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(71) Applicant: **BioNTech RNA Pharmaceuticals GmbH**
55131 Mainz (DE)

(72) Inventors:
- **SAHIN, Ugur**
  55131 Mainz (DE)
- **GÜLER, Alptekin**
  55131 Mainz (DE)
- **KUHN, Andreas**
  55131 Mainz (DE)
- **MUIK, Alexander**
  55131 Manz (DE)
- **VOGEL, Annette**
  55131 Mainz (DE)
- **WALZER, Kerstin**
  55131 Mainz (DE)
- **WITZEL, Sonja**
  55131 Mainz (DE)
- **HEIN, Stephanie**
  55131 Mainz (DE)
- **TÜRECI, Özlem**
  55131 Mainz (DE)

(74) Representative: **Schnappauf, Georg**
ZSP Patentanwälte PartG mbB
Hansastraße 32
80686 München (DE)

(54) CORONAVIRUS VACCINE

(57) This disclosure relates to the field of RNA to prevent or treat coronavirus infection. In particular, the present disclosure relates to methods and agents for vaccination against coronavirus infection and inducing effective coronavirus antigen-specific immune responses such as antibody and/or T cell responses. Specifically, in one embodiment, the present disclosure relates to methods comprising administering to a subject RNA encoding a peptide or protein comprising an epitope of SARS-CoV-2 spike protein (S protein) for inducing an immune response against coronavirus S protein, in particular S protein of SARS-CoV-2, in the subject, i.e., vaccine RNA encoding vaccine antigen.

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Description

[0001] This disclosure relates to the field of RNA to prevent or treat coronavirus infection. In particular, the present disclosure relates to methods and agents for vaccination against coronavirus infection and inducing effective coronavirus antigen-specific immune responses such as antibody and/or T cell responses. These methods and agents are, in particular, useful for the prevention or treatment of coronavirus infection. Administration of RNA disclosed herein to a subject can protect the subject against coronavirus infection. Specifically, in one embodiment, the present disclosure relates to methods comprising administering to a subject RNA encoding a peptide or protein comprising an epitope of SARS-CoV-2 spike protein (S protein) for inducing an immune response against coronavirus S protein, in particular S protein of SARS-CoV-2, in the subject, i.e., vaccine RNA encoding vaccine antigen. Administering to the subject RNA encoding vaccine antigen may provide (following expression of the RNA by appropriate target cells) vaccine antigen for inducing an immune response against vaccine antigen (and disease-associated antigen) in the subject.

[0002] In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China and it became clear that a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was the underlying cause. The genetic sequence of SARS-CoV-2 became available to the WHO and public (MN908947.3) and the virus was categorized into the betacoronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, namely the Middle East respiratory syndrome (MERS) virus. On February 2nd, a total of 14'557 cases were globally confirmed in 24 countries including Germany and a subsequent self-sustaining, human-to-human virus spread resulted in that SARS-CoV-2 became a global epidemic.

[0003] Coronaviruses are positive-sense, single-stranded RNA ((+)ssRNA) enveloped viruses that encode for a total of four structural proteins, spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N). The spike protein (S protein) is responsible for receptor-recognition, attachment to the cell, infection via the endosomal pathway, and the genomic release driven by fusion of viral and endosomal membranes. Though sequences between the different family members vary, there are conserved regions and motifs within the S protein making it possible to divide the S protein into two subdomains: S1 and S2. While the S2, with its transmembrane domain, is responsible for membrane fusion, the S1 domain recognizes the virus-specific receptor and binds to the target host cell. Within several coronavirus isolates, the receptor binding domain (RBD) was identified and a general structure of the S protein defined (Figure 1).

[0004] Vaccine approaches and therapeutics against SARS-CoV-2 are currently not available, but urgently needed.

[0005] Due to the importance of the S protein in host cell recognition and entry, as well as in the induction of virus neutralising antibodies by the host immune system, we decided to target the viral S protein of SARS-CoV-2 and subdomains of the S protein such as S1 or RBD for vaccine development. Mutations within the regions important for conformation might be beneficial for inducing a stronger protective immune response. Therefore, we envision testing several constructs (Figure 2). As the naive S protein is a trimer and this trimeric structure has most likely an effect on the stability of the protein and the antigenicity, we included a strategy based on a stabilized construct introducing the T4 bacteriophage fibritin domain which is also in use in HIV for generating stable gp140 trimers and functional for SARS RBD-constructs.

Summary

[0006] The present invention generally embraces the immunotherapeutic treatment of a subject comprising the administration of RNA, i.e., vaccine RNA, encoding an amino acid sequence, i.e., a vaccine antigen, comprising SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, i.e., an antigenic peptide or protein. Thus, the vaccine antigen comprises an epitope of SARS-CoV-2 S protein for inducing an immune response against coronavirus S protein, in particular SARS-CoV-2 S protein, in the subject. RNA encoding vaccine antigen is administered to provide (following expression of the polynucleotide by appropriate target cells) antigen for induction, i.e., stimulation, priming and/or expansion, of an immune response, e.g., antibodies and/or immune effector cells, which is targeted to target antigen (coronavirus S protein, in particular SARS-CoV-2 S protein) or a procession product thereof. In one embodiment, the immune response which is to be induced according to the present disclosure is a B cell-mediated immune response, i.e., an antibody-mediated immune response. Additionally or alternatively, in one embodiment, the immune response which is to be induced according to the present disclosure is a T cell-mediated immune response. In one embodiment, the immune response is an anti-coronavirus, in particular anti-SARS-CoV-2 immune response.

[0007] The vaccine described herein comprises as the active principle single-stranded RNA that may be translated into the respective protein upon entering cells of a recipient. In addition to wildtype or codon-optimized sequences encoding the antigen sequence, the RNA may contain one or more structural elements optimized for maximal efficacy of the RNA with respect to stability and translational efficiency (5' cap, 5' UTR, 3' UTR, poly(A)-tail). In one embodiment,

the RNA contains all of these elements. In one embodiment, beta-S-ARCA(D1) ($m_2^{7,2'\text{-}O}$GppSpG) or $m_2^{7,3'\text{-}O}$G-ppp($m_1^{2'\text{-}O}$)ApG may be utilized as specific capping structure at the 5'-end of the RNA drug substances. As 5'-UTR sequence, the 5'-UTR sequence of the human alpha-globin mRNA, optionally with an optimized 'Kozak sequence' to increase translational efficiency may be used. As 3'-UTR sequence, a combination of two sequence elements (FI element) derived from the "amino terminal enhancer of split" (AES) mRNA (called F) and the mitochondrial encoded 12S ribosomal RNA (called I) placed between the coding sequence and the poly(A)-tail to assure higher maximum protein levels and prolonged persistence of the mRNA may be used. These were identified by an *ex vivo* selection process for sequences that confer RNA stability and augment total protein expression (see WO 2017/060314, herein incorporated by reference). Alternatively, the 3'-UTR may be two re-iterated 3'-UTRs of the human beta-globin mRNA. Furthermore, a poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence (of random nucleotides) and another 70 adenosine residues may be used. This poly(A)-tail sequence was designed to enhance RNA stability and translational efficiency.

[0008] Furthermore, a secretory signal peptide (sec) may be fused to the antigen-encoding regions preferably in a way that the sec is translated as N terminal tag. In one embodiment, sec corresponds to the secreotory signal peptide of the S protein. Sequences coding for short linker peptides predominantly consisting of the amino acids glycine (G) and serine (S), as commonly used for fusion proteins may be used as GS/Linkers.

[0009] The vaccine RNA described herein may be complexed with proteins and/or lipids, preferably lipids, to generate RNA-particles for administration. If a combination of different RNAs is used, the RNAs may be complexed together or complexed separately with proteins and/or lipids to generate RNA-particles for administration.

[0010] In one aspect, the invention relates to a composition or medical preparation comprising RNA encoding an amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof.

[0011] In one embodiment, an immunogenic fragment of the SARS-CoV-2 S protein comprises the S1 subunit of the SARS-CoV-2 S protein, or the receptor binding domain (RBD) of the S1 subunit of the SARS-CoV-2 S protein.

[0012] In one embodiment, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is able to form a multimeric complex, in particular a trimeric complex. To this end, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof may comprise a domain allowing the formation of a multimeric complex, in particular a trimeric complex of the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof. In one embodiment, the domain allowing the formation of a multimeric complex comprises a trimerization domain, for example, a trimerization domain as described herein.

[0013] In one embodiment, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof is encoded by a coding sequence which is codon-optimized and/or the G/C content of which is increased compared to wild type coding sequence, wherein the codon-optimization and/or the increase in the G/C content preferably does not change the sequence of the encoded amino acid sequence.

[0014] In one embodiment,

(i) the RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the nucleotide sequence of nucleotides 979 to 1584 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 979 to 1584 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 979 to 1584 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 979 to 1584 of SEQ ID NO: 2, 8 or 9; and/or
(ii) a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, or an immunogenic fragment of the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 327 to 528 of SEQ ID NO: 1.

[0015] In one embodiment,

(i) the RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the nucleotide sequence of nucleotides

49 to 2055 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 2055 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 49 to 2055 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 2055 of SEQ ID NO: 2, 8 or 9; and/or

(ii) a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the amino acid sequence of amino acids 17 to 685 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 685 of SEQ ID NO: 1, or an immunogenic fragment of the amino acid sequence of amino acids 17 to 685 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 685 of SEQ ID NO: 1.

[0016] In one embodiment,

(i) the RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 49 to 3819 of SEQ ID NO: 2, 8 or 9; and/or

(ii) a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or an immunogenic fragment of the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 17 to 1273 of SEQ ID NO: 1 or 7.

[0017] In one embodiment, the amino acid sequence comprising a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises a secretory signal peptide.

[0018] In one embodiment, the secretory signal peptide is fused, preferably N-terminally, to a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof.

[0019] In one embodiment,

(i) the RNA encoding the secretory signal peptide comprises the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or a fragment of the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of nucleotides 1 to 48 of SEQ ID NO: 2, 8 or 9; and/or

(ii) the secretory signal peptide comprises the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, an amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or a functional fragment of the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1, or the amino acid sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the amino acid sequence of amino acids 1 to 16 of SEQ ID NO: 1.

[0020] In one embodiment,

(i) the RNA encoding a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the nucleotide sequence of SEQ ID NO: 6, a nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 6, or a fragment of the nucleotide sequence of SEQ ID NO: 6, or the nucleotide sequence having at least 99%, 98%, 97%, 96%, 95%, 90%, 85%, or 80% identity to the nucleotide sequence of SEQ ID NO: 6; and/or

(ii) a SARS-CoV-2 S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof comprises the amino acid sequence of SEQ ID NO: 5, an amino acid

<220>
<223> Epitope

<400> 57

Val Tyr Asp Pro Leu Gln Pro Glu Leu
1 5

Claims

1. A composition comprising RNA encoding an amino acid sequence that comprises a SARS-CoV-2S protein, an immunogenic variant thereof, or an immunogenic fragment of the SARS-CoV-2 S protein or the immunogenic variant thereof, wherein the RNA is formulated in lipid nanoparticles comprising a cationically ionizable lipid, a neutral lipid, a steroid, and a pegylated lipid.

2. The composition of claim 1, wherein the immunogenic variant of SARS-CoV-2 S protein is SARS-CoV-2 S protein which is modified in such a way that the prototypical prefusion conformation is stabilized.

3. The composition of claim 1, wherein the immunogenic fragment comprises the receptor binding domain (RBD) of a SARS-CoV-2 S protein or an immunogenic variant thereof.

4. The composition of any one of claims 1 to 3, wherein the RNA is a modified RNA, which is modified by substitution of some or all uridine residues by modified uridine.

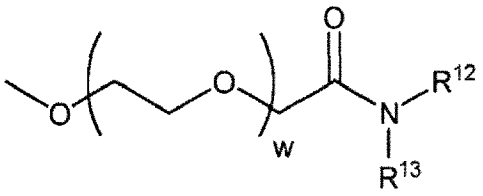
5. The composition of claim 4, wherein the modified uridine is N1-methyl-pseudouridine.

6. The composition of any one of claims 1 to 5, wherein the neutral lipid comprises a phospholipid.

7. The composition of claim 6, wherein the phospholipid comprises 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC).

8. The composition of any one of claims 1 to 7, wherein the steroid comprises cholesterol.

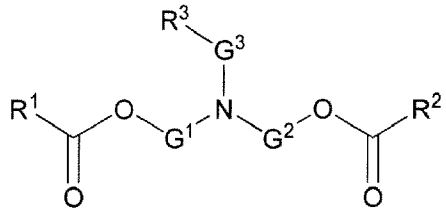
9. The composition of any one of claims 1 to 8, wherein the pegylated lipid is a compound having the structure:



or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:
R^{12} and R^{13} are each independently a straight or branched, saturated or unsaturated alkyl chain containing from 10 to 30 carbon atoms, wherein the alkyl chain is optionally interrupted by one or more ester bonds; and w has a mean value ranging from 30 to 60.

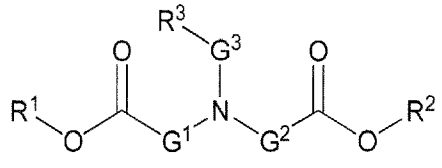
10. The composition of any one of claims 1 to 9, wherein the pegylated lipid is 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide.

11. The composition of any one of claims 1 to 10, wherein the cationically ionizable lipid is a compound having the following structure:



(IIIE)

or

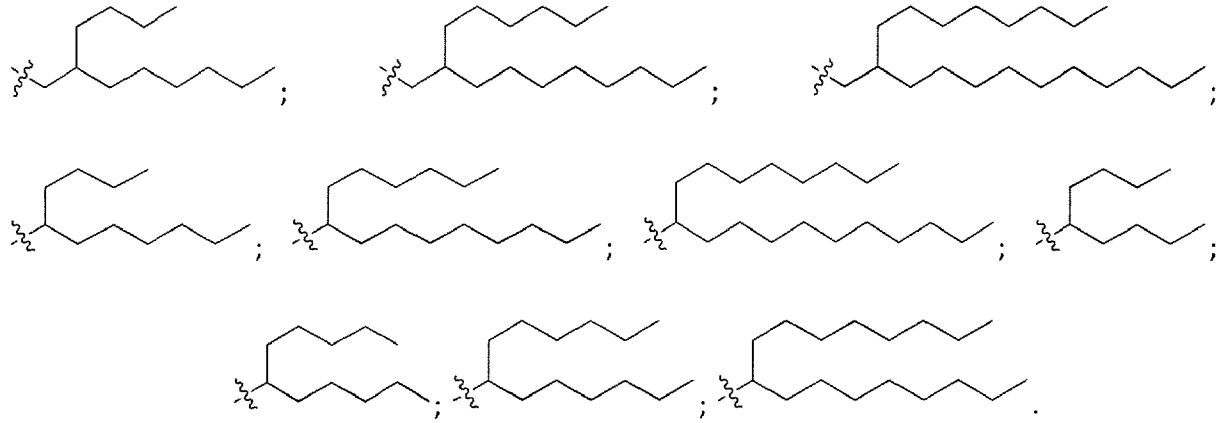


(IIIF)

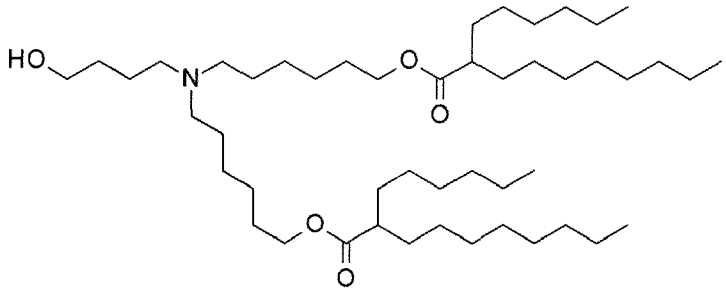
or a pharmaceutically acceptable salt, tautomer or stereoisomer thereof, wherein:

G^1 and G^2 are each independently unsubstituted C_1-C_{12} alkylene or C_1-C_{12} alkenylene;
G^3 is C_1-C_{24} alkylene, C_1-C_{24} alkenylene, C_3-C_8 cycloalkylene, C_3-C_8 cycloalkenylene;
R^1 and R^2 are each independently C_6-C_{24} alkyl or C_6-C_{24} alkenyl;
R^3 is H, OR^5, CN, -C(=O)OR^4, -OC(=O)R^4 or-$NR^5C(=O)R^4$; R^4 is C_1-C_{12} alkyl; and
R^5 is H or C_1-C_6 alkyl.

12. The composition of claim 11, wherein R^1 or R^2, or both, has one of the following structures:



13. The composition of any one of claims 1 to 12, wherein the cationically ionizable lipid has the following structure:



14. The composition of any one of claims 1 to 13, wherein the lipid nanoparticles comprise ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyidecanoate), 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide, 1,2-distearoyl-sn-glycero-3-phosphocholine, and cholesterol.

15. The composition of any one of claims 1 to 14 for pharmaceutical use.

16. The composition of any one of claims 1 to 15 for use in a method of inducing an immune response against coronavirus in a subject.

17. The composition of claim 16, wherein the coronavirus is SARS-CoV-2.

18. The composition of claim 16 or 17, wherein the subject is a human.

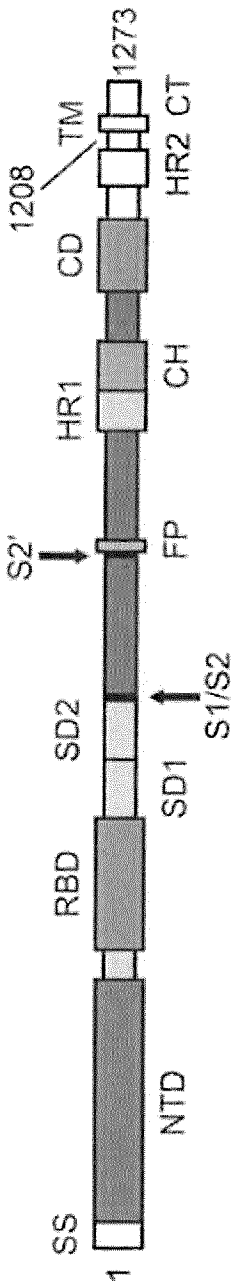
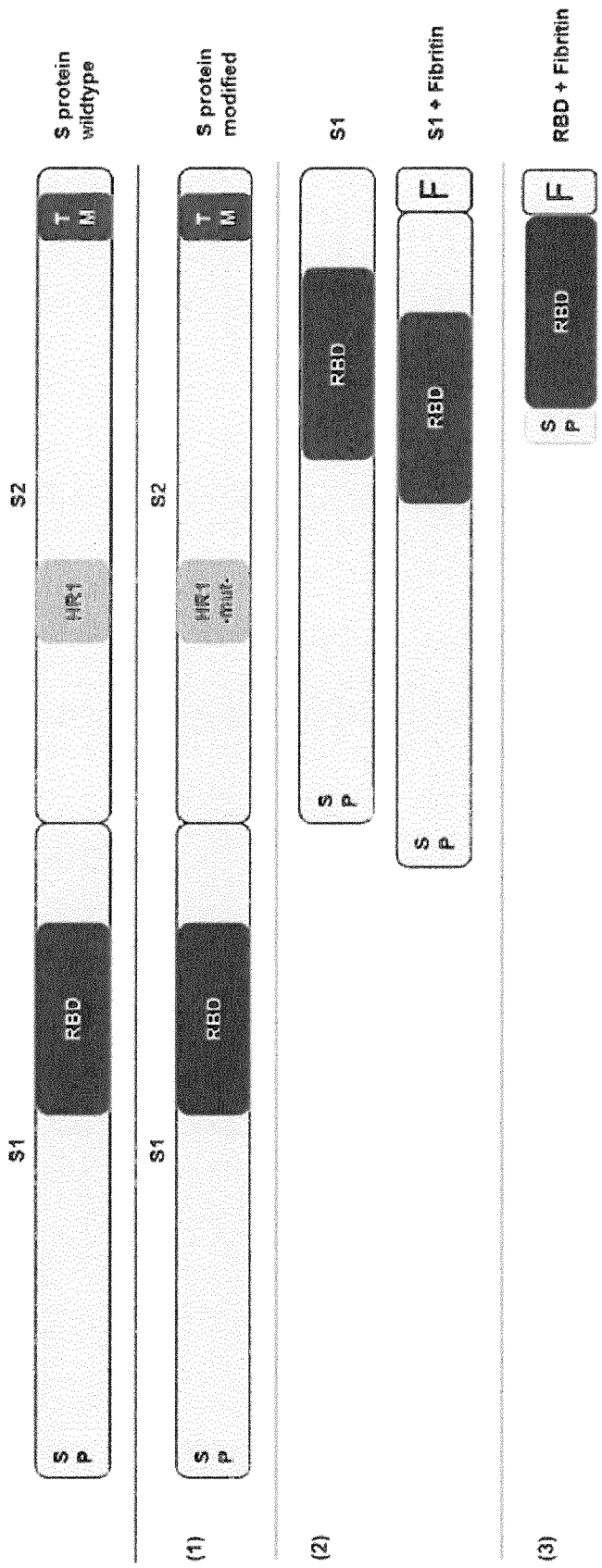


Figure 1

Figure 2


S protein wildtype
S protein modified
S1
S1 + Fibritin
RBD + Fibritin
S2
S1
RBD
HR1
T
M
S
P
F
(1)
(2)
(3)

Europäisches Patentamt
European Patent Office
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EUROPEAN SEARCH REPORT

Application Number
EP 21 16 8950

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Y	Penn Medicine: "COVID-19 Symposium: Nucleoside-modified mRNA Vaccines Against SARS-CoV-2 ¦ Dr. Norbert Pardi", , 8 April 2020 (2020-04-08), page 1, XP054982196, Retrieved from the Internet: URL:https://www.youtube.com/watch?v=wT4VzNUQ9Vs [retrieved on 2021-09-03] * page 5 *	4,5	

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TECHNICAL FIELDS SEARCHED (IPC)
F25D
A61K
B65D
C12N
C40B
C07H

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	7 September 2021	Wagner, René

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EUROPEAN SEARCH REPORT

Application Number
EP 21 16 8950

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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EUROPEAN SEARCH REPORT

Application Number
EP 21 16 8950

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	DATABASE EMBL [Online] EBI; 15 January 2020 (2020-01-15), Zhang Y.-Z. ET AL: "Wuhan seafood market pneumonia virus isolate Wuhan-Hu-1, complete genome.", XP055796635, Database accession no. MN908947 * abstract * -----	1-18	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	7 September 2021	Wagner, René

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A	Cohen Jon: "Scientists are moving at record speed to create new coronavirus vaccines-but they may come too late ¦ Science ¦ AAAS", Sciencemagazine, 27 January 2020 (2020-01-27), XP055807314, Retrieved from the Internet: URL:https://www.sciencemag.org/news/2020/01/scientists-are-moving-record-speed-create-new-coronavirus-vaccines-they-may-come-too [retrieved on 2021-05-25] * the whole document * -----	1-18	

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