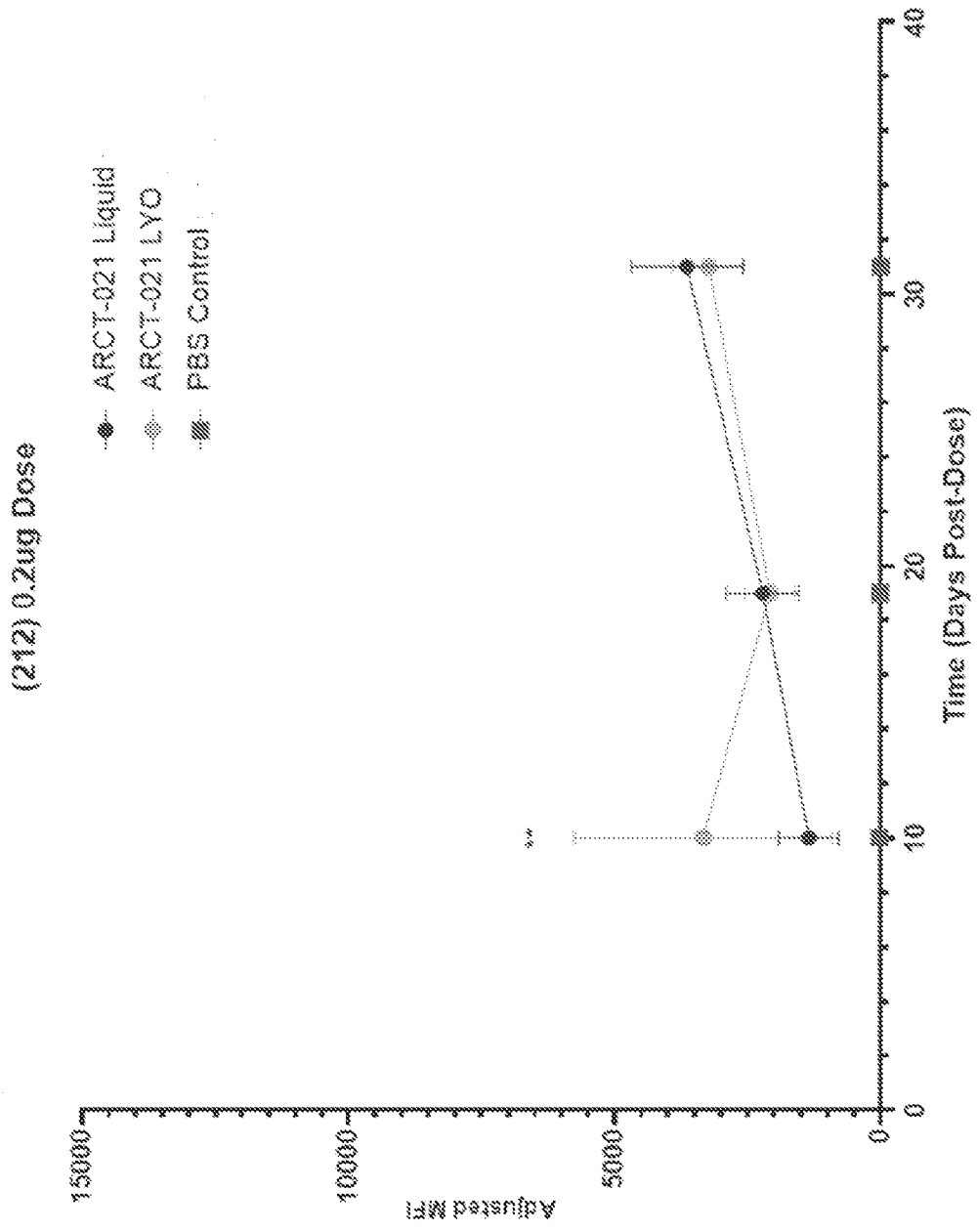

(212) 0.2ug Dose
ARCT-021 Liquid
ARCT-021 LYO
PBS Control
Adjusted MFI
15000
10000
5000
0
0
10
20
30
40
Time (Days Post-Dose)

FIG. 16A

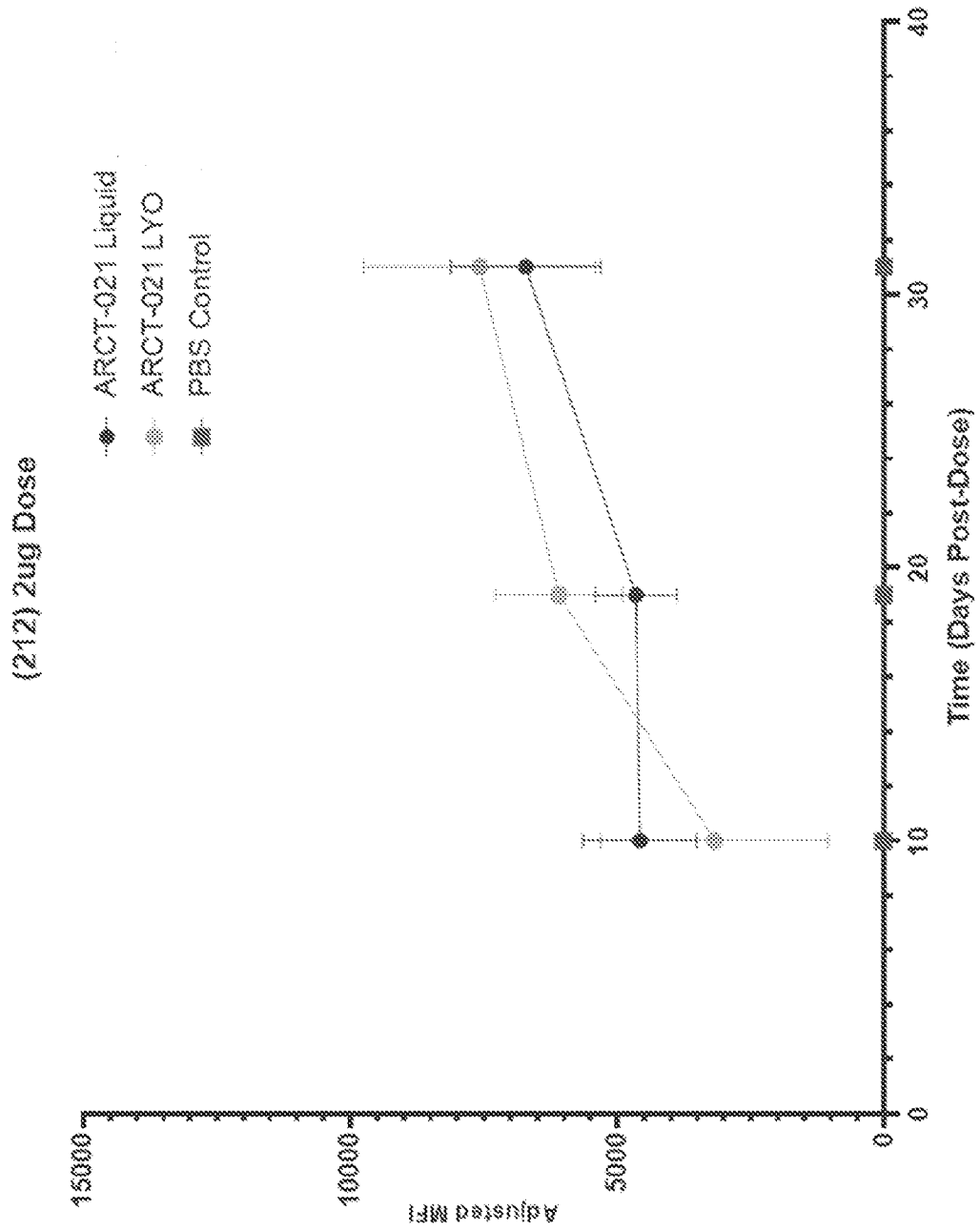

(212) 2ug Dose
ARCT-021 Liquid
ARCT-021 LYO
PBS Control
Adjusted MFI
15000
10000
5000
0
0
10
20
30
40
Time (Days Post-Dose)

FIG. 16B

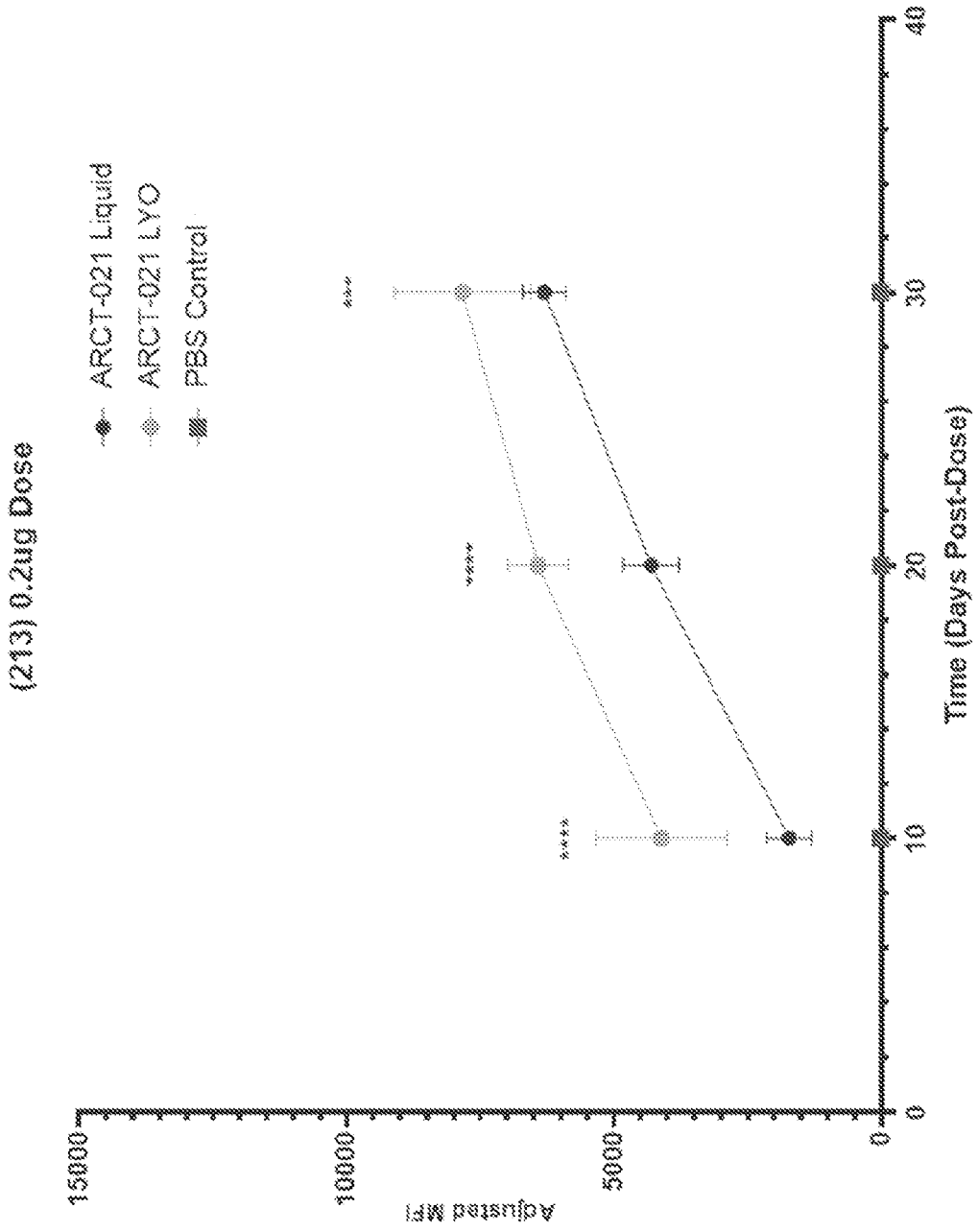

(213) 0.2ug Dose
ARCT-021 Liquid
ARCT-021 LYO
PBS Control
Adjusted MFI
15000
10000
5000
0
0
10
20
30
40
Time (Days Post-Dose)
****
****
***

FIG. 16C

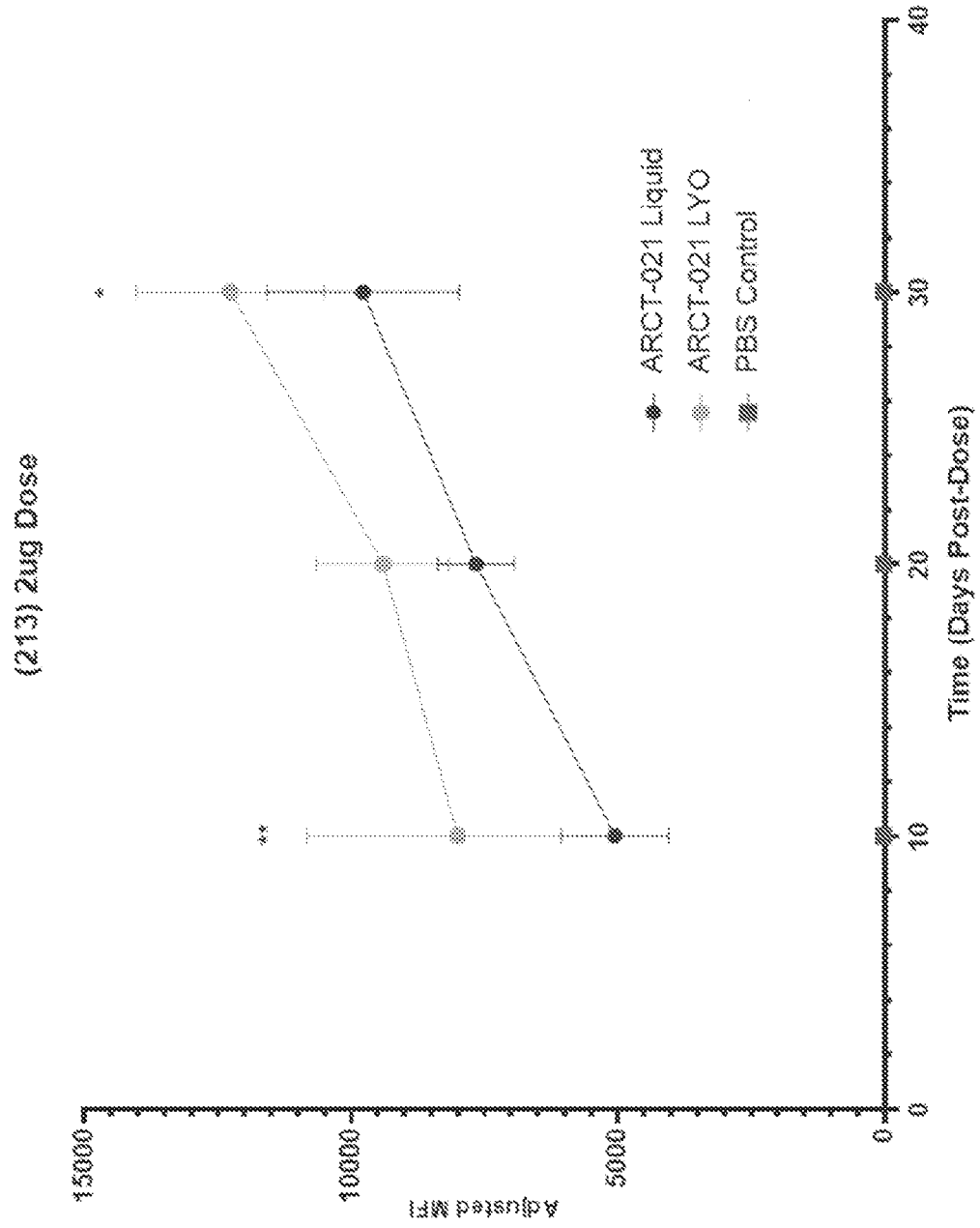

(213) 2ug Dose
ARCT-021 Liquid
ARCT-021 LYO
PBS Control
Adjusted MFI
Time (Days Post-Dose)
15000
10000
5000
0
0
10
20
30
40
*
**

FIG. 16D

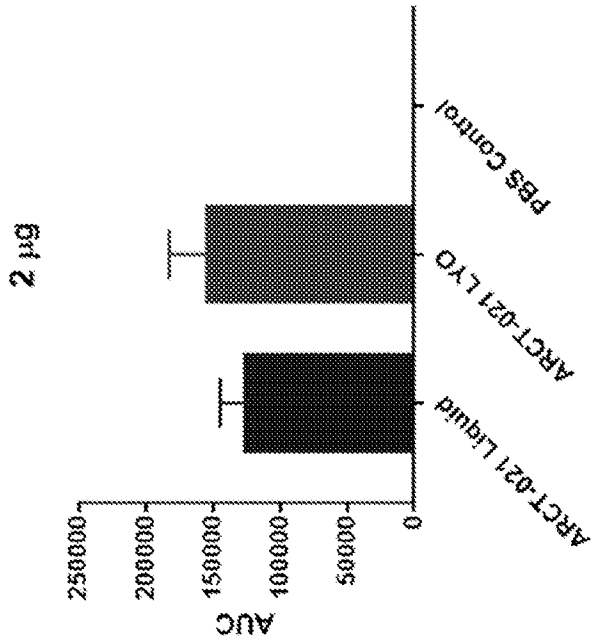


FIG. 17B

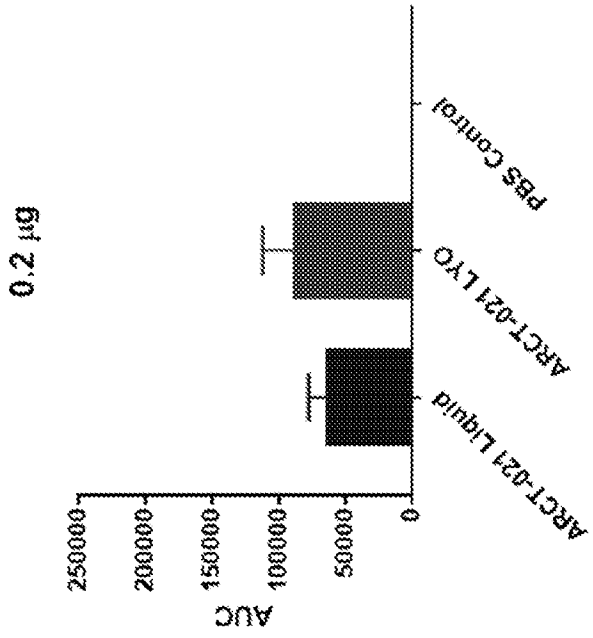


FIG. 17A

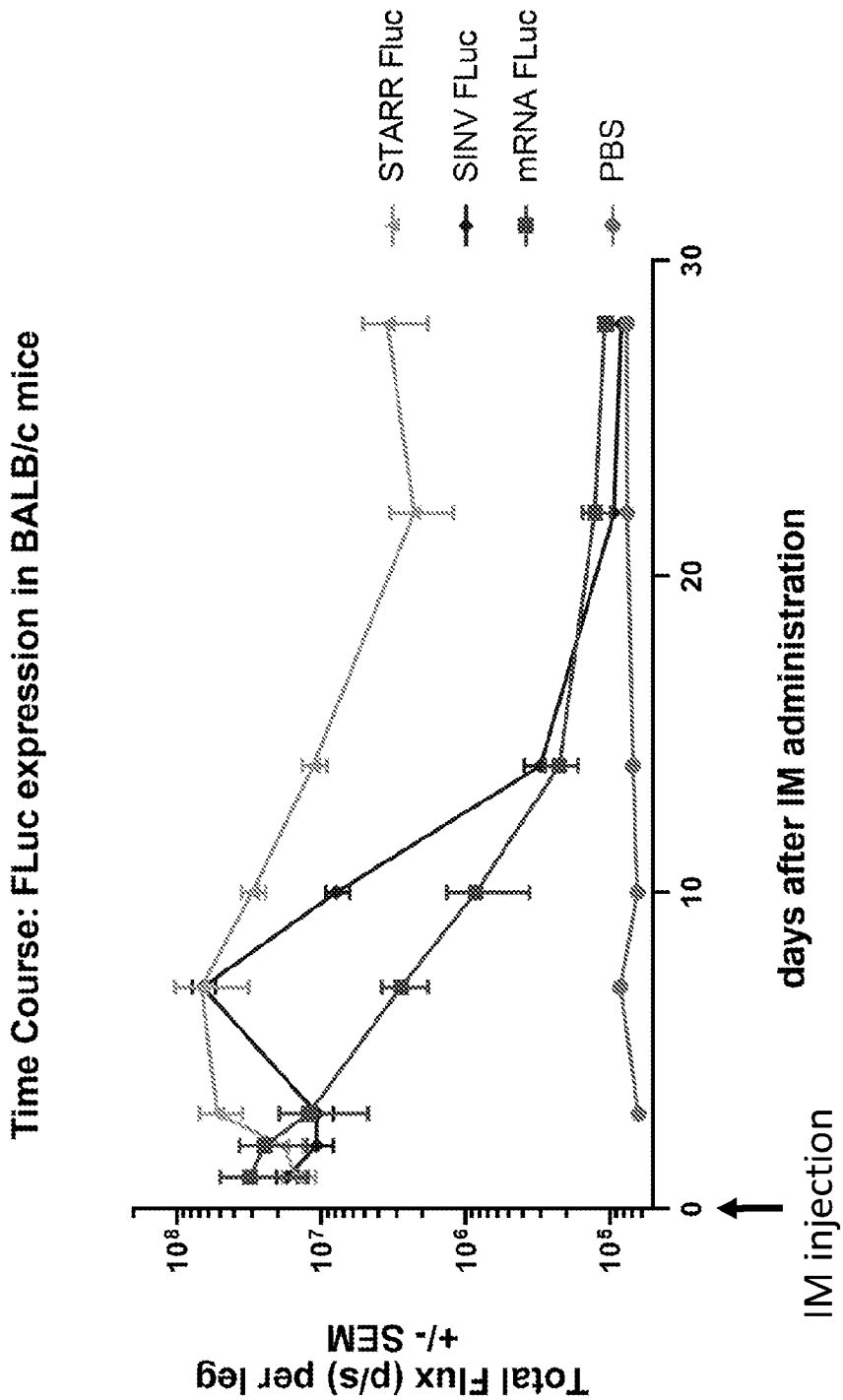

Time Course: FLuc expression in BALB/c mice
STARR Fluc
SINV FLuc
mRNA FLuc
PBS
Total Flux (p/s) per leg
+/- SEM
IM injection
days after IM administration

FIG. 18A

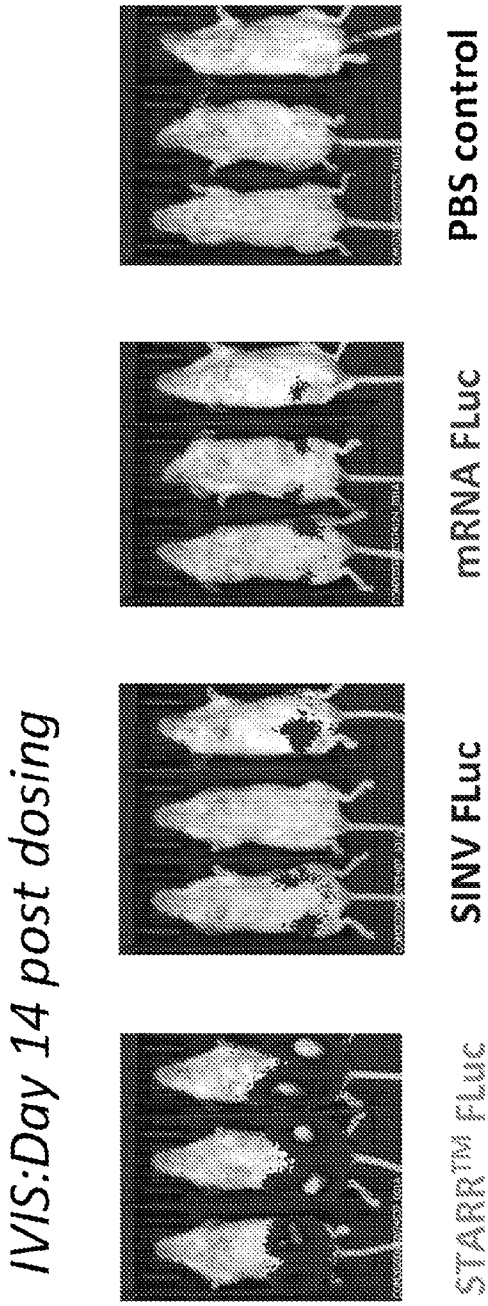

IVIS:Day 14 post dosing
STARR™ FLuc
SINV FLuc
mRNA FLuc
PBS control

FIG. 18B

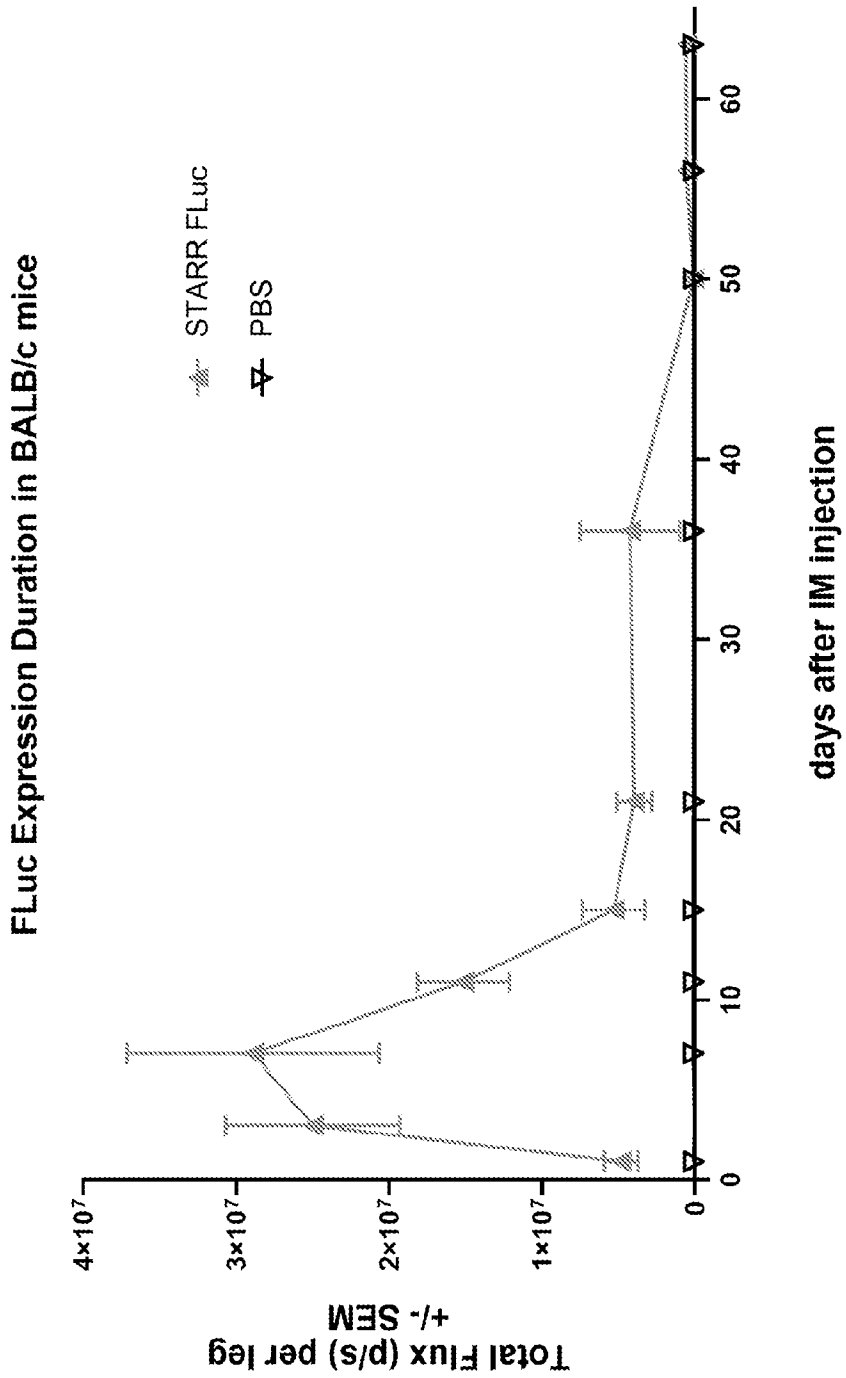

FLuc Expression Duration in BALB/c mice
STARR FLuc
PBS
Total Flux (p/s) per leg
+/- SEM
4×10^7
3×10^7
2×10^7
1×10^7
0
0
10
20
30
40
50
60
days after IM injection

FIG. 18C

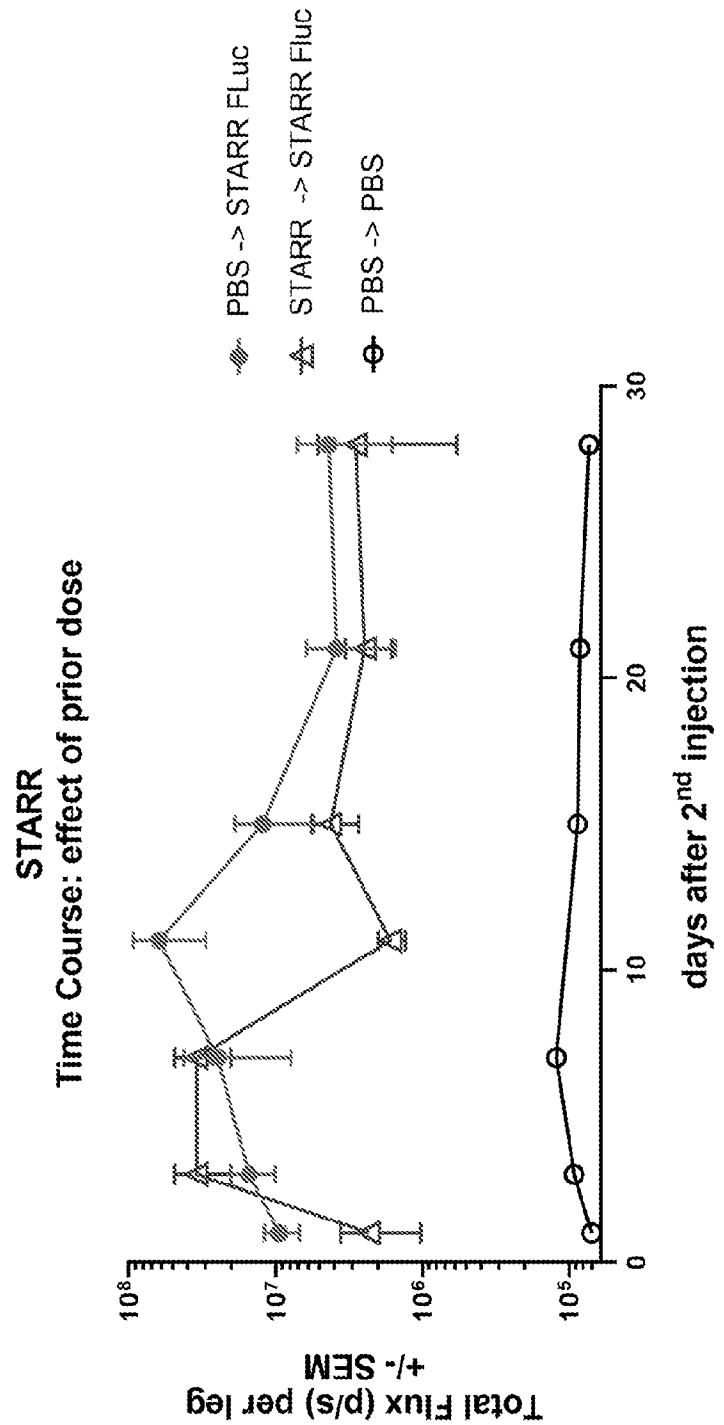

STARR
Time Course: effect of prior dose
PBS -> STARR FLuc
STARR -> STARR Fluc
PBS -> PBS
Total Flux (p/s) per leg
+/- SEM
10^8
10^7
10^6
10^5
0
10
20
30
days after 2nd injection

FIG. 18D

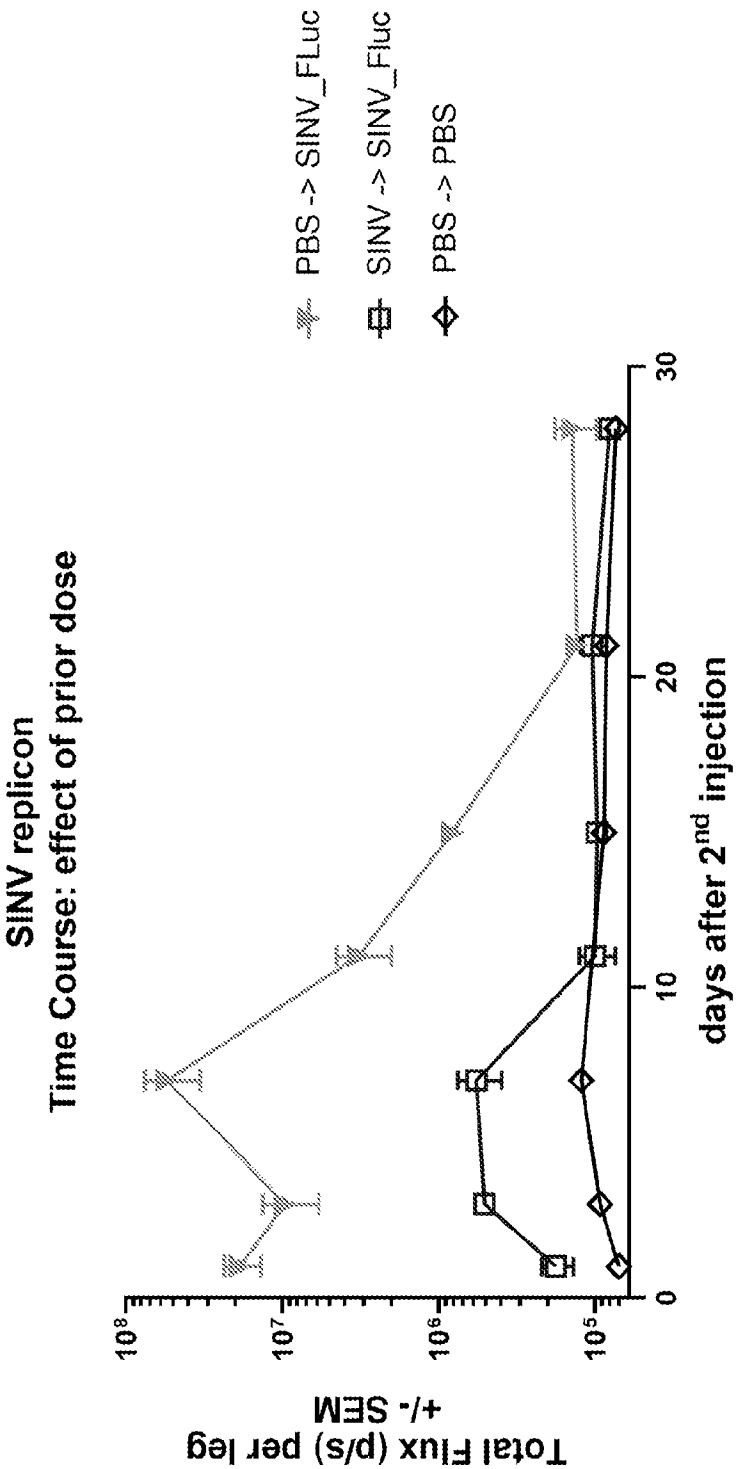


FIG. 18D (continued)

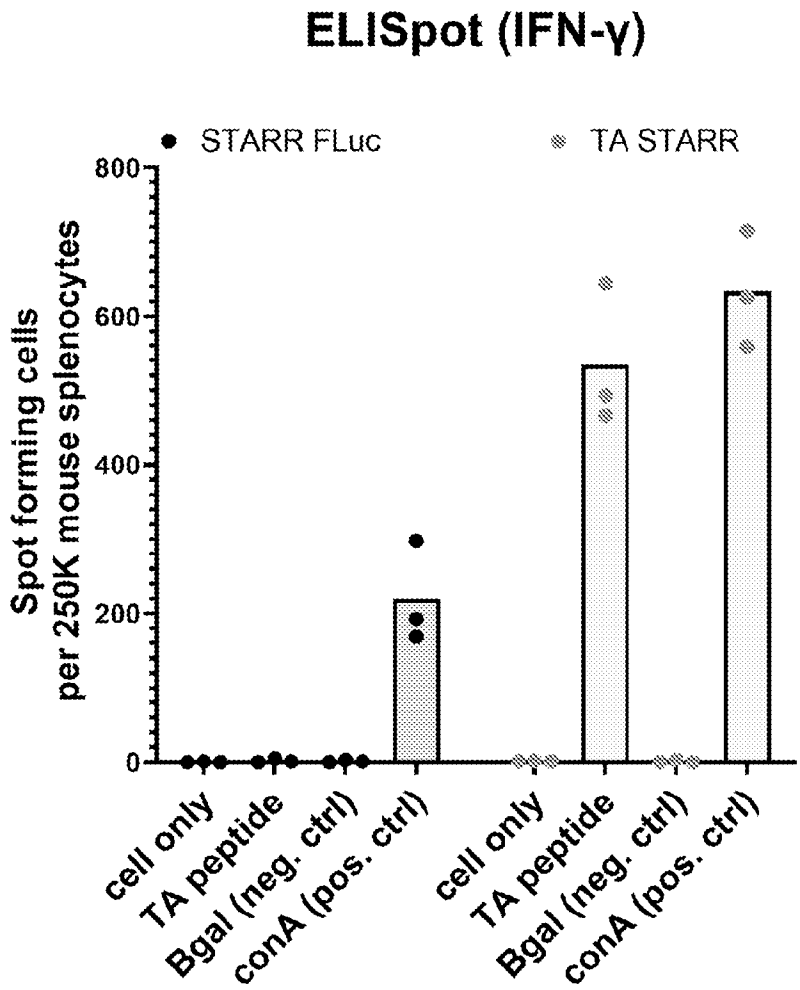

ELISpot (IFN-γ)
STARR FLuc
TA STARR
Spot forming cells
per 250K mouse splenocytes
800
600
400
200
0
cell only
TA peptide
Bgal (neg. ctrl)
conA (pos. ctrl)
cell only
TA peptide
Bgal (neg. ctrl)
conA (pos. ctrl)

FIG. 19

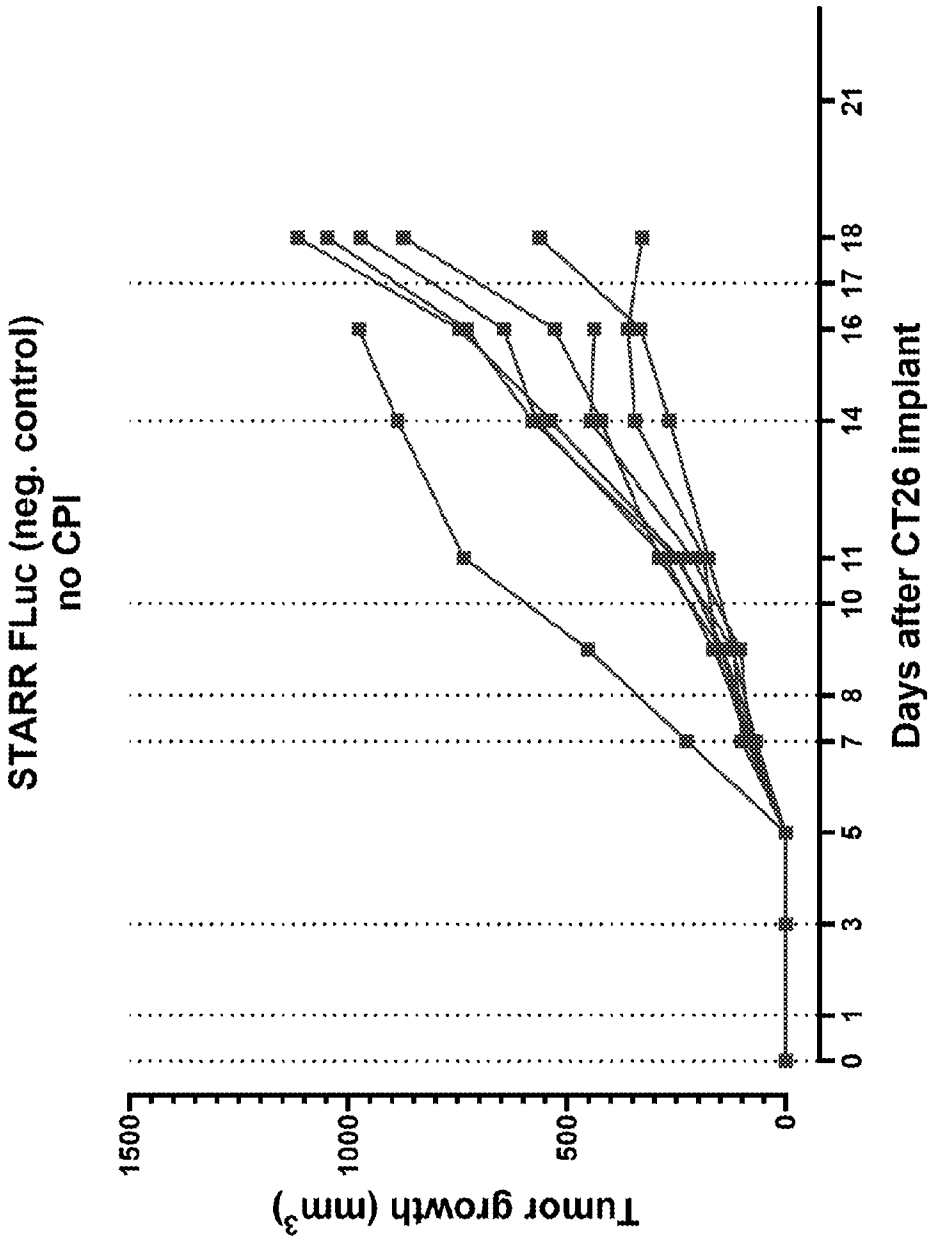

STARR FLuc (neg. control)
no CPI
Tumor growth (mm3)
1500
1000
500
0
0 1 3 5 7 8 10 11 14 16 17 18 21
Days after CT26 implant

FIG. 20A

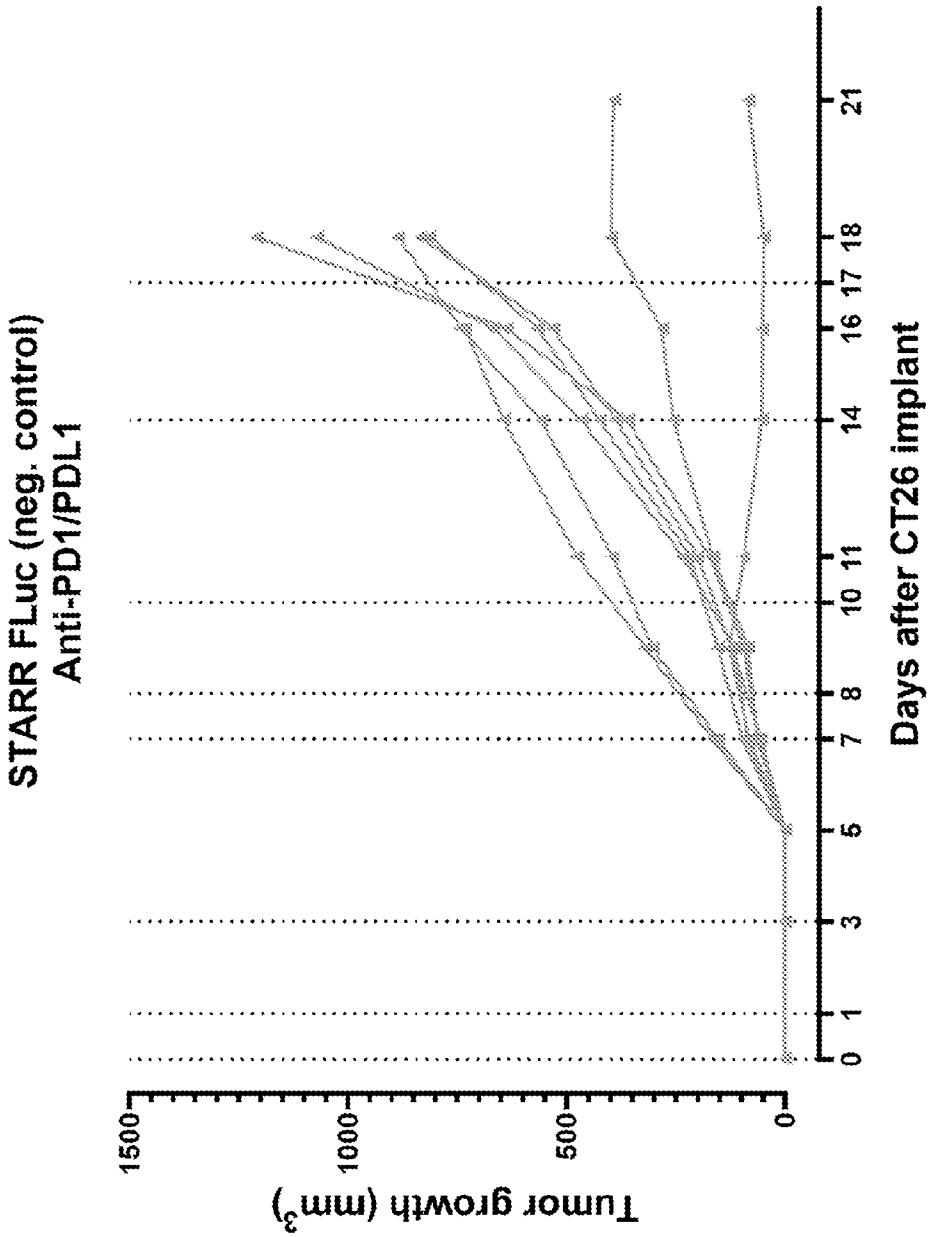

STARR FLuc (neg. control)
Anti-PD1/PDL1
Tumor growth (mm³)
1500
1000
500
0
0 1 3 5 7 8 10 11 14 16 17 18 21
Days after CT26 implant

FIG. 20B

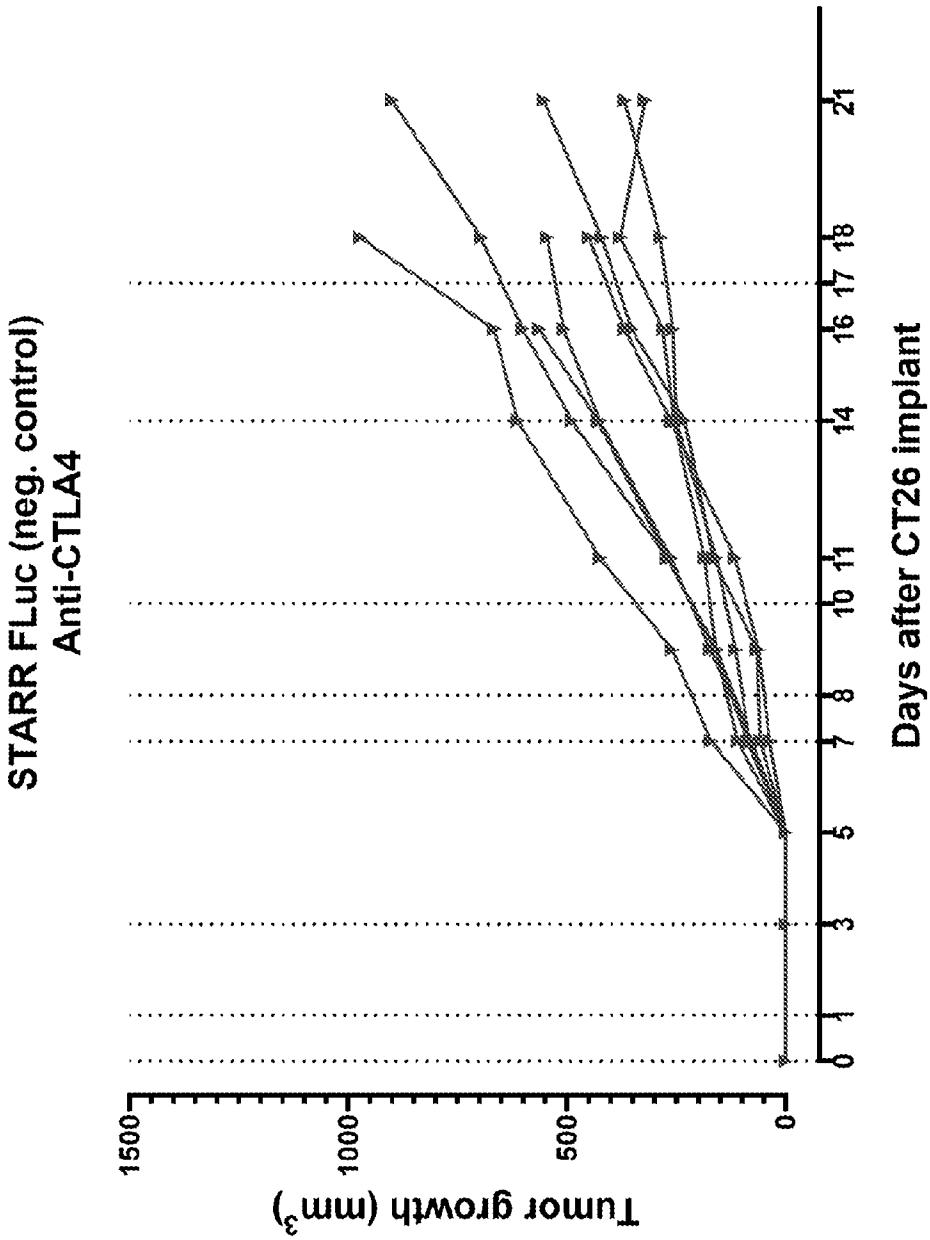

STARR FLuc (neg. control)
Anti-CTLA4
Tumor growth (mm3)
1500
1000
500
0
0
1
3
5
7
8
10
11
14
16
17
18
21
Days after CT26 implant

FIG. 20C

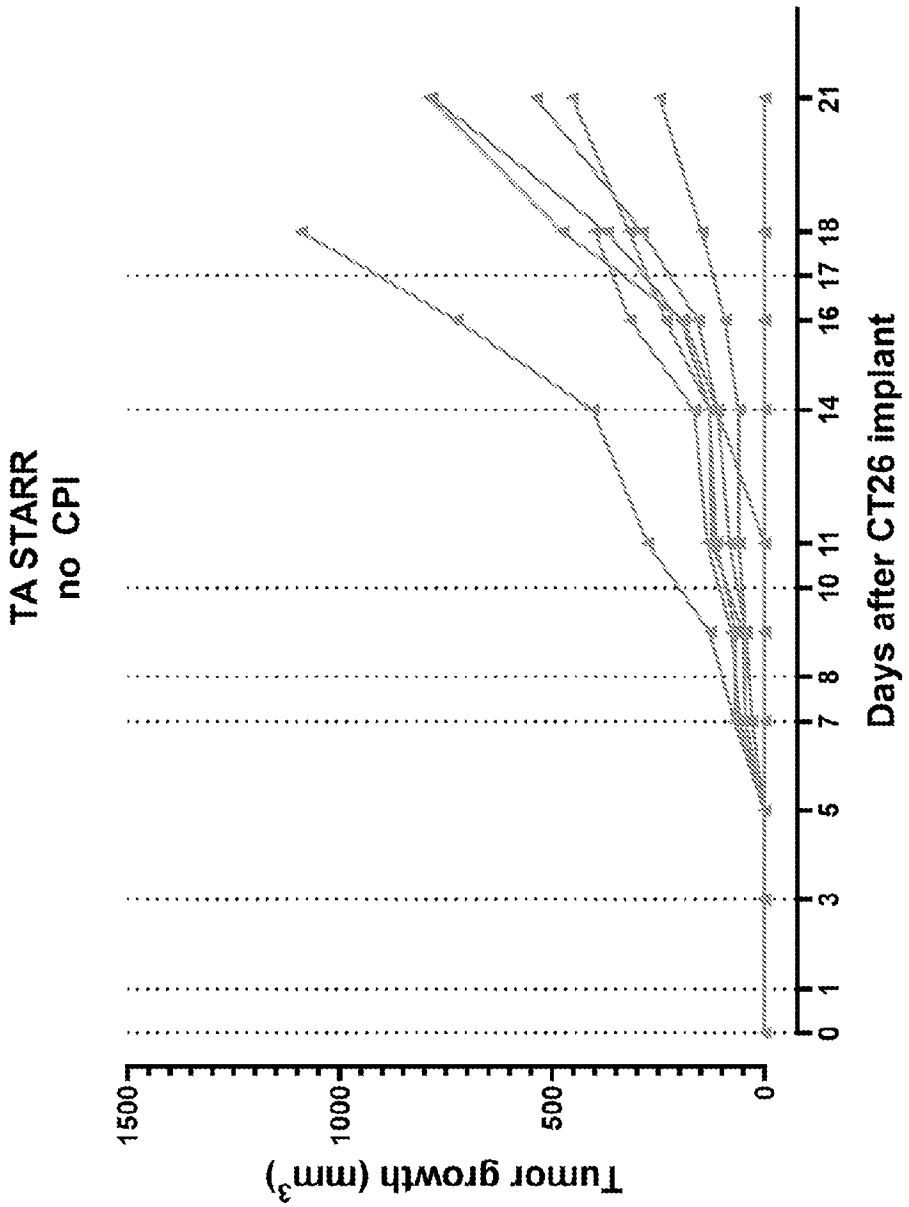

TA STARR
no CPI
Tumor growth (mm³)
1500
1000
500
0
0 1 3 5 7 8 10 11 14 16 17 18 21
Days after CT26 implant

FIG. 20D

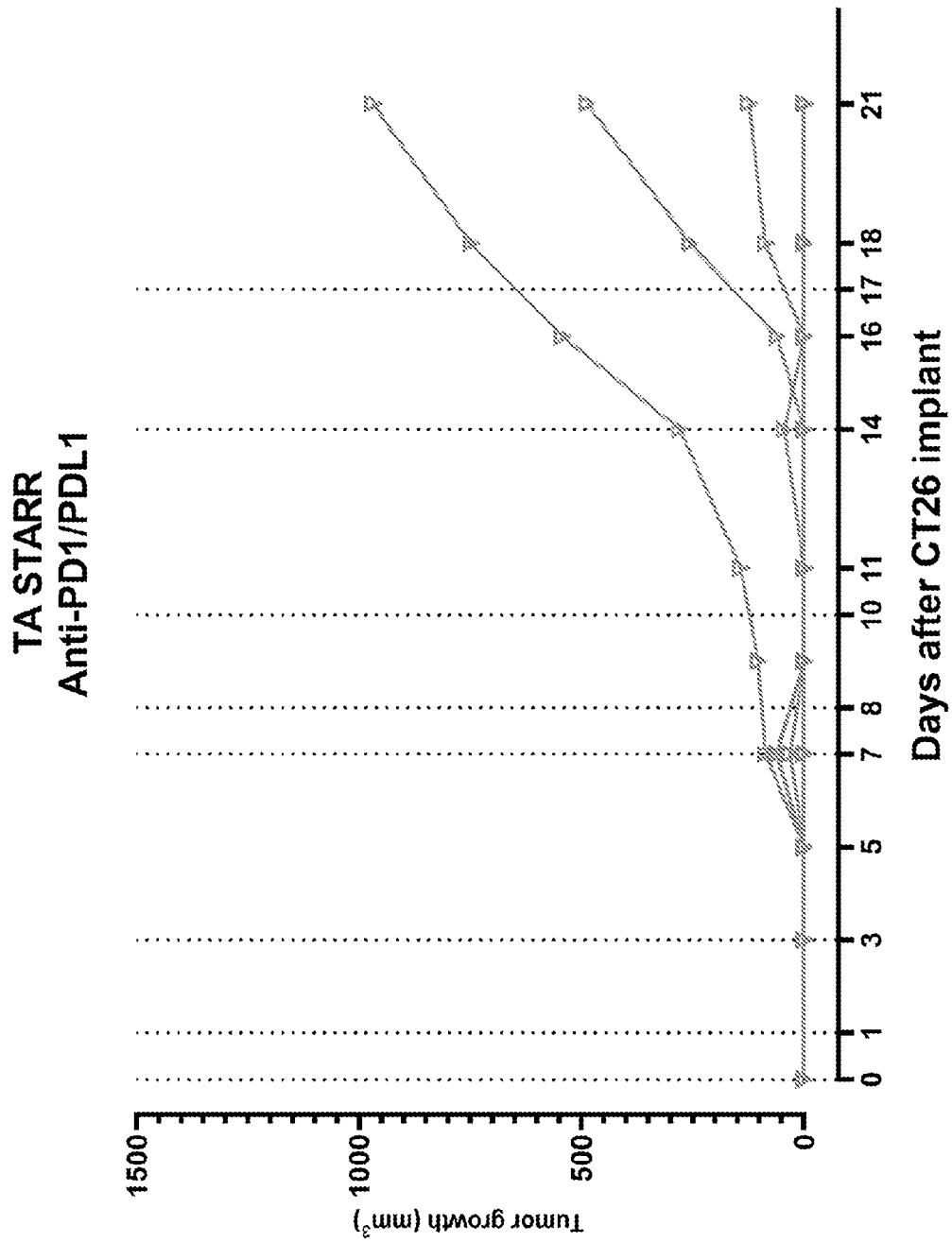

TA STARR
Anti-PD1/PDL1
Tumor growth (mm³)
1500
1000
500
0
0 1 3 5 7 8 10 11 14 16 17 18 21
Days after CT26 implant

FIG. 20E

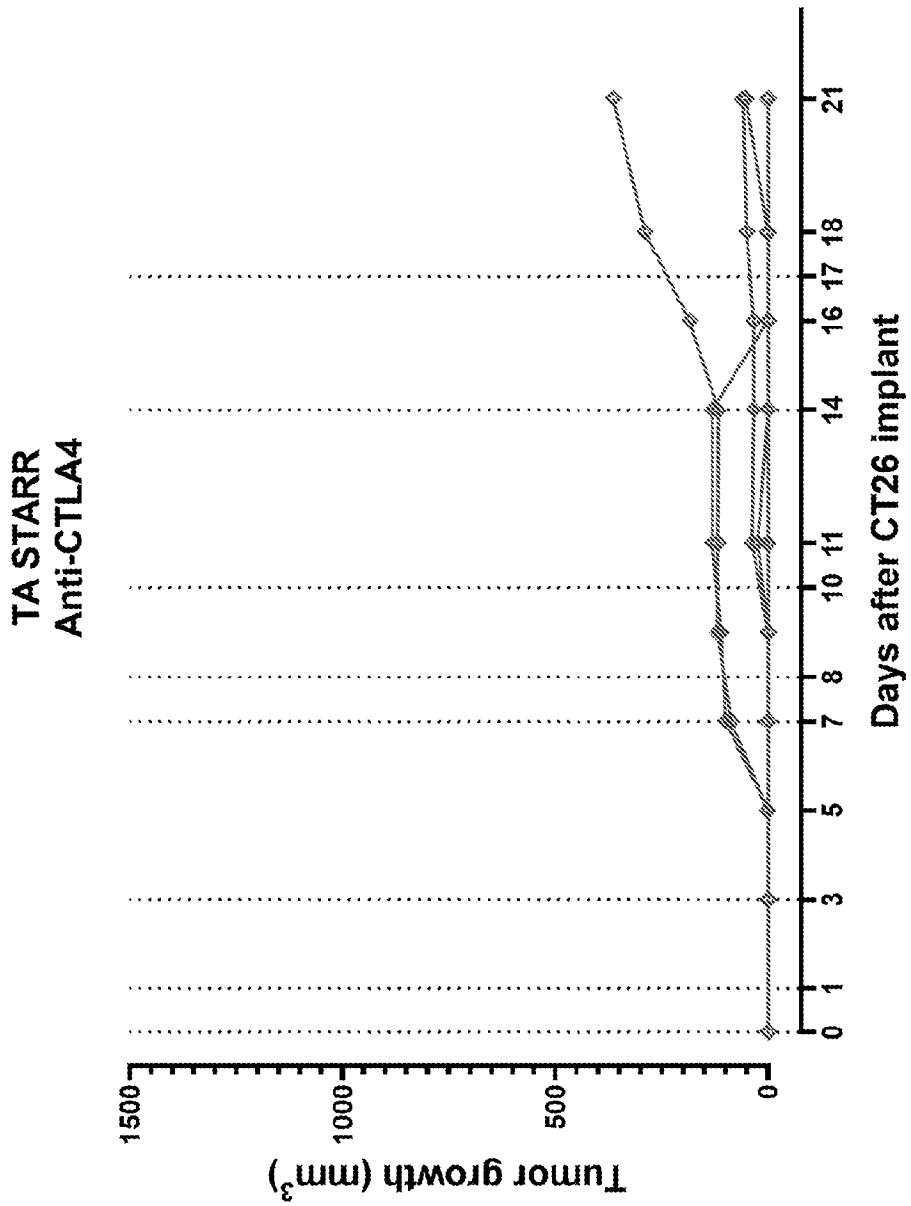

TA STARR
Anti-CTLA4
Tumor growth (mm³)
1500
1000
500
0
0
1
3
5
7
8
10
11
14
16
17
18
21
Days after CT26 implant

FIG. 20F

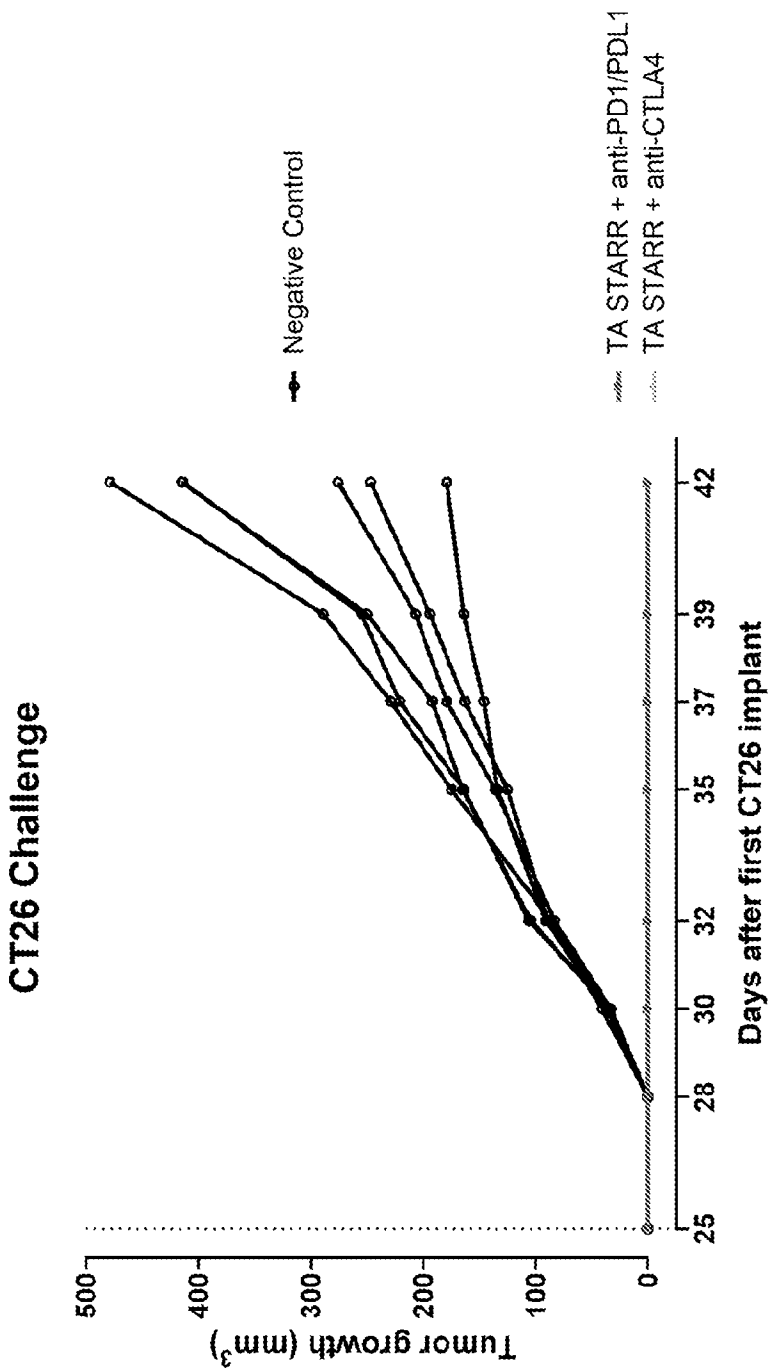

CT26 Challenge
Negative Control
TA STARR + anti-PD1/PDL1
TA STARR + anti-CTLA4
Tumor growth (mm³)
0
100
200
300
400
500
25
28
30
32
35
37
39
42
Days after first CT26 implant

FIG. 21

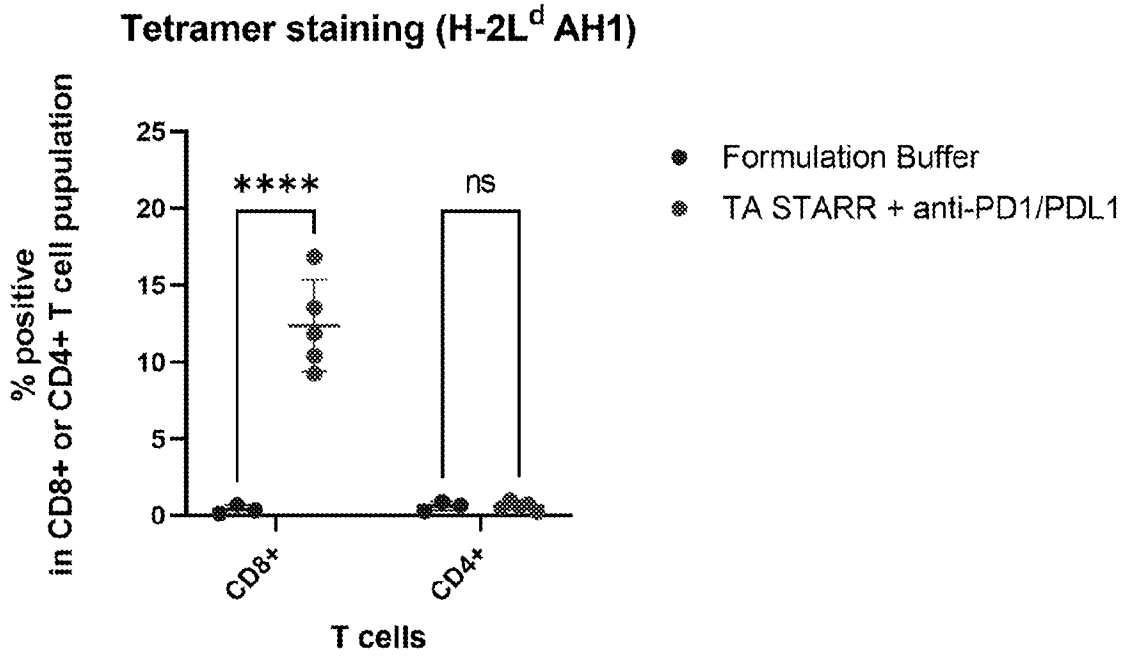

Tetramer staining (H-2L^d AH1)
% positive
in CD8+ or CD4+ T cell pupulation
25
20
15
10
5
0
****
ns
CD8+
CD4+
T cells
Formulation Buffer
TA STARR + anti-PD1/PDL1

FIG. 22A

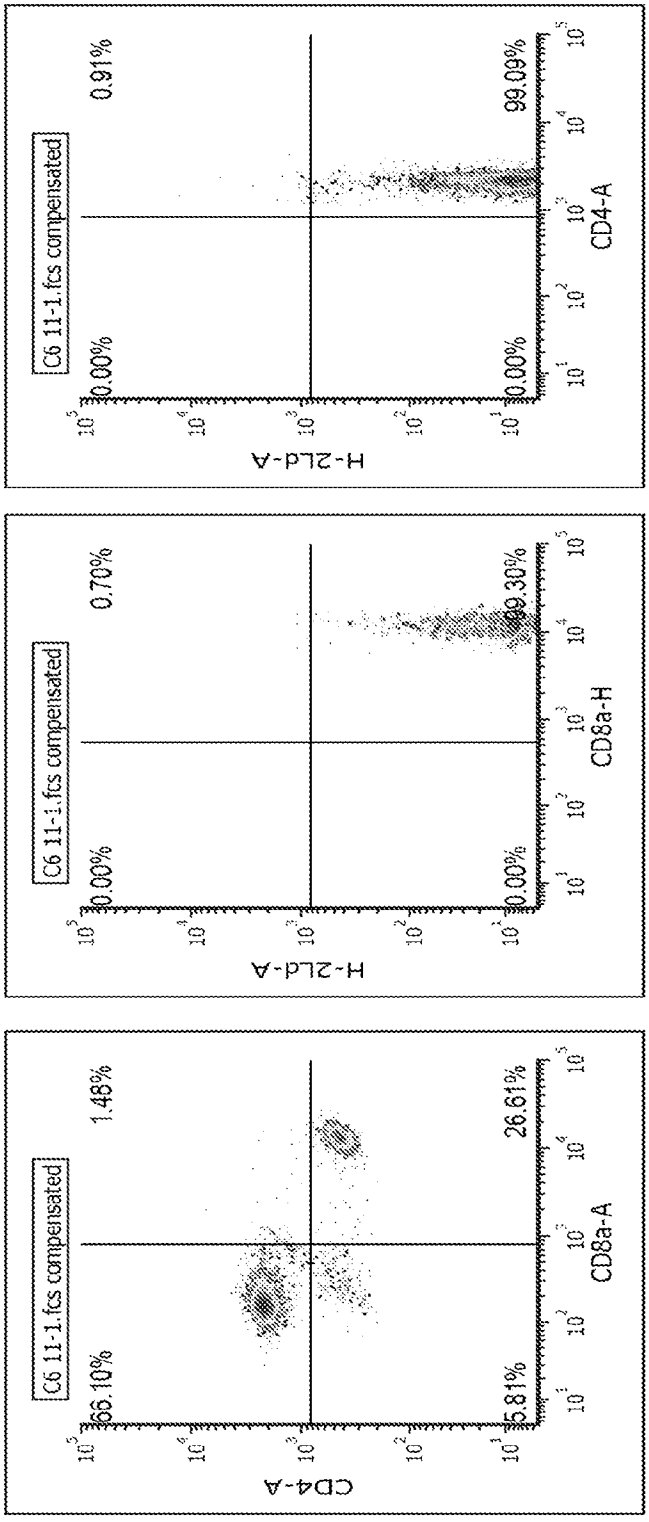

C6 11-1.fcs compensated
1.48%
66.10%
26.61%
5.81%
CD4-A
CD8a-A
C6 11-1.fcs compensated
0.70%
0.00%
99.30%
0.00%
H-2Ld-A
CD8a-H
C6 11-1.fcs compensated
0.91%
0.00%
99.09%
0.00%
H-2Ld-A
CD4-A

FIG. 22B

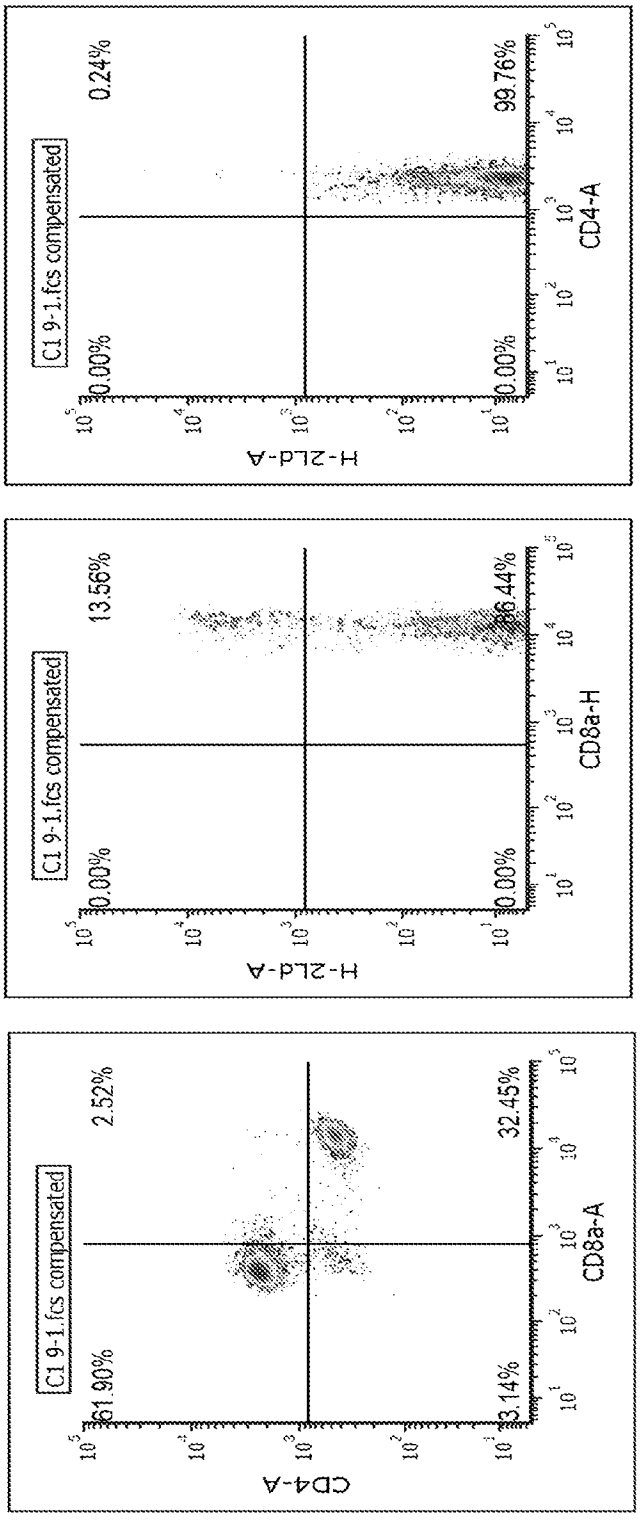

C1 9-1.fcs compensated
0.24%
99.76%
0.00%
0.00%
H-2Ld-A
CD4-A
C1 9-1.fcs compensated
13.56%
86.44%
0.00%
0.00%
H-2Ld-A
CD8a-H
C1 9-1.fcs compensated
2.52%
32.45%
61.90%
3.14%
CD4-A
CD8a-A

FIG. 22C

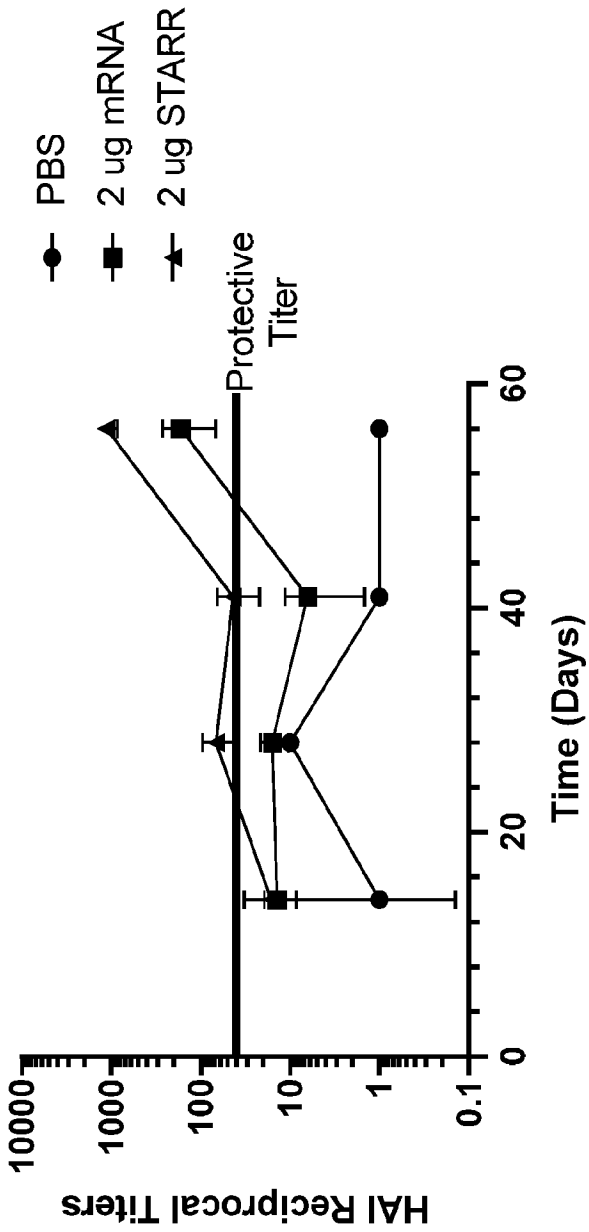

PBS
2 ug mRNA
2 ug STARR
Protective Titer
HAI Reciprocal Titers
10000
1000
100
10
1
0.1
0
20
40
60
Time (Days)

FIG. 23

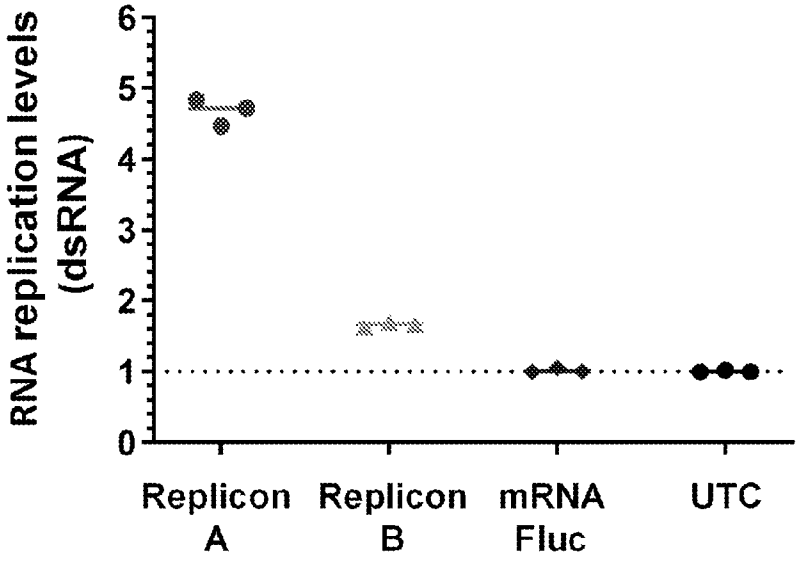


FIG. 24A

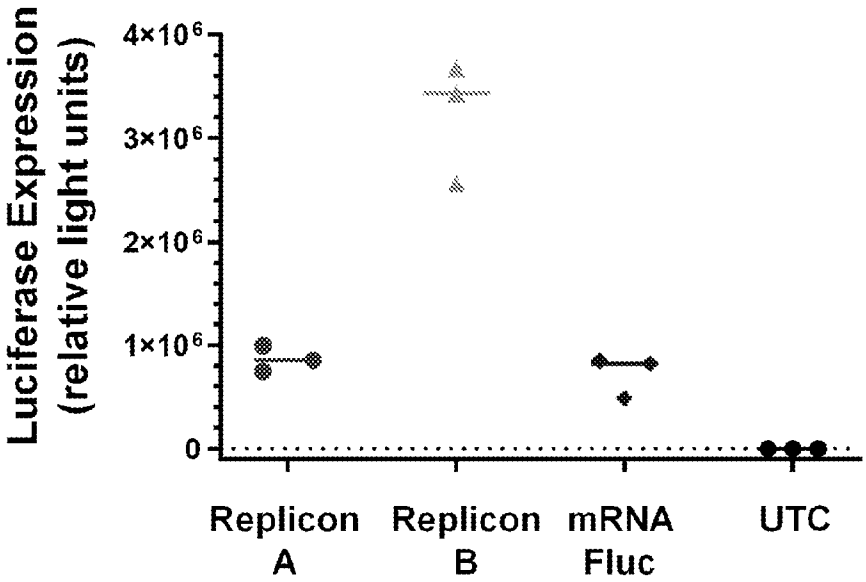


FIG. 24B

SEQUENCE LISTING

<110> Arcturus Therapeutics, Inc.
Sullivan, Sean Michael
Sagi, Amit
Matsuda, Daiki
Tachikawa, Kiyoshi
Chivukula, Padmanabh
Karmali, Priya Prakash
Davis, Jared Henry
Bao, Yanjie

<120> Coronavirus Vaccine Compositions and Methods

<130> 049386-538001WO

<150> US 62/987,191
<151> 2020-03-09

<150> US 63/073,900
<151> 2020-09-02

<160> 129

<170> PatentIn version 3.5

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<210> 2
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<212> RNA
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<220>
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agcaauuuaa aucauuucuu uuaaagcaaa agcaauuuuc ugaaaauuuu caccauuuac 120

gaacgauag 129

<210> 6
<211> 28
<212> RNA
<213> Artificial sequence

<220>
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<400> 6
auuauuacau caaaacaaaa agccgcca 28

<210> 7
<211> 245
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<223> Synthetic polynucleotide

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uggugcccca ggcccugcuc uuggucccgc ugcugguguu cccccucugc uucggcaagu 120

uccccaucua caccaucccc gacaagcugg ggccguggag ccccaucgac auccaccacc 180

uguccugccc caacaaccuc guggucgagg acgagggcug caccaaccug agcggguucu 240

ccuac 245

<210> 8
<211> 177
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cggugaguac accggaauug ccgggaagac uggguccuuu cuuggauaaa cccacucuau 120

gcccggccau uugggcgugc ccccgcaaga cugcuagccg aguaguguug gguugcg 177

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<211> 89
<212> RNA
<213> Artificial sequence

<220>
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uucugucaac cccacacgcc uuuggcaca 89

<210> 10
<211> 569
<212> RNA
<213> Artificial sequence

<220>
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cuggcccugu cuucuugacg agcauuccua gggggucuuuc cccucucgcc aaaggaaugc 180

aaggucuguu gaaugucgug aaggaagcag uuccucugga agcuucuuga agacaaacaa 240

cgucuguagc gacccuuugc aggcagcgga acccccccacc uggcgacagg ugccucugcg 300

gccaaaagcc acguguauaa gauacaccug caaaggcggc acaaccccag ugccacguug 360

ugaguuggau aguuguggaa agagucaaau ggcucuccuc aagcguauuc aacaaggggc 420

ugaaggaugc ccagaaggua ccccauugua ugggaucuga ucuggggccu cggugcacau 480

gcuuuacgug uguuuagucg agguuaaaaa acgucuaggc cccccgaacc acggggacgu 540

gguuuuccuu ugaaaaacac gaugauaau 569

<210> 11
<211> 44
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

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gucagcuuuc aaacucuuug uuucuuguuu guugauugag aaua 44

<210> 12
<211> 54
<212> RNA
<213> Artificial sequence

<220>
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<400> 12
cucucgccug agaaaaaaaa uccacgaacc aauuucucag caaccagcag cacg 54

<210> 13
<211> 52
<212> RNA
<213> Artificial sequence

<220>
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<400> 13
accugugagg guucgaagga aguagcagug uuuuuuguuc cuagaggaag ag 52

<210> 14
<211> 71
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

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uucgcaaaga c 71

<210> 15
<211> 52
<212> RNA
<213> Artificial sequence

<220>
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<400> 15
cagaaaaauu ugcuacauug uuucacaaac uucaaauauu auucauuuau uu 52

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<211> 158
<212> RNA
<213> Artificial sequence

<220>
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cucuaagcua cauaauacca acuuacacuu acaaaauguu gucccccaaa auguagccau 120

ucguaucugc uccuaauaaa aagaaaguuu cuucacau 158

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uggacgggag uggacaggag uggaugcgau aagauguggu uugaagcuga ugggugccag 120

cccugcauug cugagucaau caauaaagag cuuucuuuug acccau 166

<210> 18
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cugcagcggg agacccuguc cccgccccag ccguccuccu gggguggacc cuaguuuaau 120

aaagauucac caaguuucac gca 143

<210> 19
<211> 220
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 19
uagagcggca aacccuagcu acacuccaua gcuaguuucu uuuuuuuuug uuuuuuuuuu 60

uuuuuuuuuu uuuuuuuuuu uuuuuuuuuc cuuucuuuuc cuucuuuuuu uccucuuuuc 120

uugguggcuc caucuuagcc cuagucacgg cuagcuguga aagguccgug agccgcauga 180

cugcagagag ugccguaacu ggucucucug cagaucaugu 220

<210> 20
<211> 170
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<400> 20
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acucaucuuu ucuguuggug uaaaaucaac acccuaagga acacaaauuu cuuuaaacau 120

uugacuucuu gucucugugc ugcaauuaau aaaaaaugga aagaaucuac 170

<210> 21
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<212> RNA
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<400> 21
gcuggagccu cgguagccgu uccuccugcc cgcugggccu cccaacgggc ccuccucccc 60

uccuugcacc ggcccuuccu ggucuuugaa uaaagucuga gugggcagca 110

<210> 22
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<212> RNA
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<220>
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<400> 22
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uacugcagac aggguucuuc uacuuugcaa gauagucuag aguaguaaaa uaaauaguau 120

aag 123

<210> 23
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<212> RNA
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<400> 23
gccacc 6

<210> 24
<211> 4
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<220>
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<400> 24
gcca 4

<210> 25
<211> 21
<212> RNA
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<400> 25
cacaaagagu aaagaagaac a 21

<210> 26
<211> 21
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aacacuaaaa guagaagaaa a 21

<210> 27
<211> 21
<212> RNA
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cucagaaaga uaagaucagc c 21

<210> 28
<211> 21
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<220>
<223> Synthetic polynucleotide

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aaccaaucga aagaaaccaa a 21

<210> 29
<211> 21
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 29
cucuaaucac caggaguaaa a 21

<210> 30
<211> 21
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 30
gagagagauc uuaacaaaaa a 21

<210> 31
<211> 21
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<220>
<223> Synthetic polynucleotide

<400> 31
uguguaacaa caacaacaac a 21

<210> 32
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<212> RNA
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<220>
<223> Synthetic polynucleotide

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ccgcaguagg aagagaaagc c 21

<210> 33
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<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 33
aaaaaaaaaa gaaaucauaa a 21

<210> 34
<211> 21
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

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<210> 35
<211> 21
<212> RNA
<213> Artificial sequence

<220>
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<400> 35
caauuaaaaa uacuuaccaa a 21

<210> 36
<211> 21
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<223> Synthetic polynucleotide

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gcaaacagag uaagcgaaac g 21

<210> 37
<211> 21
<212> RNA
<213> Artificial sequence

<220>
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<400> 37
gcgaagaaga cgaacgcaaa g 21

<210> 38
<211> 21
<212> RNA
<213> Artificial sequence

<220>
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<400> 38
uuaggacugu auugacuggc c 21

<210> 39
<211> 21
<212> RNA
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<220>
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<400> 39
aucaucggaa uucggaaaaa g 21

<210> 40
<211> 21
<212> RNA
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<220>
<223> Synthetic polynucleotide

<400> 40
aaaacaaaag uuaaagcaga c 21

<210> 41
<211> 21
<212> RNA
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<220>
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<400> 41
uuuaucucaa auaagaaggc a 21

<210> 42
<211> 21
<212> RNA
<213> Artificial sequence

<220>
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Lys Leu Ile Glu Thr Glu Val Asp Pro Ser Asp Thr Ile Leu Asp Ile
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Gly Ser Ala Pro Ala Arg Arg Met Tyr Ser Lys His Lys Tyr His Cys
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Ile Cys Pro Met Arg Cys Ala Glu Asp Pro Asp Arg Leu Tyr Lys Tyr
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Asp Lys Lys Met Lys Glu Leu Ala Ala Val Met Ser Asp Pro Asp Leu
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Glu Thr Glu Thr Met Cys Leu His Asp Asp Glu Ser Cys Arg Tyr Glu
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Gly Gln Val Ala Val Tyr Gln Asp Val Tyr Ala Val Asp Gly Pro Thr
145                 150                 155                 160

Ser Leu Tyr His Gln Ala Asn Lys Gly Val Arg Val Ala Tyr Trp Ile
                165                 170                 175

Gly Phe Asp Thr Thr Pro Phe Met Phe Lys Asn Leu Ala Gly Ala Tyr
            180                 185                 190

Pro Ser Tyr Ser Thr Asn Trp Ala Asp Glu Thr Val Leu Thr Ala Arg
        195                 200                 205

Asn Ile Gly Leu Cys Ser Ser Asp Val Met Glu Arg Ser Arg Arg Gly
    210                 215                 220

Met Ser Ile Leu Arg Lys Lys Tyr Leu Lys Pro Ser Asn Asn Val Leu
225                 230                 235                 240

Phe Ser Val Gly Ser Thr Ile Tyr His Glu Lys Arg Asp Leu Leu Arg
                245                 250                 255

Ser Trp His Leu Pro Ser Val Phe His Leu Arg Gly Lys Gln Asn Tyr
            260                 265                 270

Thr Cys Arg Cys Glu Thr Ile Val Ser Cys Asp Gly Tyr Val Val Lys
        275                 280                 285

Arg Ile Ala Ile Ser Pro Gly Leu Tyr Gly Lys Pro Ser Gly Tyr Ala
    290                 295                 300
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Ala Thr Met His Arg Glu Gly Phe Leu Cys Cys Lys Val Thr Asp Thr
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Leu Asn Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Val Pro Ala
                325                 330                 335

Thr Leu Cys Asp Gln Met Thr Gly Ile Leu Ala Thr Asp Val Ser Ala
            340                 345                 350

Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val Val
        355                 360                 365

Asn Gly Arg Thr Gln Arg Asn Thr Asn Thr Met Lys Asn Tyr Leu Leu
    370                 375                 380

Pro Val Val Ala Gln Ala Phe Ala Arg Trp Ala Lys Glu Tyr Lys Glu
385                 390                 395                 400

Asp Gln Glu Asp Glu Arg Pro Leu Gly Leu Arg Asp Arg Gln Leu Val
                405                 410                 415

Met Gly Cys Cys Trp Ala Phe Arg Arg His Lys Ile Thr Ser Ile Tyr
            420                 425                 430

Lys Arg Pro Asp Thr Gln Thr Ile Ile Lys Val Asn Ser Asp Phe His
        435                 440                 445

Ser Phe Val Leu Pro Arg Ile Gly Ser Asn Thr Leu Glu Ile Gly Leu
    450                 455                 460

Arg Thr Arg Ile Arg Lys Met Leu Glu Glu His Lys Glu Pro Ser Pro
465                 470                 475                 480

Leu Ile Thr Ala Glu Asp Val Gln Glu Ala Lys Cys Ala Ala Asp Glu
                485                 490                 495

Ala Lys Glu Val Arg Glu Ala Glu Glu Leu Arg Ala Ala Leu Pro Pro
            500                 505                 510

Leu Ala Ala Asp Val Glu Glu Pro Thr Leu Glu Ala Asp Val Asp Leu
        515                 520                 525
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Met Leu Gln Glu Ala Gly Ala Gly Ser Val Glu Thr Pro Arg Gly Leu
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Ile Lys Val Thr Ser Tyr Asp Gly Glu Asp Lys Ile Gly Ser Tyr Ala
545                 550                 555                 560

Val Leu Ser Pro Gln Ala Val Leu Lys Ser Glu Lys Leu Ser Cys Ile
                565                 570                 575

His Pro Leu Ala Glu Gln Val Ile Val Ile Thr His Ser Gly Arg Lys
            580                 585                 590

Gly Arg Tyr Ala Val Glu Pro Tyr His Gly Lys Val Val Val Pro Glu
        595                 600                 605

Gly His Ala Ile Pro Val Gln Asp Phe Gln Ala Leu Ser Glu Ser Ala
    610                 615                 620

Thr Ile Val Tyr Asn Glu Arg Glu Phe Val Asn Arg Tyr Leu His His
625                 630                 635                 640

Ile Ala Thr His Gly Gly Ala Leu Asn Thr Asp Glu Glu Tyr Tyr Lys
                645                 650                 655

Thr Val Lys Pro Ser Glu His Asp Gly Glu Tyr Leu Tyr Asp Ile Asp
            660                 665                 670

Arg Lys Gln Cys Val Lys Lys Glu Leu Val Thr Gly Leu Gly Leu Thr
        675                 680                 685

Gly Glu Leu Val Asp Pro Pro Phe His Glu Phe Ala Tyr Glu Ser Leu
    690                 695                 700

Arg Thr Arg Pro Ala Ala Pro Tyr Gln Val Pro Thr Ile Gly Val Tyr
705                 710                 715                 720

Gly Val Pro Gly Ser Gly Lys Ser Gly Ile Ile Lys Ser Ala Val Thr
                725                 730                 735
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Lys Lys Asp Leu Val Val Ser Ala Lys Lys Glu Asn Cys Ala Glu Ile
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Val Asp Ser Val Leu Leu Asn Gly Cys Lys His Pro Val Glu Thr Leu
    770                 775                 780

Tyr Ile Asp Glu Ala Phe Ala Cys His Ala Gly Thr Leu Arg Ala Leu
785                 790                 795                 800

Ile Ala Ile Ile Arg Pro Lys Lys Ala Val Leu Cys Gly Asp Pro Lys
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Gln Cys Gly Phe Phe Asn Met Met Cys Leu Lys Val His Phe Asn His
            820                 825                 830

Glu Ile Cys Thr Gln Val Phe His Lys Ser Ile Ser Arg Arg Cys Thr
        835                 840                 845

Lys Ser Val Thr Ser Val Val Ser Thr Leu Phe Tyr Asp Lys Lys Met
    850                 855                 860

Arg Thr Thr Asn Pro Lys Glu Thr Lys Ile Val Ile Asp Thr Thr Gly
865                 870                 875                 880

Ser Thr Lys Pro Lys Gln Asp Asp Leu Ile Leu Thr Cys Phe Arg Gly
                885                 890                 895

Trp Val Lys Gln Leu Gln Ile Asp Tyr Lys Gly Asn Glu Ile Met Thr
            900                 905                 910

Ala Ala Ala Ser Gln Gly Leu Thr Arg Lys Gly Val Tyr Ala Val Arg
        915                 920                 925

Tyr Lys Val Asn Glu Asn Pro Leu Tyr Ala Pro Thr Ser Glu His Val
    930                 935                 940

Asn Val Leu Leu Thr Arg Thr Glu Asp Arg Ile Val Trp Lys Thr Leu
945                 950                 955                 960
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           980                 985                 990

Arg His Ile Leu Glu Arg Pro Asp  Pro Thr Asp Val Phe  Gln Asn Lys
        995                 1000                1005

Ala Asn  Val Cys Trp Ala Lys  Ala Leu Val Pro Val  Leu Lys Thr
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Ala Gly  Ile Asp Met Thr Thr  Glu Gln Trp Asn Thr  Val Asp Tyr
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Phe Glu  Thr Asp Lys Ala His  Ser Ala Glu Ile Val  Leu Asn Gln
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Leu Cys  Val Arg Phe Phe Gly  Leu Asp Leu Asp Ser  Gly Leu Phe
    1055                1060                1065

Ser Ala  Pro Thr Val Pro Leu  Ser Ile Arg Asn Asn  His Trp Asp
    1070                1075                1080

Asn Ser  Pro Ser Pro Asn Met  Tyr Gly Leu Asn Lys  Glu Val Val
    1085                1090                1095

Arg Gln  Leu Ser Arg Arg Tyr  Pro Gln Leu Pro Arg  Ala Val Ala
    1100                1105                1110

Thr Gly  Arg Val Tyr Asp Met  Asn Thr Gly Thr Leu  Arg Asn Tyr
    1115                1120                1125

Asp Pro  Arg Ile Asn Leu Val  Pro Val Asn Arg Arg  Leu Pro His
    1130                1135                1140

Ala Leu  Val Leu His His Asn  Glu His Pro Gln Ser  Asp Phe Ser
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Ser Phe  Val Ser Lys Leu Lys  Gly Arg Thr Val Leu  Val Val Gly
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Glu Lys  Leu Ser Val Pro Gly  Lys Met Val Asp Trp  Leu Ser Asp
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Arg Pro  Glu Ala Thr Phe Arg  Ala Arg Leu Asp Leu  Gly Ile Pro
    1190                1195                1200

Gly Asp  Val Pro Lys Tyr Asp  Ile Ile Phe Val Asn  Val Arg Thr
    1205                1210                1215

Pro Tyr  Lys Tyr His His Tyr  Gln Gln Cys Glu Asp  His Ala Ile
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Lys Leu  Ser Met Leu Thr Lys  Lys Ala Cys Leu His  Leu Asn Pro
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Gly Gly  Thr Cys Val Ser Ile  Gly Tyr Gly Tyr Ala  Asp Arg Ala
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Ser Glu  Ser Ile Ile Gly Ala  Ile Ala Arg Leu Phe  Lys Phe Ser
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Arg Val  Cys Lys Pro Lys Ser  Ser Leu Glu Glu Thr  Glu Val Leu
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Phe Val  Phe Ile Gly Tyr Asp  Arg Lys Ala Arg Thr  His Asn Pro
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Tyr Lys  Leu Ser Ser Thr Leu  Thr Asn Ile Tyr Thr  Gly Ser Arg
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Leu His  Glu Ala Gly Cys Ala  Pro Ser Tyr His Val  Val Arg Gly
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Asp Ile  Ala Thr Ala Thr Glu  Gly Val Ile Ile Asn  Ala Ala Asn
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Ser Lys  Gly Gln Pro Gly Gly  Gly Val Cys Gly Ala  Leu Tyr Lys
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Gly Pro  Asn Phe Asn Lys Val  Ser Glu Val Glu Gly  Asp Lys Gln
    1400                1405                1410

Leu Ala  Glu Ala Tyr Glu Ser  Ile Ala Lys Ile Val  Asn Asp Asn
    1415                1420                1425

Asn Tyr  Lys Ser Val Ala Ile  Pro Leu Leu Ser Thr  Gly Ile Phe
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Ser Gly  Asn Lys Asp Arg Leu  Thr Gln Ser Leu Asn  His Leu Leu
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Thr Ala  Leu Asp Thr Thr Asp  Ala Asp Val Ala Ile  Tyr Cys Arg
    1460                1465                1470

Asp Lys  Lys Trp Glu Met Thr  Leu Lys Glu Ala Val  Ala Arg Arg
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Glu Ala  Val Glu Glu Ile Cys  Ile Ser Asp Asp Ser  Ser Val Thr
    1490                1495                1500

Glu Pro  Asp Ala Glu Leu Val  Arg Val His Pro Lys  Ser Ser Leu
    1505                1510                1515

Ala Gly  Arg Lys Gly Tyr Ser  Thr Ser Asp Gly Lys  Thr Phe Ser
    1520                1525                1530

Tyr Leu  Glu Gly Thr Lys Phe  His Gln Ala Ala Lys  Asp Ile Ala
    1535                1540                1545

Glu Ile  Asn Ala Met Trp Pro  Val Ala Thr Glu Ala  Asn Glu Gln
    1550                1555                1560
```

```
Val Cys  Met Tyr Ile Leu Gly  Glu Ser Met Ser Ser  Ile Arg Ser
    1565                1570                1575

Lys Cys  Pro Val Glu Glu Ser  Glu Ala Ser Thr Pro  Pro Ser Thr
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Leu Pro  Cys Leu Cys Ile His  Ala Met Thr Pro Glu  Arg Val Gln
    1595                1600                1605

Arg Leu  Lys Ala Ser Arg Pro  Glu Gln Ile Thr Val  Cys Ser Ser
    1610                1615                1620

Phe Pro  Leu Pro Lys Tyr Arg  Ile Thr Gly Val Gln  Lys Ile Gln
    1625                1630                1635

Cys Ser  Gln Pro Ile Leu Phe  Ser Pro Lys Val Pro  Ala Tyr Ile
    1640                1645                1650

His Pro  Arg Lys Tyr Leu Val  Glu Thr Pro Pro Val  Asp Glu Thr
    1655                1660                1665

Pro Glu  Pro Ser Ala Glu Asn  Gln Ser Thr Glu Gly  Thr Pro Glu
    1670                1675                1680

Gln Pro  Pro Leu Ile Thr Glu  Asp Glu Thr Arg Thr  Arg Thr Pro
    1685                1690                1695

Glu Pro  Ile Ile Ile Glu Glu  Glu Glu Glu Asp Ser  Ile Ser Leu
    1700                1705                1710

Leu Ser  Asp Gly Pro Thr His  Gln Val Leu Gln Val  Glu Ala Asp
    1715                1720                1725

Ile His  Gly Pro Pro Ser Val  Ser Ser Ser Ser Trp  Ser Ile Pro
    1730                1735                1740

His Ala  Ser Asp Phe Asp Val  Asp Ser Leu Ser Ile  Leu Asp Thr
    1745                1750                1755

Leu Glu  Gly Ala Ser Val Thr  Ser Gly Ala Thr Ser  Ala Glu Thr
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```

```
Asn Ser  Tyr Phe Ala Lys Ser  Met Glu Phe Leu Ala  Arg Pro Val
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Pro Ala  Pro Arg Thr Val Phe  Arg Asn Pro Pro His  Pro Ala Pro
    1790                1795                1800

Arg Thr  Arg Thr Pro Ser Leu  Ala Pro Ser Arg Ala  Cys Ser Arg
    1805                1810                1815

Thr Ser  Leu Val Ser Thr Pro  Pro Gly Val Asn Arg  Val Ile Thr
    1820                1825                1830

Arg Glu  Glu Leu Glu Ala Leu  Thr Pro Ser Arg Thr  Pro Ser Arg
    1835                1840                1845

Ser Val  Ser Arg Thr Ser Leu  Val Ser Asn Pro Pro  Gly Val Asn
    1850                1855                1860

Arg Val  Ile Thr Arg Glu Glu  Phe Glu Ala Phe Val  Ala Gln Gln
    1865                1870                1875

Gln Arg  Arg Phe Asp Ala Gly  Ala Tyr Ile Phe Ser  Ser Asp Thr
    1880                1885                1890

Gly Gln  Gly His Leu Gln Gln  Lys Ser Val Arg Gln  Thr Val Leu
    1895                1900                1905

Ser Glu  Val Val Leu Glu Arg  Thr Glu Leu Glu Ile  Ser Tyr Ala
    1910                1915                1920

Pro Arg  Leu Asp Gln Glu Lys  Glu Glu Leu Leu Arg  Lys Lys Leu
    1925                1930                1935

Gln Leu  Asn Pro Thr Pro Ala  Asn Arg Ser Arg Tyr  Gln Ser Arg
    1940                1945                1950

Lys Val  Glu Asn Met Lys Ala  Ile Thr Ala Arg Arg  Ile Leu Gln
    1955                1960                1965
```

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Gly Leu  Gly His Tyr Leu Lys  Ala Glu Gly Lys Val  Glu Cys Tyr
    1970                 1975                 1980

Arg Thr  Leu His Pro Val Pro  Leu Tyr Ser Ser Ser  Val Asn Arg
    1985                 1990                 1995

Ala Phe  Ser Ser Pro Lys Val  Ala Val Glu Ala Cys  Asn Ala Met
    2000                 2005                 2010

Leu Lys  Glu Asn Phe Pro Thr  Val Ala Ser Tyr Cys  Ile Ile Pro
    2015                 2020                 2025

Glu Tyr  Asp Ala Tyr Leu Asp  Met Val Asp Gly Ala  Ser Cys Cys
    2030                 2035                 2040

Leu Asp  Thr Ala Ser Phe Cys  Pro Ala Lys Leu Arg  Ser Phe Pro
    2045                 2050                 2055

Lys Lys  His Ser Tyr Leu Glu  Pro Thr Ile Arg Ser  Ala Val Pro
    2060                 2065                 2070

Ser Ala  Ile Gln Asn Thr Leu  Gln Asn Val Leu Ala  Ala Ala Thr
    2075                 2080                 2085

Lys Arg  Asn Cys Asn Val Thr  Gln Met Arg Glu Leu  Pro Val Leu
    2090                 2095                 2100

Asp Ser  Ala Ala Phe Asn Val  Glu Cys Phe Lys Lys  Tyr Ala Cys
    2105                 2110                 2115

Asn Asn  Glu Tyr Trp Glu Thr  Phe Lys Glu Asn Pro  Ile Arg Leu
    2120                 2125                 2130

Thr Glu  Glu Asn Val Val Asn  Tyr Ile Thr Lys Leu  Lys Gly Pro
    2135                 2140                 2145

Lys Ala  Ala Ala Leu Phe Ala  Lys Thr His Asn Leu  Asn Met Leu
    2150                 2155                 2160

Gln Asp  Ile Pro Met Asp Arg  Phe Val Met Asp Leu  Lys Arg Asp
    2165                 2170                 2175
```

```
Val Lys  Val Thr Pro Gly Thr  Lys His Thr Glu Glu  Arg Pro Lys
    2180                2185                2190

Val Gln  Val Ile Gln Ala Ala  Asp Pro Leu Ala Thr  Ala Tyr Leu
    2195                2200                2205

Cys Gly  Ile His Arg Glu Leu  Val Arg Arg Leu Asn  Ala Val Leu
    2210                2215                2220

Leu Pro  Asn Ile His Thr Leu  Phe Asp Met Ser Ala  Glu Asp Phe
    2225                2230                2235

Asp Ala  Ile Ile Ala Glu His  Phe Gln Pro Gly Asp  Cys Val Leu
    2240                2245                2250

Glu Thr  Asp Ile Ala Ser Phe  Asp Lys Ser Glu Asp  Asp Ala Met
    2255                2260                2265

Ala Leu  Thr Ala Leu Met Ile  Leu Glu Asp Leu Gly  Val Asp Ala
    2270                2275                2280

Glu Leu  Leu Thr Leu Ile Glu  Ala Ala Phe Gly Glu  Ile Ser Ser
    2285                2290                2295

Ile His  Leu Pro Thr Lys Thr  Lys Phe Lys Phe Gly  Ala Met Met
    2300                2305                2310

Lys Ser  Gly Met Phe Leu Thr  Leu Phe Val Asn Thr  Val Ile Asn
    2315                2320                2325

Ile Val  Ile Ala Ser Arg Val  Leu Arg Glu Arg Leu  Thr Gly Ser
    2330                2335                2340

Pro Cys  Ala Ala Phe Ile Gly  Asp Asp Asn Ile Val  Lys Gly Val
    2345                2350                2355

Lys Ser  Asp Lys Leu Met Ala  Asp Arg Cys Ala Thr  Trp Leu Asn
    2360                2365                2370
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Met Glu Val Lys Ile Ile Asp Ala Val Val Gly Glu Lys Ala Pro
2375 2380 2385

Tyr Phe Cys Gly Gly Phe Ile Leu Cys Asp Ser Val Thr Gly Thr
2390 2395 2400

Ala Cys Arg Val Ala Asp Pro Leu Lys Arg Leu Phe Lys Leu Gly
2405 2410 2415

Lys Pro Leu Ala Ala Asp Asp Glu His Asp Asp Asp Arg Arg Arg
2420 2425 2430

Ala Leu His Glu Glu Ser Thr Arg Trp Asn Arg Val Gly Ile Leu
2435 2440 2445

Ser Glu Leu Cys Lys Ala Val Glu Ser Arg Tyr Glu Thr Val Gly
2450 2455 2460

Thr Ser Ile Ile Val Met Ala Met Thr Thr Leu Ala Ser Ser Val
2465 2470 2475

Lys Ser Phe Ser Tyr Leu Arg Gly Ala Pro Ile Thr Leu Tyr Gly
2480 2485 2490

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35 40 45

Ser Lys Leu Ile Glu Thr Glu Val Asp Pro Ser Asp Thr Ile Leu Asp
50 55 60

Ile Gly Ser Ala Pro Ala Arg Arg Met Tyr Ser Lys His Lys Tyr His
65 70 75 80

Cys Ile Cys Pro Met Arg Cys Ala Glu Asp Pro Asp Arg Leu Tyr Lys
85 90 95

Tyr Ala Thr Lys Leu Lys Lys Asn Cys Lys Glu Ile Thr Asp Lys Glu
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Leu Asp Lys Lys Met Lys Glu Leu Ala Ala Val Met Ser Asp Pro Asp
115 120 125

Leu Glu Thr Glu Thr Met Cys Leu His Asp Asp Glu Ser Cys Arg Tyr
130 135 140

Glu Gly Gln Val Ala Val Tyr Gln Asp Val Tyr Ala Val Asp Gly Pro
145 150 155 160

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Ile Gly Phe Asp Thr Thr Pro Phe Met Phe Lys Asn Leu Ala Gly Ala
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Tyr Pro Ser Tyr Ser Thr Asn Trp Ala Asp Glu Thr Val Leu Thr Ala
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Arg Asn Ile Gly Leu Cys Ser Ser Asp Val Met Glu Arg Ser Arg Arg
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Gly Met Ser Ile Leu Arg Lys Lys Tyr Leu Lys Pro Ser Asn Asn Val
225                 230                 235                 240

Leu Phe Ser Val Gly Ser Thr Ile Tyr His Glu Lys Arg Asp Leu Leu
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Arg Ser Trp His Leu Pro Ser Val Phe His Leu Arg Gly Lys Gln Asn
            260                 265                 270

Tyr Thr Cys Arg Cys Glu Thr Ile Val Ser Cys Asp Gly Tyr Val Val
        275                 280                 285

Lys Arg Ile Ala Ile Ser Pro Gly Leu Tyr Gly Lys Pro Ser Gly Tyr
    290                 295                 300

Ala Ala Thr Met His Arg Glu Gly Phe Leu Cys Cys Lys Val Thr Asp
305                 310                 315                 320

Thr Leu Asn Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Val Pro
                325                 330                 335

Ala Thr Leu Cys Asp Gln Met Thr Gly Ile Leu Ala Thr Asp Val Ser
            340                 345                 350

Ala Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val
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Glu Asp Gln Glu Asp Glu Arg Pro Leu Gly Leu Arg Asp Arg Gln Leu
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Val Met Gly Cys Cys Trp Ala Phe Arg Arg His Lys Ile Thr Ser Ile
            420                 425                 430

Tyr Lys Arg Pro Asp Thr Gln Thr Ile Ile Lys Val Asn Ser Asp Phe
        435                 440                 445

His Ser Phe Val Leu Pro Arg Ile Gly Ser Asn Thr Leu Glu Ile Gly
    450                 455                 460

Leu Arg Thr Arg Ile Arg Lys Met Leu Glu Glu His Lys Glu Pro Ser
465                 470                 475                 480

Pro Leu Ile Thr Ala Glu Asp Val Gln Glu Ala Lys Cys Ala Ala Asp
                485                 490                 495

Glu Ala Lys Glu Val Arg Glu Ala Glu Glu Leu Arg Ala Ala Leu Pro
            500                 505                 510

Pro Leu Ala Ala Asp Val Glu Glu Pro Thr Leu Glu Ala Asp Val Asp
        515                 520                 525

Leu Met Leu Gln Glu Ala Gly Ala Gly Ser Val Glu Thr Pro Arg Gly
    530                 535                 540

Leu Ile Lys Val Thr Ser Tyr Asp Gly Glu Asp Lys Ile Gly Ser Tyr
545                 550                 555                 560

Ala Val Leu Ser Pro Gln Ala Val Leu Lys Ser Glu Lys Leu Ser Cys
                565                 570                 575

Ile His Pro Leu Ala Glu Gln Val Ile Val Ile Thr His Ser Gly Arg
            580                 585                 590
```

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Lys Gly Arg Tyr Ala Val Glu Pro Tyr His Gly Lys Val Val Val Pro
        595                 600                 605

Glu Gly His Ala Ile Pro Val Gln Asp Phe Gln Ala Leu Ser Glu Ser
    610                 615                 620

Ala Thr Ile Val Tyr Asn Glu Arg Glu Phe Val Asn Arg Tyr Leu His
625                 630                 635                 640

His Ile Ala Thr His Gly Gly Ala Leu Asn Thr Asp Glu Glu Tyr Tyr
                645                 650                 655

Lys Thr Val Lys Pro Ser Glu His Asp Gly Glu Tyr Leu Tyr Asp Ile
            660                 665                 670

Asp Arg Lys Gln Cys Val Lys Lys Glu Leu Val Thr Gly Leu Gly Leu
        675                 680                 685

Thr Gly Glu Leu Val Asp Pro Pro Phe His Glu Phe Ala Tyr Glu Ser
    690                 695                 700

Leu Arg Thr Arg Pro Ala Ala Pro Tyr Gln Val Pro Thr Ile Gly Val
705                 710                 715                 720

Tyr Gly Val Pro Gly Ser Gly Lys Ser Gly Ile Ile Lys Ser Ala Val
                725                 730                 735

Thr Lys Lys Asp Leu Val Val Ser Ala Lys Lys Glu Asn Cys Ala Glu
            740                 745                 750

Ile Ile Arg Asp Val Lys Lys Met Lys Gly Leu Asp Val Asn Ala Arg
        755                 760                 765

Thr Val Asp Ser Val Leu Leu Asn Gly Cys Lys His Pro Val Glu Thr
    770                 775                 780

Leu Tyr Ile Asp Glu Ala Phe Ala Cys His Ala Gly Thr Leu Arg Ala
785                 790                 795                 800
```

```
Leu Ile Ala Ile Ile Arg Pro Lys Lys Ala Val Leu Cys Gly Asp Pro
                805                 810                 815

Lys Gln Cys Gly Phe Phe Asn Met Met Cys Leu Lys Val His Phe Asn
            820                 825                 830

His Glu Ile Cys Thr Gln Val Phe His Lys Ser Ile Ser Arg Arg Cys
        835                 840                 845

Thr Lys Ser Val Thr Ser Val Val Ser Thr Leu Phe Tyr Asp Lys Lys
    850                 855                 860

Met Arg Thr Thr Asn Pro Lys Glu Thr Lys Ile Val Ile Asp Thr Thr
865                 870                 875                 880

Gly Ser Thr Lys Pro Lys Gln Asp Asp Leu Ile Leu Thr Cys Phe Arg
                885                 890                 895

Gly Trp Val Lys Gln Leu Gln Ile Asp Tyr Lys Gly Asn Glu Ile Met
            900                 905                 910

Thr Ala Ala Ala Ser Gln Gly Leu Thr Arg Lys Gly Val Tyr Ala Val
        915                 920                 925

Arg Tyr Lys Val Asn Glu Asn Pro Leu Tyr Ala Pro Thr Ser Glu His
    930                 935                 940

Val Asn Val Leu Leu Thr Arg Thr Glu Asp Arg Ile Val Trp Lys Thr
945                 950                 955                 960

Leu Ala Gly Asp Pro Trp Ile Lys Thr Leu Thr Ala Lys Tyr Pro Gly
                965                 970                 975

Asn Phe Thr Ala Thr Ile Glu Glu Trp Gln Ala Glu His Asp Ala Ile
            980                 985                 990

Met Arg His Ile Leu Glu Arg Pro  Asp Pro Thr Asp Val  Phe Gln Asn
        995                 1000                1005

Lys Ala  Asn Val Cys Trp Ala  Lys Ala Leu Val Pro  Val Leu Lys
    1010                1015                1020
```

```
Thr Ala  Gly Ile Asp Met Thr  Thr Glu Gln Trp Asn  Thr Val Asp
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Tyr Phe  Glu Thr Asp Lys Ala  His Ser Ala Glu Ile  Val Leu Asn
    1040                1045                1050

Gln Leu  Cys Val Arg Phe Phe  Gly Leu Asp Leu Asp  Ser Gly Leu
    1055                1060                1065

Phe Ser  Ala Pro Thr Val Pro  Leu Ser Ile Arg Asn  Asn His Trp
    1070                1075                1080

Asp Asn  Ser Pro Ser Pro Asn  Met Tyr Gly Leu Asn  Lys Glu Val
    1085                1090                1095

Val Arg  Gln Leu Ser Arg Arg  Tyr Pro Gln Leu Pro  Arg Ala Val
    1100                1105                1110

Ala Thr  Gly Arg Val Tyr Asp  Met Asn Thr Gly Thr  Leu Arg Asn
    1115                1120                1125

Tyr Asp  Pro Arg Ile Asn Leu  Val Pro Val Asn Arg  Arg Leu Pro
    1130                1135                1140

His Ala  Leu Val Leu His His  Asn Glu His Pro Gln  Ser Asp Phe
    1145                1150                1155

Ser Ser  Phe Val Ser Lys Leu  Lys Gly Arg Thr Val  Leu Val Val
    1160                1165                1170

Gly Glu  Lys Leu Ser Val Pro  Gly Lys Met Val Asp  Trp Leu Ser
    1175                1180                1185

Asp Arg  Pro Glu Ala Thr Phe  Arg Ala Arg Leu Asp  Leu Gly Ile
    1190                1195                1200

Pro Gly  Asp Val Pro Lys Tyr  Asp Ile Ile Phe Val  Asn Val Arg
    1205                1210                1215
```

```
Thr Pro  Tyr Lys Tyr His His  Tyr Gln Gln Cys Glu  Asp His Ala
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Ile Lys  Leu Ser Met Leu Thr  Lys Lys Ala Cys Leu  His Leu Asn
    1235                 1240                 1245

Pro Gly  Gly Thr Cys Val Ser  Ile Gly Tyr Gly Tyr  Ala Asp Arg
    1250                 1255                 1260

Ala Ser  Glu Ser Ile Ile Gly  Ala Ile Ala Arg Leu  Phe Lys Phe
    1265                 1270                 1275

Ser Arg  Val Cys Lys Pro Lys  Ser Ser Leu Glu Glu  Thr Glu Val
    1280                 1285                 1290

Leu Phe  Val Phe Ile Gly Tyr  Asp Arg Lys Ala Arg  Thr His Asn
    1295                 1300                 1305

Pro Tyr  Lys Leu Ser Ser Thr  Leu Thr Asn Ile Tyr  Thr Gly Ser
    1310                 1315                 1320

Arg Leu  His Glu Ala Gly Cys  Ala Pro Ser Tyr His  Val Val Arg
    1325                 1330                 1335

Gly Asp  Ile Ala Thr Ala Thr  Glu Gly Val Ile Ile  Asn Ala Ala
    1340                 1345                 1350

Asn Ser  Lys Gly Gln Pro Gly  Gly Gly Val Cys Gly  Ala Leu Tyr
    1355                 1360                 1365

Lys Lys  Phe Pro Glu Ser Phe  Asp Leu Gln Pro Ile  Glu Val Gly
    1370                 1375                 1380

Lys Ala  Arg Leu Val Lys Gly  Ala Ala Lys His Ile  Ile His Ala
    1385                 1390                 1395

Val Gly  Pro Asn Phe Asn Lys  Val Ser Glu Val Glu  Gly Asp Lys
    1400                 1405                 1410

Gln Leu  Ala Glu Ala Tyr Glu  Ser Ile Ala Lys Ile  Val Asn Asp
    1415                 1420                 1425
```

```
Asn Asn  Tyr Lys Ser Val Ala  Ile Pro Leu Leu Ser  Thr Gly Ile
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Phe Ser  Gly Asn Lys Asp Arg  Leu Thr Gln Ser Leu  Asn His Leu
    1445                1450                1455

Leu Thr  Ala Leu Asp Thr Thr  Asp Ala Asp Val Ala  Ile Tyr Cys
    1460                1465                1470

Arg Asp  Lys Lys Trp Glu Met  Thr Leu Lys Glu Ala  Val Ala Arg
    1475                1480                1485

Arg Glu  Ala Val Glu Glu Ile  Cys Ile Ser Asp Asp  Ser Ser Val
    1490                1495                1500

Thr Glu  Pro Asp Ala Glu Leu  Val Arg Val His Pro  Lys Ser Ser
    1505                1510                1515

Leu Ala  Gly Arg Lys Gly Tyr  Ser Thr Ser Asp Gly  Lys Thr Phe
    1520                1525                1530

Ser Tyr  Leu Glu Gly Thr Lys  Phe His Gln Ala Ala  Lys Asp Ile
    1535                1540                1545

Ala Glu  Ile Asn Ala Met Trp  Pro Val Ala Thr Glu  Ala Asn Glu
    1550                1555                1560

Gln Val  Cys Met Tyr Ile Leu  Gly Glu Ser Met Ser  Ser Ile Arg
    1565                1570                1575

Ser Lys  Cys Pro Val Glu Glu  Ser Glu Ala Ser Thr  Pro Pro Ser
    1580                1585                1590

Thr Leu  Pro Cys Leu Cys Ile  His Ala Met Thr Pro  Glu Arg Val
    1595                1600                1605

Gln Arg  Leu Lys Ala Ser Arg  Pro Glu Gln Ile Thr  Val Cys Ser
    1610                1615                1620
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```
Ser Phe  Pro Leu Pro Lys Tyr  Arg Ile Thr Gly Val  Gln Lys Ile
    1625                1630                1635

Gln Cys  Ser Gln Pro Ile Leu  Phe Ser Pro Lys Val  Pro Ala Tyr
    1640                1645                1650

Ile His  Pro Arg Lys Tyr Leu  Val Glu Thr Pro Pro  Val Asp Glu
    1655                1660                1665

Thr Pro  Glu Pro Ser Ala Glu  Asn Gln Ser Thr Glu  Gly Thr Pro
    1670                1675                1680

Glu Gln  Pro Pro Leu Ile Thr  Glu Asp Glu Thr Arg  Thr Arg Thr
    1685                1690                1695

Pro Glu  Pro Ile Ile Ile Glu  Glu Glu Glu Glu Asp  Ser Ile Ser
    1700                1705                1710

Leu Leu  Ser Asp Gly Pro Thr  His Gln Val Leu Gln  Val Glu Ala
    1715                1720                1725

Asp Ile  His Gly Pro Pro Ser  Val Ser Ser Ser Ser  Trp Ser Ile
    1730                1735                1740

Pro His  Ala Ser Asp Phe Asp  Val Asp Ser Leu Ser  Ile Leu Asp
    1745                1750                1755

Thr Leu  Glu Gly Ala Ser Val  Thr Ser Gly Ala Thr  Ser Ala Glu
    1760                1765                1770

Thr Asn  Ser Tyr Phe Ala Lys  Ser Met Glu Phe Leu  Ala Arg Pro
    1775                1780                1785

Val Pro  Ala Pro Arg Thr Val  Phe Arg Asn Pro Pro  His Pro Ala
    1790                1795                1800

Pro Arg  Thr Arg Thr Pro Ser  Leu Ala Pro Ser Arg  Ala Cys Ser
    1805                1810                1815

Arg Thr  Ser Leu Val Ser Thr  Pro Pro Gly Val Asn  Arg Val Ile
    1820                1825                1830
```

```
Thr Arg  Glu Glu Leu Glu Ala  Leu Thr Pro Ser Arg  Thr Pro Ser
    1835                1840                1845

Arg Ser  Val Ser Arg Thr Ser  Leu Val Ser Asn Pro  Pro Gly Val
    1850                1855                1860

Asn Arg  Val Ile Thr Arg Glu  Glu Phe Glu Ala Phe  Val Ala Gln
    1865                1870                1875

Gln Gln  Arg Arg Phe Asp Ala  Gly Ala Tyr Ile Phe  Ser Ser Asp
    1880                1885                1890

Thr Gly  Gln Gly His Leu Gln  Gln Lys Ser Val Arg  Gln Thr Val
    1895                1900                1905

Leu Ser  Glu Val Val Leu Glu  Arg Thr Glu Leu Glu  Ile Ser Tyr
    1910                1915                1920

Ala Pro  Arg Leu Asp Gln Glu  Lys Glu Glu Leu Leu  Arg Lys Lys
    1925                1930                1935

Leu Gln  Leu Asn Pro Thr Pro  Ala Asn Arg Ser Arg  Tyr Gln Ser
    1940                1945                1950

Arg Lys  Val Glu Asn Met Lys  Ala Ile Thr Ala Arg  Arg Ile Leu
    1955                1960                1965

Gln Gly  Leu Gly His Tyr Leu  Lys Ala Glu Gly Lys  Val Glu Cys
    1970                1975                1980

Tyr Arg  Thr Leu His Pro Val  Pro Leu Tyr Ser Ser  Ser Val Asn
    1985                1990                1995

Arg Ala  Phe Ser Ser Pro Lys  Val Ala Val Glu Ala  Cys Asn Ala
    2000                2005                2010

Met Leu  Lys Glu Asn Phe Pro  Thr Val Ala Ser Tyr  Cys Ile Ile
    2015                2020                2025
```

```
Pro Glu  Tyr Asp Ala Tyr Leu  Asp Met Val Asp Gly  Ala Ser Cys
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Cys Leu  Asp Thr Ala Ser Phe  Cys Pro Ala Lys Leu  Arg Ser Phe
    2045                 2050                 2055

Pro Lys  Lys His Ser Tyr Leu  Glu Pro Thr Ile Arg  Ser Ala Val
    2060                 2065                 2070

Pro Ser  Ala Ile Gln Asn Thr  Leu Gln Asn Val Leu  Ala Ala Ala
    2075                 2080                 2085

Thr Lys  Arg Asn Cys Asn Val  Thr Gln Met Arg Glu  Leu Pro Val
    2090                 2095                 2100

Leu Asp  Ser Ala Ala Phe Asn  Val Glu Cys Phe Lys  Lys Tyr Ala
    2105                 2110                 2115

Cys Asn  Asn Glu Tyr Trp Glu  Thr Phe Lys Glu Asn  Pro Ile Arg
    2120                 2125                 2130

Leu Thr  Glu Glu Asn Val Val  Asn Tyr Ile Thr Lys  Leu Lys Gly
    2135                 2140                 2145

Pro Lys  Ala Ala Ala Leu Phe  Ala Lys Thr His Asn  Leu Asn Met
    2150                 2155                 2160

Leu Gln  Asp Ile Pro Met Asp  Arg Phe Val Met Asp  Leu Lys Arg
    2165                 2170                 2175

Asp Val  Lys Val Thr Pro Gly  Thr Lys His Thr Glu  Glu Arg Pro
    2180                 2185                 2190

Lys Val  Gln Val Ile Gln Ala  Ala Asp Pro Leu Ala  Thr Ala Tyr
    2195                 2200                 2205

Leu Cys  Gly Ile His Arg Glu  Leu Val Arg Arg Leu  Asn Ala Val
    2210                 2215                 2220

Leu Leu  Pro Asn Ile His Thr  Leu Phe Asp Met Ser  Ala Glu Asp
    2225                 2230                 2235
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```
Phe Asp  Ala Ile Ile Ala Glu  His Phe Gln Pro Gly  Asp Cys Val
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Leu Glu  Thr Asp Ile Ala Ser  Phe Asp Lys Ser Glu  Asp Asp Ala
    2255                2260                2265

Met Ala  Leu Thr Ala Leu Met  Ile Leu Glu Asp Leu  Gly Val Asp
    2270                2275                2280

Ala Glu  Leu Leu Thr Leu Ile  Glu Ala Ala Phe Gly  Glu Ile Ser
    2285                2290                2295

Ser Ile  His Leu Pro Thr Lys  Thr Lys Phe Lys Phe  Gly Ala Met
    2300                2305                2310

Met Lys  Ser Gly Met Phe Leu  Thr Leu Phe Val Asn  Thr Val Ile
    2315                2320                2325

Asn Ile  Val Ile Ala Ser Arg  Val Leu Arg Glu Arg  Leu Thr Gly
    2330                2335                2340

Ser Pro  Cys Ala Ala Phe Ile  Gly Asp Asp Asn Ile  Val Lys Gly
    2345                2350                2355

Val Lys  Ser Asp Lys Leu Met  Ala Asp Arg Cys Ala  Thr Trp Leu
    2360                2365                2370

Asn Met  Glu Val Lys Ile Ile  Asp Ala Val Val Gly  Glu Lys Ala
    2375                2380                2385

Pro Tyr  Phe Cys Gly Gly Phe  Ile Leu Cys Asp Ser  Val Thr Gly
    2390                2395                2400

Thr Ala  Cys Arg Val Ala Asp  Pro Leu Lys Arg Leu  Phe Lys Leu
    2405                2410                2415

Gly Lys  Pro Leu Ala Ala Asp  Asp Glu His Asp Asp  Asp Arg Arg
    2420                2425                2430
```

Arg Ala Leu His Glu Glu Ser Thr Arg Trp Asn Arg Val Gly Ile
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Leu Ser Glu Leu Cys Lys Ala Val Glu Ser Arg Tyr Glu Thr Val
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Gly Thr Ser Ile Ile Val Met Ala Met Thr Thr Leu Ala Ser Ser
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Val Lys Ser Phe Ser Tyr Leu Arg Gly Ala Pro Ile Thr Leu Tyr
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35 40 45

Lys Leu Ile Glu Thr Glu Val Asp Pro Ser Asp Thr Ile Leu Asp Ile
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```
Gly Ser Ala Pro Ala Arg Arg Met Tyr Ser Lys His Lys Tyr His Cys
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Ile Cys Pro Met Arg Cys Ala Glu Asp Pro Asp Arg Leu Tyr Lys Tyr
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Ala Thr Lys Leu Lys Lys Asn Cys Lys Glu Ile Thr Asp Lys Glu Leu
            100                 105                 110

Asp Lys Lys Met Lys Glu Leu Ala Ala Val Met Ser Asp Pro Asp Leu
        115                 120                 125

Glu Thr Glu Thr Met Cys Leu His Asp Asp Glu Ser Cys Arg Tyr Glu
    130                 135                 140

Gly Gln Val Ala Val Tyr Gln Asp Val Tyr Ala Val Asp Gly Pro Thr
145                 150                 155                 160

Ser Leu Tyr His Gln Ala Asn Lys Gly Val Arg Val Ala Tyr Trp Ile
                165                 170                 175

Gly Phe Asp Thr Thr Pro Phe Met Phe Lys Asn Leu Ala Gly Ala Tyr
            180                 185                 190

Pro Ser Tyr Ser Thr Asn Trp Ala Asp Glu Thr Val Leu Thr Ala Arg
        195                 200                 205

Asn Ile Gly Leu Cys Ser Ser Asp Val Met Glu Arg Ser Arg Arg Gly
    210                 215                 220

Met Ser Ile Leu Arg Lys Lys Tyr Leu Lys Pro Ser Asn Asn Val Leu
225                 230                 235                 240

Phe Ser Val Gly Ser Thr Ile Tyr His Glu Lys Arg Asp Leu Leu Arg
                245                 250                 255

Ser Trp His Leu Pro Ser Val Phe His Leu Arg Gly Lys Gln Asn Tyr
            260                 265                 270

Thr Cys Arg Cys Glu Thr Ile Val Ser Cys Asp Gly Tyr Val Val Lys
        275                 280                 285
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Arg Ile Ala Ile Ser Pro Gly Leu Tyr Gly Lys Pro Ser Gly Tyr Ala
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Ala Thr Met His Arg Glu Gly Phe Leu Cys Cys Lys Val Thr Asp Thr
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Leu Asn Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Val Pro Ala
                325                 330                 335

Thr Leu Cys Asp Gln Met Thr Gly Ile Leu Ala Thr Asp Val Ser Ala
            340                 345                 350

Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val Val
        355                 360                 365

Asn Gly Arg Thr Gln Arg Asn Thr Asn Thr Met Lys Asn Tyr Leu Leu
    370                 375                 380

Pro Val Val Ala Gln Ala Phe Ala Arg Trp Ala Lys Glu Tyr Lys Glu
385                 390                 395                 400

Asp Gln Glu Asp Glu Arg Pro Leu Gly Leu Arg Asp Arg Gln Leu Val
                405                 410                 415

Met Gly Cys Cys Trp Ala Phe Arg Arg His Lys Ile Thr Ser Ile Tyr
            420                 425                 430

Lys Arg Pro Asp Thr Gln Thr Ile Ile Lys Val Asn Ser Asp Phe His
        435                 440                 445

Ser Phe Val Leu Pro Arg Ile Gly Ser Asn Thr Leu Glu Ile Gly Leu
    450                 455                 460

Arg Thr Arg Ile Arg Lys Met Leu Glu Glu His Lys Glu Pro Ser Pro
465                 470                 475                 480

Leu Ile Thr Ala Glu Asp Val Gln Glu Ala Lys Cys Ala Ala Asp Glu
                485                 490                 495
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Ala Lys Glu Val Arg Glu Ala Glu Glu Leu Arg Ala Ala Leu Pro Pro
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Leu Ala Ala Asp Val Glu Glu Pro Thr Leu Glu Ala Asp Val Asp Leu
        515                 520                 525

Met Leu Gln Glu Ala Gly Ala Gly Ser Val Glu Thr Pro Arg Gly Leu
    530                 535                 540

Ile Lys Val Thr Ser Tyr Asp Gly Glu Asp Lys Ile Gly Ser Tyr Ala
545                 550                 555                 560

Val Leu Ser Pro Gln Ala Val Leu Lys Ser Glu Lys Leu Ser Cys Ile
                565                 570                 575

His Pro Leu Ala Glu Gln Val Ile Val Ile Thr His Ser Gly Arg Lys
            580                 585                 590

Gly Arg Tyr Ala Val Glu Pro Tyr His Gly Lys Val Val Val Pro Glu
        595                 600                 605

Gly His Ala Ile Pro Val Gln Asp Phe Gln Ala Leu Ser Glu Ser Ala
    610                 615                 620

Thr Ile Val Tyr Asn Glu Arg Glu Phe Val Asn Arg Tyr Leu His His
625                 630                 635                 640

Ile Ala Thr His Gly Gly Ala Leu Asn Thr Asp Glu Glu Tyr Tyr Lys
                645                 650                 655

Thr Val Lys Pro Ser Glu His Asp Gly Glu Tyr Leu Tyr Asp Ile Asp
            660                 665                 670

Arg Lys Gln Cys Val Lys Lys Glu Leu Val Thr Gly Leu Gly Leu Thr
        675                 680                 685

Gly Glu Leu Val Asp Pro Pro Phe His Glu Phe Ala Tyr Glu Ser Leu
    690                 695                 700

Arg Thr Arg Pro Ala Ala Pro Tyr Gln Val Pro Thr Ile Gly Val Tyr
705                 710                 715                 720
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Gly Val Pro Gly Ser Gly Lys Ser Gly Ile Ile Lys Ser Ala Val Thr
                725                 730                 735

Lys Lys Asp Leu Val Val Ser Ala Lys Lys Glu Asn Cys Ala Glu Ile
            740                 745                 750

Ile Arg Asp Val Lys Lys Met Lys Gly Leu Asp Val Asn Ala Arg Thr
        755                 760                 765

Val Asp Ser Val Leu Leu Asn Gly Cys Lys His Pro Val Glu Thr Leu
    770                 775                 780

Tyr Ile Asp Glu Ala Phe Ala Cys His Ala Gly Thr Leu Arg Ala Leu
785                 790                 795                 800

Ile Ala Ile Ile Arg Pro Lys Lys Ala Val Leu Cys Gly Asp Pro Lys
                805                 810                 815

Gln Cys Gly Phe Phe Asn Met Met Cys Leu Lys Val His Phe Asn His
            820                 825                 830

Glu Ile Cys Thr Gln Val Phe His Lys Ser Ile Ser Arg Arg Cys Thr
        835                 840                 845

Lys Ser Val Thr Ser Val Val Ser Thr Leu Phe Tyr Asp Lys Lys Met
    850                 855                 860

Arg Thr Thr Asn Pro Lys Glu Thr Lys Ile Val Ile Asp Thr Thr Gly
865                 870                 875                 880

Ser Thr Lys Pro Lys Gln Asp Asp Leu Ile Leu Thr Cys Phe Arg Gly
                885                 890                 895

Trp Val Lys Gln Leu Gln Ile Asp Tyr Lys Gly Asn Glu Ile Met Thr
            900                 905                 910

Ala Ala Ala Ser Gln Gly Leu Thr Arg Lys Gly Val Tyr Ala Val Arg
        915                 920                 925
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```
Tyr Lys Val Asn Glu Asn Pro Leu Tyr Ala Pro Thr Ser Glu His Val
    930                 935                 940

Asn Val Leu Leu Thr Arg Thr Glu Asp Arg Ile Val Trp Lys Thr Leu
945                 950                 955                 960

Ala Gly Asp Pro Trp Ile Lys Thr Leu Thr Ala Lys Tyr Pro Gly Asn
                965                 970                 975

Phe Thr Ala Thr Ile Glu Glu Trp Gln Ala Glu His Asp Ala Ile Met
            980                 985                 990

Arg His Ile Leu Glu Arg Pro Asp  Pro Thr Asp Val Phe  Gln Asn Lys
        995                 1000                1005

Ala Asn  Val Cys Trp Ala Lys  Ala Leu Val Pro Val  Leu Lys Thr
    1010                1015                1020

Ala Gly  Ile Asp Met Thr Thr  Glu Gln Trp Asn Thr  Val Asp Tyr
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Phe Glu  Thr Asp Lys Ala His  Ser Ala Glu Ile Val  Leu Asn Gln
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Leu Cys  Val Arg Phe Phe Gly  Leu Asp Leu Asp Ser  Gly Leu Phe
    1055                1060                1065

Ser Ala  Pro Thr Val Pro Leu  Ser Ile Arg Asn Asn  His Trp Asp
    1070                1075                1080

Asn Ser  Pro Ser Pro Asn Met  Tyr Gly Leu Asn Lys  Glu Val Val
    1085                1090                1095

Arg Gln  Leu Ser Arg Arg Tyr  Pro Gln Leu Pro Arg  Ala Val Ala
    1100                1105                1110

Thr Gly  Arg Val Tyr Asp Met  Asn Thr Gly Thr Leu  Arg Asn Tyr
    1115                1120                1125

Asp Pro  Arg Ile Asn Leu Val  Pro Val Asn Arg Arg  Leu Pro His
    1130                1135                1140
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Ala Leu  Val Leu His His Asn  Glu His Pro Gln Ser  Asp Phe Ser
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Ser Phe  Val Ser Lys Leu Lys  Gly Arg Thr Val Leu  Val Val Gly
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Glu Lys  Leu Ser Val Pro Gly  Lys Met Val Asp Trp  Leu Ser Asp
    1175                1180                1185

Arg Pro  Glu Ala Thr Phe Arg  Ala Arg Leu Asp Leu  Gly Ile Pro
    1190                1195                1200

Gly Asp  Val Pro Lys Tyr Asp  Ile Ile Phe Val Asn  Val Arg Thr
    1205                1210                1215

Pro Tyr  Lys Tyr His His Tyr  Gln Gln Cys Glu Asp  His Ala Ile
    1220                1225                1230

Lys Leu  Ser Met Leu Thr Lys  Lys Ala Cys Leu His  Leu Asn Pro
    1235                1240                1245

Gly Gly  Thr Cys Val Ser Ile  Gly Tyr Gly Tyr Ala  Asp Arg Ala
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Ser Glu  Ser Ile Ile Gly Ala  Ile Ala Arg Leu Phe  Lys Phe Ser
    1265                1270                1275

Arg Val  Cys Lys Pro Lys Ser  Ser Leu Glu Glu Thr  Glu Val Leu
    1280                1285                1290

Phe Val  Phe Ile Gly Tyr Asp  Arg Lys Ala Arg Thr  His Asn Pro
    1295                1300                1305

Tyr Lys  Leu Ser Ser Thr Leu  Thr Asn Ile Tyr Thr  Gly Ser Arg
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Leu His  Glu Ala Gly Cys Ala  Pro Ser Tyr His Val  Val Arg Gly
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Asp Ile  Ala Thr Ala Thr Glu  Gly Val Ile Ile Asn  Ala Ala Asn
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Ser Lys  Gly Gln Pro Gly Gly  Gly Val Cys Gly Ala  Leu Tyr Lys
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Lys Phe  Pro Glu Ser Phe Asp  Leu Gln Pro Ile Glu  Val Gly Lys
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Ala Arg  Leu Val Lys Gly Ala  Ala Lys His Ile Ile  His Ala Val
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Gly Pro  Asn Phe Asn Lys Val  Ser Glu Val Glu Gly  Asp Lys Gln
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Leu Ala  Glu Ala Tyr Glu Ser  Ile Ala Lys Ile Val  Asn Asp Asn
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Asn Tyr  Lys Ser Val Ala Ile  Pro Leu Leu Ser Thr  Gly Ile Phe
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Ser Gly  Asn Lys Asp Arg Leu  Thr Gln Ser Leu Asn  His Leu Leu
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Thr Ala  Leu Asp Thr Thr Asp  Ala Asp Val Ala Ile  Tyr Cys Arg
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Asp Lys  Lys Trp Glu Met Thr  Leu Lys Glu Ala Val  Ala Arg Arg
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Glu Ala  Val Glu Glu Ile Cys  Ile Ser Asp Asp Ser  Ser Val Thr
    1490                1495                1500

Glu Pro  Asp Ala Glu Leu Val  Arg Val His Pro Lys  Ser Ser Leu
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Ala Gly  Arg Lys Gly Tyr Ser  Thr Ser Asp Gly Lys  Thr Phe Ser
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Tyr Leu  Glu Gly Thr Lys Phe  His Gln Ala Ala Lys  Asp Ile Ala
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Glu Ile  Asn Ala Met Trp Pro  Val Ala Thr Glu Ala  Asn Glu Gln
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Val Cys  Met Tyr Ile Leu Gly  Glu Ser Met Ser Ser  Ile Arg Ser
    1565                1570                1575

Lys Cys  Pro Val Glu Glu Ser  Glu Ala Ser Thr Pro  Pro Ser Thr
    1580                1585                1590

Leu Pro  Cys Leu Cys Ile His  Ala Met Thr Pro Glu  Arg Val Gln
    1595                1600                1605

Arg Leu  Lys Ala Ser Arg Pro  Glu Gln Ile Thr Val  Cys Ser Ser
    1610                1615                1620

Phe Pro  Leu Pro Lys Tyr Arg  Ile Thr Gly Val Gln  Lys Ile Gln
    1625                1630                1635

Cys Ser  Gln Pro Ile Leu Phe  Ser Pro Lys Val Pro  Ala Tyr Ile
    1640                1645                1650

His Pro  Arg Lys Tyr Leu Val  Glu Thr Pro Pro Val  Asp Glu Thr
    1655                1660                1665

Pro Glu  Pro Ser Ala Glu Asn  Gln Ser Thr Glu Gly  Thr Pro Glu
    1670                1675                1680

Gln Pro  Pro Leu Ile Thr Glu  Asp Glu Thr Arg Thr  Arg Thr Pro
    1685                1690                1695

Glu Pro  Ile Ile Ile Glu Glu  Glu Glu Glu Asp Ser  Ile Ser Leu
    1700                1705                1710

Leu Ser  Asp Gly Pro Thr His  Gln Val Leu Gln Val  Glu Ala Asp
    1715                1720                1725

Ile His  Gly Pro Pro Ser Val  Ser Ser Ser Ser Trp  Ser Ile Pro
    1730                1735                1740
```

```
His Ala  Ser Asp Phe Asp Val  Asp Ser Leu Ser Ile  Leu Asp Thr
    1745                1750                1755

Leu Glu  Gly Ala Ser Val Thr  Ser Gly Ala Thr Ser  Ala Glu Thr
    1760                1765                1770

Asn Ser  Tyr Phe Ala Lys Ser  Met Glu Phe Leu Ala  Arg Pro Val
    1775                1780                1785

Pro Ala  Pro Arg Thr Val Phe  Arg Asn Pro Pro His  Pro Ala Pro
    1790                1795                1800

Arg Thr  Arg Thr Pro Ser Leu  Ala Pro Ser Arg Ala  Cys Ser Arg
    1805                1810                1815

Thr Ser  Leu Val Ser Thr Pro  Pro Gly Val Asn Arg  Val Ile Thr
    1820                1825                1830

Arg Glu  Glu Leu Glu Ala Leu  Thr Pro Ser Arg Thr  Pro Ser Arg
    1835                1840                1845

Ser Val  Ser Arg Thr Ser Leu  Val Ser Asn Pro Pro  Gly Val Asn
    1850                1855                1860

Arg Val  Ile Thr Arg Glu Glu  Phe Glu Ala Phe Val  Ala Gln Gln
    1865                1870                1875

Gln Arg  Arg Phe Asp Ala Gly  Ala Tyr Ile Phe Ser  Ser Asp Thr
    1880                1885                1890

Gly Gln  Gly His Leu Gln Gln  Lys Ser Val Arg Gln  Thr Val Leu
    1895                1900                1905

Ser Glu  Val Val Leu Glu Arg  Thr Glu Leu Glu Ile  Ser Tyr Ala
    1910                1915                1920

Pro Arg  Leu Asp Gln Glu Lys  Glu Glu Leu Leu Arg  Lys Lys Leu
    1925                1930                1935

Gln Leu  Asn Pro Thr Pro Ala  Asn Arg Ser Arg Tyr  Gln Ser Arg
    1940                1945                1950
```

```
Lys Val  Glu Asn Met Lys Ala  Ile Thr Ala Arg Arg  Ile Leu Gln
    1955                1960                1965

Gly Leu  Gly His Tyr Leu Lys  Ala Glu Gly Lys Val  Glu Cys Tyr
    1970                1975                1980

Arg Thr  Leu His Pro Val Pro  Leu Tyr Ser Ser Ser  Val Asn Arg
    1985                1990                1995

Ala Phe  Ser Ser Pro Lys Val  Ala Val Glu Ala Cys  Asn Ala Met
    2000                2005                2010

Leu Lys  Glu Asn Phe Pro Thr  Val Ala Ser Tyr Cys  Ile Ile Pro
    2015                2020                2025

Glu Tyr  Asp Ala Tyr Leu Asp  Met Val Asp Gly Ala  Ser Cys Cys
    2030                2035                2040

Leu Asp  Thr Ala Ser Phe Cys  Pro Ala Lys Leu Arg  Ser Phe Pro
    2045                2050                2055

Lys Lys  His Ser Tyr Leu Glu  Pro Thr Ile Arg Ser  Ala Val Pro
    2060                2065                2070

Ser Ala  Ile Gln Asn Thr Leu  Gln Asn Val Leu Ala  Ala Ala Thr
    2075                2080                2085

Lys Arg  Asn Cys Asn Val Thr  Gln Met Arg Glu Leu  Pro Val Leu
    2090                2095                2100

Asp Ser  Ala Ala Phe Asn Val  Glu Cys Phe Lys Lys  Tyr Ala Cys
    2105                2110                2115

Asn Asn  Glu Tyr Trp Glu Thr  Phe Lys Glu Asn Pro  Ile Arg Leu
    2120                2125                2130

Thr Glu  Glu Asn Val Val Asn  Tyr Ile Thr Lys Leu  Lys Gly Pro
    2135                2140                2145
```

```
Lys Ala  Ala Ala Leu Phe Ala  Lys Thr His Asn Leu  Asn Met Leu
    2150                 2155                 2160

Gln Asp  Ile Pro Met Asp Arg  Phe Val Met Asp Leu  Lys Arg Asp
    2165                 2170                 2175

Val Lys  Val Thr Pro Gly Thr  Lys His Thr Glu Glu  Arg Pro Lys
    2180                 2185                 2190

Val Gln  Val Ile Gln Ala Ala  Asp Pro Leu Ala Thr  Ala Tyr Leu
    2195                 2200                 2205

Cys Gly  Ile His Arg Glu Leu  Val Arg Arg Leu Asn  Ala Val Leu
    2210                 2215                 2220

Leu Pro  Asn Ile His Thr Leu  Phe Asp Met Ser Ala  Glu Asp Phe
    2225                 2230                 2235

Asp Ala  Ile Ile Ala Glu His  Phe Gln Pro Gly Asp  Cys Val Leu
    2240                 2245                 2250

Glu Thr  Asp Ile Ala Ser Phe  Asp Lys Ser Glu Asp  Asp Ala Met
    2255                 2260                 2265

Ala Leu  Thr Ala Leu Met Ile  Leu Glu Asp Leu Gly  Val Asp Ala
    2270                 2275                 2280

Glu Leu  Leu Thr Leu Ile Glu  Ala Ala Phe Gly Glu  Ile Ser Ser
    2285                 2290                 2295

Ile His  Leu Pro Thr Lys Thr  Lys Phe Lys Phe Gly  Ala Met Met
    2300                 2305                 2310

Lys Ser  Gly Met Phe Leu Thr  Leu Phe Val Asn Thr  Val Ile Asn
    2315                 2320                 2325

Ile Val  Ile Ala Ser Arg Val  Leu Arg Glu Arg Leu  Thr Gly Ser
    2330                 2335                 2340

Pro Cys  Ala Ala Phe Ile Gly  Asp Asp Asn Ile Val  Lys Gly Val
    2345                 2350                 2355
```

```
Lys Ser  Asp Lys Leu Met Ala  Asp Arg Cys Ala Thr  Trp Leu Asn
    2360                2365                2370


Met Glu  Val Lys Ile Ile Asp  Ala Val Val Gly Glu  Lys Ala Pro
    2375                2380                2385


Tyr Phe  Cys Gly Gly Phe Ile  Leu Cys Asp Ser Val  Thr Gly Thr
    2390                2395                2400


Ala Cys  Arg Val Ala Asp Pro  Leu Lys Arg Leu Phe  Lys Leu Gly
    2405                2410                2415


Lys Pro  Leu Ala Ala Asp Asp  Glu His Asp Asp Asp  Arg Arg Arg
    2420                2425                2430


Ala Leu  His Glu Glu Ser Thr  Arg Trp Asn Arg Val  Gly Ile Leu
    2435                2440                2445


Ser Glu  Leu Cys Lys Ala Val  Glu Ser Arg Tyr Glu  Thr Val Gly
    2450                2455                2460


Thr Ser  Ile Ile Val Met Ala  Met Thr Thr Leu Ala  Ser Ser Val
    2465                2470                2475


Lys Ser  Phe Ser Tyr Leu Arg  Gly Ala Pro Ile Thr  Leu Tyr Gly
    2480                2485                2490


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Met Pro Glu Lys Val His Val Asp Ile Glu Glu Asp Ser Pro Phe Leu
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Arg Ala Leu Gln Arg Ser Phe Pro Gln Phe Glu Val Glu Ala Lys Gln
            20                  25                  30
```

```
Val Thr Asp Asn Asp His Ala Asn Ala Arg Ala Phe Ser His Leu Ala
        35                  40                  45

Ser Lys Leu Ile Glu Thr Glu Val Asp Pro Ser Asp Thr Ile Leu Asp
    50                  55                  60

Ile Gly Ser Ala Pro Ala Arg Arg Met Tyr Ser Lys His Lys Tyr His
65                  70                  75                  80

Cys Ile Cys Pro Met Arg Cys Ala Glu Asp Pro Asp Arg Leu Tyr Lys
                85                  90                  95

Tyr Ala Thr Lys Leu Lys Lys Asn Cys Lys Glu Ile Thr Asp Lys Glu
            100                 105                 110

Leu Asp Lys Lys Met Lys Glu Leu Ala Ala Val Met Ser Asp Pro Asp
        115                 120                 125

Leu Glu Thr Glu Thr Met Cys Leu His Asp Asp Glu Ser Cys Arg Tyr
    130                 135                 140

Glu Gly Gln Val Ala Val Tyr Gln Asp Val Tyr Ala Val Asp Gly Pro
145                 150                 155                 160

Thr Ser Leu Tyr His Gln Ala Asn Lys Gly Val Arg Val Ala Tyr Trp
                165                 170                 175

Ile Gly Phe Asp Thr Thr Pro Phe Met Phe Lys Asn Leu Ala Gly Ala
            180                 185                 190

Tyr Pro Ser Tyr Ser Thr Asn Trp Ala Asp Glu Thr Val Leu Thr Ala
        195                 200                 205

Arg Asn Ile Gly Leu Cys Ser Ser Asp Val Met Glu Arg Ser Arg Arg
    210                 215                 220

Gly Met Ser Ile Leu Arg Lys Lys Tyr Leu Lys Pro Ser Asn Asn Val
225                 230                 235                 240
```

```
Leu Phe Ser Val Gly Ser Thr Ile Tyr His Glu Lys Arg Asp Leu Leu
                245                 250                 255

Arg Ser Trp His Leu Pro Ser Val Phe His Leu Arg Gly Lys Gln Asn
            260                 265                 270

Tyr Thr Cys Arg Cys Glu Thr Ile Val Ser Cys Asp Gly Tyr Val Val
        275                 280                 285

Lys Arg Ile Ala Ile Ser Pro Gly Leu Tyr Gly Lys Pro Ser Gly Tyr
    290                 295                 300

Ala Ala Thr Met His Arg Glu Gly Phe Leu Cys Cys Lys Val Thr Asp
305                 310                 315                 320

Thr Leu Asn Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Val Pro
                325                 330                 335

Ala Thr Leu Cys Asp Gln Met Thr Gly Ile Leu Ala Thr Asp Val Ser
            340                 345                 350

Ala Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val
        355                 360                 365

Val Asn Gly Arg Thr Gln Arg Asn Thr Asn Thr Met Lys Asn Tyr Leu
    370                 375                 380

Leu Pro Val Val Ala Gln Ala Phe Ala Arg Trp Ala Lys Glu Tyr Lys
385                 390                 395                 400

Glu Asp Gln Glu Asp Glu Arg Pro Leu Gly Leu Arg Asp Arg Gln Leu
                405                 410                 415

Val Met Gly Cys Cys Trp Ala Phe Arg Arg His Lys Ile Thr Ser Ile
            420                 425                 430

Tyr Lys Arg Pro Asp Thr Gln Thr Ile Ile Lys Val Asn Ser Asp Phe
        435                 440                 445

His Ser Phe Val Leu Pro Arg Ile Gly Ser Asn Thr Leu Glu Ile Gly
    450                 455                 460
```

```
Leu Arg Thr Arg Ile Arg Lys Met Leu Glu Glu His Lys Glu Pro Ser
465                 470                 475                 480

Pro Leu Ile Thr Ala Glu Asp Val Gln Glu Ala Lys Cys Ala Ala Asp
                485                 490                 495

Glu Ala Lys Glu Val Arg Glu Ala Glu Glu Leu Arg Ala Ala Leu Pro
            500                 505                 510

Pro Leu Ala Ala Asp Val Glu Glu Pro Thr Leu Glu Ala Asp Val Asp
        515                 520                 525

Leu Met Leu Gln Glu Ala Gly Ala Gly Ser Val Glu Thr Pro Arg Gly
    530                 535                 540

Leu Ile Lys Val Thr Ser Tyr Asp Gly Glu Asp Lys Ile Gly Ser Tyr
545                 550                 555                 560

Ala Val Leu Ser Pro Gln Ala Val Leu Lys Ser Glu Lys Leu Ser Cys
                565                 570                 575

Ile His Pro Leu Ala Glu Gln Val Ile Val Ile Thr His Ser Gly Arg
            580                 585                 590

Lys Gly Arg Tyr Ala Val Glu Pro Tyr His Gly Lys Val Val Val Pro
        595                 600                 605

Glu Gly His Ala Ile Pro Val Gln Asp Phe Gln Ala Leu Ser Glu Ser
    610                 615                 620

Ala Thr Ile Val Tyr Asn Glu Arg Glu Phe Val Asn Arg Tyr Leu His
625                 630                 635                 640

His Ile Ala Thr His Gly Gly Ala Leu Asn Thr Asp Glu Glu Tyr Tyr
                645                 650                 655

Lys Thr Val Lys Pro Ser Glu His Asp Gly Glu Tyr Leu Tyr Asp Ile
            660                 665                 670
```

```
Asp Arg Lys Gln Cys Val Lys Lys Glu Leu Val Thr Gly Leu Gly Leu
        675                 680                 685

Thr Gly Glu Leu Val Asp Pro Pro Phe His Glu Phe Ala Tyr Glu Ser
    690                 695                 700

Leu Arg Thr Arg Pro Ala Ala Pro Tyr Gln Val Pro Thr Ile Gly Val
705                 710                 715                 720

Tyr Gly Val Pro Gly Ser Gly Lys Ser Gly Ile Ile Lys Ser Ala Val
                725                 730                 735

Thr Lys Lys Asp Leu Val Val Ser Ala Lys Lys Glu Asn Cys Ala Glu
            740                 745                 750

Ile Ile Arg Asp Val Lys Lys Met Lys Gly Leu Asp Val Asn Ala Arg
        755                 760                 765

Thr Val Asp Ser Val Leu Leu Asn Gly Cys Lys His Pro Val Glu Thr
    770                 775                 780

Leu Tyr Ile Asp Glu Ala Phe Ala Cys His Ala Gly Thr Leu Arg Ala
785                 790                 795                 800

Leu Ile Ala Ile Ile Arg Pro Lys Lys Ala Val Leu Cys Gly Asp Pro
                805                 810                 815

Lys Gln Cys Gly Phe Phe Asn Met Met Cys Leu Lys Val His Phe Asn
            820                 825                 830

His Glu Ile Cys Thr Gln Val Phe His Lys Ser Ile Ser Arg Arg Cys
        835                 840                 845

Thr Lys Ser Val Thr Ser Val Val Ser Thr Leu Phe Tyr Asp Lys Lys
    850                 855                 860

Met Arg Thr Thr Asn Pro Lys Glu Thr Lys Ile Val Ile Asp Thr Thr
865                 870                 875                 880

Gly Ser Thr Lys Pro Lys Gln Asp Asp Leu Ile Leu Thr Cys Phe Arg
                885                 890                 895
```

```
Gly Trp Val Lys Gln Leu Gln Ile Asp Tyr Lys Gly Asn Glu Ile Met
            900                 905                 910

Thr Ala Ala Ala Ser Gln Gly Leu Thr Arg Lys Gly Val Tyr Ala Val
        915                 920                 925

Arg Tyr Lys Val Asn Glu Asn Pro Leu Tyr Ala Pro Thr Ser Glu His
    930                 935                 940

Val Asn Val Leu Leu Thr Arg Thr Glu Asp Arg Ile Val Trp Lys Thr
945                 950                 955                 960

Leu Ala Gly Asp Pro Trp Ile Lys Thr Leu Thr Ala Lys Tyr Pro Gly
                965                 970                 975

Asn Phe Thr Ala Thr Ile Glu Glu Trp Gln Ala Glu His Asp Ala Ile
            980                 985                 990

Met Arg His Ile Leu Glu Arg Pro  Asp Pro Thr Asp Val  Phe Gln Asn
        995                 1000                1005

Lys Ala  Asn Val Cys Trp Ala  Lys Ala Leu Val Pro  Val Leu Lys
    1010                1015                1020

Thr Ala  Gly Ile Asp Met Thr  Thr Glu Gln Trp Asn  Thr Val Asp
    1025                1030                1035

Tyr Phe  Glu Thr Asp Lys Ala  His Ser Ala Glu Ile  Val Leu Asn
    1040                1045                1050

Gln Leu  Cys Val Arg Phe Phe  Gly Leu Asp Leu Asp  Ser Gly Leu
    1055                1060                1065

Phe Ser  Ala Pro Thr Val Pro  Leu Ser Ile Arg Asn  Asn His Trp
    1070                1075                1080

Asp Asn  Ser Pro Ser Pro Asn  Met Tyr Gly Leu Asn  Lys Glu Val
    1085                1090                1095
```

```
Val Arg  Gln Leu Ser Arg Arg  Tyr Pro Gln Leu Pro  Arg Ala Val
    1100                1105                1110

Ala Thr  Gly Arg Val Tyr Asp  Met Asn Thr Gly Thr  Leu Arg Asn
    1115                1120                1125

Tyr Asp  Pro Arg Ile Asn Leu  Val Pro Val Asn Arg  Arg Leu Pro
    1130                1135                1140

His Ala  Leu Val Leu His His  Asn Glu His Pro Gln  Ser Asp Phe
    1145                1150                1155

Ser Ser  Phe Val Ser Lys Leu  Lys Gly Arg Thr Val  Leu Val Val
    1160                1165                1170

Gly Glu  Lys Leu Ser Val Pro  Gly Lys Met Val Asp  Trp Leu Ser
    1175                1180                1185

Asp Arg  Pro Glu Ala Thr Phe  Arg Ala Arg Leu Asp  Leu Gly Ile
    1190                1195                1200

Pro Gly  Asp Val Pro Lys Tyr  Asp Ile Ile Phe Val  Asn Val Arg
    1205                1210                1215

Thr Pro  Tyr Lys Tyr His His  Tyr Gln Gln Cys Glu  Asp His Ala
    1220                1225                1230

Ile Lys  Leu Ser Met Leu Thr  Lys Lys Ala Cys Leu  His Leu Asn
    1235                1240                1245

Pro Gly  Gly Thr Cys Val Ser  Ile Gly Tyr Gly Tyr  Ala Asp Arg
    1250                1255                1260

Ala Ser  Glu Ser Ile Ile Gly  Ala Ile Ala Arg Leu  Phe Lys Phe
    1265                1270                1275

Ser Arg  Val Cys Lys Pro Lys  Ser Ser Leu Glu Glu  Thr Glu Val
    1280                1285                1290

Leu Phe  Val Phe Ile Gly Tyr  Asp Arg Lys Ala Arg  Thr His Asn
    1295                1300                1305
```

```
Pro Tyr  Lys Leu Ser Ser Thr  Leu Thr Asn Ile Tyr  Thr Gly Ser
    1310                1315                1320

Arg Leu  His Glu Ala Gly Cys  Ala Pro Ser Tyr His  Val Val Arg
    1325                1330                1335

Gly Asp  Ile Ala Thr Ala Thr  Glu Gly Val Ile Ile  Asn Ala Ala
    1340                1345                1350

Asn Ser  Lys Gly Gln Pro Gly  Gly Gly Val Cys Gly  Ala Leu Tyr
    1355                1360                1365

Lys Lys  Phe Pro Glu Ser Phe  Asp Leu Gln Pro Ile  Glu Val Gly
    1370                1375                1380

Lys Ala  Arg Leu Val Lys Gly  Ala Ala Lys His Ile  Ile His Ala
    1385                1390                1395

Val Gly  Pro Asn Phe Asn Lys  Val Ser Glu Val Glu  Gly Asp Lys
    1400                1405                1410

Gln Leu  Ala Glu Ala Tyr Glu  Ser Ile Ala Lys Ile  Val Asn Asp
    1415                1420                1425

Asn Asn  Tyr Lys Ser Val Ala  Ile Pro Leu Leu Ser  Thr Gly Ile
    1430                1435                1440

Phe Ser  Gly Asn Lys Asp Arg  Leu Thr Gln Ser Leu  Asn His Leu
    1445                1450                1455

Leu Thr  Ala Leu Asp Thr Thr  Asp Ala Asp Val Ala  Ile Tyr Cys
    1460                1465                1470

Arg Asp  Lys Lys Trp Glu Met  Thr Leu Lys Glu Ala  Val Ala Arg
    1475                1480                1485

Arg Glu  Ala Val Glu Glu Ile  Cys Ile Ser Asp Asp  Ser Ser Val
    1490                1495                1500
```

```
Thr Glu  Pro Asp Ala Glu Leu  Val Arg Val His Pro  Lys Ser Ser
    1505                1510                1515

Leu Ala  Gly Arg Lys Gly Tyr  Ser Thr Ser Asp Gly  Lys Thr Phe
    1520                1525                1530

Ser Tyr  Leu Glu Gly Thr Lys  Phe His Gln Ala Ala  Lys Asp Ile
    1535                1540                1545

Ala Glu  Ile Asn Ala Met Trp  Pro Val Ala Thr Glu  Ala Asn Glu
    1550                1555                1560

Gln Val  Cys Met Tyr Ile Leu  Gly Glu Ser Met Ser  Ser Ile Arg
    1565                1570                1575

Ser Lys  Cys Pro Val Glu Glu  Ser Glu Ala Ser Thr  Pro Pro Ser
    1580                1585                1590

Thr Leu  Pro Cys Leu Cys Ile  His Ala Met Thr Pro  Glu Arg Val
    1595                1600                1605

Gln Arg  Leu Lys Ala Ser Arg  Pro Glu Gln Ile Thr  Val Cys Ser
    1610                1615                1620

Ser Phe  Pro Leu Pro Lys Tyr  Arg Ile Thr Gly Val  Gln Lys Ile
    1625                1630                1635

Gln Cys  Ser Gln Pro Ile Leu  Phe Ser Pro Lys Val  Pro Ala Tyr
    1640                1645                1650

Ile His  Pro Arg Lys Tyr Leu  Val Glu Thr Pro Pro  Val Asp Glu
    1655                1660                1665

Thr Pro  Glu Pro Ser Ala Glu  Asn Gln Ser Thr Glu  Gly Thr Pro
    1670                1675                1680

Glu Gln  Pro Pro Leu Ile Thr  Glu Asp Glu Thr Arg  Thr Arg Thr
    1685                1690                1695

Pro Glu  Pro Ile Ile Ile Glu  Glu Glu Glu Glu Asp  Ser Ile Ser
    1700                1705                1710
```

```
Leu Leu  Ser Asp Gly Pro Thr  His Gln Val Leu Gln  Val Glu Ala
    1715                1720                1725

Asp Ile  His Gly Pro Pro Ser  Val Ser Ser Ser Ser  Trp Ser Ile
    1730                1735                1740

Pro His  Ala Ser Asp Phe Asp  Val Asp Ser Leu Ser  Ile Leu Asp
    1745                1750                1755

Thr Leu  Glu Gly Ala Ser Val  Thr Ser Gly Ala Thr  Ser Ala Glu
    1760                1765                1770

Thr Asn  Ser Tyr Phe Ala Lys  Ser Met Glu Phe Leu  Ala Arg Pro
    1775                1780                1785

Val Pro  Ala Pro Arg Thr Val  Phe Arg Asn Pro Pro  His Pro Ala
    1790                1795                1800

Pro Arg  Thr Arg Thr Pro Ser  Leu Ala Pro Ser Arg  Ala Cys Ser
    1805                1810                1815

Arg Thr  Ser Leu Val Ser Thr  Pro Pro Gly Val Asn  Arg Val Ile
    1820                1825                1830

Thr Arg  Glu Glu Leu Glu Ala  Leu Thr Pro Ser Arg  Thr Pro Ser
    1835                1840                1845

Arg Ser  Val Ser Arg Thr Ser  Leu Val Ser Asn Pro  Pro Gly Val
    1850                1855                1860

Asn Arg  Val Ile Thr Arg Glu  Glu Phe Glu Ala Phe  Val Ala Gln
    1865                1870                1875

Gln Gln  Arg Arg Phe Asp Ala  Gly Ala Tyr Ile Phe  Ser Ser Asp
    1880                1885                1890

Thr Gly  Gln Gly His Leu Gln  Gln Lys Ser Val Arg  Gln Thr Val
    1895                1900                1905
```

```
Leu Ser  Glu Val Val Leu Glu  Arg Thr Glu Leu Glu  Ile Ser Tyr
    1910                 1915                 1920

Ala Pro  Arg Leu Asp Gln Glu  Lys Glu Glu Leu Leu  Arg Lys Lys
    1925                 1930                 1935

Leu Gln  Leu Asn Pro Thr Pro  Ala Asn Arg Ser Arg  Tyr Gln Ser
    1940                 1945                 1950

Arg Lys  Val Glu Asn Met Lys  Ala Ile Thr Ala Arg  Arg Ile Leu
    1955                 1960                 1965

Gln Gly  Leu Gly His Tyr Leu  Lys Ala Glu Gly Lys  Val Glu Cys
    1970                 1975                 1980

Tyr Arg  Thr Leu His Pro Val  Pro Leu Tyr Ser Ser  Ser Val Asn
    1985                 1990                 1995

Arg Ala  Phe Ser Ser Pro Lys  Val Ala Val Glu Ala  Cys Asn Ala
    2000                 2005                 2010

Met Leu  Lys Glu Asn Phe Pro  Thr Val Ala Ser Tyr  Cys Ile Ile
    2015                 2020                 2025

Pro Glu  Tyr Asp Ala Tyr Leu  Asp Met Val Asp Gly  Ala Ser Cys
    2030                 2035                 2040

Cys Leu  Asp Thr Ala Ser Phe  Cys Pro Ala Lys Leu  Arg Ser Phe
    2045                 2050                 2055

Pro Lys  Lys His Ser Tyr Leu  Glu Pro Thr Ile Arg  Ser Ala Val
    2060                 2065                 2070

Pro Ser  Ala Ile Gln Asn Thr  Leu Gln Asn Val Leu  Ala Ala Ala
    2075                 2080                 2085

Thr Lys  Arg Asn Cys Asn Val  Thr Gln Met Arg Glu  Leu Pro Val
    2090                 2095                 2100

Leu Asp  Ser Ala Ala Phe Asn  Val Glu Cys Phe Lys  Lys Tyr Ala
    2105                 2110                 2115
```

```
Cys Asn  Asn Glu Tyr Trp Glu  Thr Phe Lys Glu Asn  Pro Ile Arg
    2120                2125                2130

Leu Thr  Glu Glu Asn Val Val  Asn Tyr Ile Thr Lys  Leu Lys Gly
    2135                2140                2145

Pro Lys  Ala Ala Ala Leu Phe  Ala Lys Thr His Asn  Leu Asn Met
    2150                2155                2160

Leu Gln  Asp Ile Pro Met Asp  Arg Phe Val Met Asp  Leu Lys Arg
    2165                2170                2175

Asp Val  Lys Val Thr Pro Gly  Thr Lys His Thr Glu  Glu Arg Pro
    2180                2185                2190

Lys Val  Gln Val Ile Gln Ala  Ala Asp Pro Leu Ala  Thr Ala Tyr
    2195                2200                2205

Leu Cys  Gly Ile His Arg Glu  Leu Val Arg Arg Leu  Asn Ala Val
    2210                2215                2220

Leu Leu  Pro Asn Ile His Thr  Leu Phe Asp Met Ser  Ala Glu Asp
    2225                2230                2235

Phe Asp  Ala Ile Ile Ala Glu  His Phe Gln Pro Gly  Asp Cys Val
    2240                2245                2250

Leu Glu  Thr Asp Ile Ala Ser  Phe Asp Lys Ser Glu  Asp Asp Ala
    2255                2260                2265

Met Ala  Leu Thr Ala Leu Met  Ile Leu Glu Asp Leu  Gly Val Asp
    2270                2275                2280

Ala Glu  Leu Leu Thr Leu Ile  Glu Ala Ala Phe Gly  Glu Ile Ser
    2285                2290                2295

Ser Ile  His Leu Pro Thr Lys  Thr Lys Phe Lys Phe  Gly Ala Met
    2300                2305                2310
```

```
Met Lys  Ser Gly Met Phe Leu  Thr Leu Phe Val Asn  Thr Val Ile
    2315                 2320                 2325

Asn Ile  Val Ile Ala Ser Arg  Val Leu Arg Glu Arg  Leu Thr Gly
    2330                 2335                 2340

Ser Pro  Cys Ala Ala Phe Ile  Gly Asp Asp Asn Ile  Val Lys Gly
    2345                 2350                 2355

Val Lys  Ser Asp Lys Leu Met  Ala Asp Arg Cys Ala  Thr Trp Leu
    2360                 2365                 2370

Asn Met  Glu Val Lys Ile Ile  Asp Ala Val Val Gly  Glu Lys Ala
    2375                 2380                 2385

Pro Tyr  Phe Cys Gly Gly Phe  Ile Leu Cys Asp Ser  Val Thr Gly
    2390                 2395                 2400

Thr Ala  Cys Arg Val Ala Asp  Pro Leu Lys Arg Leu  Phe Lys Leu
    2405                 2410                 2415

Gly Lys  Pro Leu Ala Ala Asp  Asp Glu His Asp Asp  Asp Arg Arg
    2420                 2425                 2430

Arg Ala  Leu His Glu Glu Ser  Thr Arg Trp Asn Arg  Val Gly Ile
    2435                 2440                 2445

Leu Ser  Glu Leu Cys Lys Ala  Val Glu Ser Arg Tyr  Glu Thr Val
    2450                 2455                 2460

Gly Thr  Ser Ile Ile Val Met  Ala Met Thr Thr Leu  Ala Ser Ser
    2465                 2470                 2475

Val Lys  Ser Phe Ser Tyr Leu  Arg Gly Ala Pro Ile  Thr Leu Tyr
    2480                 2485                 2490

Gly
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Ala Leu Gln Arg Ser Phe Pro Gln Phe Glu Val Glu Ala Lys Gln Val
20 25 30

Thr Asp Asn Asp His Ala Asn Ala Arg Ala Phe Ser His Leu Ala Ser
35 40 45

Lys Leu Ile Glu Thr Glu Val Asp Pro Ser Asp Thr Ile Leu Asp Ile
50 55 60

Gly Ser Ala Pro Ala Arg Arg Met Tyr Ser Lys His Lys Tyr His Cys
65 70 75 80

Ile Cys Pro Met Arg Cys Ala Glu Asp Pro Asp Arg Leu Tyr Lys Tyr
85 90 95

Ala Thr Lys Leu Lys Lys Asn Cys Lys Glu Ile Thr Asp Lys Glu Leu
100 105 110

Asp Lys Lys Met Lys Glu Leu Ala Ala Val Met Ser Asp Pro Asp Leu
115 120 125

Glu Thr Glu Thr Met Cys Leu His Asp Asp Glu Ser Cys Arg Tyr Glu
130 135 140

Gly Gln Val Ala Val Tyr Gln Asp Val Tyr Ala Val Asp Gly Pro Thr
145 150 155 160

Ser Leu Tyr His Gln Ala Asn Lys Gly Val Arg Val Ala Tyr Trp Ile
165 170 175

Gly Phe Asp Thr Thr Pro Phe Met Phe Lys Asn Leu Ala Gly Ala Tyr
180 185 190

```
Pro Ser Tyr Ser Thr Asn Trp Ala Asp Glu Thr Val Leu Thr Ala Arg
        195                 200                 205

Asn Ile Gly Leu Cys Ser Ser Asp Val Met Glu Arg Ser Arg Arg Gly
    210                 215                 220

Met Ser Ile Leu Arg Lys Lys Tyr Leu Lys Pro Ser Asn Asn Val Leu
225                 230                 235                 240

Phe Ser Val Gly Ser Thr Ile Tyr His Glu Lys Arg Asp Leu Leu Arg
                245                 250                 255

Ser Trp His Leu Pro Ser Val Phe His Leu Arg Gly Lys Gln Asn Tyr
            260                 265                 270

Thr Cys Arg Cys Glu Thr Ile Val Ser Cys Asp Gly Tyr Val Val Lys
        275                 280                 285

Arg Ile Ala Ile Ser Pro Gly Leu Tyr Gly Lys Pro Ser Gly Tyr Ala
    290                 295                 300

Ala Thr Met His Arg Glu Gly Phe Leu Cys Cys Lys Val Thr Asp Thr
305                 310                 315                 320

Leu Asn Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Val Pro Ala
                325                 330                 335

Thr Leu Cys Asp Gln Met Thr Gly Ile Leu Ala Thr Asp Val Ser Ala
            340                 345                 350

Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val Val
        355                 360                 365

Asn Gly Arg Thr Gln Arg Asn Thr Asn Thr Met Lys Asn Tyr Leu Leu
    370                 375                 380

Pro Val Val Ala Gln Ala Phe Ala Arg Trp Ala Lys Glu Tyr Lys Glu
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Asp Gln Glu Asp Glu Arg Pro Leu Gly Leu Arg Asp Arg Gln Leu Val
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Met Gly Cys Cys Trp Ala Phe Arg Arg His Lys Ile Thr Ser Ile Tyr
            420                 425                 430

Lys Arg Pro Asp Thr Gln Thr Ile Ile Lys Val Asn Ser Asp Phe His
        435                 440                 445

Ser Phe Val Leu Pro Arg Ile Gly Ser Asn Thr Leu Glu Ile Gly Leu
    450                 455                 460

Arg Thr Arg Ile Arg Lys Met Leu Glu Glu His Lys Glu Pro Ser Pro
465                 470                 475                 480

Leu Ile Thr Ala Glu Asp Ile Gln Glu Ala Lys Cys Ala Ala Asp Glu
                485                 490                 495

Ala Lys Glu Val Arg Glu Ala Glu Glu Leu Arg Ala Ala Leu Pro Pro
            500                 505                 510

Leu Ala Ala Asp Phe Glu Glu Pro Thr Leu Glu Ala Asp Val Asp Leu
        515                 520                 525

Met Leu Gln Glu Ala Gly Ala Gly Ser Val Glu Thr Pro Arg Gly Leu
    530                 535                 540

Ile Lys Val Thr Ser Tyr Ala Gly Glu Asp Lys Ile Gly Ser Tyr Ala
545                 550                 555                 560

Val Leu Ser Pro Gln Ala Val Leu Lys Ser Glu Lys Leu Ser Cys Ile
                565                 570                 575

His Pro Leu Ala Glu Gln Val Ile Val Ile Thr His Ser Gly Arg Lys
            580                 585                 590

Gly Arg Tyr Ala Val Glu Pro Tyr His Gly Lys Val Val Val Pro Glu
        595                 600                 605

Gly His Ala Ile Pro Val Gln Asp Phe Gln Ala Leu Ser Glu Ser Ala
    610                 615                 620
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```
Thr Ile Val Tyr Asn Glu Arg Glu Phe Val Asn Arg Tyr Leu His His
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Ile Ala Thr His Gly Gly Ala Leu Asn Thr Asp Glu Glu Tyr Tyr Lys
                645                 650                 655

Thr Val Lys Pro Ser Glu His Asp Gly Glu Tyr Leu Tyr Asp Ile Asp
            660                 665                 670

Arg Lys Gln Cys Val Lys Lys Glu Leu Val Thr Gly Leu Gly Leu Thr
        675                 680                 685

Gly Glu Leu Val Asp Pro Pro Phe His Glu Phe Ala Tyr Glu Ser Leu
    690                 695                 700

Arg Thr Arg Pro Ala Ala Pro Tyr Gln Val Pro Thr Ile Gly Val Tyr
705                 710                 715                 720

Gly Val Pro Gly Ser Gly Lys Ser Gly Ile Ile Lys Ser Ala Val Thr
                725                 730                 735

Lys Lys Asp Leu Val Val Ser Ala Lys Lys Glu Asn Cys Ala Glu Ile
            740                 745                 750

Ile Arg Asp Val Lys Lys Met Lys Gly Leu Asp Val Asn Ala Arg Thr
        755                 760                 765

Val Asp Ser Val Leu Leu Asn Gly Cys Lys His Pro Val Glu Thr Leu
    770                 775                 780

Tyr Ile Asp Glu Ala Phe Ala Cys His Ala Gly Thr Leu Arg Ala Leu
785                 790                 795                 800

Ile Ala Ile Ile Arg Pro Lys Lys Ala Val Leu Cys Gly Asp Pro Lys
                805                 810                 815

Gln Cys Gly Phe Phe Asn Met Met Cys Leu Lys Val His Phe Asn His
            820                 825                 830
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Glu Ile Cys Thr Gln Val Phe His Lys Ser Ile Ser Arg Arg Cys Thr
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Lys Ser Val Thr Ser Val Val Ser Thr Leu Phe Tyr Asp Lys Arg Met
    850                 855                 860

Arg Thr Thr Asn Pro Lys Glu Thr Lys Ile Val Ile Asp Thr Thr Gly
865                 870                 875                 880

Ser Thr Lys Pro Lys Gln Asp Asp Leu Ile Leu Thr Cys Phe Arg Gly
                885                 890                 895

Trp Val Lys Gln Leu Gln Ile Asp Tyr Lys Gly Asn Glu Ile Met Thr
            900                 905                 910

Ala Ala Ala Ser Gln Gly Leu Thr Arg Lys Gly Val Tyr Ala Val Arg
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Tyr Lys Val Asn Glu Asn Pro Leu Tyr Ala Pro Thr Ser Glu His Val
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Asn Val Leu Leu Thr Arg Thr Glu Asp Arg Ile Val Trp Lys Thr Leu
945                 950                 955                 960

Ala Gly Asp Pro Trp Ile Lys Ile Leu Thr Ala Lys Tyr Pro Gly Asn
                965                 970                 975

Phe Thr Ala Thr Ile Glu Glu Trp Gln Ala Glu His Asp Ala Ile Met
            980                 985                 990

Arg His Ile Leu Glu Arg Pro Asp  Pro Thr Asp Val Phe  Gln Asn Lys
        995                 1000                1005

Ala Asn  Val Cys Trp Ala Lys  Ala Leu Val Pro Val  Leu Lys Thr
    1010                1015                1020

Ala Gly  Ile Asp Met Thr Thr  Glu Gln Trp Asn Thr  Val Asp Tyr
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Phe Glu  Thr Asp Lys Ala His  Ser Ala Glu Ile Val  Leu Asn Gln
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Leu Cys  Val Arg Phe Phe Gly  Leu Asp Leu Asp Ser  Gly Leu Phe
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Ser Ala  Pro Thr Val Pro Leu  Ser Ile Arg Asn Asn  His Trp Asp
    1070                1075                1080

Asn Ser  Pro Ser Pro Asn Met  Tyr Gly Leu Asn Lys  Glu Val Val
    1085                1090                1095

Arg Gln  Leu Ser Arg Arg Tyr  Pro Gln Leu Pro Arg  Ala Val Ala
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Thr Gly  Arg Val Tyr Asp Met  Asn Thr Gly Thr Leu  Arg Asn Tyr
    1115                1120                1125

Asp Pro  Arg Ile Asn Leu Val  Pro Val Asn Arg Arg  Leu Pro His
    1130                1135                1140

Ala Leu  Val Leu His His Asn  Glu His Pro Gln Ser  Asp Phe Ser
    1145                1150                1155

Ser Phe  Val Ser Lys Leu Lys  Gly Arg Thr Val Leu  Val Val Gly
    1160                1165                1170

Glu Lys  Leu Ser Val Pro Gly  Lys Lys Val Asp Trp  Leu Ser Asp
    1175                1180                1185

Gln Pro  Glu Ala Thr Phe Arg  Ala Arg Leu Asp Leu  Gly Ile Pro
    1190                1195                1200

Gly Asp  Val Pro Lys Tyr Asp  Ile Val Phe Ile Asn  Val Arg Thr
    1205                1210                1215

Pro Tyr  Lys Tyr His His Tyr  Gln Gln Cys Glu Asp  His Ala Ile
    1220                1225                1230

Lys Leu  Ser Met Leu Thr Lys  Lys Ala Cys Leu His  Leu Asn Pro
    1235                1240                1245
```

```
Gly Gly  Thr Cys Val Ser Ile  Gly Tyr Gly Tyr Ala  Asp Arg Ala
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Ser Glu  Ser Ile Ile Gly Ala  Ile Ala Arg Gln Phe  Lys Phe Ser
    1265                 1270                 1275

Arg Val  Cys Lys Pro Lys Ser  Ser His Glu Glu Thr  Glu Val Leu
    1280                 1285                 1290

Phe Val  Phe Ile Gly Tyr Asp  Arg Lys Ala Arg Thr  His Asn Pro
    1295                 1300                 1305

Tyr Lys  Leu Ser Ser Thr Leu  Thr Asn Ile Tyr Thr  Gly Ser Arg
    1310                 1315                 1320

Leu His  Glu Ala Gly Cys Ala  Pro Ser Tyr His Val  Val Arg Gly
    1325                 1330                 1335

Asp Ile  Ala Thr Ala Thr Glu  Gly Val Ile Ile Asn  Ala Ala Asn
    1340                 1345                 1350

Ser Lys  Gly Gln Pro Gly Gly  Gly Val Cys Gly Ala  Leu Tyr Lys
    1355                 1360                 1365

Lys Phe  Pro Glu Ser Phe Asp  Leu Gln Pro Ile Glu  Val Gly Lys
    1370                 1375                 1380

Ala Arg  Leu Val Lys Gly Ala  Ala Lys His Ile Ile  His Ala Val
    1385                 1390                 1395

Gly Pro  Asn Phe Asn Lys Val  Ser Glu Val Glu Gly  Asp Lys Gln
    1400                 1405                 1410

Leu Ala  Glu Ala Tyr Glu Ser  Ile Ala Lys Ile Val  Asn Asp Asn
    1415                 1420                 1425

Asn Tyr  Lys Ser Val Ala Ile  Pro Leu Leu Ser Thr  Gly Ile Phe
    1430                 1435                 1440

Ser Gly  Asn Lys Asp Arg Leu  Thr Gln Ser Leu Asn  His Leu Leu
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Thr Ala  Leu Asp Thr Thr Asp  Ala Asp Val Ala Ile  Tyr Cys Arg
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Asp Lys  Lys Trp Glu Met Thr  Leu Lys Glu Ala Val  Ala Arg Arg
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Glu Ala  Val Glu Glu Ile Cys  Ile Ser Asp Asp Ser  Ser Val Thr
    1490                1495                1500

Glu Pro  Asp Ala Glu Leu Val  Arg Val His Pro Lys  Ser Ser Leu
    1505                1510                1515

Ala Gly  Arg Lys Gly Tyr Ser  Thr Ser Asp Gly Lys  Thr Phe Ser
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Tyr Leu  Glu Gly Thr Lys Phe  His Gln Ala Ala Lys  Asp Ile Ala
    1535                1540                1545

Glu Ile  Asn Ala Met Trp Pro  Val Ala Thr Glu Ala  Asn Glu Gln
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Val Cys  Met Tyr Ile Leu Gly  Glu Ser Met Ser Ser  Ile Arg Ser
    1565                1570                1575

Lys Cys  Pro Val Glu Glu Ser  Glu Ala Ser Thr Pro  Pro Ser Thr
    1580                1585                1590

Leu Pro  Cys Leu Cys Ile His  Ala Met Thr Pro Glu  Arg Val Gln
    1595                1600                1605

Arg Leu  Lys Ala Ser Arg Pro  Glu Gln Ile Thr Val  Cys Ser Ser
    1610                1615                1620

Phe Pro  Leu Pro Lys Tyr Arg  Ile Thr Gly Val Gln  Lys Ile Gln
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Cys Ser  Gln Pro Ile Leu Phe  Ser Pro Lys Val Pro  Ala Tyr Ile
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His Pro  Arg Lys Tyr Leu Val  Glu Thr Pro Pro Val  Glu Glu Thr
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Pro Glu  Ser Pro Ala Glu Asn  Gln Ser Thr Glu Gly  Thr Pro Glu
    1670                1675                1680

Gln Pro  Ala Leu Val Asn Val  Asp Ala Thr Arg Thr  Arg Met Pro
    1685                1690                1695

Glu Pro  Ile Ile Ile Glu Glu  Glu Glu Glu Asp Ser  Ile Ser Leu
    1700                1705                1710

Leu Ser  Asp Gly Pro Thr His  Gln Val Leu Gln Val  Glu Ala Asp
    1715                1720                1725

Ile His  Gly Ser Pro Ser Val  Ser Ser Ser Ser Trp  Ser Ile Pro
    1730                1735                1740

His Ala  Ser Asp Phe Asp Val  Asp Ser Leu Ser Ile  Leu Asp Thr
    1745                1750                1755

Leu Asp  Gly Ala Ser Val Thr  Ser Gly Ala Val Ser  Ala Glu Thr
    1760                1765                1770

Asn Ser  Tyr Phe Ala Arg Ser  Met Glu Phe Arg Ala  Arg Pro Val
    1775                1780                1785

Pro Ala  Pro Arg Thr Val Phe  Arg Asn Pro Pro His  Pro Ala Pro
    1790                1795                1800

Arg Thr  Arg Thr Pro Pro Leu  Ala His Ser Arg Ala  Ser Ser Arg
    1805                1810                1815

Thr Ser  Leu Val Ser Thr Pro  Pro Gly Val Asn Arg  Val Ile Thr
    1820                1825                1830

Arg Glu  Glu Leu Glu Ala Leu  Thr Pro Ser Arg Ala  Pro Ser Arg
    1835                1840                1845

Ser Ala  Ser Arg Thr Ser Leu  Val Ser Asn Pro Pro  Gly Val Asn
    1850                1855                1860
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Arg Val  Ile Thr Arg Glu Glu  Phe Glu Ala Phe Val  Ala Gln Gln
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Gln Arg  Phe Asp Ala Gly Ala  Tyr Ile Phe Ser Ser  Asp Thr Gly
    1880                1885                1890

Gln Gly  His Leu Gln Gln Lys  Ser Val Arg Gln Thr  Val Leu Ser
    1895                1900                1905

Glu Val  Val Leu Glu Arg Thr  Glu Leu Glu Ile Ser  Tyr Ala Pro
    1910                1915                1920

Arg Leu  Asp Gln Glu Lys Glu  Glu Leu Leu Arg Lys  Lys Leu Gln
    1925                1930                1935

Leu Asn  Pro Thr Pro Ala Asn  Arg Ser Arg Tyr Gln  Ser Arg Arg
    1940                1945                1950

Val Glu  Asn Met Lys Ala Ile  Thr Ala Arg Arg Ile  Leu Gln Gly
    1955                1960                1965

Leu Gly  His Tyr Leu Lys Ala  Glu Gly Lys Val Glu  Cys Tyr Arg
    1970                1975                1980

Thr Leu  His Pro Val Pro Leu  Tyr Ser Ser Ser Val  Asn Arg Ala
    1985                1990                1995

Phe Ser  Ser Pro Lys Val Ala  Val Glu Ala Cys Asn  Ala Met Leu
    2000                2005                2010

Lys Glu  Asn Phe Pro Thr Val  Ala Ser Tyr Cys Ile  Ile Pro Glu
    2015                2020                2025

Tyr Asp  Ala Tyr Leu Asp Met  Val Asp Gly Ala Ser  Cys Cys Leu
    2030                2035                2040

Asp Thr  Ala Ser Phe Cys Pro  Ala Lys Leu Arg Ser  Phe Pro Lys
    2045                2050                2055
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Lys His  Ser Tyr Leu Glu Pro  Thr Ile Arg Ser Ala  Val Pro Ser
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Ala Ile  Gln Asn Thr Leu Gln  Asn Val Leu Ala Ala  Ala Thr Lys
    2075                2080                2085

Arg Asn  Cys Asn Val Thr Gln  Met Arg Glu Leu Pro  Val Leu Asp
    2090                2095                2100

Ser Ala  Ala Phe Asn Val Glu  Cys Phe Lys Lys Tyr  Ala Cys Asn
    2105                2110                2115

Asn Glu  Tyr Trp Glu Thr Phe  Lys Glu Asn Pro Ile  Arg Leu Thr
    2120                2125                2130

Glu Glu  Asn Val Val Asn Tyr  Ile Thr Lys Leu Lys  Gly Pro Lys
    2135                2140                2145

Ala Ala  Ala Leu Phe Ala Lys  Thr His Asn Leu Asn  Met Leu Gln
    2150                2155                2160

Asp Ile  Pro Met Asp Arg Phe  Val Met Asp Leu Lys  Arg Asp Val
    2165                2170                2175

Lys Val  Thr Pro Gly Thr Lys  His Thr Glu Glu Arg  Pro Lys Val
    2180                2185                2190

Gln Val  Ile Gln Ala Ala Asp  Pro Leu Ala Thr Ala  Asp Leu Cys
    2195                2200                2205

Gly Ile  His Arg Glu Leu Val  Arg Arg Leu Asn Ala  Val Leu Leu
    2210                2215                2220

Pro Asn  Ile His Thr Leu Phe  Asp Met Ser Ala Glu  Asp Phe Asp
    2225                2230                2235

Ala Ile  Ile Ala Glu His Phe  Gln Pro Gly Asp Cys  Val Leu Glu
    2240                2245                2250

Thr Asp  Ile Ala Ser Phe Asp  Lys Ser Glu Asp Asp  Ala Met Ala
    2255                2260                2265
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Leu Thr  Ala Leu Met Ile Leu  Glu Asp Leu Gly Val  Asp Ala Glu
    2270                2275                2280

Leu Leu  Thr Leu Ile Glu Ala  Ala Phe Gly Glu Ile  Ser Ser Ile
    2285                2290                2295

His Leu  Pro Thr Lys Thr Lys  Phe Lys Phe Gly Ala  Met Met Lys
    2300                2305                2310

Ser Gly  Met Phe Leu Thr Leu  Phe Val Asn Thr Val  Ile Asn Ile
    2315                2320                2325

Val Ile  Ala Ser Arg Val Leu  Arg Glu Arg Leu Thr  Gly Ser Pro
    2330                2335                2340

Cys Ala  Ala Phe Ile Gly Asp  Asp Asn Ile Val Lys  Gly Val Lys
    2345                2350                2355

Ser Asp  Lys Leu Met Ala Asp  Arg Cys Ala Thr Trp  Leu Asn Met
    2360                2365                2370

Glu Val  Lys Ile Ile Asp Ala  Val Val Gly Glu Lys  Ala Pro Tyr
    2375                2380                2385

Phe Cys  Gly Gly Phe Ile Leu  Cys Asp Ser Val Thr  Gly Thr Ala
    2390                2395                2400

Cys Arg  Val Ala Asp Pro Leu  Lys Arg Leu Phe Lys  Leu Gly Lys
    2405                2410                2415

Pro Leu  Ala Val Asp Asp Glu  His Asp Asp Asp Arg  Arg Arg Ala
    2420                2425                2430

Leu His  Glu Glu Ser Thr Arg  Trp Asn Arg Val Gly  Ile Leu Pro
    2435                2440                2445

Glu Leu  Cys Lys Ala Val Glu  Ser Arg Tyr Glu Thr  Val Gly Thr
    2450                2455                2460
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Ser Ile Ile Val Met Ala Met Thr Thr Leu Ala Ser Ser Val Lys
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Ser Phe Ser Tyr Leu Arg Gly Ala Pro Ile Thr Leu Tyr Gly
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caccccaaca ucuucgacgc cggggucgcc ggccugcccg acgacgaugc cggcgagcug 1440

cccgccgcag ucgucgugcu ggaacacggu aaaaccauga ccgagaagga gaucguggac 1500

uauguggcca gccagguuac aaccgccaag aagcugcgcg gugguguugu guucguggac 1560

gaggugccua aaggacugac cggcaaguug gacgcccgca agauccgcga gauucucauu 1620

aaggccaaga agggcggcaa gaucgccgug uaa 1653

<210> 87
<211> 57
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 87
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<210> 88
<211> 66
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 88
auggauccua gacgcuacgc cccaaugauc cgaccagcaa aacucgaugu acuuccgagg 60

aacuga 66

<210> 89
<211> 837

<212> RNA
<213> Artificial sequence

<220>
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<400> 89
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gagacauggg cuggaucucu gagcgaggug accggccagg gccugugcau cggcgccgug 120

cccaagaccc accaggugcu gugcaacacc acccagaaga ccagcgacgg cagcuacuac 180

cuggccgcuc ccaccggcac caccuggggcc ugcagcaccg gccugacccc uugcaucagc 240

accaccaucc ugaaccugac caccgacuac ugcgugcugg uggagcugug gcccagggug 300

accuaccaca gccccagcua cgccuaccac caguucgaga ggagggccaa guacaagagg 360

gagcccguga gccugacccu ggcccugcug cugggcggcc ugacaauggg cggcaucgcc 420

gccggcgugg gcaccggcac caccgcccug guggccaccc agcaguucca gcagcugcag 480

gccgccaugc acgacgaccu gaaggaggug gagaagucca ucaccaaccu ggagaagucc 540

cugaccagcc ugagcgaggu ggugcugcag aacaggaggg gccuggaccu gcuguuccug 600

aaggagggcg gccugugcgc cgcccugaag gaggagugcu gccuguacgc cgaccacacc 660

ggccugguga ucgugggcau ugucgcuggc cuggccgucc ucgccguggu ggugauugga 720

gcuguggucg cagcuguuau gugcagaaga aagucauccg gcggaaaggg aggcuccuac 780

ucucaggcug cuucugcuac agugccuaga gcucuuaugu guuuaucuca gcuguaa 837

<210> 90
<211> 378
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 90
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ggaggaggcu ccgggggagg aggcucccug aagaucagcc aggccgugca cgccgcccac 180

gccgagauca acgaggccgg ccgggaggug aucgugggca uugucgcugg ccuggccguc 240

cucgccgugg uggugauugg agcuguggguc gcagcuguua ugugcagaag aaagucaucc 300

ggcggaaagg gaggcuccua cucucaggcu gcuucugcua cagugccuag agcucuuaug 360

uguuuaucuc agcuguaa 378

<210> 91
<211> 876
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 91
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cccaagaccc accaggugcu gugcaacacc acccagaaga ccagcgacgg cagcuacuac 180

cuggccgcuc ccaccggcac caccuggggcc ugcagcaccg gccugacccc uugcaucagc 240

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accuaccaca gccccagcua cgccuaccac caguucgaga ggagggccaa guacaagagg 360

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gccgccaugc acgacgaccu gaaggaggug gagaagucca ucaccaaccu ggagaagucc 540

cugaccagcc ugagcgaggu ggugcugcag aacaggaggg gccuggaccu gcuguuccug 600

aaggagggcg gccugugcgc cgcccugaag gaggagugcu gccuguacgc cgaccacacc 660

ggccugguga ucgugggcau ugucgcuggc cuggccgucc ucgccguggu ggugauugga 720

gcuguggucg cagcuguuau gugcagaaga aagucauccg gcggaaaggg aggcuccuac 780

ucucaggcug cuucugcuac agugccuaga gcucuuaugu guuuaucuca gcugggcggc 840

ggaggcagcg acuacaagga cgacgaugac aaguaa 876

<210> 92
<211> 417
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 92
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ggaggaggcu ccgggggagg aggcucccug aagaucagcc aggccgugca cgccgcccac 180

gccgagauca acgaggccgg ccgggaggug aucgugggca uugucgcugg ccuggccguc 240

cucgccgugg uggugauugg agcugugguc gcagcuguua ugugcagaag aaagucaucc 300

ggcggaaagg gaggcuccua cucucaggcu gcuucugcua cagugccuag agcucuuaug 360

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<210> 93
<211> 550
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 93

Met Glu Asp Ala Lys Asn Ile Lys Lys Gly Pro Ala Pro Phe Tyr Pro
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Leu Glu Asp Gly Thr Ala Gly Glu Gln Leu His Lys Ala Met Lys Arg
20 25 30

Tyr Ala Leu Val Pro Gly Thr Ile Ala Phe Thr Asp Ala His Ile Glu
35 40 45

Val Asp Ile Thr Tyr Ala Glu Tyr Phe Glu Met Ser Val Arg Leu Ala
50 55 60

Glu Ala Met Lys Arg Tyr Gly Leu Asn Thr Asn His Arg Ile Val Val
65 70 75 80

Cys Ser Glu Asn Ser Leu Gln Phe Phe Met Pro Val Leu Gly Ala Leu
85 90 95

Phe Ile Gly Val Ala Val Ala Pro Ala Asn Asp Ile Tyr Asn Glu Arg
100 105 110

```
Glu Leu Leu Asn Ser Met Gly Ile Ser Gln Pro Thr Val Val Phe Val
        115                 120                 125

Ser Lys Lys Gly Leu Gln Lys Ile Leu Asn Val Gln Lys Lys Leu Pro
    130                 135                 140

Ile Ile Gln Lys Ile Ile Ile Met Asp Ser Lys Thr Asp Tyr Gln Gly
145                 150                 155                 160

Phe Gln Ser Met Tyr Thr Phe Val Thr Ser His Leu Pro Pro Gly Phe
                165                 170                 175

Asn Glu Tyr Asp Phe Val Pro Glu Ser Phe Asp Arg Asp Lys Thr Ile
            180                 185                 190

Ala Leu Ile Met Asn Ser Ser Gly Ser Thr Gly Leu Pro Lys Gly Val
        195                 200                 205

Ala Leu Pro His Arg Thr Ala Cys Val Arg Phe Ser His Ala Arg Asp
    210                 215                 220

Pro Ile Phe Gly Asn Gln Ile Ile Pro Asp Thr Ala Ile Leu Ser Val
225                 230                 235                 240

Val Pro Phe His His Gly Phe Gly Met Phe Thr Thr Leu Gly Tyr Leu
                245                 250                 255

Ile Cys Gly Phe Arg Val Val Leu Met Tyr Arg Phe Glu Glu Glu Leu
            260                 265                 270

Phe Leu Arg Ser Leu Gln Asp Tyr Lys Ile Gln Ser Ala Leu Leu Val
        275                 280                 285

Pro Thr Leu Phe Ser Phe Phe Ala Lys Ser Thr Leu Ile Asp Lys Tyr
    290                 295                 300

Asp Leu Ser Asn Leu His Glu Ile Ala Ser Gly Gly Ala Pro Leu Ser
305                 310                 315                 320

Lys Glu Val Gly Glu Ala Val Ala Lys Arg Phe His Leu Pro Gly Ile
                325                 330                 335
```

```
Arg Gln Gly Tyr Gly Leu Thr Glu Thr Thr Ser Ala Ile Leu Ile Thr
            340                 345                 350

Pro Glu Gly Asp Asp Lys Pro Gly Ala Val Gly Lys Val Val Pro Phe
        355                 360                 365

Phe Glu Ala Lys Val Val Asp Leu Asp Thr Gly Lys Thr Leu Gly Val
    370                 375                 380

Asn Gln Arg Gly Glu Leu Cys Val Arg Gly Pro Met Ile Met Ser Gly
385                 390                 395                 400

Tyr Val Asn Asn Pro Glu Ala Thr Asn Ala Leu Ile Asp Lys Asp Gly
                405                 410                 415

Trp Leu His Ser Gly Asp Ile Ala Tyr Trp Asp Glu Asp Glu His Phe
            420                 425                 430

Phe Ile Val Asp Arg Leu Lys Ser Leu Ile Lys Tyr Lys Gly Tyr Gln
        435                 440                 445

Val Ala Pro Ala Glu Leu Glu Ser Ile Leu Leu Gln His Pro Asn Ile
    450                 455                 460

Phe Asp Ala Gly Val Ala Gly Leu Pro Asp Asp Asp Ala Gly Glu Leu
465                 470                 475                 480

Pro Ala Ala Val Val Val Leu Glu His Gly Lys Thr Met Thr Glu Lys
                485                 490                 495

Glu Ile Val Asp Tyr Val Ala Ser Gln Val Thr Thr Ala Lys Lys Leu
            500                 505                 510

Arg Gly Gly Val Val Phe Val Asp Glu Val Pro Lys Gly Leu Thr Gly
        515                 520                 525

Lys Leu Asp Ala Arg Lys Ile Arg Glu Ile Leu Ile Lys Ala Lys Lys
    530                 535                 540
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Gly Gly Lys Ile Ala Val
545 550

<210> 94
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 94

Met Lys Leu Val Val Val Gly Ala Gly Gly Val Gly Lys Ser Ala Leu
1 5 10 15

Thr Ile

<210> 95
<211> 21
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 95

Met Asp Pro Arg Arg Tyr Ala Pro Met Ile Arg Pro Ala Lys Leu Asp
1 5 10 15

Val Leu Pro Arg Asn
20

<210> 96
<211> 278
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 96

Met Arg Val Thr Ala Pro Arg Thr Leu Leu Leu Leu Leu Trp Gly Ala
1 5 10 15

```
Val Ala Leu Thr Glu Thr Trp Ala Gly Ser Leu Ser Glu Val Thr Gly
            20                  25                  30

Gln Gly Leu Cys Ile Gly Ala Val Pro Lys Thr His Gln Val Leu Cys
        35                  40                  45

Asn Thr Thr Gln Lys Thr Ser Asp Gly Ser Tyr Tyr Leu Ala Ala Pro
    50                  55                  60

Thr Gly Thr Thr Trp Ala Cys Ser Thr Gly Leu Thr Pro Cys Ile Ser
65                  70                  75                  80

Thr Thr Ile Leu Asn Leu Thr Thr Asp Tyr Cys Val Leu Val Glu Leu
                85                  90                  95

Trp Pro Arg Val Thr Tyr His Ser Pro Ser Tyr Ala Tyr His Gln Phe
            100                 105                 110

Glu Arg Arg Ala Lys Tyr Lys Arg Glu Pro Val Ser Leu Thr Leu Ala
        115                 120                 125

Leu Leu Leu Gly Gly Leu Thr Met Gly Gly Ile Ala Ala Gly Val Gly
    130                 135                 140

Thr Gly Thr Thr Ala Leu Val Ala Thr Gln Gln Phe Gln Gln Leu Gln
145                 150                 155                 160

Ala Ala Met His Asp Asp Leu Lys Glu Val Glu Lys Ser Ile Thr Asn
                165                 170                 175

Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val Leu Gln Asn Arg
            180                 185                 190

Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu Gly Gly Leu Cys Ala Ala
        195                 200                 205

Leu Lys Glu Glu Cys Cys Leu Tyr Ala Asp His Thr Gly Leu Val Ile
    210                 215                 220

Val Gly Ile Val Ala Gly Leu Ala Val Leu Ala Val Val Val Ile Gly
225                 230                 235                 240
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```
Ala Val Val Ala Ala Val Met Cys Arg Arg Lys Ser Ser Gly Gly Lys
                245                 250                 255


Gly Gly Ser Tyr Ser Gln Ala Ala Ser Ala Thr Val Pro Arg Ala Leu
            260                 265                 270


Met Cys Leu Ser Gln Leu
        275


<210>  97
<211>  125
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic polypeptide

<400>  97

Met Arg Val Thr Ala Pro Arg Thr Leu Leu Leu Leu Leu Trp Gly Ala
1               5                   10                  15


Val Ala Leu Thr Glu Thr Trp Ala Gly Ser Tyr His Ser Pro Ser Tyr
            20                  25                  30


Ala Tyr His Gln Phe Glu Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly
        35                  40                  45


Ser Leu Lys Ile Ser Gln Ala Val His Ala Ala His Ala Glu Ile Asn
    50                  55                  60


Glu Ala Gly Arg Glu Val Ile Val Gly Ile Val Ala Gly Leu Ala Val
65                  70                  75                  80


Leu Ala Val Val Val Ile Gly Ala Val Val Ala Ala Val Met Cys Arg
                85                  90                  95


Arg Lys Ser Ser Gly Gly Lys Gly Gly Ser Tyr Ser Gln Ala Ala Ser
            100                 105                 110


Ala Thr Val Pro Arg Ala Leu Met Cys Leu Ser Gln Leu
        115                 120                 125
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<210> 98
<211> 291
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 98

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Met Arg Val Thr Ala Pro Arg Thr Leu Leu Leu Leu Trp Gly Ala
1               5                  10                  15


Val Ala Leu Thr Glu Thr Trp Ala Gly Ser Leu Ser Glu Val Thr Gly
            20                  25                  30


Gln Gly Leu Cys Ile Gly Ala Val Pro Lys Thr His Gln Val Leu Cys
        35                  40                  45


Asn Thr Thr Gln Lys Thr Ser Asp Gly Ser Tyr Tyr Leu Ala Ala Pro
    50                  55                  60


Thr Gly Thr Thr Trp Ala Cys Ser Thr Gly Leu Thr Pro Cys Ile Ser
65                  70                  75                  80


Thr Thr Ile Leu Asn Leu Thr Thr Asp Tyr Cys Val Leu Val Glu Leu
                85                  90                  95


Trp Pro Arg Val Thr Tyr His Ser Pro Ser Tyr Ala Tyr His Gln Phe
            100                 105                 110


Glu Arg Arg Ala Lys Tyr Lys Arg Glu Pro Val Ser Leu Thr Leu Ala
        115                 120                 125


Leu Leu Leu Gly Gly Leu Thr Met Gly Gly Ile Ala Ala Gly Val Gly
    130                 135                 140


Thr Gly Thr Thr Ala Leu Val Ala Thr Gln Gln Phe Gln Gln Leu Gln
145                 150                 155                 160


Ala Ala Met His Asp Asp Leu Lys Glu Val Glu Lys Ser Ile Thr Asn
                165                 170                 175
```

```
Leu Glu Lys Ser Leu Thr Ser Leu Ser Glu Val Val Leu Gln Asn Arg
            180                 185                 190

Arg Gly Leu Asp Leu Leu Phe Leu Lys Glu Gly Gly Leu Cys Ala Ala
        195                 200                 205

Leu Lys Glu Glu Cys Cys Leu Tyr Ala Asp His Thr Gly Leu Val Ile
    210                 215                 220

Val Gly Ile Val Ala Gly Leu Ala Val Leu Ala Val Val Val Ile Gly
225                 230                 235                 240

Ala Val Val Ala Ala Val Met Cys Arg Arg Lys Ser Ser Gly Gly Lys
                245                 250                 255

Gly Gly Ser Tyr Ser Gln Ala Ala Ser Ala Thr Val Pro Arg Ala Leu
            260                 265                 270

Met Cys Leu Ser Gln Leu Gly Gly Gly Gly Ser Asp Tyr Lys Asp Asp
        275                 280                 285

Asp Asp Lys
    290
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<210> 99
<211> 138
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic polypeptide

<400> 99

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Met Arg Val Thr Ala Pro Arg Thr Leu Leu Leu Leu Leu Trp Gly Ala
1               5                   10                  15

Val Ala Leu Thr Glu Thr Trp Ala Gly Ser Tyr His Ser Pro Ser Tyr
            20                  25                  30

Ala Tyr His Gln Phe Glu Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly
        35                  40                  45
```

```
Ser Leu Lys Ile Ser Gln Ala Val His Ala Ala His Ala Glu Ile Asn
    50                  55                  60

Glu Ala Gly Arg Glu Val Ile Val Gly Ile Val Ala Gly Leu Ala Val
65                  70                  75                  80

Leu Ala Val Val Val Ile Gly Ala Val Val Ala Ala Val Met Cys Arg
                85                  90                  95

Arg Lys Ser Ser Gly Gly Lys Gly Gly Ser Tyr Ser Gln Ala Ala Ser
            100                 105                 110

Ala Thr Val Pro Arg Ala Leu Met Cys Leu Ser Gln Leu Gly Gly Gly
        115                 120                 125

Gly Ser Asp Tyr Lys Asp Asp Asp Asp Lys
    130                 135
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<210> 100
<211> 9690
<212> RNA
<213> Artificial sequence

<220>
<223> Synthetic polynucleotide

<400> 100

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agguagaagc caagcagguc acugauaaug accaugcuaa ugccagagcg uuuucgcauc      180

uggcuucaaa acugaucgaa acggaggugg acccauccga cacgauccuu gacauuggaa      240

gugcgcccgc ccgcagaaug uauucuaagc acaaguauca uuguaucugu ccgaugagau      300

gugcggaaga uccggacaga uuguauaagu augcaacuaa gcugaagaaa aacuguaagg      360

aaauaacuga uaaggaauug gacaagaaaa ugaaggagcu ggccgccguc augagcgacc      420

cugaccugga aacugagacu augugccucc acgacgacga gucgugucgc uacgaagggc      480

aagucgcugu uuaccaggau guauacgccg ucgacggccc caccagccug uaccaccagg      540

ccaacaaggg cgugagggug gccuacugga ucggcuucga caccacaccc uucauguuca      600
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ccgccaggaa caucggccug ugcagcagcg acgugaugga gaggagccgg agaggcauga 720

gcauccugag gaagaaauac cugaagccca gcaacaacgu gcuguucagc gugggcagca 780

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cccggaucag gaagaugcug gaggaacaca aggagcccag cccacugauc accgccgagg 1500

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Gln Val Thr Pro Asn Asp His Ala Asn Ala Arg Ala Phe Ser His Leu
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Ala Ser Lys Leu Ile Glu Leu Glu Val Pro Thr Thr Ala Thr Ile Leu
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Asp Ile Gly Ser Ala Pro Ala Arg Arg Met Phe Ser Glu His Gln Tyr
65                  70                  75                  80


His Cys Val Cys Pro Met Arg Ser Pro Glu Asp Pro Asp Arg Met Met
                85                  90                  95


Lys Tyr Ala Ser Lys Leu Ala Glu Lys Ala Cys Lys Ile Thr Asn Lys
            100                 105                 110


Asn Leu His Glu Lys Ile Lys Asp Leu Arg Thr Val Leu Asp Thr Pro
        115                 120                 125


Asp Ala Glu Thr Pro Ser Leu Cys Phe His Asn Asp Val Thr Cys Asn
    130                 135                 140


Met Arg Ala Glu Tyr Ser Val Met Gln Asp Val Tyr Ile Asn Ala Pro
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Gly Thr Ile Tyr His Gln Ala Met Lys Gly Val Arg Thr Leu Tyr Trp
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Ile Gly Phe Asp Thr Thr Gln Phe Met Phe Ser Ala Met Ala Gly Ser
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Lys Leu Ser Ile Met Arg Lys Lys Glu Leu Lys Pro Gly Ser Arg Val
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Tyr Phe Ser Val Gly Ser Thr Leu Tyr Pro Glu His Arg Ala Ser Leu
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Gln Ser Trp His Leu Pro Ser Val Phe His Leu Asn Gly Lys Gln Ser
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Tyr Thr Cys Arg Cys Asp Thr Val Val Ser Cys Glu Gly Tyr Val Val
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Lys Lys Ile Thr Ile Ser Pro Gly Ile Thr Gly Glu Thr Val Gly Tyr
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Thr Val Lys Gly Glu Arg Val Ser Phe Pro Val Cys Thr Tyr Ile Pro
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Ala Thr Ile Cys Asp Gln Met Thr Gly Ile Met Ala Thr Asp Ile Ser
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Pro Asp Asp Ala Gln Lys Leu Leu Val Gly Leu Asn Gln Arg Ile Val
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Ile Asn Gly Arg Thr Asn Arg Asn Thr Asn Thr Met Gln Asn Tyr Leu
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Leu Pro Ile Ile Ala Gln Gly Phe Ser Lys Trp Ala Lys Glu Arg Lys
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Pro Pro Leu Val Ala Asp Lys Gly Ile Glu Ala Ala Ala Glu Val Val
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Cys Glu Val Glu Gly Leu Gln Ala Asp Ile Gly Ala Ala Leu Val Glu
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Thr Pro Arg Gly His Val Arg Ile Ile Pro Gln Ala Asn Asp Arg Met
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Ile Gly Gln Tyr Ile Val Val Ser Pro Asn Ser Val Leu Lys Asn Ala
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Lys Leu Ala Pro Ala His Pro Leu Ala Asp Gln Val Lys Ile Ile Thr
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His Ser Gly Arg Ser Gly Arg Tyr Ala Val Glu Pro Tyr Asp Ala Lys
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Ile Thr Ser Lys Thr Val Asp Ser Val Met Leu Asn Gly Cys His Lys
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Lys Val His Phe Asn His Pro Glu Lys Asp Ile Cys Thr Lys Thr Phe
        835                 840                 845


Tyr Lys Tyr Ile Ser Arg Arg Cys Thr Gln Pro Val Thr Ala Ile Val
    850                 855                 860


Ser Thr Leu His Tyr Asp Gly Lys Met Lys Thr Thr Asn Pro Cys Lys
865                 870                 875                 880


Lys Asn Ile Glu Ile Asp Ile Thr Gly Ala Thr Lys Pro Lys Pro Gly
                885                 890                 895


Asp Ile Ile Leu Thr Cys Phe Arg Gly Trp Val Lys Gln Leu Gln Ile
            900                 905                 910


Asp Tyr Pro Gly His Glu Val Met Thr Ala Ala Ala Ser Gln Gly Leu
        915                 920                 925


Thr Arg Lys Gly Val Tyr Ala Val Arg Gln Lys Val Asn Glu Asn Pro
    930                 935                 940


Leu Tyr Ala Ile Thr Ser Glu His Val Asn Val Leu Leu Thr Arg Thr
945                 950                 955                 960


Glu Asp Arg Leu Val Trp Lys Thr Leu Gln Gly Asp Pro Trp Ile Lys
                965                 970                 975


Gln Leu Thr Asn Ile Pro Lys Gly Asn Phe Gln Ala Thr Ile Glu Asp
            980                 985                 990


Trp Glu Ala Glu His Lys Gly Ile  Ile Ala Ala Ile Asn  Ser Pro Thr
        995                 1000                1005


Pro Arg  Ala Asn Pro Phe Ser  Cys Lys Thr Asn Val  Cys Trp Ala
    1010                1015                1020


Lys Ala  Leu Glu Pro Ile Leu  Ala Thr Ala Gly Ile  Val Leu Thr
    1025                1030                1035


Gly Cys  Gln Trp Ser Glu Leu  Phe Pro Gln Phe Ala  Asp Asp Lys
    1040                1045                1050
```

```
Pro His  Ser Ala Ile Tyr Ala  Leu Asp Val Ile Cys  Ile Lys Phe
    1055                1060                1065

Phe Gly  Met Asp Leu Thr Ser  Gly Leu Phe Ser Lys  Gln Ser Ile
    1070                1075                1080

Pro Leu  Thr Tyr His Pro Ala  Asp Ser Ala Arg Pro  Val Ala His
    1085                1090                1095

Trp Asp  Asn Ser Pro Gly Thr  Arg Lys Tyr Gly Tyr  Asp His Ala
    1100                1105                1110

Ile Ala  Ala Glu Leu Ser Arg  Arg Phe Pro Val Phe  Gln Leu Ala
    1115                1120                1125

Gly Lys  Gly Thr Gln Leu Asp  Leu Gln Thr Gly Arg  Thr Arg Val
    1130                1135                1140

Ile Ser  Ala Gln His Asn Leu  Val Pro Val Asn Arg  Asn Leu Pro
    1145                1150                1155

His Ala  Leu Val Pro Glu Tyr  Lys Glu Lys Gln Pro  Gly Pro Val
    1160                1165                1170

Glu Lys  Phe Leu Asn Gln Phe  Lys His His Ser Val  Leu Val Val
    1175                1180                1185

Ser Glu  Glu Lys Ile Glu Ala  Pro Arg Lys Arg Ile  Glu Trp Ile
    1190                1195                1200

Ala Pro  Ile Gly Ile Ala Gly  Ala Asp Lys Asn Tyr  Asn Leu Ala
    1205                1210                1215

Phe Gly  Phe Pro Pro Gln Ala  Arg Tyr Asp Leu Val  Phe Ile Asn
    1220                1225                1230

Ile Gly  Thr Lys Tyr Arg Asn  His His Phe Gln Gln  Cys Glu Asp
    1235                1240                1245
```

```
His Ala  Ala Thr Leu Lys Thr  Leu Ser Arg Ser Ala  Leu Asn Cys
    1250                1255                1260

Leu Asn  Pro Gly Gly Thr Leu  Val Val Lys Ser Tyr  Gly Tyr Ala
    1265                1270                1275

Asp Arg  Asn Ser Glu Asp Val  Val Thr Ala Leu Ala  Arg Lys Phe
    1280                1285                1290

Val Arg  Val Ser Ala Ala Arg  Pro Asp Cys Val Ser  Ser Asn Thr
    1295                1300                1305

Glu Met  Tyr Leu Ile Phe Arg  Gln Leu Asp Asn Ser  Arg Thr Arg
    1310                1315                1320

Gln Phe  Thr Pro His His Leu  Asn Cys Val Ile Ser  Ser Val Tyr
    1325                1330                1335

Glu Gly  Thr Arg Asp Gly Val  Gly Ala Ala Pro Ser  Tyr Arg Thr
    1340                1345                1350

Lys Arg  Glu Asn Ile Ala Asp  Cys Gln Glu Glu Ala  Val Val Asn
    1355                1360                1365

Ala Ala  Asn Pro Leu Gly Arg  Pro Gly Glu Gly Val  Cys Arg Ala
    1370                1375                1380

Ile Tyr  Lys Arg Trp Pro Thr  Ser Phe Thr Asp Ser  Ala Thr Glu
    1385                1390                1395

Thr Gly  Thr Ala Arg Met Thr  Val Cys Leu Gly Lys  Lys Val Ile
    1400                1405                1410

His Ala  Val Gly Pro Asp Phe  Arg Lys His Pro Glu  Ala Glu Ala
    1415                1420                1425

Leu Lys  Leu Leu Gln Asn Ala  Tyr His Ala Val Ala  Asp Leu Val
    1430                1435                1440

Asn Glu  His Asn Ile Lys Ser  Val Ala Ile Pro Leu  Leu Ser Thr
    1445                1450                1455
```

```
Gly Ile  Tyr Ala Ala Gly Lys  Asp Arg Leu Glu Val  Ser Leu Asn
    1460                 1465                 1470

Cys Leu  Thr Thr Ala Leu Asp  Arg Thr Asp Ala Asp  Val Thr Ile
    1475                 1480                 1485

Tyr Cys  Leu Asp Lys Lys Trp  Lys Glu Arg Ile Asp  Ala Ala Leu
    1490                 1495                 1500

Gln Leu  Lys Glu Ser Val Thr  Glu Leu Lys Asp Glu  Asp Met Glu
    1505                 1510                 1515

Ile Asp  Asp Glu Leu Val Trp  Ile His Pro Asp Ser  Cys Leu Lys
    1520                 1525                 1530

Gly Arg  Lys Gly Phe Ser Thr  Thr Lys Gly Lys Leu  Tyr Ser Tyr
    1535                 1540                 1545

Phe Glu  Gly Thr Lys Phe His  Gln Ala Ala Lys Asp  Met Ala Glu
    1550                 1555                 1560

Ile Lys  Val Leu Phe Pro Asn  Asp Gln Glu Ser Asn  Glu Gln Leu
    1565                 1570                 1575

Cys Ala  Tyr Ile Leu Gly Glu  Thr Met Glu Ala Ile  Arg Glu Lys
    1580                 1585                 1590

Cys Pro  Val Asp His Asn Pro  Ser Ser Ser Pro Pro  Lys Thr Leu
    1595                 1600                 1605

Pro Cys  Leu Cys Met Tyr Ala  Met Thr Pro Glu Arg  Val His Arg
    1610                 1615                 1620

Leu Arg  Ser Asn Asn Val Lys  Glu Val Thr Val Cys  Ser Ser Thr
    1625                 1630                 1635

Pro Leu  Pro Lys His Lys Ile  Lys Asn Val Gln Lys  Val Gln Cys
    1640                 1645                 1650
```

```
Thr Lys  Val Val Leu Phe Asn  Pro His Thr Pro Ala  Phe Val Pro
    1655                1660                1665

Ala Arg  Lys Tyr Ile Glu Val  Pro Glu Gln Pro Thr  Ala Pro Pro
    1670                1675                1680

Ala Gln  Ala Glu Glu Ala Pro  Glu Val Val Ala Thr  Pro Ser Pro
    1685                1690                1695

Ser Thr  Ala Asp Asn Thr Ser  Leu Asp Val Thr Asp  Ile Ser Leu
    1700                1705                1710

Asp Met  Asp Asp Ser Ser Glu  Gly Ser Leu Phe Ser  Ser Phe Ser
    1715                1720                1725

Gly Ser  Asp Asn Ser Ile Thr  Ser Met Asp Ser Trp  Ser Ser Gly
    1730                1735                1740

Pro Ser  Ser Leu Glu Ile Val  Asp Arg Arg Gln Val  Val Val Ala
    1745                1750                1755

Asp Val  His Ala Val Gln Glu  Pro Ala Pro Ile Pro  Pro Pro Arg
    1760                1765                1770

Leu Lys  Lys Met Ala Arg Leu  Ala Ala Ala Arg Lys  Glu Pro Thr
    1775                1780                1785

Pro Pro  Ala Ser Asn Ser Ser  Glu Ser Leu His Leu  Ser Phe Gly
    1790                1795                1800

Gly Val  Ser Met Ser Leu Gly  Ser Ile Phe Asp Gly  Glu Thr Ala
    1805                1810                1815

Arg Gln  Ala Ala Val Gln Pro  Leu Ala Thr Gly Pro  Thr Asp Val
    1820                1825                1830

Pro Met  Ser Phe Gly Ser Phe  Ser Asp Gly Glu Ile  Asp Glu Leu
    1835                1840                1845

Ser Arg  Arg Val Thr Glu Ser  Glu Pro Val Leu Phe  Gly Ser Phe
    1850                1855                1860
```

```
Glu Pro  Gly Glu Val Asn Ser  Ile Ile Ser Ser Arg  Ser Ala Val
    1865                1870                1875

Ser Phe  Pro Leu Arg Lys Gln  Arg Arg Arg Arg Arg  Ser Arg Arg
    1880                1885                1890

Thr Glu  Tyr Leu Thr Gly Val  Gly Gly Tyr Ile Phe  Ser Thr Asp
    1895                1900                1905

Thr Gly  Pro Gly His Leu Gln  Lys Lys Ser Val Leu  Gln Asn Gln
    1910                1915                1920

Leu Thr  Glu Pro Thr Leu Glu  Arg Asn Val Leu Glu  Arg Ile His
    1925                1930                1935

Ala Pro  Val Leu Asp Thr Ser  Lys Glu Glu Gln Leu  Lys Leu Arg
    1940                1945                1950

Tyr Gln  Met Met Pro Thr Glu  Ala Asn Lys Ser Arg  Tyr Gln Ser
    1955                1960                1965

Arg Lys  Val Glu Asn Gln Lys  Ala Ile Thr Thr Glu  Arg Leu Leu
    1970                1975                1980

Ser Gly  Leu Arg Leu Tyr Asn  Ser Ala Thr Asp Gln  Pro Glu Cys
    1985                1990                1995

Tyr Lys  Ile Thr Tyr Pro Lys  Pro Leu Tyr Ser Ser  Ser Val Pro
    2000                2005                2010

Ala Asn  Tyr Ser Asp Pro Gln  Phe Ala Val Ala Val  Cys Asn Asn
    2015                2020                2025

Tyr Leu  His Glu Asn Tyr Pro  Thr Val Ala Ser Tyr  Gln Ile Thr
    2030                2035                2040

Asp Glu  Tyr Asp Ala Tyr Leu  Asp Met Val Asp Gly  Thr Val Ala
    2045                2050                2055
```

```
Cys Leu  Asp Thr Ala Thr Phe  Cys Pro Ala Lys Leu  Arg Ser Tyr
    2060                2065                2070

Pro Lys  Lys His Glu Tyr Arg  Ala Pro Asn Ile Arg  Ser Ala Val
    2075                2080                2085

Pro Ser  Ala Met Gln Asn Thr  Leu Gln Asn Val Leu  Ile Ala Ala
    2090                2095                2100

Thr Lys  Arg Asn Cys Asn Val  Thr Gln Met Arg Glu  Leu Pro Thr
    2105                2110                2115

Leu Asp  Ser Ala Thr Phe Asn  Val Glu Cys Phe Arg  Lys Tyr Ala
    2120                2125                2130

Cys Asn  Asp Glu Tyr Trp Glu  Glu Phe Ala Arg Lys  Pro Ile Arg
    2135                2140                2145

Ile Thr  Thr Glu Phe Val Thr  Ala Tyr Val Ala Arg  Leu Lys Gly
    2150                2155                2160

Pro Lys  Ala Ala Ala Leu Phe  Ala Lys Thr Tyr Asn  Leu Val Pro
    2165                2170                2175

Leu Gln  Glu Val Pro Met Asp  Arg Phe Val Met Asp  Met Lys Arg
    2180                2185                2190

Asp Val  Lys Val Thr Pro Gly  Thr Lys His Thr Glu  Glu Arg Pro
    2195                2200                2205

Lys Val  Gln Val Ile Gln Ala  Ala Glu Pro Leu Ala  Thr Ala Tyr
    2210                2215                2220

Leu Cys  Gly Ile His Arg Glu  Leu Val Arg Arg Leu  Thr Ala Val
    2225                2230                2235

Leu Leu  Pro Asn Ile His Thr  Leu Phe Asp Met Ser  Ala Glu Asp
    2240                2245                2250

Phe Asp  Ala Ile Ile Ala Glu  His Phe Lys Gln Gly  Asp Pro Val
    2255                2260                2265
```

```
Leu Glu  Thr Asp Ile Ala Ser  Phe Asp Lys Ser Gln  Asp Asp Ala
    2270                2275                2280

Met Ala  Leu Thr Gly Leu Met  Ile Leu Glu Asp Leu  Gly Val Asp
    2285                2290                2295

Gln Pro  Leu Leu Asp Leu Ile  Glu Cys Ala Phe Gly  Glu Ile Ser
    2300                2305                2310

Ser Thr  His Leu Pro Thr Gly  Thr Arg Phe Lys Phe  Gly Ala Met
    2315                2320                2325

Met Lys  Ser Gly Met Phe Leu  Thr Leu Phe Val Asn  Thr Val Leu
    2330                2335                2340

Asn Val  Val Ile Ala Ser Arg  Val Leu Glu Glu Arg  Leu Lys Thr
    2345                2350                2355

Ser Arg  Cys Ala Ala Phe Ile  Gly Asp Asp Asn Ile  Ile His Gly
    2360                2365                2370

Val Val  Ser Asp Lys Glu Met  Ala Glu Arg Cys Ala  Thr Trp Leu
    2375                2380                2385

Asn Met  Glu Val Lys Ile Ile  Asp Ala Val Ile Gly  Glu Arg Pro
    2390                2395                2400

Pro Tyr  Phe Cys Gly Gly Phe  Ile Leu Gln Asp Ser  Val Thr Ser
    2405                2410                2415

Thr Ala  Cys Arg Val Ala Asp  Pro Leu Lys Arg Leu  Phe Lys Leu
    2420                2425                2430

Gly Lys  Pro Leu Pro Ala Asp  Asp Glu Gln Asp Glu  Asp Arg Arg
    2435                2440                2445

Arg Ala  Leu Leu Asp Glu Thr  Lys Ala Trp Phe Arg  Val Gly Ile
    2450                2455                2460
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Thr Gly Thr Leu Ala Val Ala Val Thr Thr Arg Tyr Glu Val Asp
    2465   2470   2475

Asn Ile Thr Pro Val Leu Leu Ala Leu Arg Thr Phe Ala Gln Ser
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Lys Arg Ala Phe Gln Ala Ile Arg Gly Glu Ile Lys His Leu Tyr
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Gly Gly Pro Lys
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ccaaaccaug acagcaacaa gggagugaca gcagccuguc cacaugcugg agccaagucc 480

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accucugcug accaacaguc ccucuaccag aaugcugacg ccuauguguu ugugggcucc 660

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20 25 30

Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn
35 40 45

Leu Leu Glu Asp Lys His Asn Gly Lys Leu Cys Lys Leu Arg Gly Val
50 55 60

Ala Pro Leu His Leu Gly Lys Cys Asn Ile Ala Gly Trp Ile Leu Gly
65 70 75 80

Asn Pro Glu Cys Glu Ser Leu Ser Thr Ala Ser Ser Trp Ser Tyr Ile
85 90 95

Val Glu Thr Pro Ser Ser Asp Asn Gly Thr Cys Tyr Pro Gly Asp Phe
100 105 110

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Ile Asp Tyr Glu Glu Leu Arg Glu Gln Leu Ser Ser Val Ser Ser Phe
        115                 120                 125

Glu Arg Phe Glu Ile Phe Pro Lys Thr Ser Ser Trp Pro Asn His Asp
    130                 135                 140

Ser Asn Lys Gly Val Thr Ala Ala Cys Pro His Ala Gly Ala Lys Ser
145                 150                 155                 160

Phe Tyr Lys Asn Leu Ile Trp Leu Val Lys Lys Gly Asn Ser Tyr Pro
                165                 170                 175

Lys Leu Ser Lys Ser Tyr Ile Asn Asp Lys Gly Lys Glu Val Leu Val
            180                 185                 190

Leu Trp Gly Ile His His Pro Ser Thr Ser Ala Asp Gln Gln Ser Leu
        195                 200                 205

Tyr Gln Asn Ala Asp Ala Tyr Val Phe Val Gly Ser Ser Arg Tyr Ser
    210                 215                 220

Lys Lys Phe Lys Pro Glu Ile Ala Ile Arg Pro Lys Val Arg Asp Gln
225                 230                 235                 240

Glu Gly Arg Met Asn Tyr Tyr Trp Thr Leu Val Glu Pro Gly Asp Lys
                245                 250                 255

Ile Thr Phe Glu Ala Thr Gly Asn Leu Val Val Pro Arg Tyr Ala Phe
            260                 265                 270

Ala Met Glu Arg Asn Ala Gly Ser Gly Ile Ile Ile Ser Asp Thr Pro
        275                 280                 285

Val His Asp Cys Asn Thr Thr Cys Gln Thr Pro Lys Gly Ala Ile Asn
    290                 295                 300

Thr Ser Leu Pro Phe Gln Asn Ile His Pro Ile Thr Ile Gly Lys Cys
305                 310                 315                 320
```

```
Pro Lys Tyr Val Lys Ser Thr Lys Leu Arg Leu Ala Thr Gly Leu Arg
                325                 330                 335

Asn Ile Pro Ser Ile Gln Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly
            340                 345                 350

Phe Ile Glu Gly Gly Trp Thr Gly Met Val Asp Gly Trp Tyr Gly Tyr
        355                 360                 365

His His Gln Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Leu Lys Ser
    370                 375                 380

Thr Gln Asn Ala Ile Asp Glu Ile Thr Asn Lys Val Asn Ser Val Ile
385                 390                 395                 400

Glu Lys Met Asn Thr Gln Phe Thr Ala Val Gly Lys Glu Phe Asn His
                405                 410                 415

Leu Glu Lys Arg Ile Glu Asn Leu Asn Lys Lys Val Asp Asp Gly Phe
            420                 425                 430

Leu Asp Ile Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Leu Glu Asn
        435                 440                 445

Glu Arg Thr Leu Asp Tyr His Asp Ser Asn Val Lys Asn Leu Tyr Glu
    450                 455                 460

Lys Val Arg Ser Gln Leu Lys Asn Asn Ala Lys Glu Ile Gly Asn Gly
465                 470                 475                 480

Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Thr Cys Met Glu Ser Val
                485                 490                 495

Lys Asn Gly Thr Tyr Asp Tyr Pro Lys Tyr Ser Glu Glu Ala Lys Leu
            500                 505                 510

Asn Arg Glu Glu Ile Asp Gly Val Lys Leu Glu Ser Thr Arg Ile Tyr
        515                 520                 525

Gln Ile Leu Ala Ile Tyr Ser Thr Val Ala Ser Ser Leu Val Leu Val
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Val Ser Leu Gly Ala Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
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Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
            340                 345                 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480
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Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545                 550                 555                 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
                565                 570                 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
            580                 585                 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
        595                 600                 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
    610                 615                 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625                 630                 635                 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
                645                 650                 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
            660                 665                 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
        675                 680                 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
    690                 695                 700
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Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705                 710                 715                 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
                725                 730                 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
            740                 745                 750

Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
        755                 760                 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
    770                 775                 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785                 790                 795                 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
                805                 810                 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
            820                 825                 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
        835                 840                 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
    850                 855                 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865                 870                 875                 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
                885                 890                 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
            900                 905                 910
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Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
        915                 920                 925


Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
    930                 935                 940


Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945                 950                 955                 960


Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
                965                 970                 975


Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
            980                 985                 990


Ile Asp Arg Leu Ile Thr Gly Arg  Leu Gln Ser Leu Gln  Thr Tyr Val
        995                 1000                1005


Thr Gln  Gln Leu Ile Arg Ala  Ala Glu Ile Arg Ala  Ser Ala Asn
    1010                1015                1020


Leu Ala  Ala Thr Lys Met Ser  Glu Cys Val Leu Gly  Gln Ser Lys
    1025                1030                1035


Arg Val  Asp Phe Cys Gly Lys  Gly Tyr His Leu Met  Ser Phe Pro
    1040                1045                1050


Gln Ser  Ala Pro His Gly Val  Val Phe Leu His Val  Thr Tyr Val
    1055                1060                1065


Pro Ala  Gln Glu Lys Asn Phe  Thr Thr Ala Pro Ala  Ile Cys His
    1070                1075                1080


Asp Gly  Lys Ala His Phe Pro  Arg Glu Gly Val Phe  Val Ser Asn
    1085                1090                1095


Gly Thr  His Trp Phe Val Thr  Gln Arg Asn Phe Tyr  Glu Pro Gln
    1100                1105                1110


Ile Ile  Thr Thr Asp Asn Thr  Phe Val Ser Gly Asn  Cys Asp Val
    1115                1120                1125
```

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Val Ile  Gly Ile Val Asn Asn  Thr Val Tyr Asp Pro  Leu Gln Pro
    1130                1135                1140

Glu Leu  Asp Ser Phe Lys Glu  Glu Leu Asp Lys Tyr  Phe Lys Asn
    1145                1150                1155

His Thr  Ser Pro Asp Val Asp  Leu Gly Asp Ile Ser  Gly Ile Asn
    1160                1165                1170

Ala Ser  Val Val Asn Ile Gln  Lys Glu Ile Asp Arg  Leu Asn Glu
    1175                1180                1185

Val Ala  Lys Asn Leu Asn Glu  Ser Leu Ile Asp Leu  Gln Glu Leu
    1190                1195                1200

Gly Lys  Tyr Glu Gln Tyr Ile  Lys Trp Pro Trp Tyr  Ile Trp Leu
    1205                1210                1215

Gly Phe  Ile Ala Gly Leu Ile  Ala Ile Val Met Val  Thr Ile Met
    1220                1225                1230

Leu Cys  Cys Met Thr Ser Cys  Cys Ser Cys Leu Lys  Gly Cys Cys
    1235                1240                1245

Ser Cys  Gly Ser Cys Cys Lys  Phe Asp Glu Asp Asp  Ser Glu Pro
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Val Leu  Lys Gly Val Lys Leu  His Tyr Thr
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aacgtgacct ggttccacgc catccacgtg agcggcacca atggcacaaa gcggttcgac 240

aatcccgtgc tgccttttaa cgatggcgtg tacttcgcct ctaccgagaa gagcaacatc 300

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tgttcttgcc tgaagggctg ctgtagctgt ggctcctgct gtaagtttga cgaggatgac 3780

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Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu
35 40 45

His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
50 55 60

Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65 70 75 80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
85 90 95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
100 105 110

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Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
        115                 120                 125

Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
    130                 135                 140

Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
145                 150                 155                 160

Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
                165                 170                 175

Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
            180                 185                 190

Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
        195                 200                 205

Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
    210                 215                 220

Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
225                 230                 235                 240

Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
                245                 250                 255

Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro
            260                 265                 270

Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala
        275                 280                 285

Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
    290                 295                 300

Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
305                 310                 315                 320
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
                325                 330                 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
            340                 345                 350

Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
    370                 375                 380

Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
385                 390                 395                 400

Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
                405                 410                 415

Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
            420                 425                 430

Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
        435                 440                 445

Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
    450                 455                 460

Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
465                 470                 475                 480

Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly
                485                 490                 495

Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val
            500                 505                 510

Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
        515                 520                 525

Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540
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```
Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
545                 550                 555                 560

Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
                565                 570                 575

Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
            580                 585                 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
        595                 600                 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
    610                 615                 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
625                 630                 635                 640

Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
                645                 650                 655

Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
            660                 665                 670

Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
        675                 680                 685

Ser Gln Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asn Ser
    690                 695                 700

Val Ala Tyr Ser Asn Asn Ser Ile Ala Ile Pro Thr Asn Phe Thr Ile
705                 710                 715                 720

Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
                725                 730                 735

Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
            740                 745                 750
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Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
        755                 760                 765

Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
    770                 775                 780

Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
785                 790                 795                 800

Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser
                805                 810                 815

Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
            820                 825                 830

Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
        835                 840                 845

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
    850                 855                 860

Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
865                 870                 875                 880

Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
                885                 890                 895

Pro Phe Ala Met Gln Met Ala Tyr Arg Phe Asn Gly Ile Gly Val Thr
            900                 905                 910

Gln Asn Val Leu Tyr Glu Asn Gln Lys Leu Ile Ala Asn Gln Phe Asn
        915                 920                 925

Ser Ala Ile Gly Lys Ile Gln Asp Ser Leu Ser Ser Thr Ala Ser Ala
    930                 935                 940

Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
945                 950                 955                 960

Thr Leu Val Lys Gln Leu Ser Ser Asn Phe Gly Ala Ile Ser Ser Val
                965                 970                 975
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Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
            980                 985                 990


Ile Asp Arg Leu Ile Thr Gly Arg  Leu Gln Ser Leu Gln  Thr Tyr Val
        995                 1000                1005


Thr Gln  Gln Leu Ile Arg Ala  Ala Glu Ile Arg Ala  Ser Ala Asn
    1010                1015                1020


Leu Ala  Ala Thr Lys Met Ser  Glu Cys Val Leu Gly  Gln Ser Lys
    1025                1030                1035


Arg Val  Asp Phe Cys Gly Lys  Gly Tyr His Leu Met  Ser Phe Pro
    1040                1045                1050


Gln Ser  Ala Pro His Gly Val  Val Phe Leu His Val  Thr Tyr Val
    1055                1060                1065


Pro Ala  Gln Glu Lys Asn Phe  Thr Thr Ala Pro Ala  Ile Cys His
    1070                1075                1080


Asp Gly  Lys Ala His Phe Pro  Arg Glu Gly Val Phe  Val Ser Asn
    1085                1090                1095


Gly Thr  His Trp Phe Val Thr  Gln Arg Asn Phe Tyr  Glu Pro Gln
    1100                1105                1110


Ile Ile  Thr Thr Asp Asn Thr  Phe Val Ser Gly Asn  Cys Asp Val
    1115                1120                1125


Val Ile  Gly Ile Val Asn Asn  Thr Val Tyr Asp Pro  Leu Gln Pro
    1130                1135                1140


Glu Leu  Asp Ser Phe Lys Glu  Glu Leu Asp Lys Tyr  Phe Lys Asn
    1145                1150                1155


His Thr  Ser Pro Asp Val Asp  Leu Gly Asp Ile Ser  Gly Ile Asn
    1160                1165                1170
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Ala Ser  Val Val Asn Ile Gln  Lys Glu Ile Asp Arg  Leu Asn Glu
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Val Ala  Lys Asn Leu Asn Glu  Ser Leu Ile Asp Leu  Gln Glu Leu
    1190                1195                1200

Gly Lys  Tyr Glu Gln Tyr Ile  Lys Trp Pro Trp Tyr  Ile Trp Leu
    1205                1210                1215

Gly Phe  Ile Ala Gly Leu Ile  Ala Ile Val Met Val  Thr Ile Met
    1220                1225                1230

Leu Cys  Cys Met Thr Ser Cys  Cys Ser Cys Leu Lys  Gly Cys Cys
    1235                1240                1245

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Val Leu  Lys Gly Val Lys Leu  His Tyr Thr
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aaccctgtcc taccatttaa tgatggtgtt tattttgctt ccactgagaa gtctaacata      300

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aataacgcta ctaatgttgt tattaaagtc tgtgaatttc aattttgtaa tgatccattt      420

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His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp
65                  70                  75                  80

Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu
                85                  90                  95

Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser
            100                 105                 110

Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile
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Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr
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Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr
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Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu
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Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr
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Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu
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Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr
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Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser
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Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys
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Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val
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Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys
                325                 330                 335

Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala
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Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu
        355                 360                 365

Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro
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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe
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Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
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Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
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Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn
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Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe
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Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys
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Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys
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Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn
    530                 535                 540

Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu
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Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val
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Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe
            580                 585                 590

Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val
        595                 600                 605

Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile
    610                 615                 620

His Ala Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser
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Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val
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Asn Asn Ser Tyr Glu Cys Asp Ile Pro Ile Gly Ala Gly Ile Cys Ala
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Ser Tyr Gln Thr Gln Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala
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Ser Val Thr Thr Glu Ile Leu Pro Val Ser Met Thr Lys Thr Ser Val
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Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu
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Leu Leu Gln Tyr Gly Ser Phe Cys Thr Gln Leu Asn Arg Ala Leu Thr
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Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln
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Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe
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Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly
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Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp
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Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu
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Leu Thr Asp Glu Met Ile Ala Gln Tyr Thr Ser Ala Leu Leu Ala Gly
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Thr Ile Thr Ser Gly Trp Thr Phe Gly Ala Gly Ala Ala Leu Gln Ile
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Leu Gly Lys Leu Gln Asp Val Val Asn Gln Asn Ala Gln Ala Leu Asn
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Leu Asn Asp Ile Leu Ser Arg Leu Asp Lys Val Glu Ala Glu Val Gln
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Ile Asp Arg Leu Ile Thr Gly Arg  Leu Gln Ser Leu Gln  Thr Tyr Val
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Arg Val  Asp Phe Cys Gly Lys  Gly Tyr His Leu Met  Ser Phe Pro
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Pro Ala  Gln Glu Lys Asn Phe  Thr Thr Ala Pro Ala  Ile Cys His
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Asp Gly  Lys Ala His Phe Pro  Arg Glu Gly Val Phe  Val Ser Asn
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His Thr  Ser Pro Asp Val Asp  Leu Gly Asp Ile Ser  Gly Ile Asn
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Ala Ser  Val Val Asn Ile Gln  Lys Glu Ile Asp Arg  Leu Asn Glu
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Val Ala  Lys Asn Leu Asn Glu  Ser Leu Ile Asp Leu  Gln Glu Leu
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Gly Lys  Tyr Glu Gln Tyr Ile  Lys Trp Pro Trp Tyr  Ile Trp Leu
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