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(12) United States Patent

Smith et al.

(54) CORONAVIRUS VACCINE FORMULATIONS

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A61K 39/215	(2006.01)
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A61K 39/00	(2006.01)

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(58) Field of Classification Search None

See application file for complete search history.

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(57) **ABSTRACT**

Disclosed herein are coronavirus Spike (S) proteins and nanoparticles comprising the same, which are suitable for use in vaccines. The nanoparticles present antigens from pathogens surrounded to and associated with a detergent core resulting in enhanced stability and good immunogenicity. Dosages, formulations, and methods for preparing the vaccines and nanoparticles are also disclosed.

20 Claims, 83 Drawing Sheets (77 of 83 Drawing Sheet(s) Filed in Color)

Specification includes a Sequence Listing.

MFVFLVLLPLVSSOCVNLTTRTOLPPAYTNSFTRGVYYPDKVFRSSVLHSTODLFLPFFSN VTWFHAIHVSGTNGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNN ATNVVIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEG KQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLLAL HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLK SFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYS VLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLP DDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGF NCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNG LTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQ VAVLYODVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNNSYECDIPIG AGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVS MTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYK TPPIKDFGGFNFSQILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICA QKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVT **ONVLYENOKLIANOFNSAIĞKIODSLSSTASALGKLODVVNONAOALNTLVKOLSSNFGA** ISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECV LGQSKRVDFCGKGYHLMSFPQSAPHGVVFLĤVTYVPÄQEKNFTTAPAICHDGKAHFPRE GVFVSNGTHWFVTQRNFYEPQHTTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEEL DKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

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NCYFPLQSYGFQPTNGVGYQPYRVVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNG
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AGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVS
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ISSVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECV
LGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPRE
GVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEEL
DKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWP
WYIWLGFIAGLIAIVMVTIMLCCMTSCCSCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

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Fig. 4



MERS does not bind ACE2 receptor

And a second 500 800 700 800 800 800 800 Time (s) 450nM 150nM 50nM 363 8 8 . 33 -200 00 ωü 8 dissociation 8 2 8 MERS 5 (BV1954) 450nM COVID 5 (BV2361) 450mM SARS S (BV444) 450nM 8 Binding DPP4 receptor: 180 MAR [-[-[association 8 2 2 88 22



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Fig. 10







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BV2365 Binding to hACE2 under stress conditions





Fig. 13A









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Fig. 15





% Weight Change (One Dose)





(98064) Weight (% Change)


























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Triple Cytokine Positive

N

~+

9







Fig. 23A



Fig. 23B



Fig. 23C







Fig. 25A













Fig. 26B















Fig. 29A







Fig. 29C









Fig. 29E

Fig. 30

BV2384: CoV-2019/GSAS/K986P/V987P (SEQ ID NO: 109)

Isoelectric Pt (pl) 5.89

Signal peptide

AGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQD VVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLD**PP**EAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASAN NGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYH KNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQG FSALEPLVDLPIGINITRFQTLLALHRSYLPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCAL DPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYS VLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSN NLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVV LSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEIL DITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVNN SYECDIPIGAGICASYQTQTNSP**GSAS**SVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSM TKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQ ILPDPSKPSKRSFIEDLLFNKVTLADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSAL LAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVFV SNGTHWEVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKELDKYFKNHTSPDVDLGDIS 3 INASVVNI QKEI DRLNEVAKNLNESLI DLQELGKYEQYI KWPWYIWLGFI AGLIAI VMVTIMLCCMTSCCSC MEVELVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGT JKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

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BV2373 (SEQ ID NO: 86)

CoV-2019/QQAQ/K986P/V987P

Inactive furin cleavage site

> Signal peptide

QI L P D P S K P S K R S F I E D L L F N K V T L A D A G F I K Q Y G D C L G D I A A R D L I C A Q K F N G L T V L P P L L T D E M I A Q Y T S A LLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSTASALGKLQ MEVELVLLPLVSSQCVNLTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGT NGTKRFDNPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSKTQSLLIVNNATNVVIKVCEFQFCNDPFLGVYYH KNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQG FSALEPLVDLPIGINITRFQTLLALHRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCA LDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADY SVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNS NNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVV LDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVN NSYECDIPIGAGICASYQTQTNSPQQAQSVASQSIIAYTMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVS MTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFS DVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRLD**PP**EAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASA NLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFPREGVF VSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGD ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTIMLCCMTSCC VLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAVRDPQTLEI SCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT



Fig. 32

Yield: 13.098mg/4.8 liter = 2.728 mg/L



Fig. 33



Fig. 34











Fig. 36A

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Fig. 36B



Fig. 37A







Fig. 38A



Fig. 38B









Fig. 38D



U.S. Patent



Mar. 23, 2021



Correlation of Anti-S lgG Titer and hACE2 Receptor Inhibition in macaques




















Fig. 41





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	8 • • • • • • • • •	* • • • •			Convalescent Sera	(
		* * }**+**	+-' • s i i ***	Dose 1/ Dose 2	25/0 50/0 26/26	Hospital Hospital
		• • • • • • • • • • • • • • • • • • •	** : !	Dose 1/ Dose 2	25/25 50/50 28/27	Day 35 patient Treated
Fig. 43B		• • •	*** * * *	Dose 1/ Dose 2	5/5 50/50 29/29	
			+++-#-# • . 1#	Dose 1/ Dose 2	25/25 0/0 25/25	
			21 + + +	Dose 1/ Dose 2	0/0 0/0 23/21	
	Neutralization 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	suniV aqv] L PI!M % (100	BV2373 (µg) Matrix-M TM I (dose 1/dose 2)	

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Fig. 44A







100 % Vild Type Virus Neutralization

Fig. 44C





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Fig. 45B



Fig. 45C



Fig. 45D

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CORONAVIRUS VACCINE FORMULATIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to the following applications, each of which is incorporated by reference in its entirety for all purposes: U.S. Provisional Application No. 62/966,271, filed Jan. 27, 2020; U.S. Provisional Application No. 62/976,858, filed Feb. 14, 2020; U.S. Provisional Application No. 62/983,180, filed Feb. 28, 2020; U.S. Provisional Application No. 63/048,945, filed Jul. 7, 2020; U.S. Provisional Application No. 63/051,706, filed Jul. 14, 2020; and U.S. Provisional Application No. 63/054,182, filed Jul. 20, 2020.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

The contents of the text file submitted electronically herewith are incorporated herein by reference in their 20 entirety: A computer readable format copy of the Sequence Listing (filename: NOVV_088_06US_SeqList_ST25.txt, date recorded: Jul. 29, 2020; file size: 514 kilobytes).

FIELD

The present disclosure is generally related to non-naturally occurring coronavirus (CoV) Spike (S) polypeptides and nanoparticles and vaccines comprising the same, which are useful for stimulating immune responses. The nanoparticles provide antigens, for example, glycoprotein antigens, optionally associated with a detergent core and are typically produced using recombinant approaches. The nanoparticles have improved stability and enhanced epitope presentation. The disclosure also provides compositions containing the nanoparticles, methods for producing them, and methods of 35 stimulating immune responses.

BACKGROUND OF THE INVENTION

Infectious diseases remain a problem throughout the 40 world. While progress has been made on developing vaccines against some pathogens, many remain a threat to human health. The outbreak of sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (also called Wuhan coronavirus and SARS-CoV-2) has infected more than 2000 45 people in China and killed at least 17 people. Recently, the SARS-CoV-2 coronavirus has spread to the United States, Thailand, South Korea, Taiwan, and Japan. The SARS-CoV-2 coronavirus belongs to the same family of viruses as severe acute respiratory syndrome coronavirus (SARS- 50 CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which have killed hundreds of people in the past 17 years. SARS-CoV-2 causes the disease COVID-19.

The development of vaccines that prevent or reduce the severity of life-threatening infectious diseases like the 55 linked immunosorbent assay (ELISA). SARS-CoV-2 coronavirus is desirable. However, human vaccine development remains challenging because of the highly sophisticated evasion mechanisms of pathogens and difficulties stabilizing vaccines. Optimally, a vaccine must both induce antibodies that block or neutralize infectious 60 agents and remain stable in various environments, including environments that do not enable refrigeration.

SUMMARY OF THE INVENTION

The present disclosure provides non-naturally occurring CoVS polypeptides suitable for inducing immune responses

against SARS-CoV-2 (also called Wuhan CoV and 2019nCoV)). The disclosure also provides nanoparticles containing the glycoproteins as well as methods of stimulating immune responses.

The present disclosure also provides CoV S polypeptides suitable for inducing immune responses against multiple coronaviruses, including SARS-CoV-2, Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome (SARS).

BRIEF DESCRIPTION OF THE DRAWINGS

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application 15 publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

FIG. 1 shows a schematic of the wild-type amino acid sequence of the SARS-CoV-2 Spike (S) protein (SEQ ID NO: 1). The furin cleavage site RRAR (SEQ ID NO: 6) is highlighted in bold, and the signal peptide is underlined.

FIG. 2 shows the primary structure of the wild-type CoV S polypeptide, which has an inactive furin cleavage site, a fusion peptide deletion, and K986P and V987P mutations. The domain positions are numbered with respect to the amino acid sequence of the wild-type CoV S polypeptide from SARS-CoV-2 containing a signal peptide (SEQ ID NO: 1).

FIG. 3 shows the primary structure of the BV2378 CoV S polypeptide, which has an inactive furin cleavage site, a fusion peptide deletion, and K986P and V987P mutations. The domain positions are numbered with respect to the amino acid sequence of the wild-type CoV S polypeptide from SARS-CoV-2 containing a signal peptide (SEQ ID NO: 1).

FIG. 4 shows purification of the CoV S polypeptides BV2364, BV2365, BV2366, BV2367, BV2368, BV2369, BV2373, BV2374, and BV2375. The data reveal that BV2365 (SEQ ID NO: 4) and BV2373 (SEQ ID NO: 87) which has an inactive furin cleavage site having an amino acid sequence of QQAQ (SEQ ID NO: 7) is expressed as a single chain (S0). In contrast, CoV S polypeptides containing an intact furin cleavage site (e.g. BV2364, BV2366, and BV2374) are cleaved, as evident by the presence of the cleavage product S2.

FIG. 5 shows that the CoV S polypeptides BV2361, BV2365, BV2369, BV2365, BV2373, and BV2374 bind to human angiotensin-converting enzyme 2 precursor (hACE2) by bio-layer interferometry.

FIG. 6 shows that BV2361 from SARS-CoV-2 does not bind the MERS-CoV receptor, dipeptidyl peptidase IV (DPP4) and the MERS S protein does not bind to human angiotensin-converting enzyme 2 precursor (hACE2) by bio-layer interferometry.

FIG. 7 shows that BV2361 binds to hACE2 by enzyme-

FIG. 8 shows the primary structure of the BV2373 CoV S polypeptide and modifications to the furin cleavage site, K986P, and V987P.

FIG. 9 shows purification of the wild type CoV S polypeptide and the CoV S polypeptides BV2365 and BV2373.

FIG. 10 shows a cryo-electron microscopy (cryoEM) structure of the BV2373 CoV S polypeptide overlaid on the cryoEM structure of the SARS-CoV-2 spike protein (EMB ID: 21374).

FIGS. 11A-F show that the CoV S Spike polypeptides BV2365 and BV2373 bind to hACE2. Bio-layer interferometry reveals that BV2365 (FIG. 11B) and BV2373 (FIG.

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11C) bind to hACE2 with similar dissociation kinetics to the wild-type CoV S polypeptide (FIG. **11**A) ELISA shows that the wild-type CoV S polypeptide (FIG. **11**D) and BV2365 (FIG. **11**E) bind to hACE2 with similar affinity while BV2373 binds to hACE2 at a higher affinity (FIG. **11**F).

FIGS. **12**A-B show the effect of stress conditions, such as temperature, two freeze/thaw cycles, oxidation, agitation, and pH extremes on binding of the CoV S polypeptides BV2373 (FIG. **12**A) and BV2365 (FIG. **12**B) to hACE2.

FIGS. **13**A-B show anti-CoV S polypeptide IgG titers 13 days, 21 days, and 28 days after immunization of mice with two doses (FIG. **13**A) and one dose of 0.1 μ g to 10 μ g of BV2373 with or without Fraction A and Fraction C iscom matrix (e.g., MATRIX-MTM) (FIG. **13**B).

FIG. **14** shows the induction of antibodies that block interaction of hACE2 in mice immunized with one dose or two doses of 0.1 μ g to 10 μ g of BV2373 with or without MATRIX-MTM.

FIG. **15** shows virus neutralizing antibodies detected in $_{20}$ mice immunized with one dose or two doses of 0.1 µg to 10 µg of BV2373 with or without MATRIX-MTM.

FIG. **16** shows the virus load (SARS-CoV-2) in the lungs of Ad/CMV/hACE2 mice immunized with either a single dose of BV2373 or two doses of BV2373 spaced 14 days 25 apart with or without MATRIX-MTM.

FIGS. **17**A-C shows weight loss exhibited by mice after immunization with BV2373. FIG. **17**A shows the effect of immunization on weight loss with a single 0.01 µg, 0.1 µg, 1 µg, or 10 µg of BV2373 plus MATRIX-MTM. FIG. **17**B 30 shows the effect of immunization on weight loss with two doses of BV2373 (0.01 µg, 0.1 µg, 1 µg) plus MATRIX-MTM. FIG. **17**C shows the effect of immunization on weight loss with two doses of BV2373 (10 µg) in the presence or absence of MATRIX-MTM. 35

FIGS. **18**A-B shows the effect of BV2373 on lung histopathology of mice four days (FIG. **18**A) or seven days (FIG. **18**B) after infection with SARS-CoV-2.

FIG. **19** shows the number of IFN- γ secreting cells after ex vivo stimulation in the spleens of mice immunized with 40 BV2373 in the absence of adjuvant compared to mice immunized with BV2373 in the presence of MATRIX-MTM. FIG. **29**A-E shows the frequency of cytokine secreting with BV2373 in the presence of MATRIX-MTM.

FIGS. **20**A-E shows the frequency of cytokine secreting CD4+ T cells in the spleens of mice immunized with BV2373 in the presence or absence of MATRIX-MTM. FIG. 45 **20**A shows the frequency of IFN- γ secreting CD4+ T cells. FIG. **20**B shows the frequency of TNF- α secreting CD4+ T cells. FIG. **20**C shows the frequency of IL-2 secreting CD4+ T cells. FIG. **20**D shows the frequency of CD4+ T cells that secrete two cytokines selected from IFN- γ , TNF- α , and 50 IL-2. FIG. **20**E shows the frequency of CD4+ T cells that express IFN- γ , TNF- α , and IL-2.

FIGS. **21**A-E shows the frequency of cytokine secreting CD8⁺ T cells in the spleens of mice immunized with BV2373 in the presence or absence of MATRIX-MTM. FIG. 55 **21**A shows the frequency of IFN- γ secreting CD8⁺ T cells. FIG. **21**B shows the frequency of TNF- α secreting CD8⁺ T cells. FIG. **21**C shows the frequency of IL-2 secreting CD8⁺ T cells. FIG. **20**D shows the frequency of CD8⁺ T cells that secrete two cytokines selected from IFN- γ , TNF- α , and 60 IL-2. FIG. **21**E shows the frequency of CD8⁺ T cells that express IFN- γ , TNF- α , and IL-2.

FIG. **22** illustrates the frequency of CD4⁺ or CD8⁺ cells that express one (single), two (double), or three (triple) cytokines selected from IFN- γ , TNF- α , and IL-2 in the 65 spleens of mice immunized with BV2373 in the presence or absence of MATRIX-MTM.

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FIGS. **23**A-C illustrate the effect of immunization with BV2373 in the presence or absence of MATRIX- M^{TM} on type 2 cytokine secretion from CD4⁺ T cells. FIG. **23**A shows the frequency of IL-4 secreting cells. FIG. **23**B shows the frequency of IL-5 CD4⁺ secreting cells. FIG. **23**C shows the ratio of IFN- γ secreting to IL-4 secreting CD4⁺ T cells.

FIGS. **24**A-B illustrate the effect of mouse immunization with BV2373 in the presence or absence of MATRIX-MTM on germinal center formation by assessing the presence of CD4⁺ T follicular helper cells (TFH). FIG. **24**A shows the frequency of CD4⁺ T follicular helper cells in spleens, and FIG. **24**B shows the phenotype (e.g. CD4⁺ CXCR5⁺ PD-1⁺) of the CD4⁺ T follicular helper cells.

FIGS. **25**A-B illustrate the effect of mouse immunization with BV2373 in the presence or absence of MATRIX-MTM on germinal center formation by assessing the presence of germinal center (GC) B cells. FIG. **25**A shows the frequency of GC B cells in spleens, and FIG. **25**B reveals the phenotype (e.g. CD19⁺ GL7⁺ CD-95⁺) of the CD4⁺ T follicular helper cells.

FIGS. **26**A-C show the effect of immunization with BV2373 in the presence or absence of MATRIX- M^{TM} on antibody response in olive baboons. FIG. **26**A shows the anti-SARS-CoV-2 S polypeptide IgG titer in baboons after immunization with BV2373. FIG. **26**B shows the presence of hACE2 receptor blocking antibodies in baboons following a single immunization with 5 µg or 25 µg of BV2373 in the presence of MATRIX- M^{TM} . FIG. **26**C shows the titer of virus neutralizing antibodies following a single immunization with BV2373 and MATRIX- M^{TM} .

FIG. **27** shows the significant correlation between anti-SARS-CoV-2 S polypeptide IgG and neutralizing antibody titers in olive baboons after immunization with BV2373.

FIG. **28** shows the frequency of IFN- γ secreting cells in peripheral blood mononuclear cells (PBMC) of olive baboons immunized with BV2373 in the presence or absence of MATRIX-MTM.

FIGS. **29**A-E shows the frequency of cytokine secreting CD4+ T cells in the PBMC of olive baboons immunized with BV2373 in the presence or absence of MATRIX-MTM. FIG. **29**A shows the frequency of IFN- γ secreting CD4+ T cells. FIG. **29**B shows the frequency of IL-2 secreting CD4+ T cells. FIG. **29**C shows the frequency of TNF- α secreting CD4+ T cells. FIG. **29**C shows the frequency of CD4+ T cells that secrete two cytokines selected from IFN- γ , TNF- α , and IL-2. FIG. **29**E shows the frequency of CD4+ T cells that express IFN- γ , TNF- α , and IL-2.

FIG. **30** shows a schematic of the coronavirus Spike (S) protein (SEQ ID NO: 109) (BV2384). The furin cleavage site GSAS (SEQ ID NO: 97) is underlined once, and the K986P and V987P mutations are underlined twice.

FIG. **31** shows a schematic of the coronavirus Spike (S) protein (SEQ ID NO: 86) (BV2373). The furin cleavage site QQAQ (SEQ ID NO: 7) is underlined once, and the K986P and V987P mutations are underlined twice.

FIG. **32** shows purification of the CoV S polypeptides BV2373 (SEQ ID NO: 87) and BV2384 (SEQ ID NO: 109). FIG. **33** shows a scanning densitometry plot of BV2384

(SEQ ID NO: 109) purity after purification. FIG. **34** shows a scanning densitometry plot of BV2373

(SEQ ID NO: 87) purity after purification

FIGS. **35**A-B illustrates induction of anti-S antibodies (FIG. **35**A) and neutralizing antibodies (FIG. **35**B) in response to administration of BV2373 and MATRIX-MTM. Cynomolgus macaques were administered one or two doses (Day 0 and Day 21) of 2.5 μ g, 5 μ g, or 25 μ g of BV2373 with

25 μ g or 50 μ g MATRIX-MTM adjuvant. Controls received neither BV2373 or MATRIX-MTM. Antibodies were measured at Days 21 and 33.

FIGS. 36A-B illustrates a decrease of SARS-CoV-2 viral replication by vaccine formulations disclosed herein as 5 assessed in broncheoalveol lavage (BAL) in Cynomolgus macaques. Cynomolgus macaques were administered BV2373 and MATRIX-M[™] as shown. Subjects were immunized Day 0 and in the groups with two doses Day 0 and Day 21. Subject animals were challenged Day 37 with 1×10^4 pfu 10 SARS-CoV-2 virus. Viral RNA (FIG. 36A, corresponding to total RNA present) and viral sub-genomic RNA (FIG. 36B, corresponding to replicating virus) levels were assessed in bronchiolar lavage (BAL) at 2 days and 4 days postchallenge with infectious virus (d2pi and d4pi). Most sub- 15 jects showed no viral RNA. At Day 2 small amounts of RNA were measured in some subjects. By Day 4, no RNA was measured except for two subjects at the lowest dose of 2.5 Sub-genomic RNA was not detected at either 2 Days or 4 days except for 1 subject, again at the lowest dose.

FIGS. 37A-B illustrates a decrease of SARS-CoV-2 viral replication by vaccine formulations disclosed herein as assessed in nasal swab in Cynomolgus macaques. Cynomolgus macaques were administered BV2373 with MATRIX-M[™] as shown. Subjects were immunized Day 0 and in the 25 groups with two doses Day 0 and Day 21. Subject animals were challenged Day 37 with 1×10^4 SARS-CoV-2 virus. Viral RNA (FIG. 37A) and viral sub-genomic (sg) RNA (FIG. 37B) were assessed by nasal swab at 2 days and 4 days post-infection (d2pi and d4pi). Most subjects showed no 30 viral RNA. At Day 2 and Day 4 small amounts of RNA were measured in some subjects. Sub-genomic RNA was not detected at either 2 Days or 4 days. Subjects were immunized Day 0 and in the groups with two doses Day 0 and Day 21. These data show that the vaccine decreases nose total 35 virus RNA by 100-1000 fold and sgRNA to undetectable levels, and confirm that immune response to the vaccine will block viral replication and prevent viral spread.

FIGS. **38**A-B show anti-CoV S polypeptide IgG titers 21 days and 35 days after immunization of Cynomolgus 40 macaques with one dose (FIG. **38**A) or two doses of BV2373 and 25 μ g or 50 μ g of MATRIX-MTM (FIG. **38**B).

FIGS. **38C-38D** shows the hACE2 inhibition titer of Cynomolgus macaques 21 days and 35 days after immunization of Cynomolgus macaques with one dose (FIG. **38**C) 45 or two doses of BV2373 (5 μ g) and MATRIX-MTM (25 μ g or 50 μ g) (FIG. **38**D).

FIG. **38**E shows the significant correlation between anti-CoV S polypeptide IgG titer and hACE2 inhibition titer in Cynomolgus macaques after administration of BV2373 and 50 Th2 cytokines IL-5 and IL-13 at the same time. MATRIX-MTM. Data is shown for Groups 2-6 of Table 4.

FIG. **39** shows the anti-CoV S polypeptide titers and hACE2 inhibition titer of Cynomolgus macaques 35 days after immunization with two doses of BV2373 and MATRIX-MTM or after immunization with convalescent 55 human serum (Groups 2, 4, and 6) of Table 4. These data show that the anti-CoV S polypeptide and hACE2 inhibition titers of Cynomologus macaques immunized with BV2373 and MATRIX-MTM is superior to Cynomolgus macaques immunized with convalescent serum. 60

FIGS. **40**A-B shows the SARS-CoV-2 neutralizing titers of Cynomolgus macaques immunized with BV2373 and MATRIX-MTM as determined by cytopathic effect (CPE) (FIG. **40**A) and plaque reduction neutralization test (PRNT) (FIG. **40**B).

FIG. **41** shows administration timings of a clinical trial that evaluated the safety and efficacy of a vaccine compris-

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ing BV2373 and optionally MATRIX-MTM. AESI denotes an adverse event of special interest. MAEE denotes a medically attended adverse event, and SAE denotes a serious adverse event.

FIGS. **42**A-B show the local (FIG. **42**A) and systemic adverse events (FIG. **42**B) experienced by patients in a clinical trial which evaluated a vaccine comprising BV2373 and MATRIX-MTM. Groups A-E are identified in Table 5. The data shows that the vaccine was well tolerated and safe.

FIGS. 43A-B show the anti-CoV S polypeptide IgG (FIG. 43A) and neutralization titers (FIG. 43B) 21 days and 35 days after immunization of participants in a clinical trial which evaluated a vaccine comprising BV2373 and MATRIX-MTM. Horizontal bars represent interquartile range (IRQ) and median area under the curve, respectively. Whisker endpoints are equal to the maximum and minimum values below or above the median ± 1.5 times the IQR. The convalescent serum panel includes specimens from PCR-20 confirmed COVID-19 participants from Baylor College of Medicine (29 specimens for ELISA and 32 specimens for microneutralization (MN IC_{>99}). Severity of COVID-19 is denoted as a red mark for hospitalized patients (including intensive care setting), a blue mark for outpatient-treated patients (sample collected in emergency department), and a green mark for asymptomatic (exposed) patients (sample collected from contact/exposure assessment).

FIGS. **44**A-C shows the correlation between anti-CoV S polypeptide IgG and neutralizing antibody titers in patients administered convalescent sera (FIG. **44**A), two 25 μ g doses of BV2373 (FIG. **44**B), and two doses (5 μ g and 25 μ g) of BV2373 with MATRIX-MTM (FIG. **44**C). A strong correlation was observed between neutralizing antibody titers and anti-CoV-S IgG titers in patients treated with convalescent sera or with adjuvanted BV2373, but not in patients treated with BV2373 in the absence of adjuvant.

FIGS. **45**A-D show the frequencies of antigen-specific CD4⁺ T cells producing T helper 1 (Th1) cytokines interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF- α), and interleukin (IL)-2 and T helper 2 (Th2) cytokines IL-5 and IL-13 indicated cytokines from participants in Groups A (placebo, FIG. **45**A), B (25 µg BV2373, FIG. **45**B), C (5 µg BV2373 and 50 MATRIX-MTM, FIG. **45**C), and D (25 µg BV2373 and 50 µg MATRIX-MTM, FIG. **45**D) following stimulation with BV2373. "Any 2" in Th1 cytokine panel means CD4⁺ T cells that can produce two types of Th1 cytokines at the same time. "All 3" indicates CD4⁺ T cells that produce IFN-γ, TNF- α , and IL-2 simultaneously. "Both" in Th2 panel means CD4⁺ T cells that can produce Th2 cytokines IL-5 and IL-13 at the same time.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, ref-60 erence to "a protein" can refer to one protein or to mixtures of such protein, and reference to "the method" includes reference to equivalent steps and/or methods known to those skilled in the art, and so forth.

As used herein, the term "adjuvant" refers to a compound that, when used in combination with an immunogen, augments or otherwise alters or modifies the immune response induced against the immunogen. Modification of the

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immune response may include intensification or broadening the specificity of either or both antibody and cellular immune responses.

As used herein, the term "about" or "approximately" when preceding a numerical value indicates the value plus or 5 minus a range of 10%. For example, "about 100" encompasses 90 and 110.

As used herein, the terms "immunogen," "antigen," and "epitope" refer to substances such as proteins, including glycoproteins, and peptides that are capable of eliciting an 10 immune response.

As used herein, an "immunogenic composition" is a composition that comprises an antigen where administration of the composition to a subject results in the development in the subject of a humoral and/or a cellular immune response 15 to the antigen.

As used herein, a "subunit" composition, for example a vaccine, that includes one or more selected antigens but not all antigens from a pathogen. Such a composition is substantially free of intact virus or the lysate of such cells or 20 particles and is typically prepared from at least partially purified, often substantially purified immunogenic polypeptides from the pathogen. The antigens in the subunit composition disclosed herein are typically prepared recombinantly, often using a baculovirus system. 25

As used herein, "substantially" refers to isolation of a substance (e.g. a compound, polynucleotide, or polypeptide) such that the substance forms the majority percent of the sample in which it is contained. For example, in a sample, a substantially purified component comprises 85%, prefer- 30 ably 85%-90%, more preferably at least 95%-99.5%, and most preferably at least 99% of the sample. If a component is substantially replaced the amount remaining in a sample is less than or equal to about 0.5% to about 10%, preferably less than about 0.5% to about 1.0%.

The terms "treat," "treatment," and "treating," as used herein, refer to an approach for obtaining beneficial or desired results, for example, clinical results. For the purposes of this disclosure, beneficial or desired results may include inhibiting or suppressing the initiation or progres- 40 sion of an infection or a disease; ameliorating, or reducing the development of, symptoms of an infection or disease; or a combination thereof.

"Prevention," as used herein, is used interchangeably with "prophylaxis" and can mean complete prevention of an 45 infection or disease, or prevention of the development of symptoms of that infection or disease; a delay in the onset of an infection or disease or its symptoms; or a decrease in the severity of a subsequently developed infection or disease or its symptoms.

As used herein an "effective dose" or "effective amount" refers to an amount of an immunogen sufficient to induce an immune response that reduces at least one symptom of pathogen infection. An effective dose or effective amount may be determined e.g., by measuring amounts of neutral- 55 izing secretory and/or serum antibodies, e.g., by plaque neutralization, complement fixation, enzyme-linked immunosorbent (ELISA), or microneutralization assay.

As used herein, the term "vaccine" refers to an immunogenic composition, such as an immunogen derived from a 60 pathogen, which is used to induce an immune response against the pathogen that provides protective immunity (e.g., immunity that protects a subject against infection with the pathogen and/or reduces the severity of the disease or condition caused by infection with the pathogen). The 65 protective immune response may include formation of antibodies and/or a cell-mediated response. Depending on con-

text, the term "vaccine" may also refer to a suspension or solution of an immunogen that is administered to a subject to produce protective immunity.

As used herein, the term "subject" includes humans and other animals. Typically, the subject is a human. For example, the subject may be an adult, a teenager, a child (2 years to 14 years of age), an infant (birth to 2 year), or a neonate (up to 2 months). In particular aspects, the subject is up to 4 months old, or up to 6 months old. In some aspects, the adults are seniors about 65 years or older, or about 60 years or older. In some aspects, the subject is a pregnant woman or a woman intending to become pregnant. In other aspects, subject is not a human; for example a non-human primate; for example, a baboon, a chimpanzee, a gorilla, or a macaque. In certain aspects, the subject may be a pet, such as a dog or cat.

As used herein, the term "pharmaceutically acceptable" means being approved by a regulatory agency of a U.S. Federal or a state government or listed in the U.S. Pharmacopeia, European Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans. These compositions can be useful as a vaccine and/or antigenic compositions for inducing a protective immune response in a vertebrate.

As used herein, the term "about" means plus or minus 10% of the indicated numerical value.

As used herein, the term "NVX-CoV2373" refers to a vaccine composition comprising the BV2373 Spike glycoprotein (SEQ ID NO: 87) and Fraction A and Fraction C iscom matrix (e.g., MATRIX-MTM).

Vaccine Compositions Containing Coronavirus (CoV) Spike (S) Proteins

The disclosure provides non-naturally occurring coronavirus (CoV) Spike (S) polypeptides, nanoparticles containing CoV S polypeptides, and immunogenic compositions and vaccine compositions containing either non-naturally occurring CoV S polypeptides or nanoparticles containing CoV S polypeptides. In embodiments, provided herein are methods of using CoV S polypeptides, nanoparticles, immunogenic compositions, and vaccine compositions to stimulate an immune response.

Also provided herein are methods of manufacturing the nanoparticles and vaccine compositions. Advantageously, the methods provide nanoparticles that are substantially free from contamination by other proteins, such as proteins associated with recombinant expression of proteins in insect cells. In embodiments, expression occurs in baculovirus/Sf9 systems.

CoV S Polypeptide Antigens

The vaccine compositions of the disclosure contain nonnaturally occurring CoV S polypeptides. CoV S polypeptides may be derived from coronaviruses, including but not limited to SARS-CoV-2, for example from SARS-CoV-2, from MERS CoV, and from SARS CoV. In contrast to the SARS-CoV S protein, the SARS-CoV-2 S protein has a four amino acid insertion in the S1/S2 cleavage site resulting in a polybasic RRAR furin-like cleavage motif. The SARS-CoV-2 S protein is synthesized as an inactive precursor (S0) that is proteolytically cleaved at the furin cleavage site into 51 and S2 subunits which remain non-covalently linked to form prefusion trimers. The S2 domain of the SARS-CoV-2 S protein comprises a fusion peptide (FP), two heptad repeats (HR1 and HR2), a transmembrane (TM) domain, and a cytoplasmic tail. The 51 domain of the SARS-CoV-2 S protein folds into four distinct domains: the N-terminal

domain (NTD) and the C-terminal domain, which contains the receptor binding domain (RBD) and two subdomains SD1 and SD2. The prefusion SARS-CoV-2 S protein trimers undergo a structural rearrangement from a prefusion to a postfusion conformation upon S-protein receptor binding 5 and cleavage.

In embodiments, the CoV S polypeptides are glycoproteins, due to post-translational glycosylation. The glycoproteins comprise one or more of an NTD, an RBD, an SD1/SD2 portion a UH domain, an intact or modified fusion 10 protein region, an HR1 domain an HR2 domain, and a TM domain. In embodiments, the amino acids for each domain are given in FIG. 2 and FIG. 3 (shown corresponding to SEQ ID NO: 1). In embodiments, each domain may have at least 95%, at least 97% or at least 99% identity to the sequences 15 for each domain as in SEQ ID NO: 1. Each domain may have a deletion or an insertion of about 10, about 20, or about 30 amino acids compared to those shown in SEQ ID NO: 1. Note that FIGS. 2 and 3 illustrate the 13-amino acid N-terminal signal peptide that is absent from the mature 20 peptide. The CoV S polypeptides may be used to stimulate immune responses against the native CoV Spike (S) polypeptide.

In embodiments, the native CoV Spike (S) polypeptide (SEQ ID NO: 2) is modified resulting in non-naturally 25 occurring CoV Spike (S) polypeptides (FIG. 1). In embodiments, the CoV Spike (S) glycoproteins comprise one or more modifications selected from the group consisting of:

(a) an inactivated mutated furin cleavage site amino acids 669-672;

(b) a deletion of one or more amino acids from amino acids 676-685;

(c) a deletion of one or more amino acids from amino acids 702-711;

(d) a deletion of one or more amino acids of the fusion 35 peptide (amino acids 806-815);

(e) mutation of amino acid 601:

(f) mutation of amino acid 973;

(g) mutation of amino acid 974;

(h) a deletion of one or more amino acids from the 40 N-terminal domain (NTD) (amino acids 1-318); and

(i) a deletion of one or more amino acids from the transmembrane and cytoplasmic domain (TMCT) (amino acids 1201-1260),

wherein the amino acids of the CoV S glycoprotein are 45 numbered with respect to SEQ ID NO: 2. FIG. **3** shows a CoV S polypeptide called BV2378, which has an inactive furin cleavage site, deleted fusion peptide, a K986P, and a V987 mutation.

In embodiments, the CoV S polypeptides described herein 50 exist in a prefusion conformation. In embodiments, the CoV S polypeptides described herein comprise a flexible HR2 domain. Unless otherwise mentioned, the flexibility of a domain is determined by transition electron microscopy (TEM) and 2D class averaging. A reduction in electron 55 density corresponds to a flexible domain.

In embodiments, the CoV S polypeptides contain a furin site (RRAR), amino acids 669 to 672 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2), that is inactivated by one or more mutations. Inactivation of the furin cleavage site 60 prevents furin from cleaving the CoV S polypeptide. In embodiments, the CoV S polypeptides described herein which contain an inactivated furin cleavage site are expressed as a single chain.

In embodiments, one or more of the amino acids com- 65 prising the native furin cleavage site is mutated to any natural amino acid. In embodiments, the amino acids are

L-amino acids. Non-limiting examples of amino acids include alanine, arginine, glycine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, serine, threonine, histidine, lysine, methionine, proline, valine, isoleucine, leucine, tyrosine, tryptophan, and phenylalanine.

In embodiments, one or more of the amino acids comprising the native furin cleavage site is mutated to glutamine. In embodiments, 1, 2, 3, or 4 amino acids may be mutated to glutamine. In embodiments, one of the arginines comprising the native furin cleavage site is mutated to glutamine. In embodiments, two of the arginines comprising the native furin cleavage site are mutated to glutamine. In embodiments, three of the arginines comprising the native furin cleavage site are mutated to glutamine.

In embodiments, one or more of the amino acids comprising the native furin cleavage site, is mutated to alanine. In embodiments, 1, 2, 3, or 4 amino acids may be mutated to alanine. embodiments, one of the arginines comprising the native furin cleavage site is mutated to alanine. In embodiments, two of the arginines comprising the native furin cleavage site are mutated to alanine. In embodiments, three of the arginines comprising the native furin cleavage site are mutated to alanine.

In embodiments, one or more of the amino acids comprising the native furin cleavage site is mutated to glycine. In embodiments, 1, 2, 3, or 4 amino acids may be mutated to glycine. In embodiments, one of the arginines of the native furin cleavage site is mutated to glycine. In embodiments, two of the arginines comprising the native furin cleavage site are mutated to glycine. In embodiments, three of the arginines comprising the native furin cleavage site are mutated to glycine.

In embodiments, one or more of the amino acids comprising the native furin cleavage site, is mutated to asparagine. For example 1, 2, 3, or 4 amino acids may be mutated to asparagine. In embodiments, one of the arginines comprising the native furin cleavage site is mutated to asparagine. In embodiments, two of the arginines comprising the native furin cleavage site are mutated to asparagine. In embodiments, three of the arginines comprising the native furin cleavage site are mutated to asparagine. In

Non-limiting examples of the amino acid sequences of the inactivated furin sites contained within the CoV S polypeptides are found in Table 1.

TABLE 1

 Inactivated Furin Cle	avage Sites	
Amino Acid Sequence of Furin Cleavage Site	Active or Inactive Furin Cleavage Site	
RRAR (SEQ ID NO: 6)	Active	
QOAQ (SEQ ID NO: 7)	Inactive	
ORAR (SEQ ID NO: 8)	Inactive	
ROAR (SEQ ID NO: 9)	Inactive	
RRAQ (SEQ ID NO: 10)	Inactive	
OOAR (SEO ID NO: 11)	Inactive	
ROAO (SEO ID NO: 12)	Inactive	
QRAQ (SEQ ID NO: 13)	Inactive	
NNAN (SEQ ID NO: 14)	Inactive	
NRAR (SEQ ID NO: 15)	Inactive	
RNAR (SEQ ID NO: 16)	Inactive	
RRAN (SEQ ID NO: 17)	Inactive	
NNAR (SEQ ID NO: 18)	Inactive	
RNAN (SEQ ID NO: 19)	Inactive	
NRAN (SEQ ID NO: 20)	Inactive	
AAAA (SEQ ID NO: 21)	Inactive	
ARAR (SEQ ID NO: 22)	Inactive	
RAAR (SEQ ID NO: 23)	Inactive	
RRAA (SEO ID NO: 24)	Inactive	

TABLE	1-continued
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Inactivated Furin Cleavage Sites								
Amino Acid Sequence of Furin Cleavage Site	Active or Inactive Furin Cleavage Site							
AAAR (SEQ ID NO: 25)	Inactive	_						
RAAA (SEQ ID NO: 26)	Inactive							
ARAA (SEQ ID NO: 27)	Inactive							
GGAG (SEQ ID NO: 28)	Inactive							
GRAR (SEQ ID NO: 29)	Inactive	1						
RGAR (SEQ ID NO: 30)	Inactive							
RRAG (SEQ ID NO: 31)	Inactive							
GGAR (SEQ ID NO: 32)	Inactive							
RGAG (SEQ ID NO: 33)	Inactive							
GRAG (SEQ ID NO: 34)	Inactive							
GSAS (SEQ ID NO: 97)	Inactive	1						
GSGA (SEQ ID NO: 113)	Inactive							

In embodiments, in lieu of an active furin cleavage site (SEQ ID NO: 6) the CoV S polypeptides described herein contain an inactivated furin cleavage site. In embodiments, 20 the amino acid sequence of the inactivated furin cleavage site is represented by any one of SEQ ID NO: 7-34 or SEQ ID NO: 97. In embodiments, the amino acid sequence of the inactivated furin cleavage site is QQAQ (SEQ ID NO: 7). In embodiments, the amino acid sequence of the inactivated 25 furin cleavage site is GSAS (SEQ ID NO: 97). In embodiments, the amino acid sequence of the inactivated furin cleavage site is GSAS (SEQ ID NO: 97). In embodiments, the amino acid sequence of the inactivated furin cleavage site is GSAS (SEQ ID NO: 97).

In embodiments, the CoV S polypeptides contain a deletion, corresponding to one or more deletions within amino 30 acids 676-685 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids of amino acids 676-685 of the native CoV Spike (S) polypeptide (SEQ ID NO:2) are deleted. In embodiments, the deletions of amino acids within amino 35 acids 676-685 are consecutive e.g. amino acids 676 and 677 are deleted or amino acids 680 and 681 are deleted. In embodiments, the deletions of amino acids within amino acids 676-685 are non-consecutive e.g. amino acids 676 and 680 are deleted or amino acids 677 and 682 are deleted. In 40 embodiments, CoV S polypeptides containing a deletion, corresponding to one or more deletions within amino acids 676-685, have an amino acid sequence selected from the group consisting of SEQ ID NO: 62 and SEQ ID NO: 63.

In embodiments, the CoV S polypeptides contain a dele- 45 tion, corresponding to one or more deletions within amino acids 702-711 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids of amino acids 702-711 of the native SARS-CoV-2 Spike (S) polypeptide (SEQ ID NO:2) are deleted. In 50 embodiments, the one or more deletions of amino acids within amino acids 702-711 are consecutive e.g. amino acids 702 and 703 are deleted or amino acids 708 and 709 are deleted. In embodiments, the deletions of amino acids within amino acids 702-711 are non-consecutive e.g. amino acids 55 702 and 704 are deleted or amino acids 707 and 710 are deleted. In embodiments, the CoVS polypeptides containing a deletion, corresponding to one or more deletions within amino acids 702-711, have an amino acid sequence selected from the group consisting of SEQ ID NO: 64 and SEQ ID 60 NO: 65

In embodiments, the CoV S polypeptides contain a deletion of the fusion peptide (SEQ ID NO: 104), which corresponds to amino acids 806-815 of SEQ ID NO: 2. In embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids of 65 the fusion peptide of the CoV Spike (S) polypeptide (SEQ ID NO:2) are deleted. In embodiments, the deletions of

amino acids within the fusion peptide are consecutive e.g. amino acids 806 and 807 are deleted or amino acids 809 and 810 are deleted. In embodiments, the deletions of amino acids within the fusion peptide are non-consecutive e.g. amino acids 806 and 808 are deleted or amino acids 810 and 813 are deleted. In embodiments, the CoV S polypeptides containing a deletion, corresponding to one or more amino acids of the fusion peptide, have an amino acid sequence selected from SEQ ID NOS: 66, 77, and 105-108.

In embodiments, the CoV S polypeptides contain a deletion of one or more amino acids from the N-terminal domain (NTD) (corresponding to amino acids 1-318 of SEQ ID NO: 2. The amino acid sequence of the NTD is represented by SEQ ID NO: 45. In embodiments, the CoV S polypeptides contain a deletion of amino acids 1-318 of the N-terminal domain (NTD) of SEQ ID NO: 2. In embodiments, deletion of the NTD enhances protein expression of the CoV Spike (S) polypeptide. In embodiments, the CoV S polypeptides which have an NTD deletion have amino acid sequences represented by SEQ ID NOS: 46, 48, 49, 51, 52, and 54. In embodiments, the CoV S polypeptides which have an NTD deletion are encoded by an isolated nucleic acid sequence selected from the group consisting of SEQ ID NO: 47, SEQ ID NO: 50, and SEQ ID NO: 53.

In embodiments, the CoV Spike (S) polypeptides contain a deletion of one or more amino acids from the transmembrane and cytoplasmic domain (TMCT) (corresponding to amino acids 1201-1260). The amino acid sequence of the TMCT is represented by SEQ ID NO: 39. In embodiments, the CoV S polypeptides which have a deletion of one or more residues of the TMCT have enhanced protein expression. In embodiments, the CoV Spike (S) polypeptides which have one or more deletions from the TMCT have an amino acid sequence selected from the group consisting of SEQ ID NO: 40, 41, 42, 52, 54, 59, 61, 88, and 89. In embodiments, the CoV S polypeptides which have one or more deletions from the TMCT are encoded by an isolated nucleic acid sequence selected from the group consisting of SEQ ID NO: 39, 43, 53, and 60.

In embodiments, the CoV S polypeptides contain a mutation at Asp-601 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, Asp-601 is mutated to any natural amino acid. In embodiments, Asp-601 is mutated to glycine.

In embodiments, the CoV S polypeptides contain mutations that stabilize the prefusion conformation of the CoV S polypeptide. In embodiments, the CoV S polypeptides contain proline substitutions which stabilize the prefusion conformation. This strategy has been utilized for to develop a prefusion stabilized MERS-CoV S protein as described in the following documents which are each incorporated by reference herein in their entirety: Proc Natl Acad Sci USA. 2017 Aug. 29; 114 (35):E7348-E7357; Sci Rep. 2018 Oct. 24; 8(1):15701; U.S. Publication No. 2020/0061185; and PCT Application No. PCT/US2017/058370.

In embodiments, the CoV S polypeptides contain a mutation at Lys-973 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, Lys-973 is mutated to any natural amino acid. In embodiments, Lys-973 is mutated to proline. In embodiments, the CoV S polypeptides containing a mutation at amino acid 973 are selected from the group consisting of SEQ ID NO: 84-89, 105-106, and 109-110.

In embodiments, the CoV S polypeptides contain a mutation at Val-974 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, Val-974 is mutated to any natural amino acid. In embodiments, Val-974 is mutated to proline. In embodiments, the CoV S polypeptides containing a mutation at amino acid 974 are selected from the group consisting of SEQ ID NO: 84-89, 105-106, and 109-110.

In embodiments, the CoV S polypeptides contain a mutation at Lys-973 and Val-974 of the native CoV Spike (S) polypeptide (SEQ ID NO: 2). In embodiments, Lys-973 and Val-974 are mutated to any natural amino acid. In embodiments, Lys-973 and Val-974 are mutated to proline. In embodiments, the CoV S polypeptides containing a mutation at amino acids 973 and 974 are selected from SEQ ID NOS: 84-89, 105-106, and 109-110.

In embodiments, the CoV S polypeptides contain a mutation at Lys-973 and Val-974 and an inactivated furin cleavage site. In embodiments, the CoV S polypeptides contain mutations of Lys-973 and Val-974 to proline and an inactivated furin cleavage site, having the amino acid sequence of QQAQ (SEQ ID NO: 7) or GSAS (SEQ ID NO: 96). An exemplary CoV S polypeptide containing a mutation at Lys-973 and Val-974 and an inactivated furin cleavage site is depicted in FIG. **8**. In embodiments, the CoV S polypeptides containing mutations of Lys-973 and Val-974 to proline and an inactivated furin cleavage site have an amino acid sequences of SEQ ID NOS: 86 or 87 and a nucleic acid sequence of SEQ ID NO: 96.

In embodiments, the CoV S polypeptides contain a muta-25 tion at Lys-973 and Val-974, an inactivated furin cleavage site, and a deletion of one or more amino acids of the fusion peptide. In embodiments, the CoV S polypeptides contain mutations of Lys-973 and Val-974 to proline, an inactivated furin cleavage site having the amino acid sequence of 30 QQAQ (SEQ ID NO: 7) or GSAS (SEQ ID NO: 96), and deletion of one or more amino acids of the fusion peptide. In embodiments, the CoV S polypeptides containing mutations of Lys-973 and Val-974 to proline, an inactivated furin cleavage site, and deletion of one or more amino acids of the 35 fusion peptide has an amino acid sequence of SEQ ID NO: 105 or 106.

In embodiments, the CoV Spike (S) polypeptides comprise a polypeptide linker. In embodiments, the polypeptide linker contains glycine and serine. In embodiments, the 40 linker has about 50%, about 55%, about 60%, about 65%, about 70%, about 55%, about 80%, about 85%, about 90%, about 95%, or about 100% glycine.

In embodiments, the polypeptide linker has a repeat of (SGGG), (SEQ ID NO: 91), wherein n is an integer from 1 45 to 50 (e.g. 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50). In embodiments, the polypeptide linker has an amino acid sequence corresponding to SEQ ID NO: 90. 50

In embodiments, the polypeptide linker has a repeat of (GGGGS), (SEQ ID NO: 93), wherein n is an integer from 1 to 50 (e.g. 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, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 55 48, 49, or 50).

In embodiments, the polypeptide linker has a repeat of (GGGS)_n (SEQ ID NO: 92), wherein n is an integer from 1 to 50 (e.g. 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, 31, 32, 60 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50).

In some aspects, the polypeptide linker is a poly-(Gly)_n linker, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 16, 17, 18, 19, or 20. In other embodiments, the linker is selected 65 from the group consisting of: dipeptides, tripeptides, and quadripeptides. In embodiments, the linker is a dipeptide

selected from the group consisting of alanine-serine (AS), leucine-glutamic acid (LE), and serine-arginine (SR).

In embodiments, the polypeptide linker comprises between 1 to 100 contiguous amino acids of a naturally occurring CoV S polypeptide or of a CoV S polypeptide disclosed herein. In embodiments, the polypeptide linker has an amino acid sequence corresponding to SEQ ID NO: 94.

In embodiments, the CoV Spike (S) polypeptides comprise a foldon. In embodiments, the TMCT is replaced with a foldon. In embodiments, a foldon causes trimerization of the CoV Spike (S) polypeptide. In embodiments, the foldon is an amino acid sequence known in the art. In embodiments, the foldon has an amino acid sequence of SEQ ID NO: 68. In embodiments, the foldon is a T4 fibritin trimerization motif. In embodiments, the T4 fibritin trimerization domain has an amino acid sequence of SEQ ID NO: 103. In embodiments, the foldon is separated in amino acid sequence from the CoV Spike (S) polypeptide by a polypeptide linker. Non-limiting examples of polypeptide linkers are found throughout this disclosure.

In embodiments, the disclosure provides CoV S polypeptides comprising a fragment of a coronavirus S protein and nanoparticles and vaccines comprising the same. In embodiments, the fragment of the coronavirus S protein is between 10 and 1500 amino acids in length (e.g. about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 150, about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, about 1000, about 1050, about 1100, about 1150, about 1200, about 1250, about 1300, about 1350, about 1400, about 1450, or about 1500 amino acids in length). In embodiments, the fragment of the coronavirus S protein is selected from the group consisting of the receptor binding domain (RBD), subdomain 1, subdomain 2, upper helix, fusion peptide, connecting region, heptad repeat 1, central helix, heptad repeat 2, NTD, and TMCT.

In embodiments, the CoV S polypeptide comprises an RBD and a subdomain 1. In embodiments, the CoV S polypeptide comprising an RBD and a subdomain 1 is amino acids 319 to 591 of SEQ ID NO: 1.

In embodiments, the CoV S polypeptide contains a frag-45 ment of a coronavirus S protein, wherein the fragment of the coronavirus S protein is the RBD. Non-limiting examples of RBDs include the RBD of SARS-CoV-2 (amino acid sequence=SEQ ID NO: 69), the RBD of SARS (amino acid sequence=SEQ ID NO: 70), and the RBD of MERS, (amino 50 acid sequence=SEQ ID NO: 71).

In embodiments, the CoV S polypeptide contains two or more RBDs, which are connected by a polypeptide linker. In embodiments, the polypeptide linker has an amino acid sequence of SEQ ID NO: 90 or SEQ ID NO: 94.

In embodiments, the CoV S polypeptide contains 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 RBDs.

In some embodiments, the CoV S polypeptide contains two or more SARS-CoV-2 RBDs, which are connected by a polypeptide linker. In embodiments, the antigen containing two or more SARS-CoV-2 RBDs has an amino acid sequence corresponding to one of SEQ ID NOS: 72-75.

In embodiments, the CoV S polypeptide contains a SARS-CoV-2 RBD and a SARS RBD. In embodiments, the CoV S polypeptide comprises a SARS-CoV-2 RBD and a SARS RBD, wherein each RBD is separated by a polypeptide linker. In embodiments, the CoV S polypeptide com-

prising a SARS-CoV-2 RBD and a SARS RBD has an amino acid sequence selected from the group consisting of SEQ ID NOS: 76-79.

In embodiments, the CoV S polypeptide contains a SARS-CoV-2 RBD and a MERS RBD. In embodiments, the 5 CoV S polypeptide comprises a SARS-CoV-2 RBD and a MERS RBD, wherein each RBD is separated by a polypeptide linker.

In embodiments, the CoV S polypeptide comprises a SARS RBD and a MERS RBD. In embodiments, the CoV 10 S polypeptide comprises a SARS RBD and a MERS RBD, wherein each RBD is separated by a polypeptide linker.

In embodiments, the CoV S polypeptide contains a SARS-CoV-2 RBD, a SARS RBD, and a MERS RBD. In embodiments, the CoV S polypeptide contains a SARS- 15 CoV-2 RBD, a SARS RBD, and a MERS RBD, wherein each RBD is separated by a polypeptide linker. In embodiments, the CoV S polypeptide comprising a SARS-CoV-2 RBD, a SARS RBD, and a MERS RBD has an amino acid sequence selected from the group consisting of SEQ ID 20 NOS: 80-83.

In embodiments, the CoV S polypeptides described herein are expressed with an N-terminal signal peptide. In embodiments, the N-terminal signal peptide consists of an amino acid sequence of SEQ ID NO: 5 (MFVFLVLLPLVSS). In 25 embodiments, the signal peptide may be replaced with any signal peptide that enables expression of the CoV S protein. In embodiments, one or more of the CoV S protein signal peptide amino acids may be deleted or mutated. An initiating methionine residue is maintained to initiate expression. In 30 embodiments, the CoV S polypeptides are encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 35, SEQ ID NO: 37, SEQ ID NO: 95, SEQ ID NO: 43, SEQ ID NO: 47, SEQ ID NO: 50, SEQ ID NO: 53, SEQ ID NO: 55, SEQ ID NO: 57, SEQ ID NO: 96, and SEQ 35 ID NO: 60.

Following expression of the CoV S protein in a host cell, the N-terminal signal peptide is cleaved to provide the mature CoV protein sequence (SEQ ID NOS: 2, 4, 38, 41, 44, 48, 51, 54, 58, 61, 63, 65, 67, 73, 75, 78, 79, 82, 83, 85, 40 87, 89, 106, and 110). In embodiments, the signal peptide is cleaved by host cell proteases. In aspects, the full-length protein may be isolated from the host cell and the signal peptide cleaved subsequently.

Following cleavage of the signal peptide from the CoV 45 Spike (S) polypeptide with an amino acid sequence corresponding to SEQ ID NOS: 1, 3, 36, 40, 42, 46, 49, 52, 56, 59, 62, 64, 66, 72, 74, 76, 77, 80, 81, 84, 86, 87, 105, 107, 88, and 109 during expression and purification, a mature polypeptide having an amino acid sequence selected from 50 the group consisting of SEQ ID NOS: 2, 4, 38, 41, 44, 48, 51, 54, 58, 61, 63, 65, 67, 73, 75, 78, 79, 82, 83, 85, 106, 108, 89, and 110 is obtained and used to produce a CoV S nanoparticle vaccine or CoV S nanoparticles.

Advantageously, the disclosed CoV S polypeptides may 55 have enhanced protein expression and stability relative to the native CoV Spike (S) protein.

In embodiments, the CoV S polypeptides described herein contain further modifications from the native coronavirus S protein (SEQ ID NO: 2). In embodiments, the coronavirus S proteins described herein exhibit at least 80%, or at least 90%, or at least 95%, or at least 97%, or at least 99% identity to the native coronavirus S protein. A person of skill in the art would use known techniques to calculate the percent identity of the recombinant coronavirus S protein to the 65 native protein. For example, percentage identity can be calculated using the tools CLUSTALW2 or Basic Local

Alignment Search Tool (BLAST), which are available online. The following default parameters may be used for CLUSTALW2 Pairwise alignment: Protein Weight Matrix=Gonnet; Gap Open=10; Gap Extension=0.1.

In embodiments, the CoV S polypeptides described herein comprise about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 substitutions compared to the coronavirus S protein (SEQ ID NO: 87).

In embodiments, the coronavirus S polypeptide is extended at the N-terminus, the C-terminus, or both the N-terminus and the C-terminus. In some aspects, the extension is a tag useful for a function, such as purification or detection. In some aspects the tag contains an epitope. For example, the tag may be a polyglutamate tag, a FLAG-tag, a HA-tag, a polyHis-tag (having about 5-10 histidines) (SEQ ID NO: 101), a hexahistidine tag (SEQ ID NO: 100), an 8x-His-tag (having eight histidines) (SEQ ID NO: 102), a Myc-tag, a Glutathione-S-transferase-tag, a Green fluorescent protein-tag, Maltose binding protein-tag, a Thioredoxin-tag, or an Fc-tag. In other aspects, the extension may be an N-terminal signal peptide fused to the protein to enhance expression. While such signal peptides are often cleaved during expression in the cell, some nanoparticles may contain the antigen with an intact signal peptide. Thus, when a nanoparticle comprises an antigen, the antigen may contain an extension and thus may be a fusion protein when incorporated into nanoparticles. For the purposes of calculating identity to the sequence, extensions are not included. In embodiments, the tag is a protease cleavage site. Nonlimiting examples of protease cleavage sites include the HRV3C protease cleavage site, chymotrypsin, trypsin, elastase, endopeptidase, caspase-1, caspase-2, caspase-3, caspase-4, caspase-5, caspase-6, caspase-7, caspase-8, caspase-9, caspase-10, enterokinase, factor Xa, Granzyme B, TEV protease, and thrombin. In embodiments, the protease cleavage site is an HRV3C protease cleavage site. In embodiments, the protease cleavage site comprises an amino acid sequence of SEQ ID NO: 98.

In embodiments, the CoV S glycoprotein comprises a fusion protein. In embodiments, the CoV S glycoprotein comprises an N-terminal fusion protein. In embodiments, the Cov S glycoprotein comprises a C-terminal fusion protein. In embodiments, the fusion protein encompasses a tag useful for protein expression, purification, or detection. In embodiments, the tag is a polyHis-tag (having about 5-10 histidines), a Myc-tag, a Glutathione-S-transferase-tag, a Green fluorescent protein-tag, Maltose binding protein-tag, a Thioredoxin-tag, a Strep-tag, a Twin-Strep-tag, or an Fc-tag. In embodiments, the tag is an Fc-tag. In embodiments, the Fc-tag is monomeric, dimeric, or trimeric. In embodiments, the tag is a hexahistidine tag, e.g. a polyHistag which contains six histidines (SEQ ID NO: 100). In embodiments, the tag is a Twin-Strep-tag with an amino acid sequence of SEQ ID NO: 99.

In embodiments, the CoV S polypeptide is a fusion protein comprising another coronavirus protein. In embodiments, the other coronavirus protein is from the same coronavirus. In embodiments, the other coronavirus protein is from a different coronavirus.

In some aspects, the CoV S protein may be truncated. For example, the N-terminus may be truncated by about 10 amino acids, about 30 amino acids, about 50 amino acids, about 75 amino acids, about 100 amino acids, or about 200 amino acids. The C-terminus may be truncated instead of or in addition to the N-terminus. For example, the C-terminus may be truncated by about 10 amino acids, about 30 amino acids, about 50 amino acids, about 75 amino acids, about 100 amino acids, or about 200 amino acids. For purposes of calculating identity to the protein having truncations, identity is measured over the remaining portion of the protein. Nanoparticles Containing CoV Spike (S) Polypeptides

In embodiments, the mature CoV S polypeptide antigens are used to produce a vaccine comprising coronavirus S nanoparticles. In embodiments, nanoparticles of the present 10 disclosure comprise the CoV S polypeptides described herein. In embodiments, the nanoparticles of the present disclosure comprise CoV S polypeptides associated with a detergent core. The presence of the detergent facilitates formation of the nanoparticles by forming a core that 15 organizes and presents the antigens. In embodiments, the nanoparticles may contain the CoV S polypeptides assembled into multi-oligomeric glycoprotein-detergent (e.g. PS80) nanoparticles with the head regions projecting outward and hydrophobic regions and PS80 detergent form- 20 ing a central core surrounded by the glycoprotein. In embodiments, the CoV S polypeptide inherently contains or is adapted to contain a transmembrane domain to promote association of the protein into a detergent core. In embodiments, the CoV S polypeptide contains a head domain. FIG. 25 10 shows an exemplary structure of a CoV S polypeptide of the disclosure. Primarily the transmembrane domains of a CoV S polypeptide trimer associate with detergent; however, other portions of the polypeptide may also interact. Advantageously, the nanoparticles have improved resistance 30 to environmental stresses such that they provide enhanced stability and/or improved presentation to the immune system due to organization of multiple copies of the protein around the detergent.

In embodiments, the detergent core is a non-ionic detergent core. In embodiments, the CoV S polypeptide is associated with the non-ionic detergent core. In embodiments, the detergent is selected from the group consisting of polysorbate-20 (PS20), polysorbate-40 (PS40), polysorbate-60 (PS60), polysorbate-65 (PS65) and polysorbate-80 (PS80). 40 In embodiments, the detergent is PS80.

In embodiments, the CoVS polypeptide forms a trimer. In embodiments, the CoV S polypeptide nanoparticles are composed of multiple polypeptide trimers surrounding a non-ionic detergent core. In embodiments, the nanoparticles 45 contain at least about 1 trimer or more. In embodiments, the nanoparticles contain at least about 5 trimers to about 30 trimers of the Spike protein. In embodiments, each nanoparticle may contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 15, 20, 25, or 30 trimers, including all values and ranges in 50 between. Compositions disclosed herein may contain nanoparticles having different numbers of trimers. For example, a composition may contain nanoparticles where the number of trimers ranges from 2-9; in embodiments, the nanoparticles in a composition may contain from 2-6 trimers. In 55 embodiments, the compositions contain a heterogeneous population of nanoparticles having 2 to 6 trimers per nanoparticle, or 2 to 9 trimers per nanoparticle. In embodiments, the compositions may contain a substantially homogenous population of nanoparticles. For example, the population 60 may contain about 95% nanoparticles having 5 trimers.

The nanoparticles disclosed herein range in particle size. In embodiments, the nanoparticles disclosed herein range in particle size from a Z-ave size from about 20 nm to about 60 nm, about 20 nm to about 50 nm, about 20 nm to about 45 65 nm, about 20 nm to about 35 nm, about 20 nm to about 30 nm, about 25 nm to about 35 nm, or about 25 nm to about

45 nm. Particle size (Z-ave) is measured by dynamic light scattering (DLS) using a Zetasizer NanoZS (Malvern, UK), unless otherwise specified.

In embodiments, the nanoparticles comprising the CoV S polypeptides disclosed herein have a reduced particle size compared to nanoparticles comprising a wild-type CoV S polypeptide. In embodiments, the CoV S polypeptides are at least about 40% smaller in particle size, for example, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 65%, at least about 65%, at least about 75%, at least about 80%, or at least about 85% smaller in particle size.

The nanoparticles comprising CoV S polypeptides disclosed herein are more homogenous in size, shape, and mass than nanoparticles comprising a wild-type CoV S polypeptide. The polydispersity index (PDI), which is a measure of heterogeneity, is measured by dynamic light scattering using a Malvern Setasizer unless otherwise specified. In embodiments, the particles measured herein have a PDI from about 0.2 to about 0.45, for example, about 0.2, about 0.25, about 0.29, about 0.3, about 0.35, about 0.40, or about 0.45. In embodiments, the nanoparticles measured herein have a PDI that is at least about 25% smaller than the PDI of nanoparticles comprising the wild-type CoV S polypeptide, for example, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, or at least about 60%, smaller.

The CoV S polypeptides and nanoparticles comprising the same have improved thermal stability as compared to the wild-type CoV S polypeptide or a nanoparticle thereof. The thermal stability of the CoV S polypeptides is measured using differential scanning calorimetry (DSC) unless otherwise specified. The enthalpy of transition (Δ Hcal) is the energy required to unfold a CoV S polypeptide. In embodiments, the CoV S polypeptides have an increased Δ Hcal as compared to the wild-type CoV S polypeptide. In embodiments, the Δ Hcal of a CoV S polypeptide is about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, or about 10-fold greater than the Δ Hcal of a wild-type CoV S polypeptide.

Several nanoparticle types may be included in vaccine compositions disclosed herein. In some aspects, the nanoparticle type is in the form of an anisotropic rod, which may be a dimer or a monomer. In other aspects, the nanoparticle type is a spherical oligomer. In yet other aspects, the nanoparticle may be described as an intermediate nanoparticle, having sedimentation properties intermediate between the first two types. Formation of nanoparticle types may be regulated by controlling detergent and protein concentration during the production process. Nanoparticle type may be determined by measuring sedimentation co-efficient. Production of Nanoparticles Containing CoV S Polypeptide

Antigens

The nanoparticles of the present disclosure are nonnaturally occurring products, the components of which do not occur together in nature. Generally, the methods disclosed herein use a detergent exchange approach wherein a first detergent is used to isolate a protein and then that first detergent is exchanged for a second detergent to form the nanoparticles.

The antigens contained in the nanoparticles are typically produced by recombinant expression in host cells. Standard recombinant techniques may be used. In embodiments, the CoV S polypeptides are expressed in insect host cells using a baculovirus system. In embodiments, the baculovirus is a cathepsin-L knock-out baculovirus, a chitinase knock-out baculovirus. Optionally, the baculovirus is a double knockout for both cathepsin-L and chitinase. High level expression may be obtained in insect cell expression systems. Non limiting examples of insect cells are, Spodoptera frugiperda (Sf) cells, e.g. Sf9, Sf21, Trichoplusiani cells, e.g. High Five 5 cells, and Drosophila S2 cells. In embodiments, the CoV S polypeptide described herein are produced in any suitable host cell. In embodiments, the host cell is an insect cell. In embodiments, the insect cell is an Sf9 cell.

Typical transfection and cell growth methods can be used 10 to culture the cells. Vectors, e.g., vectors comprising polynucleotides that encode fusion proteins, can be transfected into host cells according to methods well known in the art. For example, introducing nucleic acids into eukaryotic cells can be achieved by calcium phosphate co-precipitation, 15 electroporation, microinjection, lipofection, and transfection employing polyamine transfection reagents. In one embodiment, the vector is a recombinant baculovirus.

Methods to grow host cells include, but are not limited to, batch, batch-fed, continuous and perfusion cell culture tech- 20 niques. Cell culture means the growth and propagation of cells in a bioreactor (a fermentation chamber) where cells propagate and express protein (e.g. recombinant proteins) for purification and isolation. Typically, cell culture is performed under sterile, controlled temperature and atmo- 25 spheric conditions in a bioreactor. A bioreactor is a chamber used to culture cells in which environmental conditions such as temperature, atmosphere, agitation and/or pH can be monitored. In one embodiment, the bioreactor is a stainless steel chamber. In another embodiment, the bioreactor is a 30 pre-sterilized plastic bag (e.g. Cellbag®, Wave Biotech, Bridgewater, N.J.). In other embodiment, the pre-sterilized plastic bags are about 50 L to 3500 L bags.

Extraction and Purification of Nanoparticles Containing CoV Spike (S) Protein Antigens

After growth of the host cells, the protein may be harvested from the host cells using detergents and purification protocols. Once the host cells have grown for 48 to 96 hours, the cells are isolated from the media and a detergentcontaining solution is added to solubilize the cell membrane, 40 debris using centrifugation. In embodiments, gradient cenreleasing the protein in a detergent extract. Triton X-100 and TERGITOL® nonylphenol ethoxylate, also known as NP-9, are each preferred detergents for extraction. The detergent may be added to a final concentration of about 0.1% to about 1.0%. For example, the concentration may be about 0.1%, 45about 0.2%, about 0.3%, about 0.5%, about 0.7%, about 0.8%, or about 1.0%. The range may be about 0.1% to about 0.3%. In aspects, the concentration is about 0.5%.

In other aspects, different first detergents may be used to isolate the protein from the host cell. For example, the first 50 detergent may be Bis(polyethylene glycol bis[imidazoylcarbonyl]), nonoxynol-9, Bis(polyethylene glycol bis[imidazoyl carbonyl]), BRIJ® Polyethylene glycol dodecyl ether 35, BRIJ® Polyethylene glycol (3) cetyl ether 56, BRIJ® alcohol ethoxylate 72, BRIJ® Polyoxyl 2 stearyl ether 76, 55 BRIJ® polyethylene glycol monoolelyl ether 92V, BRIJ® Polyoxyethylene (10) oleyl ether 97, BRIJ® Polyethylene glycol hexadecyl ether 58P, CREMOPHOR® EL Macrogolglycerol ricinoleate, Decaethyleneglycol monododecyl ether, N-Decanoyl-N-methylglucamine, n-Decyl alpha-Dg- 60 lucopyranoside, Decyl beta-D-maltopyranoside, n-Dodecanoyl-N-methylglucamide, nDodecyl alpha-D-maltoside, n-Dodecyl beta-D-maltoside, n-Dodecyl beta-D-maltoside, Heptaethylene glycol monodecyl ether, Heptaethylene glycol monododecyl ether, Heptaethylene glycol monotetra- 65 decyl ether, n-Hexadecyl beta-D-maltoside, Hexaethylene glycol monododecyl ether, Hexaethylene glycol monohexa20

decyl ether, Hexaethylene glycol monooctadecyl ether, Hexaethylene glycol monotetradecyl ether, Igepal CA-630, Igepal CA-630, Methyl-6-0-(N-heptylcarbamoyl)-alpha-Dglucopyranoside, Nonaethylene glycol monododecyl ether, N-Nonanoyl-N-methylglucamine, N-NonanoylN-methylglucamine, Octaethylene glycol monodecyl ether, Octaethylene glycolmonododecyl ether, Octaethylene glycol monohexadecyl ether, Octaethylene glycol monooctadecyl ether, Octaethylene glycol monotetradecyl ether, Octyl-beta-D glucopyranoside, Pentaethylene glycol monodecyl ether, Pentaethylene glycol monododecyl ether, Pentaethylene glycol monohexadecyl ether, Pentaethylene glycol monohexyl ether, Pentaethylene glycol monooctadecyl ether, Pentaethylene glycol monooctyl ether, Polyethylene glycol diglycidyl ether, Polyethylene glycol ether W-1, Polyoxyethylene 10 tridecyl ether, Polyoxyethylene 100 stearate, Polyoxyethylene 20 isohexadecyl ether, Polyoxyethylene 20 oleyl ether, Polyoxyethylene 40 stearate, Polyoxyethylene stearate, Polyoxyethylene 8 stearate, Polyoxyethylene bis(imidazolyl carbonyl), Polyoxyethylene 25 propylene glycol stearate, Saponin from Quillaja bark, SPAN® 20 sorbitan laurate, SPAN® 40 sorbitan monopalmitate, SPAN® 60 sorbitan stearate, SPAN® 65 sorbitan tristearate, SPAN® 80 sorbitane monooleate, SPAN® 85 sorbitane trioleate, TER-GITOL® secondary alcohol ethoxylate Type 15-S-12, TER-GITOL® secondary alcohol ethoxylate Type 15-S-30, TER-GITOL® secondary alcohol ethoxylate Type 15-S-5, TERGITOL® secondary alcohol ethoxylate Type 15-S-7, TERGITOL® secondary alcohol ethoxylate Type 15-S-9, TERGITOL® nonylphenol ethoxylate Type NP-10, TER-GITOL® nonylphenol ethoxylate Type NP-4, TERGITOL® nonylphenol ethoxylate Type NP-40, TERGITOL® nonylphenol ethoxylate Type NP-7, TERGITOL® nonylphenol ethoxylate Type NP-9, TERGITOL® branched secondary alcohol ethoxylate Type TMN-10, TERGITOL® branched secondary alcohol ethoxylate Type TMN-6, TRITON™ X-100 Polyethylene glycol tert-octylphenyl ether or combinations thereof.

The nanoparticles may then be isolated from cellular trifugation, such as using cesium chloride, sucrose and iodixanol, may be used. Other techniques may be used as alternatives or in addition, such as standard purification techniques including, e.g., ion exchange, affinity, and gel filtration chromatography.

For example, the first column may be an ion exchange chromatography resin, such as FRACTOGEL® EMD methacrylate based polymeric beads TMAE (EMD Millipore), the second column may be a lentil (Lens culinaris) lectin affinity resin, and the third column may be a cation exchange column such as a FRACTOGEL® EMD methacrylate based polymeric beads S03 (EMD Millipore) resin. In other aspects, the cation exchange column may be an MMC column or a Nuvia C Prime column (Bio-Rad Laboratories, Inc). Preferably, the methods disclosed herein do not use a detergent extraction column; for example a hydrophobic interaction column. Such a column is often used to remove detergents during purification but may negatively impact the methods disclosed here.

Detergent Exchange of Nanoparticles Containing CoV S Polypeptide Antigens

To form nanoparticles, the first detergent, used to extract the protein from the host cell is substantially replaced with a second detergent to arrive at the nanoparticle structure. NP-9 is a preferred extraction detergent. Typically, the nanoparticles do not contain detectable NP-9 when measured by HPLC. The second detergent is typically selected

from the group consisting of PS20, PS40, PS60, PS65, and PS80. Preferably, the second detergent is PS80.

In particular aspects, detergent exchange is performed using affinity chromatography to bind glycoproteins via their carbohydrate moiety. For example, the affinity chromatography may use a legume lectin column. Legume lectins are proteins originally identified in plants and found to interact specifically and reversibly with carbohydrate residues. See, for example, Sharon and Lis, "Legume lectins-a large family of homologous proteins," FASEB J. 1990 November; 10 4(14):3198-208; Liener, "The Lectins: Properties, Functions, and Applications in Biology and Medicine," Elsevier, 2012. Suitable lectins include concanavalin A (con A), pea lectin, sainfoin lect, and lentil lectin. Lentil lectin is a preferred column for detergent exchange due to its binding 15 properties. Lectin columns are commercially available; for example, Capto Lentil Lectin, is available from GE Healthcare. In certain aspects, the lentil lectin column may use a recombinant lectin. At the molecular level, it is thought that the carbohydrate moieties bind to the lentil lectin. freeing the 20 amino acids of the protein to coalesce around the detergent resulting in the formation of a detergent core providing nanoparticles having multiple copies of the antigen, e.g., glycoprotein oligomers which can be dimers, trimers, or tetramers anchored in the detergent. In embodiments, the 25 CoV S polypeptides form trimers. In embodiments, the CoV S polypeptide trimers are anchored in detergent. In embodiments, each CoV S polypeptide nanoparticle contains at least one trimer associated with a non-ionic core.

The detergent, when incubated with the protein to form 30 the nanoparticles during detergent exchange, may be present at up to about 0.1% (w/v) during early purifications steps and this amount is lowered to achieve the final nanoparticles having optimum stability. For example, the non-ionic detergent (e.g., PS80) may be about 0.005% (v/v) to about 0.1% 35 (v/v), for example, about 0.005% (v/v), about 0.006% (v/v), about 0.007% (v/v), about 0.008% (v/v), about 0.009% (v/v), about 0.01% (v/v), about 0.015% (v/v), about 0.02% (v/v), about 0.025% (v/v), about 0.03% (v/v), about 0.035% (v/v), about 0.04% (v/v), about 0.045% (v/v), about 0.05% 40 (v/v), about 0.055% (v/v), about 0.06% (v/v), about 0.065% (v/v), about 0.07% (v/v), about 0.075% (v/v), about 0.08% (v/v), about 0.085% (v/v), about 0.09% (v/v), about 0.095% (v/v), or about 0.1% (v/v) PS80. In embodiments, the nanoparticle contains about 0.03% to about 0.05% PS80. In 45 embodiments, the nanoparticle contains about 0.01% (v/v) PS80.

In embodiments, purified CoV S polypeptides are dialyzed. In embodiments, dialysis occurs after purification. In embodiments, the CoV S polypeptides are dialyzed in a 50 solution comprising sodium phosphate, NaCl, and PS80. In embodiments, the dialysis solution comprising sodium phosphate contains between about 5 mM and about 100 mM of sodium phosphate, for example, about 5 mM, about 10 mM, about 15 mM, about 20 mM, about 25 mM, about 30 mM, 55 about 35 mM, about 40 mM, about 45 mM, about 50 mM, about 55 mM, about 60 mM, about 65 mM, about 70 mM, about 75 mM, about 80 mM, about 85 mM, about 90 mM, about 95 mM, or about 100 mM sodium phosphate. In embodiments, the pH of the solution comprising sodium 60 phosphate is about 6.5, about 6.6, about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, or about 7.5. In embodiments, the dialysis solution comprising sodium chloride comprises about 50 mM NaCl to about 500 mM NaCl, for example, about 50 mM, about 60 mM, about 65 70 mM, about 80 mM, about 90 mM, about 100 mM, about 110 mM, about 120 mM, about 130 mM, about 140 mM,

about 150 mM, about 160 mM, about 170 mM, about 180 mM, about 190 mM, about 200 mM, about 210 mM, about 220 mM, about 230 mM, about 240 mM, about 250 mM, about 260 mM, about 270 mM, about 280 mM, about 290 mM, about 300 mM, about 310 mM, about 320 mM, about 330 mM, about 340 mM, about 350 mM, about 360 mM, about 370 mM, about 380 mM, about 390 mM, about 400 mM, about 410 mM, about 420 mM, about 430 mM, about 440 mM, about 450 mM, about 460 mM, about 470 mM, about 480 mM, about 490 mM, or about 500 mM NaCl. In embodiments, the dialysis solution comprising PS80 comprises about 0.005% (v/v), about 0.006% (v/v), about 0.007% (v/v), about 0.008% (v/v), about 0.009% (v/v), about 0.01% (v/v), about 0.015% (v/v), about 0.02% (v/v), about 0.025% (v/v), about 0.03% (v/v), about 0.035% (v/v), about 0.04% (v/v), about 0.045% (v/v), about 0.05% (v/v), about 0.055% (v/v), about 0.06% (v/v), about 0.065% (v/v), about 0.07% (v/v), about 0.075% (v/v), about 0.08% (v/v), about 0.085% (v/v), about 0.09% (v/v), about 0.095% (v/v), or about 0.1% (v/v) PS80. In embodiments, the dialvsis solution comprises about 25 mM sodium phosphate (pH 7.2), about 300 mM NaCl, and about 0.01% (v/v) PS80.

Detergent exchange may be performed with proteins purified as discussed above and purified, frozen for storage, and then thawed for detergent exchange.

Stability of compositions disclosed herein may be measured in a variety of ways. In one approach, a peptide map may be prepared to determine the integrity of the antigen protein after various treatments designed to stress the nanoparticles by mimicking harsh storage conditions. Thus, a measure of stability is the relative abundance of antigen peptides in a stressed sample compared to a control sample. For example, the stability of nanoparticles containing the CoV S polypeptides may be evaluated by exposing the nanoparticles to various pHs, proteases, salt, oxidizing agents, including but not limited to hydrogen peroxide, various temperatures, freeze/thaw cycles, and agitation. FIGS. 12A-B show that BV2373 (SEQ ID NO: 87) and BV2365 (SEQ ID NO: 4) retain binding to hACE2 under a variety of stress conditions. It is thought that the position of the glycoprotein anchored into the detergent core provides enhanced stability by reducing undesirable interactions. For example, the improved protection against protease-based degradation may be achieved through a shielding effect whereby anchoring the glycoproteins into the core at the molar ratios disclosed herein results in steric hindrance blocking protease access. Stability may also be measured by monitoring intact proteins. FIG. 33 and FIG. 34 compare nanoparticles containing CoV polypeptides having amino acid sequences of SEQ ID NOS: 109 and 87, respectively. FIG. 34 indicates that CoV polypeptides having an amino acid sequence of SEQ ID NO: 87 show particularly good stability during purification. The polypeptide of FIG. 34 comprises a furin cleavage site having an amino acid sequence of QQAQ (SEQ ID NO: 7).

Vaccine Compositions Containing CoV S Polypeptide Antigens

The disclosure provides vaccine compositions comprising CoV S polypeptides, for example, in a nanoparticle. In some aspects, the vaccine composition may contain nanoparticles with antigens from more than one viral strain from the same species of virus. In another embodiment, the disclosures provide for a pharmaceutical pack or kit comprising one or more containers filled with one or more of the components of the vaccine compositions.

Compositions disclosed herein may be used either prophylactically or therapeutically, but will typically be prophylactic. Accordingly, the disclosure includes methods for treating or preventing infection. The methods involve administering to the subject a therapeutic or prophylactic amount of the immunogenic compositions of the disclosure. Preferably, the pharmaceutical composition is a vaccine 5 composition that provides a protective effect. In other aspects, the protective effect may include amelioration of a symptom associated with infection in a percentage of the exposed population. For example, the composition may prevent or reduce one or more virus disease symptoms 10 selected from: fever fatigue, muscle pain, headache, sore throat, vomiting, diarrhea, rash, symptoms of impaired kidney and liver function, internal bleeding and external bleeding, compared to an untreated subject.

The nanoparticles may be formulated for administration 15 as vaccines in the presence of various excipients, buffers, and the like. For example, the vaccine compositions may contain sodium phosphate, sodium chloride, and/or histidine. Sodium phosphate may be present at about 10 mM to about 50 mM, about 15 mM to about 25 mM, or about 25 20 mM; in particular cases, about 22 mM sodium phosphate is present. Histidine may be present about 0.1% (w/v), about 0.5% (w/v), about 0.7% (w/v), about 1% (w/v), about 1.5% (w/v), about 2% (w/v), or about 2.5% (w/v). Sodium chloride, when present, may be about 150 mM. In certain 25 compositions, the sodium chloride may be present in higher concentrations, for example from about 200 mM to about 500 mM. In embodiments, the sodium chloride is present in a high concentration, including but not limited to about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 30 400 mM, about 450 mM, or about 500 mM.

In embodiments, the nanoparticles described herein have improved stability at certain pH levels. In embodiments, the nanoparticles are stable at slightly acidic pH levels. For example, the nanoparticles that are stable at a slightly acidic 35 pH, for example from pH 5.8 to pH 7.0. In embodiments, the nanoparticles and compositions containing nanoparticles may be stable at pHs ranging from about pH 5.8 to about pH 7.0, including about pH 5.9 to about pH 6.8, about pH 6.0 to about pH 6.5, about pH 6.1 to about pH 6.4, about pH 6.1 40 to about pH 6.3, or about pH 6.2. In embodiments, the nanoparticles and compositions described herein are stabile at neutral pHs, including from about pH 7.0 to about pH 7.4. In embodiments, the nanoparticles and compositions described herein are stable at slightly alkaline pHs, for 45 example from about pH 7.0 to about pH 8.5, from about pH 7.0 to about pH 8.0, or from about pH 7.0 to about pH 7.5, including all values and ranges in between. Adjuvants

In certain embodiments, the compositions disclosed 50 herein may be combined with one or more adjuvants to enhance an immune response. In other embodiments, the compositions are prepared without adjuvants, and are thus available to be administered as adjuvant-free compositions. Advantageously, adjuvant-free compositions disclosed 55 herein may provide protective immune responses when administered as a single dose. Alum-free compositions that induce robust immune responses are especially useful in adults about 60 and older. 60

Aluminum-Based Adjuvants

In embodiments, the adjuvant may be alum (e.g. AlPO₄ or Al(OH)₃). Typically, the nanoparticle is substantially bound to the alum. For example, the nanoparticle may be at least 80% bound, at least 85% bound, at least 90% bound or at least 95% bound to the alum. Often, the nanoparticle is 92% 65 to 97% bound to the alum in a composition. The amount of alum is present per dose is typically in a range between

about 400 µg to about 1250 µg. For example, the alum may be present in a per dose amount of about 300 µg to about 900 μ g, about 400 μ g to about 800 μ g, about 500 μ g to about 700 µg, about 400 µg to about 600 µg, or about 400 µg to about 500 µg. Typically, the alum is present at about 400 µg for a dose of 120 µg of the protein nanoparticle.

Saponin Adjuvants

Adjuvants containing saponin may also be combined with the immunogens disclosed herein. Saponins are glycosides derived from the bark of the Quillaja saponaria Molina tree. Typically, saponin is prepared using a multi-step purification process resulting in multiple fractions. As used, herein, the term "a saponin fraction from Quillaja saponaria Molina" is used generically to describe a semi-purified or defined saponin fraction of Quillaja saponaria or a substantially pure fraction thereof.

Saponin Fractions

Several approaches for producing saponin fractions are suitable. Fractions A, B, and C are described in U.S. Pat. No. 6,352,697 and may be prepared as follows. A lipophilic fraction from Quil A, a crude aqueous Quillaja saponaria Molina extract, is separated by chromatography and eluted with 70% acetonitrile in water to recover the lipophilic fraction. This lipophilic fraction is then separated by semipreparative HPLC with elution using a gradient of from 25% to 60% acetonitrile in acidic water. The fraction referred to herein as "Fraction A" or "QH-A" is, or corresponds to, the fraction, which is eluted at approximately 39% acetonitrile. The fraction referred to herein as "Fraction B" or "QH-B" is, or corresponds to, the fraction, which is eluted at approximately 47% acetonitrile. The fraction referred to herein as "Fraction C" or "QH-C" is, or corresponds to, the fraction, which is eluted at approximately 49% acetonitrile. Additional information regarding purification of Fractions is found in U.S. Pat. No. 5,057,540. When prepared as described herein, Fractions A, B and C of Quillaja saponaria Molina each represent groups or families of chemically closely related molecules with definable properties. The chromatographic conditions under which they are obtained are such that the batch-to-batch reproducibility in terms of elution profile and biological activity is highly consistent.

Other saponin fractions have been described. Fractions B3. B4 and B4b are described in EP 0436620. Fractions OA1-OA22 are described EP03632279 B2, O-VAC (Nor-Feed, AS Denmark), Quillaja saponaria Molina Spikoside (Isconova AB, Ultunaallén 2B, 756 51 Uppsala, Sweden). Fractions QA-1, QA-2, QA-3, QA-4, QA-5, QA-6, QA-7, QA-8, QA-9, QA-10, QA-11, QA-12, QA-13, QA-14, QA-15, QA-16, QA-17, QA-18, QA-19, QA-20, QA-21, and QA-22 of EP 0 3632 279 B2, especially QA-7, QA-17, QA-18, and QA-21 may be used. They are obtained as described in EP 0 3632 279 B2, especially at page 6 and in Example 1 on page 8 and 9.

The saponin fractions described herein and used for forming adjuvants are often substantially pure fractions; that is, the fractions are substantially free of the presence of contamination from other materials. In particular aspects, a substantially pure saponin fraction may contain up to 40% by weight, up to 30% by weight, up to 25% by weight, up to 20% by weight, up to 15% by weight, up to 10% by weight, up to 7% by weight, up to 5% by weight, up to 2% by weight, up to 1% by weight, up to 0.5% by weight, or up to 0.1% by weight of other compounds such as other saponins or other adjuvant materials.

ISCOM Structures

Saponin fractions may be administered in the form of a cage-like particle referred to as an ISCOM (Immune Stimulating COMplex). ISCOMs may be prepared as described in EP0109942B1, EP0242380B1 and EP0180546 B1. In par-5 ticular embodiments a transport and/or a passenger antigen may be used, as described in EP 9600647-3 (PCT/SE97/ 00289).

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Matrix Adjuvants

In embodiments, the ISCOM is an ISCOM matrix complex. An ISCOM matrix complex comprises at least one saponin fraction and a lipid. The lipid is at least a sterol, such as cholesterol. In particular aspects, the ISCOM matrix complex also contains a phospholipid. The ISCOM matrix complexes may also contain one or more other immunomodulatory (adjuvant-active) substances, not necessarily a glycoside, and may be produced as described in EP0436620B1, which is incorporated by reference in its entirety herein.

In other aspects, the ISCOM is an ISCOM complex. An ISCOM complex contains at least one saponin, at least one lipid, and at least one kind of antigen or epitope. The ISCOM complex contains antigen associated by detergent treatment such that that a portion of the antigen integrates 25 crude saponin fraction may be integrated into one ISCOM into the particle. In contrast, ISCOM matrix is formulated as an admixture with antigen and the association between ISCOM matrix particles and antigen is mediated by electrostatic and/or hydrophobic interactions.

According to one embodiment, the saponin fraction inte- 30 grated into an ISCOM matrix complex or an ISCOM complex, or at least one additional adjuvant, which also is integrated into the ISCOM or ISCOM matrix complex or mixed therewith, is selected from fraction A, fraction B, or fraction C of Quillaja saponaria, a semipurified preparation 35 of Quillaja saponaria, a purified preparation of Quillaja saponaria, or any purified sub-fraction e.g., QA 1-21.

In particular aspects, each ISCOM particle may contain at least two saponin fractions. Any combinations of weight % of different saponin fractions may be used. Any combination 40 of weight % of any two fractions may be used. For example, the particle may contain any weight % of fraction A and any weight % of another saponin fraction, such as a crude saponin fraction or fraction C, respectively. Accordingly, in particular aspects, each ISCOM matrix particle or each 45 ISCOM complex particle may contain from 0.1 to 99.9 by weight, 5 to 95% by weight, 10 to 90% by weight 15 to 85% by weight, 20 to 80% by weight, 25 to 75% by weight, 30 to 70% by weight, 35 to 65% by weight, 40 to 60% by weight, 45 to 55% by weight, 40 to 60% by weight, or 50% 50 by weight of one saponin fraction, e.g. fraction A and the rest up to 100% in each case of another saponin e.g. any crude fraction or any other faction e.g. fraction C. The weight is calculated as the total weight of the saponin fractions. Examples of ISCOM matrix complex and ISCOM complex 55 first ISCOM matrix or ISCOM complex particle is Fraction adjuvants are disclosed in U.S Published Application No. 2013/0129770, which is incorporated by reference in its entirety herein.

In particular embodiments, the ISCOM matrix or ISCOM complex comprises from 5-99% by weight of one fraction, 60 e.g. fraction A and the rest up to 100% of weight of another fraction e.g. a crude saponin fraction or fraction C. The weight is calculated as the total weight of the saponin fractions.

In another embodiment, the ISCOM matrix or ISCOM 65 complex comprises from 40% to 99% by weight of one fraction, e.g. fraction A and from 1% to 60% by weight of

another fraction, e.g. a crude saponin fraction or fraction C. The weight is calculated as the total weight of the saponin fractions.

In yet another embodiment, the ISCOM matrix or ISCOM complex comprises from 70% to 95% by weight of one fraction e.g., fraction A, and from 30% to 5% by weight of another fraction, e.g., a crude saponin fraction, or fraction C. The weight is calculated as the total weight of the saponin fractions. In other embodiments, the saponin fraction from Quillaja saponaria Molina is selected from any one of QA 1-21.

In addition to particles containing mixtures of saponin fractions, ISCOM matrix particles and ISCOM complex particles may each be formed using only one saponin fraction. Compositions disclosed herein may contain multiple particles wherein each particle contains only one saponin fraction. That is, certain compositions may contain one or more different types of ISCOM-matrix complexes particles and/or one or more different types of ISCOM 20 complexes particles, where each individual particle contains one saponin fraction from Quillaja saponaria Molina, wherein the saponin fraction in one complex is different from the saponin fraction in the other complex particles.

In particular aspects, one type of saponin fraction or a matrix complex or particle and another type of substantially pure saponin fraction, or a crude saponin fraction, may be integrated into another ISCOM matrix complex or particle. A composition or vaccine may comprise at least two types of complexes or particles each type having one type of saponins integrated into physically different particles.

In the compositions, mixtures of ISCOM matrix complex particles and/or ISCOM complex particles may be used in which one saponin fraction Quillaja saponaria Molina and another saponin fraction Quillaja saponaria Molina are separately incorporated into different ISCOM matrix complex particles and/or ISCOM complex particles.

The ISCOM matrix or ISCOM complex particles, which each have one saponin fraction, may be present in composition at any combination of weight %. In particular aspects, a composition may contain 0.1% to 99.9% by weight, 5% to 95% by weight, 10% to 90% by weight, 15% to 85% by weight, 20% to 80% by weight, 25% to 75% by weight, 30% to 70% by weight, 35% to 65% by weight, 40% to 60% by weight, 45% to 55% by weight, 40 to 60% by weight, or 50% by weight, of an ISCOM matrix or complex containing a first saponin fraction with the remaining portion made up by an ISCOM matrix or complex containing a different saponin fraction. In some aspects, the remaining portion is one or more ISCOM matrix or complexes where each matrix or complex particle contains only one saponin fraction. In other aspects, the ISCOM matrix or complex particles may contain more than one saponin fraction.

In particular compositions, the only saponin fraction in a A and the only saponin fraction in a second ISCOM matrix or ISCOM complex particle is Fraction C.

Preferred compositions comprise a first ISCOM matrix containing Fraction A and a second ISCOM matrix containing Fraction C, wherein the Fraction A ISCOM matrix constitutes about 70% per weight of the total saponin adjuvant, and the Fraction C ISCOM matrix constitutes about 30% per weight of the total saponin adjuvant. In another preferred composition, the Fraction A ISCOM matrix constitutes about 85% per weight of the total saponin adjuvant, and the Fraction C ISCOM matrix constitutes about 15% per weight of the total saponin adjuvant. Thus, in

certain compositions, the Fraction A ISCOM matrix is present in a range of about 70% to about 85%, and Fraction C ISCOM matrix is present in a range of about 15% to about 30%, of the total weight amount of saponin adjuvant in the composition. In embodiments, the Fraction A ISCOM 5 matrix accounts for 50-96% by weight and Fraction C ISCOM matrix accounts for the remainder, respectively, of the sums of the weights of Fraction A ISCOM matrix and Fraction C ISCOM in the adjuvant. In a particularly preferred composition, referred to herein as MATRIX-MTM, the 10 Fraction A ISCOM matrix is present at about 85% and Fraction C ISCOM matrix is present at about 15% of the total weight amount of saponin adjuvant in the composition. MATRIX-MTM may be referred to interchangeably as Matrix-M1.

Exemplary QS-7 and QS-21 fractions, their production and their use is described in U.S. Pat. Nos. 5,057,540; 6,231,859; 6,352,697; 6,524,584; 6,846,489; 7,776,343, and 8,173,141, which are incorporated by reference herein.

In some, compositions other adjuvants may be used in 20 addition or as an alternative. The inclusion of any adjuvant described in Vogel et al., "A Compendium of Vaccine Adjuvants and Excipients (2nd Edition)," herein incorporated by reference in its entirety for all purposes, is envisioned within the scope of this disclosure. Other adjuvants 25 include complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed Mycobacterium tuberculosis), incomplete Freund's adjuvants and aluminum hydroxide adjuvant. Other adjuvants comprise GMCSP, BCG, MDP compounds, such as thur-MDP and 30 nor-MDP, CGP (MTP-PE), lipid A, and monophosphoryl lipid A (MPL), MF-59, RIBI, which contains three components extracted from bacteria, MPL, trehalose dimycolate (TDM) and cell wall skeleton (CWS) in a 2% squalene/ TWEEN® polysorbate 80 emulsion. In embodiments, the 35 adjuvant may be a paucilamellar lipid vesicle; for example, NOVASOMES®. NOVASOMES® are paucilamellar nonphospholipid vesicles ranging from about 100 nm to about 500 nm. They comprise BRIJ® alcohol ethoxylate 72, cholesterol, oleic acid and squalene. NOVASOMES® have 40 been shown to be an effective adjuvant (see, U.S. Pat. Nos. 5,629,021, 6,387,373, and 4,911,928.

Administration and Dosage

In embodiments, the disclosure provides a method for eliciting an immune response against one or more corona- 45 viruses. In embodiments, the response is against one or more of the SARS-CoV-2 virus, MERS, and SARS. The method involves administering an immunologically effective amount of a composition containing a nanoparticle or containing a recombinant CoV Spike (S) polypeptide to a 50 subject. Advantageously, the proteins disclosed herein induce one or more of particularly useful anti-coronavirus responses.

In embodiments, the nanoparticles or CoV S polypeptides are administered with an adjuvant. In other aspects, the 55 nanoparticles or CoV S polypeptides are administered without an adjuvant. In some aspects, the adjuvant may be bound to the nanoparticle, such as by a non-covalent interaction. In other aspects, the adjuvant is co-administered with the nanoparticle but the adjuvant and nanoparticle do not inter-60 act substantially.

In embodiments, the nanoparticles may be used for the prevention and/or treatment of one or more of a SARS-CoV-2 infection, a SARS infection, or a MERS infection. Thus, the disclosure provides a method for eliciting an 65 immune response against one or more of the SARS-CoV-2 virus, MERS, and SARS. The method involves administer-

ing an immunologically effective amount of a composition containing a nanoparticle or a CoV S polypeptide to a subject. Advantageously, the proteins disclosed herein induce particularly useful anti-coronavirus responses.

Compositions disclosed herein may be administered via a systemic route or a mucosal route or a transdermal route or directly into a specific tissue. As used herein, the term "systemic administration" includes parenteral routes of administration. In particular, parenteral administration includes subcutaneous, intraperitoneal, intravenous, intraarterial, intramuscular, or intrasternal injection, intravenous, or kidney dialytic infusion techniques. Typically, the systemic, parenteral administration is intramuscular injection. As used herein, the term "mucosal administration" includes oral, intranasal, intravaginal, intra-rectal, intra-tracheal, intestinal and ophthalmic administration. Preferably, administration is intramuscular.

Compositions may be administered on a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunization schedule or in a booster immunization schedule. In a multiple dose schedule the various doses may be given by the same or different routes e.g., a parenteral prime and mucosal boost, a mucosal prime and parenteral boost, etc. In some aspects, a follow-on boost dose is administered about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, or about 6 weeks after the prior dose. In embodiments, the follow-on boost dose is administered 3 weeks after administration of the prior dose. In embodiments, the first dose is administered at day 0, and the boost dose is administered at day 21. In embodiments, the first dose is administered at day 28.

In embodiments, the dose, as measured in μ g, may be the total weight of the dose including the solute, or the weight of the CoV S polypeptide nanoparticles, or the weight of the CoV S polypeptide. Dose is measured using protein concentration assay either A280 or ELISA.

The dose of antigen, including for pediatric administration, may be in the range of about 5 µg to about 25 µg, about 1 µg to about 300 µg, about 90 µg to about 270 µg, about 100 µg to about 160 µg, about 110 µg to about 150 µg, about 120 μg to about 140 $\mu g,$ or about 140 μg to about 160 $\mu g.$ In embodiments, the dose is about 120 µg, administered with alum. In some aspects, a pediatric dose may be in the range of about 1 µg to about 90 µg. In embodiments, the dose of CoV Spike (S) polypeptide is about 1 µg, about 2 µg, about 3 µg, about 4 µg, about 5 µg, about 6 µg, about 7 µg, about 8 µg, about 9 µg, about 10 µg, about 11 µg, about 12 µg, about 13 µg, about 14 µg, about 15 µg, about 16 µg, about $17 \,\mu\text{g}$, about $18 \,\mu\text{g}$, about $19 \,\mu\text{g}$, about $20 \,\mu\text{g}$, about 21, about 22, about 23, about 24, about 25 $\mu g,$ about 26 $\mu g,$ about 27 μg, about 28 μg, about 29 μg, about 30 μg, about 40 μg, about 50, about 60, about 70, about 80, about 90 about 100 µg, about 110 µg, about 120 µg, about 130 µg, about 140 µg, about 150 $\mu g,$ about 160 $\mu g,$ about 170 $\mu g,$ about 180 $\mu g,$ about 190 $\mu g,$ about 200 $\mu g,$ about 210 $\mu g,$ about 220 $\mu g,$ about 230 µg, about 240 µg, about 250 µg, about 260 µg, about 270 µg, about 280 µg, about 290 µg, or about 300 µg, including all values and ranges in between. In embodiments, the dose of CoV S polypeptide is 5 μ g. In embodiments, the dose of CoV S polypeptide is 25 µg.

Certain populations may be administered with or without adjuvants. In certain aspects, compositions may be free of added adjuvant. In such circumstances, the dose may be increased by about 10%.

In embodiments, the dose of the adjuvant administered with a non-naturally occurring CoV S polypeptide is from

about 1 µg to about 100 µg, for example, about 1 µg, about 2 µg, about 3 µg, about 4 µg, about 5 µg, about 6 µg, about 7 µg, about 8 µg, about 9 µg, about 10 µg, about 11 µg, about 12 μ g, about 13 μ g, about 14 μ g, about 15 μ g, about 16 μ g, about 17 µg, about 18 µg, about 19 µg, about 20 µg, about 5 21, about 22, about 23, about 24, about 25 µg, about 26 µg, about 27 µg, about 28 µg, about 29 µg, about 30 µg, about 31 µg, about 32 µg, about 33 µg, about 34 µg, about 35 µg, about 36 µg, about 37 µg, about 38 µg, about 39 µg, about 40 µg, about 41 µg, about 42 µg, about 43 µg, about 44 µg, 10 about 45 µg, about 46 µg, about 47 µg, about 48 µg, about 49 µg, about 50 µg, about 51 µg, about 52 µg, about 53 µg, about 54 µg, about 55 µg, about 56 µg, about 57 µg, about 58 µg, about 59 µg, about 60 µg, about 61 µg, about 62 µg, about 63 µg, about 64 µg, about 65 µg, about 66 µg, about 15 67 µg, about 68 µg, about 69 µg, about 70 µg, about 71 µg, about 72 µg, about 73 µg, about 74 µg, about 75 µg, about 76 µg, about 77 µg, about 78 µg, about 79 µg, about 80 µg, about 81 µg, about 82 µg, about 83 µg, about 84 µg, about 85 µg, about 86 µg, about 87 µg, about 88 µg, about 89 µg, 20 about 90 µg, about 91 µg, about 92 µg, about 93 µg, about 94 µg, about 95 µg, about 96 µg, about 97 µg, about 98 µg, about 99 µg, or about 100 µg of adjuvant. In embodiments, the dose of adjuvant is about 50 µg. In embodiments, the adjuvant is a saponin adjuvant, e.g., MATRIX-MTM.

In embodiments, the dose is administered in a volume of about 0.1 mL to about 1.5 mL, for example, about 0.1 mL, about 0.2 mL, about 0.25 mL, about 0.3 mL, about 0.4 mL, about 0.5 mL, about 0.6 mL, about 0.7 mL, about 0.8 mL, about 0.9 mL, about 1.0 mL, about 1.1 mL, about 1.2 mL, 30 about 1.3 mL, about 1.4 mL, or about 1.5 mL. In embodiments, the dose is administered in a volume of 0.25 mL. In embodiments, the dose is administered in a volume of 0.5 mL. In embodiments, the dose is administered in a volume of 0.5 mL. In embodiments, the dose is administered in a volume of 0.5 mL. In embodiments, the dose is administered in a volume of 0.5 mL. In embodiments, the dose is administered in a volume of 0.6 mL.

In particular embodiments for a vaccine against MERS, SARS, or the SARS-CoV-2 coronavirus, the dose may comprise a CoV S polypeptide concentration of about 1 μ g/mL to about 50 μ g/mL, 10 μ g/mL to about 100 μ g/mL, about 100 μ g/mL, about 100 μ g/mL to about 50 μ g/mL, about 175 μ g/mL to 40 about 325 μ g/mL, about 200 μ g/mL to about 300 μ g/mL, about 220 μ g/mL to about 280 μ g/mL, or about 240 μ g/mL to about 260 μ g/mL.

In another embodiment, the disclosure provides a method of formulating a vaccine composition that induces immunity 45 to an infection or at least one disease symptom thereof to a mammal, comprising adding to the composition an effective dose of a nanoparticle or a CoV S polypeptide. The disclosed CoV S polypeptides and nanoparticles are useful for preparing compositions that stimulate an immune response that 50 confers immunity or substantial immunity to infectious agents. Thus, in one embodiment, the disclosure provides a method of inducing immunity to infections or at least one disease symptom thereof in a subject, comprising administering at least one effective dose of a nanoparticle and/or a 55 CoV S polypeptide.

In embodiments, the CoV S polypeptides or nanoparticles comprising the same are administered in combination with an additional immunogenic composition. In embodiments, the additional immunogenic composition induces an 60 immune response against SARS-CoV-2. In embodiments, the additional immunogenic composition is administered within about 1 minute, about 5 minutes, about 10 minutes, about 20 minutes, about 5 minutes, about 40 minutes, about 50 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about

12 hours, about 13 hours, about 14 hours, about 15 hours, about 16 hours, about 17 hours, about 18 hours, about 19 hours, about 20 hours, about 21 hours, about 22 hours, about 23 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 7 days, about 8 days, about 9 days, about 10 days, about 11 days, about 12 days, about 13 days, about 14 days, about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days, or about 31 days of the disclosed CoV S polypeptides or nanoparticles comprising the same. In embodiments, the additional composition is administered with a first dose of a composition comprising a CoV S polypeptide or nanoparticle comprising the same. In embodiments, the additional composition is administered with a boost dose of a composition comprising a CoV S polypeptide or nanoparticle comprising the same.

In embodiments, the additional immunogenic composition comprises an mRNA encoding a SARS-Cov-2 Spike glycoprotein, a plasmid DNA encoding a SARS-Cov-2 Spike glycoprotein, an viral vector encoding a SARS-Cov-2 Spike glycoprotein, or an inactivated SARS-CoV-2 virus.

In embodiments, the additional immunogenic composi-25 tion comprises mRNA that encodes for a CoV S polypeptide. In embodiments, the mRNA encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1. In embodiments, the mRNA encodes for a CoV S polypeptide comprising an intact furin cleavage site. In embodiments, the mRNA encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an intact furin cleavage site. In embodiments, the mRNA encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an inactive furin cleavage site. In embodiments, the mRNA encodes for a CoV S polypeptide having an amino acid sequence of SEQ ID NO: 87. In embodiments, the mRNA encoding for a CoV S polypeptide is encapsulated in a lipid nanoparticle. An exemplary immunogenic composition comprising mRNA that encodes for a CoV S polypeptide is described in Jackson et al. N. Eng. J. Med. 2020. An mRNA Vaccine against SARS-CoV-2-preliminary report, which is incorporated by reference in its entirety herein. In embodiments, the composition comprising mRNA that encodes for a CoV S polypeptide is administered at a dose of 25 µg, 100 µg, or 250 ug.

In embodiments, the additional immunogenic composition comprises an adenovirus vector encoding for a CoV S polypeptide. In embodiments, the AAV vector encodes for a wild-type CoV S polypeptide. In embodiments, the AAV vector encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an intact furin cleavage site. In embodiments, the AAV vector encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an inactive furin cleavage site. In embodiments, the AAV vector encodes for a CoV S polypeptide having an amino acid sequence of SEQ ID NO: 87. The following publications describe immunogenic compositions comprising an adenovirus vector encoding for a CoV S polypeptide, each of which is incorporated by reference in its entirety herein: van Doremalen N. et al. A single dose of ChAdOx1 MERS provides protective immunity in rhesus macaques. Science Advances, 2020; van Doremalen N. et al. ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. bioRxiv, (2020).

In embodiments, the additional immunogenic composition comprises deoxyribonucleic acid (DNA). In embodiments, the additional immunogenic composition comprises plasmid DNA. In embodiments, the plasmid DNA encodes for a CoV S polypeptide. In embodiments, the DNA encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an intact furin cleavage site. In embodiments, the DNA encodes for a CoV S polypeptide comprising proline substitutions at positions 986 and 987 of SEQ ID NO: 1 and an inactive furin cleavage site. In embodiments, the DNA encodes for a CoV S polypeptide having an amino acid sequence of SEQ ID NO: 87.

In embodiments, the additional immunogenic composi- 15 tion comprises an inactivated virus vaccine.

In embodiments, the CoV S proteins or nanoparticles comprising CoV S proteins are useful for preparing immunogenic compositions to stimulate an immune response that confers immunity or substantial immunity to one or more of MERS, SARS, and SARS-CoV-2. Both mucosal and cellular immunity may contribute to immunity to infection and disease. Antibodies secreted locally in the upper respiratory tract are a major factor in resistance to natural infection. 25 Secretory immunoglobulin A (sIgA) is involved in protection of the upper respiratory tract and serum IgG in protection of the lower respiratory tract. The immune response induced by an infection protects against reinfection with the same virus or an antigenically similar viral strain. The 30 antibodies produced in a host after immunization with the nanoparticles disclosed herein can also be administered to others, thereby providing passive administration in the subject.

In embodiments, the present disclosure provides a method of producing one or more of high affinity anti-MERS-CoV, anti-SARS-CoV, and anti-SARS-CoV-2 virus antibodies. The high affinity antibodies produced by immunization with the nanoparticles disclosed herein are produced by administering an immunogenic composition comprising an S CoV polypeptide or a nanoparticle comprising an S CoV polypeptide to an animal, collecting the serum and/or plasma from the animal, and purifying the antibody from the serum/ and or plasma. In one embodiment, the animal is a human. In embodiments, the animal is a chicken, mouse, guinea pig, rat, rabbit, goat, human, horse, sheep, or cow. In one embodiment, the animal is bovine or equine. In another embodiment, the bovine or equine animal is transgenic. In yet a further embodiment, the transgenic bovine or equine animal produces human antibodies. In embodiments, the animal produces monoclonal antibodies. In embodiments, 55 the animal produces polyclonal antibodies. In one embodiment, the method further comprises administration of an adjuvant or immune stimulating compound. In a further embodiment, the purified high affinity antibody is adminis- 60 tered to a human subject. In one embodiment, the human subject is at risk for infection with one or more of MERS, SARS, and SARS-CoV-2.

All patents, patent applications, references, and journal 65 articles cited in this disclosure are expressly incorporated herein by reference in their entireties for all purposes.

EXAMPLES

Example 1

Expression and Purification of Coronavirus Spike (S) Polypeptide Nanoparticles

The native coronavirus Spike (S) polypeptide (SEQ ID NO: 1 and SEQ ID NO:2) and CoV Spike polypeptides which have amino acid sequences corresponding to SEQ ID NOS: 3, 4, 38, 41, 44, 48, 51, 54, 58, 61, 63, 65, 67, 73, 75, 78, 79, 82, 83, 85, 87, 106, 108, and 89 have been expressed in a baculovirus expression system and recombinant plaques expressing the coronavirus Spike (S) polypeptides were picked and confirmed. In each case the signal peptide is SEQ ID NO: 5. FIG. 4 and FIG. 9 show successful purification of the CoV Spike polypeptides BV2364, BV2365, BV2366, BV2367, BV2368, BV2369, BV2373, BV2374, and BV2375. Table 2 shows the sequence characteristics of the aforementioned CoV Spike polypeptides.

TABLE 2

CoV S polypeptide	Modification	SEQ ID NO.
BV2364	Deleted N-Terminal Domain	48
BV2365	Inactive furin cleavage site	4
BV2361/BV2366	Wild-type	2
BV2367	Deletion of amino acids 676-	63
	685, inactive furin cleavage site	
BV2368	Deletion of amino acids 702- 711, inactive furin cleavage site	65
BV2369	Deletion of amino acids 806- 815, inactive furin cleavage	67
BV2373, formulated into a composition referred to herein as "NVX-CoV2373"	Inactive furin cleavage site, K973P mutation, V974P mutation	87
BV2374	K973P mutation, V974P mutation	85
BV2374	Inactive furin cleavage site and His-tag	58
BV2384	Inactive furin cleavage site (GSAS), K973P, V974P mutation	110

The wild-type BV2361 protein (SEQ ID NO: 2) binds to human angiotensin-converting enzyme 2 precursor (hACE2). Bio-layer interferometry and ELISA were performed to assess binding of the CoV S polypeptides. Bio-Layer Interferometry (BLI):

The BLI experiments were performed using an Octet QK384 system (Pall Forte Bio, Fremont, Calif.). His-tagged human ACE2 (2 µg mL-1) was immobilized on nickelcharged Ni-NTA biosensor tips. After baseline, SARS-CoV-2 S protein containing samples were 2-fold serially diluted and were allowed to associate for 600 seconds followed by dissociation for an additional 900 sec. Data was analyzed with Octet software HT 101:1 global curve fit.

The CoV S polypeptides BV2361, BV2365, BV2369, BV2365, BV2373, BV2374 retain the ability to bind to hACE2 (FIG. 5, FIGS. 11A-C). Dissociation kinetics showed that the S-proteins remained tightly bound as evident by minimal or no dissociation over 900 seconds of observation in the absence of fluid phase S protein (FIGS. 11A-C).

Furthermore, binding is specific. The wild-type CoV S protein, BV2361 and the CoV S polypeptides BV2365 and

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BV2373 do not bind the MERS-CoV receptor, dipeptidyl peptidase IV (DPP4). Additionally, the MERS S protein does not bind to human angiotensin-converting enzyme 2 precursor (hACE2) (FIG. 6 and FIGS. 11D-F). ELISA

The specificity of the CoV S polypeptides for hACE2 was confirmed by ELISA. Ninety-six well plates were coated with 100 µL SARS-CoV-2 spike protein (2 µg/mL) overnight at 4° C. Plates were washed with phosphate buffered saline with 0.05% Tween (PBS-T) buffer and blocked with TBS Startblock blocking buffer (ThermoFisher, Scientific). His-tagged hACE2 and hDPP4 receptors were 3-fold serially diluted (5-0.0001 µg mL-1) and added to coated wells for 2 hours at room temperature. The plates were washed with PBS-T. Optimally diluted horseradish peroxidase (HRP) conjugated anti-histidine was added and color developed by addition of and 3,3',5,5'-tetramethylbenzidine peroxidase substrate (TMB, T0440-IL, Sigma, St. Louis, Mo., USA). Plates were read at an OD of 450 nm with a 20 SpectraMax Plus plate reader (Molecular Devices, Sunnyvale, Calif., USA) and data analyzed with SoftMax software. EC50 values were calculated by 4-parameter fitting using GraphPad Prism 7.05 software.

The ELISA results showed that the wild-type CoV S 25 polypeptide (BV2361), BV2365, and BV2373 proteins specifically bound hACE2 but failed to bind the hDPP-4 receptor used by MERS-CoV (IC50>5000 ng mL-1). The wild-type CoV S polypeptide and BV2365 bound to hACE2 with similar affinity (IC₅₀=36-38 ng/mL), while BV2373 $_{30}$ attained 50% saturation of hACE2 binding at 2-fold lower concentration (IC₅₀=18 ng/mL) (FIG. 7, FIGS. 11D-F). Protein and Nanoparticle Production

The recombinant virus is amplified by infection of Sf9 insect cells. A culture of insect cells is infected at ~3 MOI 35 µg BV2373 and MATRIX-M[™] had elevated anti-S IgG (Multiplicity of infection=virus ffu or pfu/cell) with baculovirus. The culture and supernatant is harvested 48-72 hrs post-infection. The crude cell harvest, approximately 30 mL, is clarified by centrifugation for 15 minutes at approximately 800×g. The resulting crude cell harvests containing the 40 coronavirus Spike (S) protein are purified as nanoparticles as described below.

To produce nanoparticles, non-ionic surfactant TERGI-TOL® nonylphenol ethoxylate NP-9 is used in the membrane protein extraction protocol. Crude extraction is further 45 purified by passing through anion exchange chromatography, lentil lectin affinity/HIC and cation exchange chromatography. The washed cells are lysed by detergent treatment and then subjected to low pH treatment which leads to precipitation of BV and Sf9 host cell DNA and protein. The 50 neutralized low pH treatment lysate is clarified and further purified on anion exchange and affinity chromatography before a second low pH treatment is performed.

Affinity chromatography is used to remove 519/BV proteins, DNA and NP-9, as well as to concentrate the corona- 55 virus Spike (S) protein. Briefly, lentil lectin is a metalloprotein containing calcium and manganese, which reversibly binds polysaccharides and glycosylated proteins containing glucose or mannose. The coronavirus Spike (S) proteincontaining anion exchange flow through fraction is loaded 60 onto the lentil lectin affinity chromatography resin (Capto Lentil Lectin, GE Healthcare). The glycosylated coronavirus Spike (S) protein is selectively bound to the resin while non-glycosylated proteins and DNA are removed in the column flow through. Weakly bound glycoproteins are 65 removed by buffers containing high salt and low molar concentration of methyl alpha-D-mannopyranoside (MMP).

The column washes are also used to detergent exchange the NP-9 detergent with the surfactant polysorbate 80 (PS80). The coronavirus Spike (S) polypeptides are eluted in nanoparticle structure from the lentil lectin column with a high concentration of MMP. After elution, the coronavirus Spike (S) protein trimers are assembled into nanoparticles composed of coronavirus Spike (S) protein trimers and PS80 contained in a detergent core.

Example 2

Immunogenicity of Coronavirus Spike (S) Polypeptide Nanoparticle Vaccines in Mice

The coronavirus Spike (S) protein composition comprising a CoV S polypeptide of SEQ ID NO: 87 (also called "BV2373") as described in Example 1 was evaluated for immunogenicity and toxicity in a murine model, using female BALB/c mice (7-9 weeks old; Harlan Laboratories Inc., Frederick, Md.). The compositions were evaluated in the presence and in the absence of a saponin adjuvant, e.g., MATRIX-MTM. Compositions containing MATRIX-MTM contained 5 µg of MATRIX-MTM. Vaccines containing coronavirus Spike (S) polypeptide at various doses, including 0.01 µg, 0.1 µg, 1 µg, and 10 µg, were administered intramuscularly as a single dose (also referred to as a single priming dose) (study day 14) or as two doses (also referred to as a prime/boost regimen) spaced 14-days apart (study day 0 and 14). A placebo group served as a non-immunized control. Serum was collected for analysis on study days -1, 13, 21, and 28. Vaccinated and control animals were intranasally challenged with SARS-CoV-2 42 days following one (a single dose) or two (two doses) immunizations.

Vaccine Immunogenicity

Animals immunized with a single priming dose of 0.1-10 titers that were detected 21-28 days after a single immunization (FIG. 13B). Mice immunized with a 10 µg dose of BV2373 and MATRIX-MTM produced antibodies that blocked hACE2 receptor binding to the CoV S protein and virus neutralizing antibodies that were detected 21-28 days after a single priming dose (FIG. 14 and FIG. 15). Animals immunized with the prime/boost regimen (two doses) had significantly elevated anti-S IgG titers that were detected 7-16 days following the booster immunization across all dose levels (FIG. 13A). Animals immunized with BV2373 (1 µg and 10 µg) and MATRIX-MTM had similar high anti-S IgG titers following immunization (GMT=139,000 and 84,000, respectively). Mice immunized with BV2373 (0.1 µg, 1 µg, or 10 µg) and MATRIX-M[™] had significantly (p≤0.05 and p≤0.0001) higher anti-S IgG titers compared to mice immunized with 10 µg BV2373 without adjuvant (FIG. 13A). These results indicate the potential for 10- to 100-fold dose sparing provided by the MATRIX-M[™] adjuvant. Furthermore, immunization with two doses of BV2373 and MATRIX-MTM elicited high titer antibodies that blocked hACE2 receptor binding to S-protein (IC50=218-1642) and neutralized the cytopathic effect (CPE) of SARS-CoV-2 on Vero E6 cells (100% blocking of CPE=7680-20,000) across all dose levels (FIG. 14 and FIG. 15).

SARS CoV-2 Challenge

To evaluate the induction of protective immunity, immunized mice were challenged with SARS-CoV-2. Since mice do not support replication of the wild-type SARS-CoV-2 virus, on day 52 post initial vaccination, mice were intranasally infected with an adenovirus expressing hACE2 (Ad/hACE2) to render them permissive. Mice were intranasally inoculated with 1.5×10^5 pfu of SARS-CoV-2 in 50

 μ L divided between nares. Challenged mice were weighed on the day of infection and daily for up to 7 days post infection. At 4- and 7-days post infection, 5 mice were sacrificed from each vaccination and control group, and lungs were harvested and prepared for pulmonary histology. 5

The viral titer was quantified by a plaque assay. Briefly, the harvested lungs were homogenized in PBS using 1.0 mm glass beads (Sigma Aldrich) and a Beadruptor (Omini International Inc.). Homogenates were added to Vero E6 near confluent cultures and SARS-CoV-2 virus titers determined by counting plaque forming units (pfu) using a 6-point dilution curve

At 4 days post infection, placebo-treated mice had 10^4 SARS-CoV-2 pfu/lung, while the mice immunized with BV2363 without MATRIX-MTM had 10^3 pfu/lung (FIG. **16**). 15 The BV2373 with MATRIX-MTM prime-only groups of mice exhibited a dose dependent reduction in virus titer, with recipients of the 10 µg BV2373 dose having no detectable virus at day 4 post infection. Mice receiving 1 µg, 0.1 µg and 0.01 µg BV2373 doses all showed a marked reduction in 20 titer compared to placebo-vaccinated mice. In the prime/ boost groups, mice immunized with 10 µg, 1 µg and 0.1 µg doses had almost undetectable lung virus loads, while the 0.01 µg group displayed a reduction of 1 log reduction relative to placebo animals. 25

Weight loss paralleled the viral load findings. Animals receiving a single dose of BV2373 ($0.1 \mu g$, $1 \mu g$, and $10 \mu g$) and MATRIX-M[™] showed marked protection from weight loss compared to the unvaccinated placebo animals (FIG. 17A). The mice receiving a prime and boost dose with 30 adjuvant also demonstrated significant protection against weight loss at all dose levels (FIGS. 17B-C). The effect of the presence of adjuvant on protection against weight loss was evaluated. Mice receiving the prime/boost (two doses) plus adjuvant were significantly protected from weight loss 35 relative to placebo, while the group immunized without adjuvant was not (FIG. 17C). These results showed that BV2373 confers protection against SARS-CoV-2 and that low doses of the vaccine associated with lower serologic responses do not exacerbate weight loss or demonstrate 40 exaggerated illness.

Lung histopathology was evaluated on days 4 and day 7 post infection (FIG. **18**A and FIG. **18**B). At day 4 post infection, placebo-immunized mice showed denudation of epithelial cells in the large airways with thickening of the 45 alveolar septa surrounded by a mixed inflammatory cell population. Periarteriolar cuffing was observed throughout the lungs with inflammatory cells consisting primarily of neutrophils and macrophages. By day 7 post infection, the placebo-treated mice displayed peribronchiolar inflamma-50 tion with increased periarteriolar cuffing. The thickened alveolar septa remained with increased diffuse interstitial inflammation throughout the alveolar septa (FIG. **18**B).

The BV2373 immunized mice showed significant reduction in lung pathology at both day 4 and day 7 post infection 55 in a dose-dependent manner. The prime only group displays reduced inflammation at the 10 μ g and 1 μ g dose with a reduction in inflammation surrounding the bronchi and arterioles compared to placebo mice. In the lower doses of the prime-only groups, lung inflammation resembles that of 60 the placebo groups, correlating with weight loss and lung virus titer. The prime/boost immunized groups displayed a significant reduction in lung inflammation for all doses tested, which again correlated with lung viral titer and weight loss data. The epithelial cells in the large and small 65 bronchi at day 4 and 7 were substantially preserved with minimal bronchiolar sloughing and signs of viral infection.

The arterioles of animals immunized with 10 μ g, 1 μ g and 0.1 μ g doses have minimal inflammation with only moderate cuffing seen with the 0.01 μ g dose, similar to placebo. Alveolar inflammation was reduced in animals that received the higher doses with only the lower 0.01 μ g dose associated with inflammation (FIGS. **18A-18**B). These data demonstrate that BV2373 reduces lung inflammation after challenge and that even doses and regimens of BV2373 that elicit minimal or no detectable neutralizing activity are not associated with exacerbation of the inflammatory response to the virus. Furthermore, the vaccine does not cause vaccine associated enhanced respiratory disease (VAERD) in challenged mice.

T Cell Response

The effect of the vaccine composition comprising a CoV S polypeptide of SEQ ID NO: 87 on the T cell response was evaluated. BALB/c mice (N=6 per group) were immunized intramuscularly with 10 μ g BV2373 with or without 5 μ g MATRIX-MTM in 2 doses spaced 21-days apart. Spleens were collected 7-days after the second immunization (study day 28). A non-vaccinated group (N=3) served as a control.

Antigen-specific T cell responses were measured by ELISPOTTM enzyme linked immunosorbent assay and intracellular cytokine staining (ICCS) from spleens collected 7-days after the second immunization (study day 28). The number of IFN- γ secreting cells after ex vivo stimulation increased 20-fold (p=0.002) in spleens of mice immunized with BV2373 and MATRIX-M[™] compared to BV2373 alone as measured by the ELISPOTTM assay (FIG. 19). In order to examine CD4+ and CD8+ T cell responses separately, ICCS assays were performed in combination with surface marker staining. Data shown are gated on CD44hi CD62L-effector memory T cell population. The frequency of IFN- γ +, TNF- α +, and IL-2+ cytokine-secreting CD4+ and CD8+ T cells was significantly higher (p<0.0001) in spleens from mice immunized with BV2373 as compared to mice immunized without adjuvant (FIG. 20A-C and FIG. 21A-C). Further, the frequency of multifunctional CD4+ and CD8+ T cells, which simultaneously produce at least two or three cytokines was also significantly increased (p<0.0001) in spleens from the BV2373/MATRIX-MTM immunized mice as compared to mice immunized in the absence of adjuvant (FIGS. 20D-E and FIGS. 21D-E). Immunization with BV2373/MATRIX-M[™] resulted in higher proportions of multifunctional phenotypes (e.g., T cells that secrete more than one of IFN- γ , TNF- α , and IL-2) within both CD4+ and CD8+T cell populations. The proportions of multifunctional phenotypes detected in memory CD4+ T cells were higher than those in CD8+ T cells (FIG. 22).

Type 2 cytokine IL-4 and IL-5 secretion from CD4+ T cells was also determined by ICCS and ELISPOTTM respectively. Immunization with BV2373/MATRIX-MTM also increased type 2 cytokine IL-4 and IL-5 secretion (2-fold) compared to immunization with BV2373 alone, but to a lesser degree than enhancement of type 1 cytokine production (e.g. IFN- γ increased 20-fold) (FIGS. **23**A-C). These results indicate that administration of the MATRIX-MTM adjuvant skewed the CD4+ T cell development toward Th1 responses.

The effect of immunization on germinal center formation was assessed by measuring the frequency of CD4+T follicular helper (TFH) cells and germinal center (GC) B cells in spleens. MATRIX-MTM administration significantly increased the frequency of TFH cells (CD4+ CXCR5+PD-1+) was significantly increased (p=0.01), as well as the frequency of GC B cells (CD19+GL7+CD95+) (p=0.0002) in spleens (FIGS. **24**A-B and FIGS. **25**A-B).

Example 3

Immunogenicity of Coronavirus Spike (S) Polypeptide Nanoparticle Vaccines in Olive Baboons

The immunogenicity of a vaccine composition compris-⁵ ing BV2373 in baboons was assessed. Adult olive baboons were immunized with a dose range (1 μg, 5 μg and 25 μg) of BV2373 and 50 μg MATRIX-MTM adjuvant administered by intramuscular (IM) injection in two doses spaced 21-days apart. To assess the adjuvanting activity of MATRIX-MTM in ¹⁰ non-human primates, another group of animals was immunized with 25 μg of BV2373 without MATRIX-MTM. Anti-S protein IgG titers were detected within 21-days of a single priming immunization in animals immunized with BV2373/ MATRIX-MTM across all the dose levels (GMT=1249-19, ¹⁵ 000). Anti-S protein IgG titers increased over a log (GMT=33,000-174,000) within 1 to 2 weeks following a booster immunization (days 28 and 35) across all of the dose levels. (FIG. **26**A).

Low levels of hACE2 receptor blocking antibodies were 20 detected in animals following a single immunization with BV2373 (5 μg or 25 μg) and MATRIX-MTM (GMT=22-37). Receptor blocking antibody titers were significantly increased within one to two weeks of the booster immunization across all groups immunized with BV2373/MATRIX- 25 MTM (GMT=150-600) (FIG. 26B). Virus neutralizing antibodies were elevated (GMT=190-446) across all dose groups after a single immunization with BV2373/MATRIX-MTM. Animals immunized with 25 μ g BV2373 alone had no detectable antibodies that block S-protein binding to hACE2 30 (FIG. 26C). Neutralizing titers were increased 6- to 8-fold one week following the booster immunization (GMT=1160-3846). Neutralizing titers increased an additional 25- to 38-fold following the second immunization (GMT=6400-17,000) (FIG. 26C). There was a significant correlation ³⁵ (p<0.0001) between anti-S IgG levels and neutralizing antibody titers (FIG. 27). The immunogenicity of the adjuvanted vaccine in nonhuman primates is consistent with the results of Example 2 and further supports the role of MATRIX-MTM in promoting the generation of neutralizing antibodies and 40 dose sparing.

PBMCs were collected 7 days after the second immunization (day 28), and the T cell response was measured by ELISPOT assay. PBMCs from animals immunized with BV2373 (5 μg or 25 μg) and MATRIX-MTM had the highest 45 number of IFN-γ secreting cells, which was 5-fold greater compared to animals immunized with 25 μg BV2373 alone or BV2373 (1 μg) and MATRIX-MTM (FIG. **28**). By ICCS analysis, immunization with BV2373 (5 μg) and MATRIX-MTM showed the highest frequency of IFN-γ+, IL-2+, and 50 TNF-α+CD4+ T cells (FIGS. **29**A-C). This trend was also true for multifunctional CD4+ T cells, in which at least two or three type 1 cytokines were produced simultaneously (FIGS. **29**D-E).

Example 4

Structural Characterization of Coronavirus Spike (S) Polypeptide Nanoparticle Vaccines

Transmission electron microscopy (TEM) and two dimen- 60 sional (2D) class averaging were used to determine the ultrastructure of BV2373. High magnification (67,000× and 100,000×) TEM images of negatively stained BV2373 showed particles corresponding to S-protein homotrimers.

An automated picking protocol was used to construct 2D class average images (Lander G. C. et al. *J Struct Biol.* 166, 95-102 (2009); Sorzano C. O. et al., *J Struct Biol.* 148,

194-204 (2004).). Two rounds of 2D class averaging of homotrimeric structures revealed a triangular particle appearance with a 15 nm length and 13 nm width (FIG. 10, top left). Overlaying the recently solved cryoEM structure of the SARS-CoV-2 spike protein (EMD ID: 21374) over the 2D BV2373 image showed a good fit with the crown-shaped 51 (NTD and RBD) and the S2 stem (FIG. 10, bottom left). Also apparent in the 2D images was a faint projection that protruded from the tip of the trimeric structure opposite of the NTD/RBD crown (FIG. 10, top right). 2D class averaging using a larger box size showed these faint projections form a connection between the S-trimer and an amorphous structure. (FIG. 10, bottom right).

Dynamic light scattering (DLS) show that the wild-type CoV S protein had a Z-avg particle diameter of 69.53 nm compared to a 2-fold smaller particle size of BV2365 (33.4 nm) and BV2373 (27.2 nm). The polydispersity index (PDI) indicated that BV2365 and BV2373 particles were generally uniform in size, shape, and mass (PDI=0.25-0.29) compared to the wild-type spike-protein (PDI=0.46) (Table 3).

TABLE 3

Particle Size and Thermostability of SARS-CoV-2 Trimeric Spike Proteins									
	Differential Scanning Dynamic Lig Calorimetry (DSC) Scattering (D								
SARS-CoV-2 S protein	T _{max} (° C.)	ΔHcal (kJ/mol)	Z- avg diameter ² (nm)	PDI ³					
Wild-type BV2365 BV2373	58.6 61.3 60.4	153 466 732	69.53 33.40 27.21	0.46 0.25 0.29					

 ${}^{1}T_{max}$: melting temperature

²Z-avg: Z-average particle size

³PDI: polydispersity index

The thermal stability of the S-trimers was determined by differential scanning calorimetry (DSC). The thermal transition temperature of the wild-type CoV S-protein (T_{max} =58.6° C.) was similar to BV2365 and BV2373 with a T_{max} =61.3° C. and 60.4° C., respectively (Table 3). Of greater significance, was the 3-5 fold increased enthalpy of transition required to unfold the BV2365 and BV2373 variants (Δ Hcal=466 and 732 kJ/mol, respectively) compared to the lower enthalpy required to unfold the WT spike protein (Δ Hcal=153 kJ/mol). These results are consistent with improved thermal stability of the BV2365 and BV2373 compared to that of WT spike protein (Table 3).

50 The stability of the CoV Spike (S) polypeptide nanoparticle vaccines was evaluated by dynamic light scattering. Various pHs, temperatures, salt concentrations, and proteases were used to compare the stability of the CoV Spike (S) polypeptide nanoparticle vaccines to nanoparticle 55 vaccines containing the native CoV Spike (S) polypeptide.

Example 5

Stability of Coronavirus Spike (S) Polypeptide Nanoparticle Vaccines

The stability of the CoV Spike (S) polypeptide nanoparticle vaccines was evaluated by dynamic light scattering. Various pHs, temperatures, salt concentrations, and proteases were used to compare the stability of the CoV Spike (S) polypeptide nanoparticle vaccines to nanoparticle vaccines containing the native CoV Spike (S) polypeptide. The stability of BV2365 without the 2-proline substitutions

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and BV2373 with two prolines substitution was assessed under different environmental stress conditions using the hACE2 capture ELISA. Incubation of BV2373 at pH extremes (48 hours at pH 4 and pH 9), with prolonged agitation (48 hours), and through freeze/thaw (2 cycles), and elevated temperature (48 hours at 25° C. and 37° C.) had no effect on hACE2 receptor binding (IC50=14.0-18.3 ng mL-1).

Oxidizing conditions with hydrogen peroxide reduced binding of hACE2 binding to BV2373 8-fold (IC50=120 ng mL-1) (FIG. **12**A). BV2365 without the 2-proline substitutions was less stable as determined by a significant loss of hACE2 binding under multiple conditions (FIG. **12**B).

The stability of BV2384 (SEQ ID NO: 110) and BV2373 (SEQ ID NO: 87) were compared. BV2384 has a furin ¹⁵ cleavage site sequence of GSAS (SEQ ID NO: 97), whereas BV2373 has a furin cleavage site of QQAQ (SEQ ID NO: 7). As demonstrated by SDS-PAGE and Western Blot, BV2384 showed extensive degradation in comparison to BV2373 (FIG. **32**). Furthermore, scanning densitometry and ²⁰ recovery data demonstrate the unexpected loss of full length CoV S protein BV2384, lower purity, and recovery (FIG. **33**) in comparison to BV2373 (FIG. **34**).

Example 6

Immune Response in Cynomolgus Macaques

We assessed the immune response induced by BV2373 in a Cynomolgus macaque model of SARS-CoV-2 infection. Groups 1-6 were treated as shown in Table 4.

TABLE 4

Groups 1-6 of Cynomolgus macaque study									
Group (N = 4)	BV2373 Dose	MATRIX M ™ Dose	- Immunization (Days)	Blood Draw (days)	Challenge (Day)	3			
1	Placebo		0, 21	0, 21, 33	35				
2	2.5 μg	25 μg	0, 21	0, 21, 33	35	4			
3	Σμg	25 µg	0	0, 21, 33	35	40			
4	5 µg	50 µg	0, 21	0, 21, 33	35				
5	5 µg	50 μg	0	0, 21, 33	35				
6	25 μg	50 µg	0, 21	0, 21, 33	35				

Administration of a vaccine comprising BV2373 resulted 45 in the induction of anti-CoV-S antibodies (FIG. 35A) including neutralizing antibodies (FIG. 35B). Anti-CoV-S antibodies were induced after administration of one (FIG. 38A) or two doses (FIG. 38B) of BV2373. Administration of the vaccine comprising BV2373 also resulted in the production 50 of antibodies that blocked binding of the CoV S protein to hACE2 (FIG. 38C and FIG. 38D). There was a significant correlation between anti-CoV S polypeptide IgG titer and hACE2 inhibition titer in Cynomolgus macaques after administration of BV2373 (FIG. 38E). The ability of 55 BV2373 to induce the production of neutralizing antibodies was evaluated by cytopathic effect (CPE) (FIG. 40A) and plaque reduction neutralization test (PRNT) (FIG. 40B). The data revealed that vaccine formulations of Table 4 produced SARS-CoV-2 neutralizing titers, in contrast to the control. 60

The vaccine comprising BV2373's ability to induce anti-CoV-S antibodies and antibodies that block binding of hACE2 to the CoV S protein in Cynomolgus macaques was compared to human convalescent serum. The data revealed that the BV2373 vaccine formulation induced superior anti-CoV S polypeptide and hACE2 inhibition titers as compared to human convalescent serum (FIG. **39**). 40

The BV2373 vaccine formulation also caused a decrease of SARS-CoV-2 viral replication (FIGS. 36A-B). Viral RNA (FIG. 36A, corresponding to total RNA present) and viral sub-genomic RNA (sgRNA) (FIG. 36B, corresponding to replicating virus) levels were assessed in bronchiolar lavage (BAL) at 2 days and 4 days post-challenge with infectious virus (d2pi and d4pi). Most subjects showed no viral RNA. At Day 2 small amounts of RNA were measured in some subjects. By Day 4, no RNA was measured except for two subjects at the lowest dose of 2.5 µg. Sub-genomic RNA was not detected at either 2 days or 4 days except for 1 subject, again at the lowest dose. Viral RNA (FIG. 37A) and viral sub-genomic (sg) RNA (FIG. 37B) were assessed by nasal swab at 2 days and 4 days post-infection (d2pi and d4pi). Most subjects showed no viral RNA. At Day 2 and Day 4 small amounts of RNA were measured in some subjects. Sub-genomic RNA was not detected at either 2 Days or 4 days. Subjects were immunized Day 0 and in the groups with two doses Day 0 and Day 21. These data show that the vaccine decreases nose total virus RNA by 100-1000 fold and sgRNA to undetectable levels, and confirm that immune response to the vaccine will block viral replication and prevent viral spread.

Example 7

Evaluation of CoV S Polypeptide Nanoparticle Vaccines in Humans

We assessed the safety and efficacy of a vaccine comprising BV2373 in a randomized, observer-blinded, placebocontrolled Phase 1 clinical trial in 131 healthy participants 18-59 years of age. Participants were immunized with two intramuscular injections, 21 days apart. Participants received BV2373 with or without MATRIX-MTM (n=106) or placebo (n=25). Groups A-E were treated as shown in Table 5. FIG. **41** shows a timeline of the evaluation of clinical endpoints.

TABLE 5

Groups A-E of Phase 1 Human Study											
	Partic	ipants	Da	ay 0	Day 21 (+5 days)						
Group (N = 25)	Ran- domized	Sentinel	BV2373 Dose	MATRIX- M ™ Dose	BV2373 Dose	MATRIX- M ™ Dose					
A	25	_	0 μg	0 μg	0 μg	0 μg					
В С	25 25	3	25 μg 5 μg	0 μg 50 μg	25 μg 5 μg	0 μg 50 μg					
D	25	3	25 μg	50 μg	25 μg	50 μg					
Е	25	_	25 µg	50 µg	0 μg	0 µg					

Overall reactogenicity was mild, and the vaccinations were well tolerated. Local reactogenicity was more frequent in patients treated with BV2373 and MATRIX-MTM (FIGS. **42**A-B).

The immunogenicity of BV2373 with and without MATRIX-MTM was evaluated. 21 days after vaccination, anti-CoV-S antibodies were detected for all vaccine regimens (FIG. **43**A). Geometric mean fold rises (GMFR) in vaccine regimens comprising MATRIX-MTM exceeded those induced by unadjuvanted BV2373. 7 days after a second vaccination (day 28), the anti-CoV-S titer increased an additional eight-fold over responses seen with first vaccination and within 14 days (Day 35) responses had more than doubled yet again, achieving GMFRs approximately 100-fold over those observed with BV2373 alone. A single vaccination with BV2373/MATRIX-MTM achieved similar

anti-CoV-S titer levels to those in asymptomatic (exposed) COVID-19 patients. A second vaccination achieved GMEU levels that exceeded convalescent serum from outpatienttreated COVID-19 patients by six-fold, achieved levels similar to convalescent serum from patients hospitalized 5 with COVID-19, and exceeded overall convalescent serum anti-CoV-S antibodies by nearly six-fold. The responses in the two-dose 5-µg and 25-µg BV2373/MATRIX-MTM regimens were similar. This highlights the ability of the adjuvant (MATRIX-MTM) to enable dose sparing. 10

Neutralizing antibodies were induced in all groups treated with BV2373 (FIG. **43**B). Groups treated with BV2373 and MATRIX-MTM regimens exhibited an approximately fivefold GMFR than groups treated with BV2373 alone (FIG. **43**B). Second vaccinations with adjuvant had a profound 15 effect on neutralizing antibody titers—inducing >100 fold rise over single vaccinations without adjuvant. When compared to convalescent serum, second vaccinations with BV2373/MATRIX-MTM achieved GMT levels four-fold greater than outpatient-treated COVID-19 patients, levels 20 spanning those of patients hospitalized with COVID-19, and exceeded overall convalescent serum GMT by four fold.

Convalescent serum, obtained from COVID-19 patients with clinical symptoms requiring medical care, demonstrated proportional anti-CoV-S IgG and neutralization titers 25 that increased with illness severity (FIGS. **43**A-B).

A strong correlation was observed between neutralizing antibody titers and anti-CoV-S IgG in patients treated with

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BV2373 and MATRIX-MTM (r=0.9466, FIG. 44C) similar to that observed in patients treated with convalescent sera (r=0.958) (FIG. 44A). This correlation was not observed in subjected administered unadjuvanted BV2373 (r=0.7616) (FIG. 44B). Both 5 μ g and 25 μ g BV2373/MATRIX-MTM groups (groups C-E of Table 5) demonstrated similar magnitudes of two-dose responses and every participant seroconverted using either assay measurement when a two-dose regimen was utilized.

T-cell responses in 16 participants (four participants from each of Groups A through D) showed that BV2373/MA-TRIX-MTM regimens induced antigen-specific polyfunctional CD4+ T-cell responses in terms of IFN- γ , IL-2, and TNF- α production upon stimulation with BV2373. There was a strong bias toward production of Th1 cytokines (FIGS. **45**A-D).

INCORPORATION BY REFERENCE

All references, articles, publications, patents, patent publications, and patent applications cited herein are incorporated by reference in their entireties for all purposes. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as, an acknowledgment or any form of suggestion that they constitute valid prior art or form part of the common general knowledge in any country in the world.

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<400)> SI	EQUEI	NCE:	1											
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Thr	Arg	Gly 35	Val	Tyr	Tyr	Pro	Asp 40	Lys	Val	Phe	Arg	Ser 45	Ser	Val	Leu
His	Ser 50	Thr	Gln	Asp	Leu	Phe 55	Leu	Pro	Phe	Phe	Ser 60	Asn	Val	Thr	Trp
Phe 65	His	Ala	Ile	His	Val 70	Ser	Gly	Thr	Asn	Gly 75	Thr	Lys	Arg	Phe	Asp 80
Asn	Pro	Val	Leu	Pro 85	Phe	Asn	Asp	Gly	Val 90	Tyr	Phe	Ala	Ser	Thr 95	Glu
Lys	Ser	Asn	Ile 100	Ile	Arg	Gly	Trp	Ile 105	Phe	Gly	Thr	Thr	Leu 110	Asp	Ser
Lys	Thr	Gln 115	Ser	Leu	Leu	Ile	Val 120	Asn	Asn	Ala	Thr	Asn 125	Val	Val	Ile
Lys	Val 130	Сүз	Glu	Phe	Gln	Phe 135	Суз	Asn	Asp	Pro	Phe 140	Leu	Gly	Val	Tyr
Tyr 145	His	Lys	Asn	Asn	Lys 150	Ser	Trp	Met	Glu	Ser 155	Glu	Phe	Arg	Val	Tyr 160
Ser	Ser	Ala	Asn	Asn 165	Cys	Thr	Phe	Glu	Tyr 170	Val	Ser	Gln	Pro	Phe 175	Leu
Met	Asp	Leu	Glu 180	Gly	Lys	Gln	Gly	Asn 185	Phe	Lys	Asn	Leu	Arg 190	Glu	Phe
------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------	------------
Val	Phe	Lys 195	Asn	Ile	Asp	Gly	Tyr 200	Phe	Lys	Ile	Tyr	Ser 205	Lys	His	Thr
Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
Pro 225	Leu	Val	Aab	Leu	Pro 230	Ile	Gly	Ile	Asn	Ile 235	Thr	Arg	Phe	Gln	Thr 240
Leu	Leu	Ala	Leu	His 245	Arg	Ser	Tyr	Leu	Thr 250	Pro	Gly	Asp	Ser	Ser 255	Ser
Gly	Trp	Thr	Ala 260	Gly	Ala	Ala	Ala	Tyr 265	Tyr	Val	Gly	Tyr	Leu 270	Gln	Pro
Arg	Thr	Phe 275	Leu	Leu	ГÀа	Tyr	Asn 280	Glu	Asn	Gly	Thr	Ile 285	Thr	Asp	Ala
Val	Asp 290	Cys	Ala	Leu	Asp	Pro 295	Leu	Ser	Glu	Thr	Lys 300	Сув	Thr	Leu	Lys
Ser 305	Phe	Thr	Val	Glu	Lys 310	Gly	Ile	Tyr	Gln	Thr 315	Ser	Asn	Phe	Arg	Val 320
Gln	Pro	Thr	Glu	Ser 325	Ile	Val	Arg	Phe	Pro 330	Asn	Ile	Thr	Asn	Leu 335	Сүз
Pro	Phe	Gly	Glu 340	Val	Phe	Asn	Ala	Thr 345	Arg	Phe	Ala	Ser	Val 350	Tyr	Ala
Trp	Asn	Arg 355	Lys	Arg	Ile	Ser	Asn 360	Cys	Val	Ala	Asp	Tyr 365	Ser	Val	Leu
Tyr	Asn 370	Ser	Ala	Ser	Phe	Ser 375	Thr	Phe	Lys	Суз	Tyr 380	Gly	Val	Ser	Pro
Thr 385	Lys	Leu	Asn	Asp	Leu 390	Суз	Phe	Thr	Asn	Val 395	Tyr	Ala	Asp	Ser	Phe 400
Val	Ile	Arg	Gly	Asp 405	Glu	Val	Arg	Gln	Ile 410	Ala	Pro	Gly	Gln	Thr 415	Gly
rÀa	Ile	Ala	Asp 420	Tyr	Asn	Tyr	Lys	Leu 425	Pro	Asp	Asp	Phe	Thr 430	Gly	Сүз
Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	ГЛа	Val 445	Gly	Gly	Asn
Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	Lys	Ser	Asn 460	Leu	Lys	Pro	Phe
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Gln	Cys	Val	Asn	Leu	Thr	Thr	Arg	Th:	r G	ln I	Leu	Pr	o Pro	o Ala	а Туз	r Thr
1		Dho	Th∼	5	G1	Val	- ₩17~	π.	1(r D-) ro 7	lar	L.e.	a 17-1	ן האם	15	n C a≁
ASU	set.	rne	20	ΨīÂ	сту	vaı	түт	1y: 25	- FJ	.0 /	чар	чγ	ວ va.	30	= Arç	y ser
Ser	Val	Leu 35	His	Ser	Thr	Gln	Asp 40	Lei	u Pł	ne I	Leu	Pr	o Pho 45	e Pho	e Sei	r Asn
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Glu 465	Arg	Asp	Ile	Ser	Thr 470	Glu	Ile	Tyr	Gln	Ala 475	Gly	Ser	Thr	Pro	Cys 480
Asn	Gly	Val	Glu	Gly 485	Phe	Asn	Суз	Tyr	Phe 490	Pro	Leu	Gln	Ser	Tyr 495	Gly
Phe	Gln	Pro	Thr 500	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val
Leu	Ser	Phe 515	Glu	Leu	Leu	His	Ala 520	Pro	Ala	Thr	Val	Cys 525	Gly	Pro	Lys
ГÀа	Ser 530	Thr	Asn	Leu	Val	Lys 535	Asn	Lys	Суз	Val	Asn 540	Phe	Asn	Phe	Asn
Gly 545	Leu	Thr	Gly	Thr	Gly 550	Val	Leu	Thr	Glu	Ser 555	Asn	ГЛа	Lys	Phe	Leu 560
Pro	Phe	Gln	Gln	Phe 565	Gly	Arg	Asp	Ile	Ala 570	Asp	Thr	Thr	Asp	Ala 575	Val
Arg	Asp	Pro	Gln 580	Thr	Leu	Glu	Ile	Leu 585	Asp	Ile	Thr	Pro	Сув 590	Ser	Phe
Gly	Gly	Val 595	Ser	Val	Ile	Thr	Pro 600	Gly	Thr	Asn	Thr	Ser 605	Asn	Gln	Val
Ala	Val 610	Leu	Tyr	Gln	Asp	Val 615	Asn	Суз	Thr	Glu	Val 620	Pro	Val	Ala	Ile
His 625	Ala	Asp	Gln	Leu	Thr 630	Pro	Thr	Trp	Arg	Val 635	Tyr	Ser	Thr	Gly	Ser 640
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Ser	Val	Thr	Thr	Glu 725	Ile	Leu	Pro	Val	Ser 730	Met	Thr	Lys	Thr	Ser 735	Val
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Gly	Ile 770	Ala	Val	Glu	Gln	Asp 775	Lys	Asn	Thr	Gln	Glu 780	Val	Phe	Ala	Gln
Val 785	Lys	Gln	Ile	Tyr	Lys 790	Thr	Pro	Pro	Ile	Lys 795	Asp	Phe	Gly	Gly	Phe 800
Asn	Phe	Ser	Gln	Ile 805	Leu	Pro	Asp	Pro	Ser 810	Lys	Pro	Ser	Lys	Arg 815	Ser
Phe	Ile	Glu	Asp 820	Leu	Leu	Phe	Asn	Lys 825	Val	Thr	Leu	Ala	Asp 830	Ala	Gly
Phe	Ile	Lys 835	Gln	Tyr	Gly	Asp	Суз 840	Leu	Gly	Asp	Ile	Ala 845	Ala	Arg	Asp

Leu Ile Cys Ala Gln Lys Phe Asn Gly Leu Thr Val Leu Pro Pro Leu 850 855 860

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Thr Ile Thr Ser Gly 885	Trp Thr Phe Gly Al	a Gly Ala Ala Leu Glr 0 895	n Ile
Pro Phe Ala Met Gln	Met Ala Tyr Arg Pr	e Asn Gly Ile Gly Val	Thr
900	905	910	
Gln Asn Val Leu Tyr	Glu Asn Gln Lys Le	u Ile Ala Asn Gln Phe	e Asn
915	920	925	
Ser Ala Ile Gly Lys	Ile Gln Asp Ser Le	u Ser Ser Thr Ala Ser	Ala
930	935	940	
Leu Gly Lys Leu Gln	Asp Val Val Asn GI	n Asn Ala Gln Ala Leu	1 Asn
945	950	955	960
Thr Leu Val Lys Gln	Leu Ser Ser Asn Ph	e Gly Ala Ile Ser Ser	val
965	97	0 975	
Leu Asn Asp Ile Leu	Ser Arg Leu Asp Ly	rs Val Glu Ala Glu Val	. Gln
980	985	990	
Ile Asp Arg Leu Ile 995	Thr Gly Arg Leu (In Ser Leu Gln Thr 1	Yr Val
Thr Gln Gln Leu Il	Arg Ala Ala Glu	Ile Arg Ala Ser Ala	Asn
Leu Ala Ala Thr Ly	Met Ser Glu Cys	Val Leu Gly Gln Ser	Lys
1025	1030	1035	Pro
Arg Val Asp Phe Cy	s Gly Lys Gly Tyr	His Leu Met Ser Phe	
1040	1045	1050	Val
Gln Ser Ala Pro Hi	s Gly Val Val Phe	Leu His Val Thr Tyr	
1055	1060	1065	
Pro Ala Gln Glu Ly	3 Asn Phe Thr Thr	Ala Pro Ala Ile Cys	His
1070	1075	1080	
Asp Gly Lys Ala Hi	9 Phe Pro Arg Glu	Gly Val Phe Val Ser	Asn
1085	1090	1095	
Gly Thr His Trp Ph	e Val Thr Gln Arg	Asn Phe Tyr Glu Pro	Gln
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Ile Ile Thr Thr As	Asn Thr Phe Val	Ser Gly Asn Cys Asp	Val
1115	1120	1125	
Val Ile Gly Ile Va	l Asn Asn Thr Val	Tyr Asp Pro Leu Gln	Pro
1130	1135	1140	
Glu Leu Asp Ser Ph	e Lys Glu Glu Leu	Asp Lys Tyr Phe Lys	Asn
1145	1150	1155	
His Thr Ser Pro As	y Val Asp Leu Gly	Asp Ile Ser Gly Ile	Asn
1160	1165	1170	
Ala Ser Val Val As:	n Ile Gln Lys Glu	Ile Asp Arg Leu Asn	Glu
1175	1180	1185	
Val Ala Lys Asn Le [.]	ı Asn Glu Ser Leu	Ile Asp Leu Gln Glu	Leu
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Gly Lys Tyr Glu Gl:	n 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	
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ser Cys Glv Ser Cv	1240 S Cys Lys Phe Asp	Glu Asp Asp Ser Glu	Pro
1250	1255	1260	

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350 360 367 Val Sam Val Sam
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App Ser Phe Val Lie App Glu App Glu App Glu App Glu App A
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Gin Thr Giy Lys lie Ala Asp Tyr Asn Tyr Lys Leu Pro Anp Asp Pre 405 Thr Giy Cys Val 11e Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val 425 Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu 445 Tyr Pro Phe Glu Arg Asp 11e Ser Thr Glu 11e Tyr Gin Ala Gly Ser 450 Thr Pro Cys Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln 465 Tyr Gly Phe Gln Pro Thr Asn Gly Val Gly Tyr Gin Pro Tyr Arg 455 Val Val Val Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys 510 Gly Pro Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe 515 545 Pro Phe Asn Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys 550 Gly Pro Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe 515 550 Gln Ala Val Arg Asg Pro Gln Gln Phe Gly Arg Asg 149 740 Ass 75 Cys Ser Phe Gly Gly Val Ser Val 11e Thr Gly Val Leu Thr Gly Kas Asn Lys 550 Gly Pro Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe 515 550 Gln Ang Ala Val Arg Asg Pro Gln Thr Leu Glu Ieu Leu Asg II Thr Thr 545 545 Cys Ser Phe Gly Gly Val Ser Val 11e Thr Pro Gly Thr Asn Thr Ser 550 Cys Ser Phe Gly Gly Val Ser Val 11e Thr Pro Gly Thr Asn Thr Ser 550 Cys Ser Phe Gly Gly Val Ser Val 11e Thr Pro Thr Trg Arg Val Tyr Ser 610 11e His Ala Asg Gln Leu Thr Gln Asp Val Asn Cys Thr Glu Val Pro 620 Cya Ala Val Asg Asg Ser Tyr Gln Asg Ala Gly Cys Leu IIe Gly Ala 625 Clu His Val Asn Asn Ser Tyr Glu Cys Asg IIe Pro IIe Gly Ala Gly 640 Glu His Val Asn Asn Ser Tyr Glu Cys Asg IIe Pro IIe Gly Ala Gly 655 Cle Val Ala Ser Tyr Gln Thr Gln Thr Asg Ala Gly Cys Leu IIe Gly Ala 640 Glu Ass Ser Val Ala Ser Tyr Gln Thr Gln Thr Asg Ass Ser Pro Gln Gln Ala Gln 655 Clu Ash Ass Asn Ass Ser Tyr Gln Thr Gln Thr Met Ser Leu Gly Ala 650 Clu Ash Ser Val Ala Tyr Ser Ash Ash Ser IIe Ala The Pro Thr Ash 655 Clu Ash Ser Val Ala Tyr Ser Ash Ash Ser IIe Ala The Pro Thr Ash 655 Clu Ash Ser Val Ala Tyr Thr Gln Glu Thr Glu Cys Tr 730 Chr Ser Val Ala Ser Val Thr Thr Glu Thr Glu Cys Tr 735 Chr Ash Leu Leu Leu Gln Tyr Gly Ser Pro Cys Thr Gln Clu Val 735 Chr Ash Leu Thr Gly IIe Ala Val Glu Gln Asp Vas Thr Gln Clu Val 7
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Area Cya Area Cya Cya </td
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Norm Pie Gas Pie Ass Gas Yes Fie Pie Ass Val Val Leu
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Val Val Leu See Phe Glu Leu His Ala Pro Ala Thr Sul Cys Sul S
G1y Fyro Lyro Lyro Lyro Lyro Lyro Cyro Val Lyro San Lyro San Phe Asn Pho Asn G1y Leu Thr G1y Cul Thr G1y Val Leu Thr G1y Cul Thr G1y Val Leu Thr G1u San Pho G1u San Luro Thr G1u Cul Thr G1u Cul Thr G1u Cul Thr San Ason Cul San Luro Thr G1u Cul Thr San Cul Thr San Ason San Luro Thr San San Cul Ason Thr San San Ason Thr Ason San San Val Ason Thr San G1u Ason Thr San San Thr San San Thr San San San Thr San San San Thr San San San Thr S
Giv Fib Jys Jys Jei III Asin Lieu Val Jys Asin Lys Sei Val Asin File Asin Phe Asin Gly Leu Thr Gly Thr Gly Val Leu Thr Gly Sei Val Asin Lys Sei Val Asin Phe Asin Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Sei Val Leu Thr Glu Sei Val Lys Sei Val Luu Thr Glu Sei Val Luu Thr Glu Sei Val Luu Thr Sei Val Luu Thr Sei Val Luu Thr Sei Sei Val Luu Asin Val Asin Val Asin Val Luu Tyr Sei Sei Val Asin Cys Thr Glu Val Thr Sei Sei Val Asin Cys Thr Glu Val Tyr Sei Sei Val Asin Cys Thr Glu Val Tyr Sei Sei Val Asin Cys Thr Glu Val Tyr Sei Sei Sei Val Asin Val Pro Sei Val Asin Cys Thr Glu Val Tyr Sei Sei Sei Val Asin Cys Thr Glu Cys Asin Cys Thr Glu Cys Asin Cys Cys Luu Ile Gly Ala Gly Giv Cie
AnnPhoAnnGlyLeuPhoGlyPhoGlySinGlyPhoGluPhoGlyPhoSinPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPhoPh
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580 580 580 580 580 590 590 11 Asn Gln Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile His Ala Asp Gln Leu Thr Pro Thr Thr Arg Val Tyr Ser Thr Gly Ser Asn Val Asp Gln Thr Arg Ala Gly Val Tyr Ser Gly Ser Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Gly A
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Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe 770 775 780
FileFi

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Thr Ala Ser Phe Tyr	Tyr Asn 1010 Lys 1025 Pro 1040 Val 1055	Val 995 Leu Arg Glr Pro	Thr Ala Val Ser	Gln Ala Asp Asp Ala Gln	Gln Thr Phe Prc Glu	Leu Ly: 101 Cy: Cy: 103 Hi: 104 Ly: 106	Ile 1000 8 Me 5 80 80 80 80 80 80 80 80 80 80 80	Arq Arq Ex Se Ly Ly Ly Va	g Ala er G] /S G] al Va ne Th	a Ala Lu Cy Ly Ty al Ph nr Th	a Glu 75 Va 10 77 H: 10 ne La 10 nr A: 10	1 II 10 20 15 20 15 20 20 20 20 20 20 20 20 20 20	e A 05 Leu Leu His	rg A Gly Met Val Ala	la Ser Gln Ser Thr Ile
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Thr Ala Ser Phe Tyr Cys Ser	Tyr Asn 1010 Lys 1025 Pro 1040 Val 1055 His 1070 Asn 1085	Val 995 Lev Arc Glr Prc Asp Gly	Thr Als Val Ser Als Gly Thr	Gln Ala Asp Ala Gln Zura Lys This	Gln 1 Thr 1 Prc 1 Glu 3 Ala 3 Trp	Leu Leu 101 2 Cys 103 0 His 104 104 104 105 107 107 105 105 105 105 105 105 105 105	Ile 1000 3 Me 5 3 G: 3 G: 3 G: 3 G: 3 As 60 9 Pt 75 Va 00	Arq) ly Ly Ly Va bn Ph ne Ph ne Ph	g Alá er Gl vs Gl al Va al Va ne Th co An	a Ala Lu Cy Ly Ty al Př Dr Tř Crg Gl	vs Va lo vr H: lo lo lo lo lo lo lo lo lo lo lo lo lo	1 II 100 100 100 100 100 100 100 1	e A 05 Leu Leu His Pro Val	rg A Gly Met Val Ala Phe Tyr	la Ser Gln Ser Thr Ile Val Glu
Thr Ala Ser Phe Tyr Cys Ser Pro	Tyr Asn 1010 Lys 1025 Pro 1040 Val 1055 His 1070 Asn 1085 Gln 1100	Val 995 Lev Glr Prc Asp Gly Ile	Thr Thr Val Val Ser Ala Gly Thr E	Gln Ala Asp Asp Ala Gln Uys Clys Clys This Thr	Gln Thr Phe Glu Glu Ala Trp Trp	Leu Lys 103 2 Cys 103 2 Cys 104 104 104 104 106 107 2 Asp 110	Ile 1000 3 Me 5 3 G 3 G 3 G 3 G 3 G 4 5 6 0 5 9 0 0 0 0 0 0 0 0 0 0 0 0 0	Arg P Ly Ly Ly Va Son PP Po P Al Th Son Th	g Ala er G vs G al Va al Va co An r G nr G	a Ala lu Cy ly Ty al PH rr TH rg Gl ln An ne Va	a Glu 75 V2 10 77 H: 10 10 10 10 10 10 10 10 10 10 10 10 10	1 II. 100 1020 105 1035 1	e A 05 Leu His Pro Val Phe Gly	rg A Gly Met Val Ala Phe Tyr Asn	la Ser Gln Ser Thr Ile Val Glu Cys
Thr Ala Ser Phe Tyr Cys Ser Pro Asp	Tyr Asn 1010 Lys Pro 1040 Val 1055 His 1070 Asn 1085 Gln 1100 Val 1115	Val 995 Lev Glr Prc Gly Gly Ile Val	Thr Als Val Ser Als Als Gly Thr Thr Ile	Gln A Ala Asp Asp Ala Gln Uys This This Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala	Gln 1 Thr 9 Phe 1 Prc 1 Glu 1 Glu 2 Ala 2 Trp 7 Thr 7 Ile	Leu Ly: Ly: Cy: 103 104 104 104 104 104 106 107 Phe 107 208 107 107 107 107 107 107 107 107	Ile 1000 3 Me 5 3 GI 5 GI 5 GI 5 As 60 5 Pl 75 60 0 As 60 0 As 60 0 0 As 60 0 As 60 0 As 60 0 As 60 0 As 60 0 As 60 0 0 0 0 0 0 0 0 0 0 0 0 0	Arg P P Arg S S S S S S S S S S S S S	g Ala er G Vs G Al Va Al Va Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va	a Ala lu Cy ly Ty al Ph nr Th cg GJ ln An ne Va	A Glu VS Va 10 VT H: 10 10 10 10 10 10 10 10 10 10	1 11 10 al 1020 is 035 eu 050 la 065 ly 080 sn 100 95 er 110 77 .25	e A 05 Leu Leu His Pro Val Phe Gly Asp	rg A Gly Met Val Ala Tyr Tyr Asn Pro	la Ser Gln Ser Thr Ile Val Glu Cys Leu
Thr Ala Ser Phe Tyr Cys Ser Pro Asp Gln	Tyr Asn 1025 Pro 1040 Val 1055 His 1070 Asn 1070 Asn 1100 Val 1115 Pro 1130	Val 995 Lev Glr Pro Glr Gly Ile Val	Thr Thr Ala Val Ser Ala Ala Ala Ala Ile Lev	Gln A Ala A Asp A Gln A Gln 7 Lys F His F His S Thr A Sp A Asp	Gln Thr Phe Glu Glu Glu Glu Glu Glu Glu Glu	Leu Leu 101 Cys 103 Cys 104 104 104 106 106 107 Phe 107 107 207 107 207 107 207 107 207 107 207 107 207 107 207 107 207 107 207 107 107 107 107 107 107 107 1	Ile 1000 3 Ma 5 3 G: 5 3 G: 5 4 5 5 5 60 5 60 60 60 60 60 60 60 60 60 60	Arg P P Arg Ly Ly Ly Ly Ly Va an PP P P P P P P P P P P P P	g Ala er Gl vs Gl al Va al Va al Va al Va al Va br Fr Hu Gl Lu Gl	a Ala lu Cy ly Ty al PH ar Th ar Tha	a Glu 10 77 H: 10 10 10 10 10 10 10 10 10 10 10 10 10	1 II. 10 10 10 10 10 10 10 10 10 10	e A 05 Leu Leu His Pro Val Phe Gly Asp Lys	rg A Gly Met Val Ala Phe Tyr Asn Pro Tyr	la Ser Gln Ser Thr Ile Val Glu Cys Leu Phe
Thr Ala Ser Phe Tyr Cys Ser Pro Asp Gln Lys	Tyr Asn 1025 1025 Pro Val 1040 Val 1085 Gln 1100 Val 1115 Pro 1130 Asn 1145	Val 995 Lev Glr Pro Glr Gly Ile Val	Thr Thr Als Val Ser Als Als Als Als Thr Thr Thr Thr Thr Thr Thr Thr	Gln Ala Asp Ala Gln Gln Gln Gln Gln Gln Scr Scr Scr Scr	Gln Thr Phe Pro Glu Glu Ala Trp Trp Ser Pro	Leu Leu 101 2 Cys 103 104 104 104 105 2 Asp 110 2 Phe 113 2 Phe 113 3 Asp 115	Ile 1000 3 Me 5 S 3 G 3 G 4 S 4 S 5 Me 5 Me 6 Me 6 Me 6 Me 6 Me 7 S 1 Ae 1	Arg o ly Ly Ly Ly Va sn Pf ne Pf ne Pf ne Pf ne Ff Sn As	g Ala er G Vs G Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va Al Va G I Va G I Vs G I Vs G Vs G I Vs G I Vs G Vs G Vs G Vs G Vs G Vs G Vs G Vs G	a Ala lu Cy ly Ty al PP nr TP cg GJ ln An ne Va nr Va lu Le su GJ	a Glu 75 Vi 10 77 H: 10 10 10 10 10 10 10 10 10 10 11 11 11	al 10 al 10 220 is 50 50 10 10 50 50 50 50 50 50 50 50 50 5	e A 05 Leu Leu His Pro Val Phe Gly Lys Lys	rg A Gly Met Val Ala Phe Tyr Asn Pro Tyr Ser	la Ser Gln Ser Thr Ile Val Glu Cys Leu Phe Gly
Thr Ala Ser Phe Tyr Cys Ser Pro Asp Gln Lys Ile	Tyr Asn 1025 Pro 1040 Val 1055 His 1070 Asn 1100 Val 1115 Pro 1130 Asn 1145 Asn 1145	Val 995 Lev Glr Pro Glr Gly Gly Ual Glv His Als	Thr Thr Ala Val Ser Ala Ala Ala Ala Ile Lev Lev Thr Ser Ser	Gln A Ala A Asp A Gln A Gln 7 Lys C His A Gly A Asp C Ser C Val	Gln Thr Phe Pro Glu Glu Glu Glu Glu Score	Leu Leu Cys 103 Cys 104 Lys 106 Lys 106 105 C Asp 110 C Asp 112 C Phe 113 C Asp 115 L Asp 116	Ile 1000 3 Me 5 G 3 G 3 G 3 Ar 5 P 7 S 8 V 6 0 0 Ar 6 0 1 Ar 6 0 1 Ar 6 0 1 Ar 6 0 1 S 5 T 1 S	Arg P P Arg Ly Ly Ly V P P P P P P P P P P P P P	g Ala er G ys G al Va ne Th co An nr G nr Ph th G th G th L u G ln Ly	a Ala lu Cy ly Ty al PP nr TP rg GJ ln An ne Va cg GJ lu Le eu GJ ys GJ	A GIU 75 V2 10 77 H: 10 10 10 10 10 10 10 10 10 10 10 10 10	1 II. 10 10 10 10 10 10 10 10 10 10	e A 05 Leu Leu His Pro Val Phe Gly Lys Lys Ile	rg A Gly Met Val Ala Phe Tyr Asn Pro Tyr Ser Arg	la Ser Gln Ser Thr Ile Val Glu Cys Leu Phe Gly Leu

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Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
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Gln	Pro	Thr	Glu	Ser 325	Ile	Val	Arg	Phe	Pro 330	Asn	Ile	Thr	Asn	Leu 335	Сув
Pro	Phe	Gly	Glu 340	Val	Phe	Asn	Ala	Thr 345	Arg	Phe	Ala	Ser	Val 350	Tyr	Ala
Trp	Asn	Arg 355	Lys	Arg	Ile	Ser	Asn 360	Сүз	Val	Ala	Asp	Tyr 365	Ser	Val	Leu
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Val	Ile	Arg	Gly	Asp 405	Glu	Val	Arg	Gln	Ile 410	Ala	Pro	Gly	Gln	Thr 415	Gly
Lug	Tle	Ala	Asn	Tur	Agn	Tvr	Ivs	Leu	Pro	Asn	Asn	Phe	Thr	Glv	Cvs

Val 11e Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn $\frac{435}{450}$ Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe $\frac{450}{450}$ Glu Arg Asp Ile Ser Thr Glu 11e Tyr Gln Ala Gly Ser Thr Pro Cys $\frac{400}{475}$ Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly $\frac{400}{495}$ Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val Val $\frac{550}{520}$ Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys $\frac{550}{520}$ Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn $\frac{540}{540}$ Pro Phe Gln Gln Pho Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val $\frac{550}{540}$ Pro Phe Gln Gln Pho Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val $\frac{550}{540}$ Asg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe $\frac{585}{540}$ Gly Leu Thr Gly Thr Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val $\frac{575}{570}$ Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe $\frac{560}{540}$ Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val $\frac{615}{630}$ Asg Asp Gln Leu Thr Gln Asp Val Ash Cys Thr Glu Val Pro Val Ala Ile $\frac{610}{610}$ Asg Asp Gln Leu Thr Pro Thr Trp Arg Val Tyr Ser Thr Gly Ser $\frac{635}{540}$ Asg Asp Gln Leu Thr Asg Ala Gly Cys Leu Ile Gly Ala Glu His Val $\frac{645}{640}$ Asg Na Gln Thr Gln Thr Asg Ala Gly Cys Leu Ile Gly Ala Glu His Val $\frac{645}{640}$ Asg Na Ser Tyr Gln Thr Asg Ala Gly Cys Leu Ile Gly Ala Glu His Val $\frac{645}{640}$ Asg Asg Ser Ile Ile Ala Tyr Thr Met Ser Leu Gly Ala Glu Asg Ser $\frac{7}{700}$ Asg Cys Thr Met Tyr Ile Cys Gly Asg Ser Thr Glu Cys Ser Asg Lue Trr $\frac{7}{700}$ Asg Cys Thr Met Tyr Ile Cys Gly Asg Ser Thr Glu Cys Ser Asg Leu Trr $\frac{7}{760}$ Cly 11e Ala Val Glu Glu Gln Asg Lys Asg The Glu Glu Cys Asg The $\frac{640}{745}$ Cly 11e Ala Val Glu Glu Asg Fyr Ser Thr Glu Cys Asg The $\frac{7}{760}$ Cly Thr Asg Val Glu Glu Gln Asg Lys Asg The Glu Glu Glu Asg Arg Ala Arg Asg Cys Thr Met Tyr Ile Cys Gly Asg Ser Thr Glu Cys Ser Asg Leu Trr $\frac{7}{760}$ Cly Thr Met Tyr Try Gly Ser Phe Cys Thr Glu Cys Asg Asg Leu Thr $\frac{7}{760$				420					425					430		
Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe 455 (1) Arg Asp IIe Ser Thr Glu IIe Tyr Gln Ala Gly Ser Thr Pro Cys 466 (2) (2) (2) (2) (2) (2) (2) (2) (2) (2)	Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	Гла	Val 445	Gly	Gly	Asn
Glu Arg Asp Ie Ser Thr Glu Ie Tyr Gln Ala Gly Ser Thr Pro Cys Aso Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly 485 Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val 500 Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys 515 Clys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn 530 Gly Leu Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu 545 Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe 590 Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val 600 Fro Phe Gln Gln Asp Val Ieu Thr Gly Thr Asn Thr Ser Asn Gln Val 595 Gly Gly Val Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val 600 Asn Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala I field Asp Gln Leu Thr Pro Thr Thr Asp Ala Val 610 Asn Val Phe Gln Thr Leu Glu Ie Leu Asp IIe Gly Ala Glu His Val 625 Asn Asn Ser Tyr Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile 630 Asn Val Phe Gln Thr Asg Ala Gly Cys Leu Ile Gly Ala Glu His Val 645 Asn Asn Ser Tyr Glu Cys Asp Ile Pro Thr Arg Arg Ala Arg Ser Val Ala 665 Ser Gln Ser Ile Ile Ala Tyr Thr Me Ser Leu Gly Ala Gly His Cys Ala 675 Asn Asn Ser Tyr Glu Thr Asn Ser Pro Arg Arg Ala Arg Ser Val Ala 665 Ser Gln Ser Ile Ile Ala Tyr Thr Me Ser Leu Gly Ala Gly Asn Ser 710 Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Fr Asn Lue 720 Ser Val Thr Thr Glu Thr Cys Ile Ala Cys Thr Glu Cys Fr Asn Lue 720 Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Ser Asn Leu 720 Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Asp Ala Leu Thr 725 Cly Ile Ala Val Glu Gln Asp Ser Tro Gln Cys Thr Glu Cys Fr Asn Leu 726 Asp Cys Thr Met Tyr Ile Cys Gly Asp Ser Thr Glu Cys Asp Ala Leu Thr 725 Cly Ile Ala Val Glu Gln Asp Cys Thr Gln Glu Cys Asp Ala Cys Thr Glu Cys Asp Ala Leu Thr 726 Cly Ile Ala Val Glu Gln Asp Ser Tro Gln Glu Asp Arg Ala Leu Thr 726 Cly Ile Ala Val Glu Gln Asp Cys Thr Gln Glu Cys Fr Asn Leu 726 Cly Ile Ala Val Glu Gln Asp Cys Thr Gln Glu Cys Asp Thr Chn Gln Cys Fr Asp Ala Leu Thr 726 Cly Thr Chn Thr Glu Gln Asp Cys Thr Gln Gl	Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	Lys	Ser	Asn 460	Leu	Lys	Pro	Phe
Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly 495Cyr 495Cyr 495<	Glu 465	Arg	Asp	Ile	Ser	Thr 470	Glu	Ile	Tyr	Gln	Ala 475	Gly	Ser	Thr	Pro	Cys 480
Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val Val Val Val Soo Phe Glu Pro Tyr Arg Val Val Val Val Val Soo Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys 530 Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn 530 Thr Gly Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu 565 Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Thr Asp Ala Val Son Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Asp Ile Thr Pro Cys Ser Phe 580 Thr Son Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val 610 Phe 610 Ang Pro Son Pro Gly Thr Asp Val Asp Thr Asp Ala Val 555 Arg Asp Pro Gln Thr Leu Glu Ile Leu Asp Asp Ile Thr Pro Cys Ser Phe 580 Thr Son Son Chr Thr Pro Gly Thr Asn Thr Ser Asn Gln Val 610 Phe 610 Ang Pro Gln Asp Val Asn Cys Thr Glu Val Pro Val Ala Ile 610 Phe 610 For Phe 610 Ang Pro Thr Thr Pro Gly Thr Asn Thr Ser Asn Gln Val 610 For 580 Pro Gln Thr Leu Glu Ile Leu Asp Asp Ile Thr Pro Cys Ser Phe 580 Ang Asp Pro Gln Thr Leu Glu Asp Cys Thr Glu Val Pro Val Ala Ile 610 Pro Thr Try Arg Val Tyr Ser Thr Gly Ser 640 Asp Val Asp Cys Thr Glu Cys Asp Ile Pro Ile Gly Ala Glu His Val 645 Pro Gln Thr Asp Ala Cys Ile 700 Pro Val Ala Ile 655 Asp Asn Asn Ser Tyr Glu Cys Asp Ile Pro Arg Arg Ala Arg Ser Val Ala Ser 660 Pro For Core 700 Pro	Asn	Gly	Val	Glu	Gly 485	Phe	Asn	Суз	Tyr	Phe 490	Pro	Leu	Gln	Ser	Tyr 495	Gly
Leu Ser Phe Glu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Asn Phe Asn Phe Asn Phe Asn Phe Asn Fas Leu Thr Gly Val Leu Thr Gly Leu Thr Gly Val Leu Thr Glu Thr Gly Val Leu Thr Glu Thr Gly Asn Phe Asn Phe Asn Phe Ser Phe Leu Ser Phe Ser Phe Ser Phe Ser Phe Ser Phe Leu Ser Phe Glu Val Asn Phe Ser	Phe	Gln	Pro	Thr 500	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val
Lys Ser Thr Asn Leu Val Lys Asn Lys Cys Val Asn Phe Glu Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu For Phe Gln Glu Thr Gly Asp Asp For Gln Glu For Ser Gln Thr Leu Glu Ile Leu Asp Thr Thr Asp	Leu	Ser	Phe 515	Glu	Leu	Leu	His	Ala 520	Pro	Ala	Thr	Val	Cys 525	Gly	Pro	Lys
Gly Leu Thr Gly Val Leu Thr Glu Ser Asn Lys Lys Phe Leu Pro Phe Gln Gln Phe Gly Arg Asp Ile Ala Asp Thr Asp Asp Pro Gln Thr Leu Glu Ile Leu Asp Ile Thr Pro Cys Ser Phe Gly Gly Val Ser Val Ile Thr Pro Cys Ser Phe Gln Val Phe Gln Na Phe Gln Asp Sar Cros Thr Phr Phr Sar Gln Sar Sar Gln Asp Sar Gln Asp Sar Sar Sar S	Lys	Ser 530	Thr	Asn	Leu	Val	Lys 535	Asn	Гла	Суз	Val	Asn 540	Phe	Asn	Phe	Asn
Pro Phe Gln Gln Phe Gln Phe Gln Phe Gln Thr Leu Glu Ile Leu Glu Ile Leu Glu Ile Leu Glu Thr Asp Pro Ser Phe Gly Gly Val Ser Val Ile Thr Pro Glu Thr Ser Pro Ser Ser Ser Pro Ser Ser Ser Pro Ser Ser Ser Pro Ser Ser Ser Ser Pro Ser	Gly 545	Leu	Thr	Gly	Thr	Gly 550	Val	Leu	Thr	Glu	Ser 555	Asn	ГЛа	Lys	Phe	Leu 560
Arg Asp Pro Gln Thr Leu Glu Ile Asp Ile Thr Asp Sec Asp Ile Thr Asp Glo Gly Thr Sec Asp Ile Thr Pro Gly Thr Sec Asp Glo Gly Thr Asp Sec Asp Glo Sec Thr Glo Thr Sec Thr Glo Thr Sec Thr Glo Thr Sec Thr Glo Thr Glo Sec Thr Glo Glo Thr Asp Asp Glo Clo Sec Glo Glo Thr Asp Sec Glo Glo Glo Thr Glo Sec Glo Glo Glo Thr Glo Glo Glo Sec G	Pro	Phe	Gln	Gln	Phe 565	Gly	Arg	Asp	Ile	Ala 570	Asp	Thr	Thr	Asp	Ala 575	Val
Gly Gly Yal Ser Val Ile Thr Pro Gly Thr Asn Thr Ser Asn Gln Val Ala Val Leu Tyr Gln Asp Val Asn Cys Thr Glu Val Asn Ile His Ala Asp Gln Leu Thr Pro Thr Try Aga Val Fro Val Ala Ile Asn Ala Asp Gln Leu Thr Pro Thr Try Arga Gln Asp Fro Thr Arga Gln Cys Leu Fro Gln Gln Ser Gln Asp Asp Asp Gln Thr Asp Asp Gln Thr Asp Gln Cys Asp Ile Gln Gln Cys Asp Ile Gln Fro Gln Gln Asp Fro Gln Gln Cys Asp Gln Asp Cys Asp Gln Asp <td< td=""><td>Arg</td><td>Asp</td><td>Pro</td><td>Gln 580</td><td>Thr</td><td>Leu</td><td>Glu</td><td>Ile</td><td>Leu 585</td><td>Asp</td><td>Ile</td><td>Thr</td><td>Pro</td><td>Cys 590</td><td>Ser</td><td>Phe</td></td<>	Arg	Asp	Pro	Gln 580	Thr	Leu	Glu	Ile	Leu 585	Asp	Ile	Thr	Pro	Cys 590	Ser	Phe
Ala Val Leu Tyr Gln Asp Asp Gln Leu Thr Trop Arg Val Trop Gln Ser Trop Trop Arg Val Trop Gln Ser Trop Trop Arg Val Trop Ser Trop Gln Trop Asp Asp Ser Trop Gln Trop Asp Ser Trop Gln Trop Asp Ser Gln Ser Asp Ser Trop Gln Trop Asp Ser Trop Ser Gln Ser Trop Ser Gln Ser Trop Ser Asp Ser Ser Gln Trop Ser Se	Gly	Gly	Val 595	Ser	Val	Ile	Thr	Pro 600	Gly	Thr	Asn	Thr	Ser 605	Asn	Gln	Val
His Ala Asp Gln Leu Thr Gln Thr Thr Arg Als Gln Gln Thr Ala Gln Cus Gln Gln Thr Arg Ala Gln Cus Far Gln Gln Thr Ala Gln Cus Far Gln Gln Far Ala Gln Cus Far Far Gln Gln Far Ala Gln Cus Far Far Gln Gln Far Ala Gln Far F	Ala	Val 610	Leu	Tyr	Gln	Asp	Val 615	Asn	Суз	Thr	Glu	Val 620	Pro	Val	Ala	Ile
AsnValPheGlnThr G45ArgAlaGlyCysLeu G50IleGlyAlaGluHisValAsnAsnSerTyr G60GluCysAspI.ePro G65I.eGlyAlaGlyI.gCysAlaSerTyr G90GlnThrGlnThrAsnSer G80ProArgAlaArg ArgArgArgArgAlaAlaSerGln G90SerI.eAlaTyrAlaTyrAlaTyrAlaArg G95SerValAlaVal 705AlaTyrSerAsnAsnSer AsnThrMetSerLeuGluAsnSerVal 705AlaTyrSerAsnAsnAsnSerI.eAlaI.eNoSerVal 705AlaTyrSerAsnAsnAsnSerI.eAlaI.eNoSerI.eSerI.eNoSerI.eI.eI.eI.eI.eNoSerI.eI.eI.eI.eI.eI.eI.eSerI.e<	His 625	Ala	Asp	Gln	Leu	Thr 630	Pro	Thr	Trp	Arg	Val 635	Tyr	Ser	Thr	Gly	Ser 640
AsnAsnSerTyrGluCysAspIleProIleGlyAlaGlyIleCysAlaSerTyrGlnThrGlnThrAsnSerProArgAlaArgArgSerValAlaSerGlnSerIleAlaTyrThrAsnSerProArgAlaArgSerValAlaSerGlnSerIleIleAlaTyrThrMetSerLeuGlyAlaGluAsnSerValAlaTyrSerAsnAsnSerIleAlaTyrThrMetSerLeuGlyAlaAsnSerValYalAlaTyrSerAsnAsnSerIleAlaSerIleAsnSerIleSerIleTr <td>Asn</td> <td>Val</td> <td>Phe</td> <td>Gln</td> <td>Thr 645</td> <td>Arg</td> <td>Ala</td> <td>Gly</td> <td>Суз</td> <td>Leu 650</td> <td>Ile</td> <td>Gly</td> <td>Ala</td> <td>Glu</td> <td>His 655</td> <td>Val</td>	Asn	Val	Phe	Gln	Thr 645	Arg	Ala	Gly	Суз	Leu 650	Ile	Gly	Ala	Glu	His 655	Val
SerTyrGlnThrGlnThrAsnSerArgArgArgArgArgSerValAlaSerGlnSerIIeIIeAlaTyrThrMetSerLeuGlyAlaGluAsnSerValAlaTyrSerAsnAsnSerIIeAlaIIeAlaIIeProThrAsnSerValAlaTyrSerAsnAsnSerIIeAlaIIeProThrAsnPheThrIIeValAlaTyrSerAsnAsnSerIIeAlaIIeProThrAsnPheThrIIeSerValThrThrGluIIeLeuProValSerMetThrAsnPheThrIIeSerValThrThrGluIIeCysGlyAspSerThrGluCysSerAsnIeuThrAspCysThrMetTyrIIeCysGlyAspSerThrGluCysSerAsnIeuThrAspCysThrMetTyrIIeCysGlyAspSerThrGluCysSerAsnIeuThrLeuLeuGlnTyrGlySerPheCysThrGlnCysSerAsnAspAsiIeu </td <td>Asn</td> <td>Asn</td> <td>Ser</td> <td>Tyr 660</td> <td>Glu</td> <td>Суз</td> <td>Asp</td> <td>Ile</td> <td>Pro 665</td> <td>Ile</td> <td>Gly</td> <td>Ala</td> <td>Gly</td> <td>Ile 670</td> <td>Суз</td> <td>Ala</td>	Asn	Asn	Ser	Tyr 660	Glu	Суз	Asp	Ile	Pro 665	Ile	Gly	Ala	Gly	Ile 670	Суз	Ala
SerGlnSerIleIleAlaTyrThrMetSerLeuGlyAlaGluAsnSerValAlaTyrSerAsnAsnSerIleAlaIleProThrAsnPheThrIle705AlaTyrSerAsnAsnSerIleAlaIleProThrAsnPheThrIleSerValThrThrGluIleLeuProValSerAsnSerThrLysThrSerValAspCysThrMetTyrIleCysGlyAspSerThrGluCysSerAsnLeuLeuLeuGlnTyrGlySerPheCysThrGlnGluValPheAlaLeuGlyIleAlaValGluGluAspLysAsnThrGluValPheAlaGluToTheAlaValGluGluAspLysAsnThrGluAspAspSerThrAlaAlaLeuThrGlyIleAlaValGluGluAspLysAsnThrGluNaAlaAlaAlaToTheTheTheTheTheTheTheTheTheTheTheTheLeuLeuTheThe <td< td=""><td>Ser</td><td>Tyr</td><td>Gln 675</td><td>Thr</td><td>Gln</td><td>Thr</td><td>Asn</td><td>Ser 680</td><td>Pro</td><td>Arg</td><td>Arg</td><td>Ala</td><td>Arg 685</td><td>Ser</td><td>Val</td><td>Ala</td></td<>	Ser	Tyr	Gln 675	Thr	Gln	Thr	Asn	Ser 680	Pro	Arg	Arg	Ala	Arg 685	Ser	Val	Ala
ValAlaTyrSerAsnSerIleAlaIleProThrProThrAsnPheThrPleThrSerValThrThrGluIleLeuProValSerMetThrLysThrSerValAspCysThrMetTyrIleCysGlyAspSerThrGluCysSerAspSerAspCysSerAspSerAspCysSerAspSerAspCysSerAspSerAspSerAspSerThrGluCysSerAspAspAspAspAspAspSerAspSerAsp	Ser	Gln 690	Ser	Ile	Ile	Ala	Tyr 695	Thr	Met	Ser	Leu	Gly 700	Ala	Glu	Asn	Ser
Ser ValThrGluIleLeuProValSerMetThrLysThrSerValAspCysThrMetTyrIleCysGlyAspSerThrGluCysSerAsnLeuLeuLeuGlnTyrGlySerPheCysThrGlnLeuAsnArgAlaLeuThrGlyIleAlaValGluGlnAspLysAsnThrGlnGluValPheAlaGlnGlyIleAlaValGluGlnAspLysAsnThrGlnGluValPheAlaGlnTroTroNaNaSerNaNaThrGlnGluValPheAlaGlnTroTroNaNaSerNaTroSerNaThrSerNaNaNaTroNaNaSerNaNaNaThrSerNaNaNaNaNaTroNa <td>Val 705</td> <td>Ala</td> <td>Tyr</td> <td>Ser</td> <td>Asn</td> <td>Asn 710</td> <td>Ser</td> <td>Ile</td> <td>Ala</td> <td>Ile</td> <td>Pro 715</td> <td>Thr</td> <td>Asn</td> <td>Phe</td> <td>Thr</td> <td>Ile 720</td>	Val 705	Ala	Tyr	Ser	Asn	Asn 710	Ser	Ile	Ala	Ile	Pro 715	Thr	Asn	Phe	Thr	Ile 720
AspCysThrMetTyrIleCysGlyAspSerThrGluCysSerAsnLeuLeuGlnTyrGlySerPheCysThrGlnLeuAsnArgAlaLeuThrCluLeuGlnTyrGlySerPheCysThrGlnLeuAsnArgAlaLeuThrGlyIleAlaValGluGlnAspLysAsnThrGlnGluValPheAlaGln770770775775775780780780780780765	Ser	Val	Thr	Thr	Glu 725	Ile	Leu	Pro	Val	Ser 730	Met	Thr	ГЛа	Thr	Ser 735	Val
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	Asp	Суа	Thr	Met 740	Tyr	Ile	Суз	Gly	Asp 745	Ser	Thr	Glu	Суа	Ser 750	Asn	Leu
Gly Ile Ala Val Glu Gln Asp Lys Asn Thr Gln Glu Val Phe Ala Gln 770 775 780	Leu	Leu	Gln 755	Tyr	Gly	Ser	Phe	Cys 760	Thr	Gln	Leu	Asn	Arg 765	Ala	Leu	Thr
	Gly	Ile 770	Ala	Val	Glu	Gln	Asp 775	Lys	Asn	Thr	Gln	Glu 780	Val	Phe	Ala	Gln
Val Lys Gln Ile Tyr Lys Thr Pro Pro Ile Lys Asp Phe Gly Gly Phe 785 790 795 800	Val 785	Lys	Gln	Ile	Tyr	Lys 790	Thr	Pro	Pro	Ile	Lys 795	Asp	Phe	Gly	Gly	Phe 800
Asn Phe Ser Gln Ile Leu Pro Asp Pro Ser Lys Pro Ser Lys Arg Ser 805 810 815	Asn	Phe	Ser	Gln	Ile 805	Leu	Pro	Asp	Pro	Ser 810	Lys	Pro	Ser	Lys	Arg 815	Ser
Phe Ile Glu Asp Leu Leu Phe Asn Lys Val Thr Leu Ala Asp Ala Gly	Phe	Ile	Glu	Asp 820	Leu	Leu	Phe	Asn	Lys 825	Val	Thr	Leu	Ala	Aab	Ala	Gly
Phe Ile Lys Gln Tyr Gly Asp Cys Leu Gly Asp Ile Ala Ala Arg Asp	Phe	Ile	Lys	Gln	Tyr	Gly	Asp	Cys	Leu	Gly	Asp	Ile	Ala	Ala	Arg	Asp

Leu	Ile 850	Cya	Ala	Gln	Lys	Phe 855	Asn	Gly	Leu	Thr	Val 860	Leu	Pro	Pro) Leu
Leu 865	Thr	Asp	Glu	Met	Ile 870	Ala	Gln	Tyr	Thr	Ser 875	Ala	Leu	Leu	Ala	Gly 880
Thr	Ile	Thr	Ser	Gly 885	Trp	Thr	Phe	Gly	Ala 890	Gly	Ala	Ala	Leu	Glr 895	ı Ile
Pro	Phe	Ala	Met 900	Gln	Met	Ala	Tyr	Arg 905	Phe	Asn	Gly	Ile	Gly 910	Val	. Thr
Gln	Asn	Val 915	Leu	Tyr	Glu	Asn	Gln 920	Lys	Leu	Ile	Ala	Asn 925	Gln	Phe	e Asn
Ser	Ala 930	Ile	Gly	rÀa	Ile	Gln 935	Asp	Ser	Leu	Ser	Ser 940	Thr	Ala	Ser	Ala
Leu 945	Gly	Lys	Leu	Gln	Asp 950	Val	Val	Asn	Gln	Asn 955	Ala	Gln	Ala	Leu	Asn 960
Thr	Leu	Val	Lys	Gln 965	Leu	Ser	Ser	Asn	Phe 970	Gly	Ala	Ile	Ser	Ser 975	Val
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Ile	Asp	Arg 995	Leu	Ile	Thr	Gly	Arg 1000	Lei	ı Glr	n Sei	r Le	u Gl 10	n T 05	hr 1	Yr Val
Thr	Gln 1010	Gln	Leu	lle	Arg	Ala 101	1 A] .5	la Gi	lu Il	le Ai	rg A 1	la 020	Ser	Ala	Asn
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Arg	Val 1040	Asp	Phe	суа	Gly	Цуз 104	9 G] 5	Ly Ty	yr Hi	is Le	eu M 1	et 050	Ser	Phe	Pro
Gln	Ser 1055	Ala	Pro	His	Gly	Val 106	. Va 0	al Pł	ne Le	eu Hi	ls V 1	al 065	Thr	Tyr	Val
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Glu	Leu 1145	Asp	Ser	Phe	Lys	Glu 115	ι G] 50	lu Le	eu As	ар ГЛ	/s T 1	yr 155	Phe	Lys	Asn
His	Thr 1160	Ser	Pro	Asp	Val	Asp 116) Le	eu G	ly As	ab I]	le S 1	er 170	Gly	Ile	Asn
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Val	Ala 1190	Lya	Asn	. Leu	. Asn	Glu 119	ıS∉ 95	er Le	∋u Il	le As	эр L 1	eu 200	Gln	Glu	Leu
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Leu	Cvs	Cvs	Met	Thr	Ser	Cve	: ('t	zs Se	∍r ('n	zs Le	-11 T.	vs	Glv	Cvs	Cvs

CysCysMetThrSerCysCysLeuLysGlyCysCys123512401245

-continued

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aaggtettee gttetteagt getgeactea acteaggaee tgtteetgee ettettetee 180
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aacccagtgc tgcctttcaa cgacggtgtc tacttcgctt caaccgagaa gtccaacatc 300
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89

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<400> SEOUENCE: 38

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Val	Thr 50	Trp	Phe	His	Ala	Ile 55	His	Val	Ser	Gly	Thr 60	Asn	Gly	Thr	Lys
Arg 65	Phe	Asp	Asn	Pro	Val 70	Leu	Pro	Phe	Asn	Asp 75	Gly	Val	Tyr	Phe	Ala 80
Ser	Thr	Glu	Lys	Ser 85	Asn	Ile	Ile	Arg	Gly 90	Trp	Ile	Phe	Gly	Thr 95	Thr
Leu	Asp	Ser	Lys 100	Thr	Gln	Ser	Leu	Leu 105	Ile	Val	Asn	Asn	Ala 110	Thr	Asn
Val	Val	Ile 115	Lys	Val	Cys	Glu	Phe 120	Gln	Phe	Суз	Asn	Asp 125	Pro	Phe	Leu
Gly	Val 130	Tyr	Tyr	His	rÀa	Asn 135	Asn	Lys	Ser	Trp	Met 140	Glu	Ser	Glu	Phe
Arg 145	Val	Tyr	Ser	Ser	Ala 150	Asn	Asn	Сув	Thr	Phe 155	Glu	Tyr	Val	Ser	Gln 160
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Arg	Glu	Phe	Val 180	Phe	Lys	Asn	Ile	Asp 185	Gly	Tyr	Phe	ГÀа	Ile 190	Tyr	Ser
Lys	His	Thr 195	Pro	Ile	Asn	Leu	Val 200	Arg	Asp	Leu	Pro	Gln 205	Gly	Phe	Ser
Ala	Leu 210	Glu	Pro	Leu	Val	Asp 215	Leu	Pro	Ile	Gly	Ile 220	Asn	Ile	Thr	Arg
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Ser	Ser	Ser	Gly	Trp 245	Thr	Ala	Gly	Ala	Ala 250	Ala	Tyr	Tyr	Val	Gly 255	Tyr
Leu	Gln	Pro	Arg 260	Thr	Phe	Leu	Leu	Lys 265	Tyr	Asn	Glu	Asn	Gly 270	Thr	Ile
Thr	Asp	Ala 275	Val	Aab	Cys	Ala	Leu 280	Asp	Pro	Leu	Ser	Glu 285	Thr	Lys	Суз
Thr	Leu 290	Lys	Ser	Phe	Thr	Val 295	Glu	Lys	Gly	Ile	Tyr 300	Gln	Thr	Ser	Asn
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Asn	Leu	Суз	Pro	Phe 325	Gly	Glu	Val	Phe	Asn 330	Ala	Thr	Arg	Phe	Ala 335	Ser
Val	Tyr	Ala	Trp 340	Asn	Arg	Lys	Arg	Ile 345	Ser	Asn	Суз	Val	Ala 350	Asp	Tyr
Ser	Val	Leu 355	Tyr	Asn	Ser	Ala	Ser 360	Phe	Ser	Thr	Phe	Lys 365	Суз	Tyr	Gly
Val	Ser 370	Pro	Thr	Lys	Leu	Asn 375	Asp	Leu	Cys	Phe	Thr 380	Asn	Val	Tyr	Ala
Asp 385	Ser	Phe	Val	Ile	Arg 390	Gly	Asp	Glu	Val	Arg 395	Gln	Ile	Ala	Pro	Gly 400
Gln	Thr	Gly	Lys	Ile 405	Ala	Aap	Tyr	Asn	Tyr 410	Lys	Leu	Pro	Aab	Asp 415	Phe
Thr	Gly	Cys	Val 420	Ile	Ala	Trp	Asn	Ser 425	Asn	Asn	Leu	Asp	Ser 430	Lys	Val

Gly	Gly	Asn 435	Tyr	Asn	Tyr	Leu	Tyr 440	Arg	Leu	Phe	Arg	Lys 445	Ser	Asn	Leu
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Gly	Pro	Lys 515	Lys	Ser	Thr	Asn	Leu 520	Val	Lys	Asn	Lys	Cys 525	Val	Asn	Phe
Asn	Phe 530	Asn	Gly	Leu	Thr	Gly 535	Thr	Gly	Val	Leu	Thr 540	Glu	Ser	Asn	Lys
Lys 545	Phe	Leu	Pro	Phe	Gln 550	Gln	Phe	Gly	Arg	Asp 555	Ile	Ala	Aab	Thr	Thr 560
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Ser	Val	Ala	Ser	Gln	Ser	Ile	Ile	Ala	Tyr	Thr	Met	Ser	Leu	Gly	Ala
Glu	Asn	۰/5 Ser	Val	Ala	Tyr	Ser	680 Asn	Asn	Ser	Ile	Ala	٥85 Ile	Pro	Thr	Asn
Phe	690 Thr	Ile	Ser	Val	Thr	695 Thr	Glu	Ile	Leu	Pro	Val	Ser	Met	Thr	Lys
705 Thr	Ser	Val	Asp	Суз	710 Thr	Met	Tyr	Ile	Сув	715 Gly	Asp	Ser	Thr	Glu	720 Cys
Ser	Asn	Leu	Leu	725 Leu	Gln	Tyr	Gly	Ser	730 Phe	Суз	Thr	Gln	Leu	735 Asn	Arg
Ala	Leu	Thr	740 Gly	Ile	Ala	Val	Glu	745 Gln	Asp	Lys	Asn	Thr	750 Gln	Glu	Val
Phe	Ala	755 Gln	Val	Lvs	Gln	Ile	760 Tyr	Lys	- Thr	- Pro	Pro	765 Ile	Lys	Asp	Phe
Glv	770	 Phe	Aan	Dhe	Ser	775 Glp	 T10	1~ Lev	Pro	 ∆er	780 Pro	Cer	1~ Lare	Pro	Cer
сту 785	ч	FIIE	ASU	rne	5er 790	GTU	тте	ьец	PTO	нэр 795	PIO	ser	пуа	PIO	800
ŗλa	Arg	Ser	Phe	Ile 805	Glu	Asp	Leu	Leu	Phe 810	Asn	Гла	Val	Thr	Leu 815	Ala
Asp	Ala	Gly	Phe 820	Ile	ГÀа	Gln	Tyr	Gly 825	Asp	Сүз	Leu	Gly	Aap 830	Ile	Ala
Ala	Arg	Asp 835	Leu	Ile	Сув	Ala	Gln 840	Lys	Phe	Asn	Gly	Leu 845	Thr	Val	Leu
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Leu	Gln	Ile	Pro	Phe 885	Ala	Met	Gln	Met	Ala 890	Тут	: A1	rg Phe	e Asr	n Gly 895	7 Ile 5
Gly	Val	Thr	Gln 900	Asn	Val	Leu	Tyr	Glu 905	Asn	Glr	ı Lj	ys Lei	1 Ile 910	e Ala	a Asn
Gln	Phe	Asn 915	Ser	Ala	Ile	Gly	Lys 920	Ile	Gln	Asp) S€	er Leu 925	ı Sei S	s Sei	r Thr
Ala	Ser 930	Ala	Leu	Gly	ГЛа	Leu 935	Gln	Asp	Val	Val	. As 94	sn Glr 40	ı Asr	n Ala	a Gln
Ala 945	Leu	Asn	Thr	Leu	Val 950	Lys	Gln	Leu	Ser	Ser 955	r As	sn Phe	e Gly	/ Ala	a Ile 960
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Glu	Val	Gln	Ile 980	Asp	Arg	Leu	Ile	Thr 985	Gly	Arg	j L€	∋u Glr	n Sei 990	r Leu)	ı Gln
Thr	Tyr	Val 995	Thr	Gln	Gln	Leu	Ile 1000	Arg D	g Al	a Al	.a (Glu II 10	le 2	Arg A	Ala Ser
Ala	Asn 1010	Leu)	ı Ala	a Ala	a Thr	: Lys 101	8 Me .5	et S	er G	lu C	ÇAa	Val 1020	Leu	Gly	Gln
Ser	Lys 1025	Arç 5	g Val	L Asp	> Phe	e Cya 103	8 G. 80	ly L	ya G	ly 1	'yr	His 1035	Leu	Met	Ser
Phe	Pro 1040	Glr)	n Ser	r Ala	a Pro) His 104	8 G. 15	ly Va	al V	al F	he	Leu 1050	His	Val	Thr
Tyr	Val 1055	Pro	> Ala	a Glr	n Glu	1 Lys 106	3 A: 50	sn Pl	he T	hr 1	'hr	Ala 1065	Pro	Ala	Ile
САа	His 1070	Asp)	⊳ Gl}	/ Lуз	3 Ala	His 107	3 Pl 75	ne P:	ro A	rg G	lu	Gly 1080	Val	Phe	Val
Ser	Asn 1085	Gly	7 Thi	f His	; Trp) Phe 109	e Va 90	al TÌ	hr G	ln A	Arg	Asn 1095	Phe	Tyr	Glu
Pro	Gln 1100	Ile)	e Ile	e Thr	Thr	Asp 110) A:	sn Tl	hr P	he V	/al	Ser 1110	Gly	Asn	Сүз
Asp	Val 1115	Val 5	. Ile	e Gly	/ Ile	e Val 112	L A: 20	sn A	sn T	hr V	/al	Tyr 1125	Asp	Pro	Leu
Gln	Pro 1130	Glu)	ı Leu	ı As <u>r</u>) Ser	Phe 113	e Ly 85	γs G	lu G	lu I	Jeu	Asp 1140	Lys	Tyr	Phe
ГЛа	Asn 1145	His 5	5 Thr	r Ser	Pro	Asp 115	50 Va	al A	ab T	eu C	ly	Asp 1155	Ile	Ser	Gly
Ile	Asn 1160	Ala)	a Ser	r Val	. Val	. Asr 116	n I. 55	le G	ln L	λa Q	Ju	Ile 1170	Asp	Arg	Leu
Asn	Glu 1175	Va]	. Ala	a Lys	a Asr	118	1 A: 30	sn G	lu S	er I	Jeu	Ile 1185	Asp	Leu	Gln
Glu	Leu 1190	Gl ₃	/ Цуз	з Туг	Glu	ı Glr 119	1 T <u>3</u> 95	yr I	le L	ya 1	rp	Pro 1200	Trp	Tyr	Ile
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Ile	Met 1220	Leu)	ı Cys	з Суз	; Met	: Thi 122	: Se 25	er C	ys C	ya S	Ser	Cys 1230	Leu	Lys	Gly
Сүз	Cys 1235	Sei 5	CYS	; Gly	/ Ser	Cys 124	8 C <u>3</u> 10	ya Li	ys P	he A	/ab	Glu 1245	Asp	Asp	Ser
Glu	Pro 1250	Val	. Leu	ı Lys	; Gly	7 Va] 125	L L <u>3</u>	ys Le	eu H	is 1	'yr	Thr 1260	His	His	His

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_	COILC	TITUC	u

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Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro 370 375 380
The Ive Iou Ace Iou Cye Deo The Iou Vol Twe Ale Ace Cor Deo
The Lys Led Ash Asp Led Cys File The Ash Var Tyr Ara Asp Set File
Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly Gln Thr Gly
Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys
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
465470475480Asn 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 Tvr Gln Pro Tvr Arg Val Val Val
500 505 510
Set Set The Gru Bed Hed his Ala FIO Ala fill val cys Gly FIO Bys 515 520 Lya Set The Jap Ley Val Lya Jap Ley Cha Val Jap De Jap Cha Jap
Lys Ser Inr Asn Leu val Lys Asn Lys Cys val 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 Phe580585590
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
Asn Val Phe Gln Thr Arg Ala Gly Cys Leu Ile Gly Ala Glu His Val

Asn	Asn	Ser	Tyr 660	Glu	Сүз	Asp	Ile	Pro 665	Ile	Gly	Ala	Gly	Ile 670	Сув	Ala
Ser	Tyr	Gln 675	Thr	Gln	Thr	Asn	Ser 680	Pro	Arg	Arg	Ala	Arg 685	Ser	Val	Ala
Ser	Gln 690	Ser	Ile	Ile	Ala	Tyr 695	Thr	Met	Ser	Leu	Gly 700	Ala	Glu	Asn	Ser
Val 705	Ala	Tyr	Ser	Asn	Asn 710	Ser	Ile	Ala	Ile	Pro 715	Thr	Asn	Phe	Thr	Ile 720
Ser	Val	Thr	Thr	Glu 725	Ile	Leu	Pro	Val	Ser 730	Met	Thr	Lys	Thr	Ser 735	Val
Asp	Cys	Thr	Met 740	Tyr	Ile	Сүз	Gly	Asp 745	Ser	Thr	Glu	Сүз	Ser 750	Asn	Leu
Leu	Leu	Gln 755	Tyr	Gly	Ser	Phe	Cys 760	Thr	Gln	Leu	Asn	Arg 765	Ala	Leu	Thr
Gly	Ile 770	Ala	Val	Glu	Gln	Asp 775	Lys	Asn	Thr	Gln	Glu 780	Val	Phe	Ala	Gln
Val 785	Lya	Gln	Ile	Tyr	Lys 790	Thr	Pro	Pro	Ile	Lys 795	Asp	Phe	Gly	Gly	Phe 800
Asn	Phe	Ser	Gln	Ile 805	Leu	Pro	Asp	Pro	Ser 810	Lys	Pro	Ser	rÀa	Arg 815	Ser
Phe	Ile	Glu	Asp 820	Leu	Leu	Phe	Asn	Lys 825	Val	Thr	Leu	Ala	Asp 830	Ala	Gly
Phe	Ile	Lys 835	Gln	Tyr	Gly	Asp	Cys 840	Leu	Gly	Asp	Ile	Ala 845	Ala	Arg	Asp
Leu	Ile 850	Суз	Ala	Gln	Lys	Phe 855	Asn	Gly	Leu	Thr	Val 860	Leu	Pro	Pro	Leu
Leu 865	Thr	Asp	Glu	Met	Ile 870	Ala	Gln	Tyr	Thr	Ser 875	Ala	Leu	Leu	Ala	Gly 880
Thr	Ile	Thr	Ser	Gly 885	Trp	Thr	Phe	Gly	Ala 890	Gly	Ala	Ala	Leu	Gln 895	Ile
Pro	Phe	Ala	Met 900	Gln	Met	Ala	Tyr	Arg 905	Phe	Asn	Gly	Ile	Gly 910	Val	Thr
Gln	Asn	Val 915	Leu	Tyr	Glu	Asn	Gln 920	Lys	Leu	Ile	Ala	Asn 925	Gln	Phe	Asn
Ser	Ala 930	Ile	Gly	Lys	Ile	Gln 935	Asp	Ser	Leu	Ser	Ser 940	Thr	Ala	Ser	Ala
Leu 945	Gly	Lys	Leu	Gln	Asp 950	Val	Val	Asn	Gln	Asn 955	Ala	Gln	Ala	Leu	Asn 960
Thr	Leu	Val	Lys	Gln 965	Leu	Ser	Ser	Asn	Phe 970	Gly	Ala	Ile	Ser	Ser 975	Val
Leu	Asn	Asp	Ile 980	Leu	Ser	Arg	Leu	Asp 985	Гла	Val	Glu	Ala	Glu 990	Val	Gln
Ile	Asp	Arg 995	Leu	Ile	Thr	Gly	Arg 1000	Lei	ı Glr	n Sei	r Leı	ı Glr 100	n Tł 05	nr Ty	yr Val
Thr	Gln 1010	Glr)	n Leu	ı Il€	e Arç	g Ala 10:	a A: 15	La GI	lu II	le Ai	rg A] 10	La \$ 020	Ser A	Ala A	Asn
Leu	Ala 1025	Ala 5	a Thi	r Ly:	3 Met	: Sei 103	c GI 30	Lu Cy	ys Va	al Le	eu GI	Ly (035	3ln §	Ser I	ууа
Arg	Val 1040) Asl) Phe	е Су:	∃ Gl	/ Ly: 104	9 GI 15	∟у т∑	yr Hi	ls L€	eu Me 10	et \$ 050	Ger H	Phe I	?ro
Gln	Ser 1055	Ala 5	a Pro	> Hi:	a Gly	7 Va 100	L Va 50	al Pł	ne Le	eu H:	is Va 1(al : 065	[hr]	[yr \	/al

Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr $% \mathbb{C}^{2}$ Ser Pro Asp Val Asp $% \mathbb{C}^{2}$ Leu Gly Asp Ile Ser $% \mathbb{C}^{2}$ Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro 1205 1210 <210> SEO ID NO 41 <211> LENGTH: 1200 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: RECOMBINANT SPIKE PROTEIN <400> SEQUENCE: 41 Gln Cys Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser

Lys His Thr Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser 195 200 205

Ala	Leu 210	Glu	Pro	Leu	Val	Asp 215	Leu	Pro	Ile	Gly	Ile 220	Asn	Ile	Thr	Arg
Phe 225	Gln	Thr	Leu	Leu	Ala 230	Leu	His	Arg	Ser	Tyr 235	Leu	Thr	Pro	Gly	Asp 240
Ser	Ser	Ser	Gly	Trp 245	Thr	Ala	Gly	Ala	Ala 250	Ala	Tyr	Tyr	Val	Gly 255	Tyr
Leu	Gln	Pro	Arg 260	Thr	Phe	Leu	Leu	Lys 265	Tyr	Asn	Glu	Asn	Gly 270	Thr	Ile
Thr	Asp	Ala 275	Val	Asp	Сүз	Ala	Leu 280	Asp	Pro	Leu	Ser	Glu 285	Thr	Lys	СЛа
Thr	Leu 290	Lys	Ser	Phe	Thr	Val 295	Glu	Lys	Gly	Ile	Tyr 300	Gln	Thr	Ser	Asn
Phe 305	Arg	Val	Gln	Pro	Thr 310	Glu	Ser	Ile	Val	Arg 315	Phe	Pro	Asn	Ile	Thr 320
Asn	Leu	Cys	Pro	Phe 325	Gly	Glu	Val	Phe	Asn 330	Ala	Thr	Arg	Phe	Ala 335	Ser
Val	Tyr	Ala	Trp 340	Asn	Arg	Lys	Arg	Ile 345	Ser	Asn	Суз	Val	Ala 350	Asp	Tyr
Ser	Val	Leu 355	Tyr	Asn	Ser	Ala	Ser 360	Phe	Ser	Thr	Phe	Lys 365	Сүз	Tyr	Gly
Val	Ser 370	Pro	Thr	Lys	Leu	Asn 375	Asp	Leu	Сув	Phe	Thr 380	Asn	Val	Tyr	Ala
Asp 385	Ser	Phe	Val	Ile	Arg 390	Gly	Asp	Glu	Val	Arg 395	Gln	Ile	Ala	Pro	Gly 400
Gln	Thr	Gly	Lys	Ile 405	Ala	Asp	Tyr	Asn	Tyr 410	Lys	Leu	Pro	Asp	Asp 415	Phe
Thr	Gly	Сув	Val 420	Ile	Ala	Trp	Asn	Ser 425	Asn	Asn	Leu	Asp	Ser 430	Lys	Val
Gly	Gly	Asn 435	Tyr	Asn	Tyr	Leu	Tyr 440	Arg	Leu	Phe	Arg	Lys 445	Ser	Asn	Leu
Lys	Pro 450	Phe	Glu	Arg	Asp	Ile 455	Ser	Thr	Glu	Ile	Tyr 460	Gln	Ala	Gly	Ser
Thr 465	Pro	Cys	Asn	Gly	Val 470	Glu	Gly	Phe	Asn	Cys 475	Tyr	Phe	Pro	Leu	Gln 480
Ser	Tyr	Gly	Phe	Gln 485	Pro	Thr	Asn	Gly	Val 490	Gly	Tyr	Gln	Pro	Tyr 495	Arg
Val	Val	Val	Leu 500	Ser	Phe	Glu	Leu	Leu 505	His	Ala	Pro	Ala	Thr 510	Val	Сув
Gly	Pro	Lys 515	Lys	Ser	Thr	Asn	Leu 520	Val	Lys	Asn	Гла	Cys 525	Val	Asn	Phe
Asn	Phe 530	Asn	Gly	Leu	Thr	Gly 535	Thr	Gly	Val	Leu	Thr 540	Glu	Ser	Asn	Гла
Lys 545	Phe	Leu	Pro	Phe	Gln 550	Gln	Phe	Gly	Arg	Asp 555	Ile	Ala	Asp	Thr	Thr 560
Asp	Ala	Val	Arg	Asp 565	Pro	Gln	Thr	Leu	Glu 570	Ile	Leu	Asp	Ile	Thr 575	Pro
Суз	Ser	Phe	Gly 580	Gly	Val	Ser	Val	Ile 585	Thr	Pro	Gly	Thr	Asn 590	Thr	Ser
Asn	Gln	Val 595	Ala	Val	Leu	Tyr	Gln 600	Asp	Val	Asn	Сув	Thr 605	Glu	Val	Pro
Val	Ala 610	Ile	His	Ala	Asp	Gln 615	Leu	Thr	Pro	Thr	Trp 620	Arg	Val	Tyr	Ser
Thr	Gly	Ser	Asn	Val	Phe	Gln	Thr	Arg	Ala	Gly	Суз	Leu	Ile	Gly	Ala

625					630					635					640
Glu	His	Val	Asn	Asn 645	Ser	Tyr	Glu	Сүз	Asp 650	Ile	Pro	Ile	Gly	Ala 655	Gly
Ile	Суз	Ala	Ser 660	Tyr	Gln	Thr	Gln	Thr 665	Asn	Ser	Pro	Arg	Arg 670	Ala	Arg
Ser	Val	Ala 675	Ser	Gln	Ser	Ile	Ile 680	Ala	Tyr	Thr	Met	Ser 685	Leu	Gly	Ala
Glu	Asn 690	Ser	Val	Ala	Tyr	Ser 695	Asn	Asn	Ser	Ile	Ala 700	Ile	Pro	Thr	Asn
Phe	Thr	Ile	Ser	Val	Thr	Thr	Glu	Ile	Leu	Pro	Val	Ser	Met	Thr	Lys
705 Thr	Ser	Val	Asp	Сув	710 Thr	Met	Tyr	Ile	Суз	/15 Gly	Asp	Ser	Thr	Glu	720 . Cys
Ser	Asn	Leu	Leu	725 Leu	Gln	Tvr	Glv	Ser	730 Phe	Cvs	Thr	Gln	Leu	735 Asn	Ara
		u	740			- 1 -		745		- , ,		· · ·	750		
AIA	Leu	755	σту	тте	Ala	va⊥	G1u 760	GIN	Asb	гда	Asn	765	GIN	GLU	.va⊥
Phe	Ala 770	Gln	Val	Lys	Gln	Ile 775	Tyr	Lys	Thr	Pro	Pro 780	Ile	Lys	Asp	Phe
Gly 785	Gly	Phe	Asn	Phe	Ser 790	Gln	Ile	Leu	Pro	Asp 795	Pro	Ser	Lys	Pro	Ser 800
Lys	Arg	Ser	Phe	Ile 805	Glu	Asp	Leu	Leu	Phe 810	Asn	ГЛа	Val	Thr	Leu 815	Ala
Asp	Ala	Gly	Phe 820	Ile	Гла	Gln	Tyr	Gly 825	Asp	Суз	Leu	Gly	830 830	Ile	Ala
Ala	Arg	Asp	Leu	Ile	СЛа	Ala	Gln	ГЛЗ	Phe	Asn	Gly	Leu	. Thr	Val	Leu
Pro	Pro	835 Leu	Leu	Thr	Asp	Glu	840 Met	Ile	Ala	Gln	Tyr	845 Thr	Ser	Ala	Leu
Leu	850 Ala	Glv	Thr	Ile	Thr	855 Ser	Glv	Tro	Thr	Phe	860 Glv	Ala	Glv	Ala	Ala
865					870					875					880
Leu	Gln	Iĺe	Pro	Phe 885	Ala	Met	Gln	Met	Ala 890	Tyr	Arg	Phe	Asn	Gly 895	Ile
Gly	Val	Thr	Gln 900	Asn	Val	Leu	Tyr	Glu 905	Asn	Gln	Lys	Leu	. Ile 910	Ala	Asn
Gln	Phe	Asn 915	Ser	Ala	Ile	Gly	Lys 920	Ile	Gln	Asp	Ser	Leu 925	Ser	Ser	Thr
Ala	Ser 930	Ala	Leu	Gly	Lys	Leu 935	Gln	Asp	Val	Val	Asn 940	Gln	Asn	Ala	Gln
Ala 945	Leu	Asn	Thr	Leu	Val 950	ГЛа	Gln	Leu	Ser	Ser 955	Asn	Phe	Gly	Ala	Ile 960
Ser	Ser	Val	Leu	Asn	Asb	Ile	Leu	Ser	Arg	Leu	Asp	Lys	Val	Glu	Ala
Glu	Val	Gln	Ile	965 Asp	Ara	Leu	Ile	Thr	970 Glv	Ara	Leu	Gln	Ser	975 Leu	Gln
			980			4		985	1	9			990		
Thr	Tyr	Val 995	Thr	Gln	Gln	Leu	Ile 1000	Arq D	g Ala	a Al.	a Gl	u Il 10	e A 05	rg A	la Se
Ala	Asn 1010	Lei	ı Ala	a Ala	a Thi	r Ly: 10:	s Me 15	et Se	er G	lu C	ys V 1	al 020	Leu	Gly	Gln
Ser	Lys 1025	Arç	g Val	l Asj	p Phe	∋ Cy: 10'	a GI 30	ly Ly	ys G	ly T	yr H 1	is 035	Leu	Met	Ser
Phe	Pro	Glı	n Se:	r Ala	a Pro	> Hi	s GI	ly Va	al Va	al Pl	he L	eu	His	Val	Thr
	1040)				104	45				1	050			

Tyr Val Pro Ala Gln Glu Lys Asn Phe Thr Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe Pro Arg Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr Phe Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp $% \mathbb{C}^{2}$ Val Asp Leu Gly Asp $% \mathbb{C}^{2}$ Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys Glu Ile Asp Arg Leu Asn Glu Val Ala Lys Asn Leu Asn Glu Ser Leu Ile Asp Leu Gln Glu Leu Gly Lys Tyr Glu Gln Tyr Ile Lys Trp Pro <210> SEQ ID NO 42 <211> LENGTH: 1219 <212> TYPE: PRT <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: RECOMBINANT SPIKE PROTEIN <400> SEQUENCE: 42 Met Phe Val Phe Leu Val Leu Leu Pro Leu Val Ser Ser Gln Cys Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe 2.0 Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr

Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
Pro 225	Leu	Val	Asp	Leu	Pro 230	Ile	Gly	Ile	Asn	Ile 235	Thr	Arg	Phe	Gln	Thr 240
Leu	Leu	Ala	Leu	His 245	Arg	Ser	Tyr	Leu	Thr 250	Pro	Gly	Asp	Ser	Ser 255	Ser
Gly	Trp	Thr	Ala 260	Gly	Ala	Ala	Ala	Tyr 265	Tyr	Val	Gly	Tyr	Leu 270	Gln	Pro
Arg	Thr	Phe 275	Leu	Leu	Lys	Tyr	Asn 280	Glu	Asn	Gly	Thr	Ile 285	Thr	Asp	Ala
Val	Asp 290	Cys	Ala	Leu	Asp	Pro 295	Leu	Ser	Glu	Thr	Lуз 300	Сүз	Thr	Leu	Lys
Ser 305	Phe	Thr	Val	Glu	Lys 310	Gly	Ile	Tyr	Gln	Thr 315	Ser	Asn	Phe	Arg	Val 320
Gln	Pro	Thr	Glu	Ser 325	Ile	Val	Arg	Phe	Pro 330	Asn	Ile	Thr	Asn	Leu 335	Сүв
Pro	Phe	Gly	Glu 340	Val	Phe	Asn	Ala	Thr 345	Arg	Phe	Ala	Ser	Val 350	Tyr	Ala
Trp	Asn	Arg 355	Lys	Arg	Ile	Ser	Asn 360	Суз	Val	Ala	Asp	Tyr 365	Ser	Val	Leu
Tyr	Asn 370	Ser	Ala	Ser	Phe	Ser 375	Thr	Phe	Lys	Суз	Tyr 380	Gly	Val	Ser	Pro
Thr 385	Lys	Leu	Asn	Asp	Leu 390	Сүз	Phe	Thr	Asn	Val 395	Tyr	Ala	Asp	Ser	Phe 400
Val	Ile	Arg	Gly	Asp 405	Glu	Val	Arg	Gln	Ile 410	Ala	Pro	Gly	Gln	Thr 415	Gly
Lys	Ile	Ala	Asp 420	Tyr	Asn	Tyr	Lys	Leu 425	Pro	Asp	Asp	Phe	Thr 430	Gly	Сүв
Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	Lys	Val 445	Gly	Gly	Asn
Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	Lys	Ser	Asn 460	Leu	Lys	Pro	Phe
Glu 465	Arg	Aab	Ile	Ser	Thr 470	Glu	Ile	Tyr	Gln	Ala 475	Gly	Ser	Thr	Pro	Cys 480
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Phe	Gln	Pro	Thr 500	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val
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Arg	Asp	Pro	Gln 580	Thr	Leu	Glu	Ile	Leu 585	Asp	Ile	Thr	Pro	Суз 590	Ser	Phe
Gly	Gly	Val 595	Ser	Val	Ile	Thr	Pro 600	Gly	Thr	Asn	Thr	Ser 605	Asn	Gln	Val
Ala	Val 610	Leu	Tyr	Gln	Asp	Val 615	Asn	Cys	Thr	Glu	Val 620	Pro	Val	Ala	Ile

His 625	Ala	Asp	Gln	Leu	Thr 630	Pro	Thr	Trp	Arg	Val 635	Tyr	Ser	Thr	Gly	Ser 640	
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Val 705	Ala	Tyr	Ser	Asn	Asn 710	Ser	Ile	Ala	Ile	Pro 715	Thr	Asn	Phe	Thr	Ile 720	
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Val 785	Lys	Gln	Ile	Tyr	Lys 790	Thr	Pro	Pro	Ile	Lys 795	Asp	Phe	Gly	Gly	Phe 800	
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Phe	Ile	Glu	Asp 820	Leu	Leu	Phe	Asn	Lys 825	Val	Thr	Leu	Ala	Asp 830	Ala	Gly	
Phe	Ile	Lys 835	Gln	Tyr	Gly	Asp	Cys 840	Leu	Gly	Asp	Ile	Ala 845	Ala	Arg	Asp	
Leu	Ile 850	Cys	Ala	Gln	Lys	Phe 855	Asn	Gly	Leu	Thr	Val 860	Leu	Pro	Pro	Leu	
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Ser	Ala 930	Ile	Gly	Lys	Ile	Gln 935	Asp	Ser	Leu	Ser	Ser 940	Thr	Ala	Ser	Ala	
Leu 945	Gly	Lys	Leu	Gln	Asp 950	Val	Val	Asn	Gln	Asn 955	Ala	Gln	Ala	Leu	Asn 960	
Thr	Leu	Val	Lys	Gln 965	Leu	Ser	Ser	Asn	Phe 970	Gly	Ala	Ile	Ser	Ser 975	Val	
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Ile	Asp	Arg 995	Leu	Ile	Thr	Gly	Arg 1000	Lei)	ı Glı	ı Se:	r Leı	1 Gli 100	n TÌ 05	hr T	yr Val	
Thr	Gln 1010	Glr	ı Leı	ı Ile	e Arç	g Ala 10:	a A: 15	la Gi	lu I	Le A:	rg Al 10	La : 020	Ser A	Ala i	Asn	
Leu	Ala 1025	Ala	a Thi	r Ly:	3 Met	: Sei 103	r G: 30	lu Cy	γs Va	al Le	eu GI	Ly ()35	Gln :	Ser 1	Lys	
Arg	Val	Asī	Phe	e Cys	∃ Glչ	/ Ly:	∃ G	ly Ty	yr H:	is Le	eu Me	et :	Ser 1	Phe 1	Pro	
	1040					1045					1050					
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Gln	Ser 1055	Ala	Pro	His	Gly	Val 1060	Val	Phe	Leu	His	Val 1065	Thr	Tyr	Val		
Pro	Ala 1070	Gln	Glu	Гла	Asn	Phe 1075	Thr	Thr	Ala	Pro	Ala 1080	Ile	Суз	His		
Asp	Gly 1085	Lys	Ala	His	Phe	Pro 1090	Arg	Glu	Gly	Val	Phe 1095	Val	Ser	Asn		
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-	COL			LLU.		u.
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Tyr 145	His	Lys	Asn	Asn	Lys 150	Ser	Trp	Met	Glu	Ser 155	Glu	Phe	Arg	Val	Tyr 160
Ser	Ser	Ala	Asn	Asn 165	Сүз	Thr	Phe	Glu	Tyr 170	Val	Ser	Gln	Pro	Phe 175	Leu
Met	Asp	Leu	Glu 180	Gly	Lys	Gln	Gly	Asn 185	Phe	Lys	Asn	Leu	Arg 190	Glu	Phe
Val	Phe	Lys 195	Asn	Ile	Asp	Gly	Tyr 200	Phe	Lys	Ile	Tyr	Ser 205	Lys	His	Thr
Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
Pro 225	Leu	Val	Asp	Leu	Pro 230	Ile	Gly	Ile	Asn	Ile 235	Thr	Arg	Phe	Gln	Thr 240
Leu	Leu	Ala	Leu	His 245	Arg	Ser	Tyr	Leu	Thr 250	Pro	Gly	Asp	Ser	Ser 255	Ser
Gly	Trp	Thr	Ala 260	Gly	Ala	Ala	Ala	Tyr 265	Tyr	Val	Gly	Tyr	Leu 270	Gln	Pro
Arg	Thr	Phe 275	Leu	Leu	Lys	Tyr	Asn 280	Glu	Asn	Gly	Thr	Ile 285	Thr	Asp	Ala
Val	Asp 290	Cys	Ala	Leu	Asp	Pro 295	Leu	Ser	Glu	Thr	Lys 300	Суз	Thr	Leu	Lya
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Gln	Pro	Thr	Glu	Ser 325	Ile	Val	Arg	Phe	Pro 330	Asn	Ile	Thr	Asn	Leu 335	Сүз
Pro	Phe	Gly	Glu 340	Val	Phe	Asn	Ala	Thr 345	Arg	Phe	Ala	Ser	Val 350	Tyr	Ala
Trp	Asn	Arg 355	Lys	Arg	Ile	Ser	Asn 360	Суз	Val	Ala	Asp	Tyr 365	Ser	Val	Leu
Tyr	Asn 370	Ser	Ala	Ser	Phe	Ser 375	Thr	Phe	Lys	Суз	Tyr 380	Gly	Val	Ser	Pro

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Lys	Ile	Ala	Asp 420	Tyr	Asn	Tyr	Lys	Leu 425	Pro	Asp	Asp	Phe	Thr 430	Gly	Сүз
Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	Lys	Val 445	Gly	Gly	Asn
Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	ГЛа	Ser	Asn 460	Leu	Гλа	Pro	Phe
Glu 465	Arg	Asp	Ile	Ser	Thr 470	Glu	Ile	Tyr	Gln	Ala 475	Gly	Ser	Thr	Pro	Сув 480
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Phe	Gln	Pro	Thr 500	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val
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Lys	Ser 530	Thr	Asn	Leu	Val	Lys 535	Asn	Lys	Сүз	Val	Asn 540	Phe	Asn	Phe	Asn
Gly 545	Leu	Thr	Gly	Thr	Gly 550	Val	Leu	Thr	Glu	Ser 555	Asn	Γλa	Lys	Phe	Leu 560
Pro	Phe	Gln	Gln	Phe 565	Gly	Arg	Asp	Ile	Ala 570	Asp	Thr	Thr	Aab	Ala 575	Val
Arg	Asp	Pro	Gln 580	Thr	Leu	Glu	Ile	Leu 585	Aab	Ile	Thr	Pro	Cys 590	Ser	Phe
Gly	Gly	Val 595	Ser	Val	Ile	Thr	Pro 600	Gly	Thr	Asn	Thr	Ser 605	Asn	Gln	Val
Ala	Val 610	Leu	Tyr	Gln	Asp	Val 615	Asn	Суз	Thr	Glu	Val 620	Pro	Val	Ala	Ile
His 625	Ala	Aab	Gln	Leu	Thr 630	Pro	Thr	Trp	Arg	Val 635	Tyr	Ser	Thr	Gly	Ser 640
Asn	Val	Phe	Gln	Thr 645	Arg	Ala	Gly	Сүз	Leu 650	Ile	Gly	Ala	Glu	His 655	Val
Asn	Asn	Ser	Tyr 660	Glu	СЛа	Asp	Ile	Pro 665	Ile	Gly	Ala	Gly	Ile 670	Сүз	Ala
Ser	Tyr	Gln 675	Thr	Gln	Thr	Asn	Ser 680	Pro	Gln	Gln	Ala	Gln 685	Ser	Val	Ala
Ser	Gln 690	Ser	Ile	Ile	Ala	Tyr 695	Thr	Met	Ser	Leu	Gly 700	Ala	Glu	Asn	Ser
Val 705	Ala	Tyr	Ser	Asn	Asn 710	Ser	Ile	Ala	Ile	Pro 715	Thr	Asn	Phe	Thr	Ile 720
Ser	Val	Thr	Thr	Glu 725	Ile	Leu	Pro	Val	Ser 730	Met	Thr	Lys	Thr	Ser 735	Val
Asp	Cys	Thr	Met 740	Tyr	Ile	Суз	Gly	Asp 745	Ser	Thr	Glu	Суз	Ser 750	Asn	Leu
Leu	Leu	Gln 755	Tyr	Gly	Ser	Phe	Cys 760	Thr	Gln	Leu	Asn	Arg 765	Ala	Leu	Thr
Gly	Ile 770	Ala	Val	Glu	Gln	Asp 775	Lys	Asn	Thr	Gln	Glu 780	Val	Phe	Ala	Gln
Val 785	Lys	Gln	Ile	Tyr	Lys 790	Thr	Pro	Pro	Ile	Lys 795	Asp	Phe	Gly	Gly	Phe 800

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Asn	Phe	Ser	Gln	Ile 805	Leu	Pro	Asp	Pro	Ser 810	Lys	Pr	o S	er	Lys	Arg 815	Ser	
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Phe	Ile	Lys 835	Gln	Tyr	Gly	Asp	Cys 840	Leu	Gly	Asp) Il	.e A 8	la 45	Ala	Arg	Asp	
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Leu	Asn	Asp	Ile 980	Leu	Ser	Arg	Leu	Asp 985	Lys	Val	. G1	u A	la	Glu 990	Val	Gln	
Ile	Asp	Arg 995	Leu	Ile	Thr	Gly	Arg 1000	Lei)	ı Gl	n S∈	er L	eu	Gl1 100	n T. 05	hr T	yr Val	1
Thr	Gln 1010	Glr	n Leu	ı Il€	e Arç	9 Ala 101	. A] .5	la Gi	lu I	le A	rg	Ala 102	0	Ser .	Ala .	Asn	
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Gln	Ser 1055	Ala	a Pro) His	∃ Gly	7 Val 106	. Va 0	al Pl	ne L	eu H	lis	Val 106	5	Thr	Tyr	Val	
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Val	Ile 1130	Gl ₃	/ Ile	e Val	l Asr	n Asr 113	1 Tł 5	nr Va	al T	yr A	ab	Prc 114	0	Leu	Gln	Pro	
Glu	Leu 1145	Asp) Sei	: Phe	e Lys	5 Glu 115	G]	lu L	eu A	ap I	ya	Tyr 115	5	Phe	Lys	Asn	
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Ala	Ser 1175	Val	l Val	. Asr	n Il€	e Glr 118	ь Lչ	/s G	lu I	le A	'ab	Arg 118	I 5	Leu .	Asn	Glu	
Val	Ala 1190	Ly:	s Asr	ı Leu	ı Asr	1 Glu	L S€	er Le	∋u I	le A	'ab	Leu		Gln	Glu	Leu	
Gly	Гуа	Туз	r Glu	ı Glr	ı Tyr	: Ile	ε LΣ	/s T:	rp P	ro I	rp	Tyr	• :	Ile	Trp	Leu	

173

1205

1220

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1250

1265

<210> SEQ ID NO 57 <211> LENGTH: 3837 <212> TYPE: DNA

<400> SEQUENCE: 57

<220> FEATURE:

His

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1260

1320

1380

1440

1500

1560

1620

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175

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176

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<210> SEQ ID NO 58 <211> LENGTH: 1266 <212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: RECOMBINANT SPIKE PROTEIN <400> SEQUENCE: 58 Gln Cys Val Asn Leu Thr Thr Arg Thr Gln Leu Pro Pro Ala Tyr Thr Asn Ser Phe Thr Arg Gly Val Tyr Tyr Pro Asp Lys Val Phe Arg Ser Ser Val Leu His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe Ser Asn Val Thr Trp Phe His Ala Ile His Val Ser Gly Thr Asn Gly Thr Lys Arg Phe Asp Asn Pro Val Leu Pro Phe Asn Asp Gly Val Tyr Phe Ala Ser Thr Glu Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser Lys Thr Gln Ser Leu Leu Ile Val Asn Asn Ala Thr Asn Val Val Ile Lys Val Cys Glu Phe Gln Phe Cys Asn Asp Pro Phe Leu Gly Val Tyr Tyr His Lys Asn Asn Lys Ser Trp Met Glu Ser Glu Phe Arg Val Tyr Ser Ser Ala Asn Asn Cys Thr Phe Glu Tyr Val Ser Gln Pro Phe Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu Arg Glu Phe Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile Tyr Ser Lys His Thr Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly Phe Ser Ala Leu Glu Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile Thr Arg Phe Gln Thr Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro Gly Asp Ser Ser Ser Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val Gly Tyr Leu Gln Pro Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly Thr Ile Thr Asp Ala Val Asp Cys Ala Leu Asp Pro Leu Ser Glu Thr Lys Cys Thr Leu Lys Ser Phe Thr Val Glu Lys Gly Ile Tyr Gln Thr Ser Asn Phe Arg Val Gln Pro Thr Glu Ser Ile Val Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Arg Phe Ala Ser Val Tyr Ala Trp Asn Arg Lys Arg Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Ala Ser Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Pro Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val Arg Gln Ile Ala Pro Gly

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Gly	Gly	Asn 435	Tyr	Asn	Tyr	Leu	Tyr 440	Arg	Leu	Phe	Arg	Lys 445	Ser	Asn	Leu
Lys	Pro 450	Phe	Glu	Arg	Asp	Ile 455	Ser	Thr	Glu	Ile	Tyr 460	Gln	Ala	Gly	Ser
Thr 465	Pro	Cys	Asn	Gly	Val 470	Glu	Gly	Phe	Asn	Cys 475	Tyr	Phe	Pro	Leu	Gln 480
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Val	Val	Val	Leu 500	Ser	Phe	Glu	Leu	Leu 505	His	Ala	Pro	Ala	Thr 510	Val	Суз
Gly	Pro	Lys 515	Lys	Ser	Thr	Asn	Leu 520	Val	Lys	Asn	Lys	Cys 525	Val	Asn	Phe
Asn	Phe 530	Asn	Gly	Leu	Thr	Gly 535	Thr	Gly	Val	Leu	Thr 540	Glu	Ser	Asn	Lys
Lys 545	Phe	Leu	Pro	Phe	Gln 550	Gln	Phe	Gly	Arg	Asp 555	Ile	Ala	Asp	Thr	Thr 560
Asp	Ala	Val	Arg	Asp 565	Pro	Gln	Thr	Leu	Glu 570	Ile	Leu	Asp	Ile	Thr 575	Pro
Суз	Ser	Phe	Gly 580	Gly	Val	Ser	Val	Ile 585	Thr	Pro	Gly	Thr	Asn 590	Thr	Ser
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Ile	Суз	Ala	Ser 660	Tyr	Gln	Thr	Gln	Thr 665	Asn	Ser	Pro	Gln	Gln 670	Ala	Gln
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Ala	Leu	Thr 755	Gly	Ile	Ala	Val	Glu 760	Gln	Asp	Lys	Asn	Thr 765	Gln	Glu	Val
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Ala	Arg	Asp 835	Leu	Ile	САа	Ala	Gln 840	Lys	Phe	Asn	Gly	Leu 845	Thr	Val	Leu
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Ala	Ser 930	Ala	Leu	Gly	Lya	Leu 935	Gln	Asp	Val	Val	Asn 940	Gln	Asn	Ala	Gln
Ala 945	Leu	Asn	Thr	Leu	Val 950	Lya	Gln	Leu	Ser	Ser 955	Asn	Phe	Gly	Ala	Ile 960
Ser	Ser	Val	Leu	Asn 965	Asp	Ile	Leu	Ser	Arg 970	Leu	Asp	ГÀа	Val	Glu 975	Ala
Glu	Val	Gln	Ile 980	Aap	Arg	Leu	Ile	Thr 985	Gly	Arg	Leu	Gln	Ser 990	Leu	Gln
Thr	Tyr	Val 995	Thr	Gln	Gln	Leu	Ile 1000	Arq D	g Ala	a Ala	a Gli	Il ג 10	e A 05	rg A	la Ser
Ala	Asn 1010	Leu)	ı Ala	a Ala	1 Thr	Ly: 101	s Me LS	∋t Se	∍r G	lu Cy	ys V. 1	al 020	Leu	Gly	Gln
Ser	Lys 1025	Arg 5	g Val	. Asr) Phe	Cya 103	5 GI 30	ly Ly	ys Gi	ly Ty	yr H. 1	is 035	Leu	Met	Ser
Phe	Pro 1040	Glr	n Ser	: Ala	a Pro	Hi: 104	9 GI 15	ly Va	al Vá	al Pl	ne L 1	eu 050	His	Val	Thr
Tyr	Val 1055	Pro	> Ala	a Glr	n Glu	Ly: 106	8 As 50	sn Pl	ne Tł	nr Tl	nr A	la 065	Pro .	Ala	Ile
Суз	His 1070	Asp)	⊳ Gl}	и Буз	3 Ala	His 107	9 Pł 75	ne Pi	ro Ai	rg G	lu G	ly 080	Val	Phe	Val
Ser	Asn 1085	Gl ₃	7 Thi	His	; Trp	Phe 109	e Va 90	al Tł	nr G	ln A:	rg A 1	sn 095	Phe	Tyr	Glu
Pro	Gln 1100	Ile)	e Ile	e Thr	Thr	Asp 110)5 As	sn Tl	nr Pl	ne Va	al S 1	∋r 110	Gly .	Asn	Суз
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Gln	Pro 1130	Glu)	ı Leu	ı Asp) Ser	Phe 113	е Цу 85	ys G	lu G	lu Le	eu A 1	ap 140	Lys	Tyr	Phe
ГЛа	Asn 1145	Hi:	5 Thr	: Sei	Pro	Asp 115	p Vá 50	al As	зр Le	eu Gi	ly A 1	зр 155	Ile	Ser	Gly
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35 40	45
His Ser Thr Gln Asp Leu Phe Leu Pro Phe Phe	e Ser Asn Val Thr Tr
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Phe His Ala Ile His Val Ser Gly Thr Asn Gly	y Thr Lys Arg Phe As
65 70 75	80
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly	y Thr Thr Leu Asp Se
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115 120	125
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Tyr His Lys Asn Asn Lys Ser Trp Met Glu Sei	r Glu Phe Arg Val Ty
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165 170	175
Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys	s Asn Leu Arg Glu Pr
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Val Phe Lys Asn Ile Asp Gly Tyr Phe Lys Ile	e Tyr Ser Lys His Tr
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Pro Ile Asn Leu Val Arg Asp Leu Pro Gln Gly	y Phe Ser Ala Leu Gl
210 215	220
Pro Leu Val Asp Leu Pro Ile Gly Ile Asn Ile	e Thr Arg Phe Gln Tr
225 230 23!	5 24
Leu Leu Ala Leu His Arg Ser Tyr Leu Thr Pro	o Gly Asp Ser Ser Se
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Gly Trp Thr Ala Gly Ala Ala Ala Tyr Tyr Val	l Gly Tyr Leu Gln Pr
260 265	270
Arg Thr Phe Leu Leu Lys Tyr Asn Glu Asn Gly	y Thr Ile Thr Asp Al
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Val	Ile	Gly	/ Ile	e Val	l Asr	1 Asr	n Tr	nr Va	al T	yr A	vab j	Pro	Leu	L G	ln H	Pro
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His															
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Val	Ile	Lys 115	Val	Суз	Glu	Phe	Gln 120	Phe	Суз	Asn	Asp	Pro 125	Phe	Leu	Gly
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His	Thr	Pro 195	Ile	Asn	Leu	Val	Arg 200	Asp	Leu	Pro	Gln	Gly 205	Phe	Ser	Ala
Leu	Glu 210	Pro	Leu	Val	Asp	Leu 215	Pro	Ile	Gly	Ile	Asn 220	Ile	Thr	Arg	Phe
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Tyr	Ala	Trp	Asn 340	Arg	Lys	Arg	Ile	Ser 345	Asn	Суз	Val	Ala	Asp 350	Tyr	Ser
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Ser	Pro 370	Thr	Lys	Leu	Asn	Asp 375	Leu	Суз	Phe	Thr	Asn 380	Val	Tyr	Ala	Asp
Ser 385	Phe	Val	Ile	Arg	Gly 390	Asp	Glu	Val	Arg	Gln 395	Ile	Ala	Pro	Gly	Gln 400
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Pro	Phe 450	Glu	Arg	Asp	Ile	Ser 455	Thr	Glu	Ile	Tyr	Gln 460	Ala	Gly	Ser	Thr
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Tyr	Gly	Phe	Gln	Pro 485	Thr	Asn	Gly	Val	Gly 490	Tyr	Gln	Pro	Tyr	Arg 495	Val
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Gly 625	Ser	Asn	Val	Phe	Gln 630	Thr	Arg	Ala	Gly	Cys 635	Leu	Ile	Gly	Ala	Glu 640
His	Val	Asn	Asn	Ser 645	Tyr	Glu	Сув	Asp	Ile 650	Pro	Ile	Gly	Ala	G1y 655	Ile
Суз	Ala	Ser	Tyr 660	Gln	Thr	Gln	Thr	Asn 665	Ser	Pro	Gln	Gln	Ala 670	Gln	Ser
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Asn	Ser 690	Val	Ala	Tyr	Ser	Asn 695	Asn	Ser	Ile	Ala	Ile 700	Pro	Thr	Asn	Phe
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Ser	Val	Aab	Сүз	Thr 725	Met	Tyr	Ile	Суа	Gly 730	Asp	Ser	Thr	Glu	Суз 735	Ser
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Ala	Gln 770	Val	Lys	Gln	Ile	Tyr 775	Lys	Thr	Pro	Pro	Ile 780	Lys	Asp	Phe	Gly
Gly 785	Phe	Asn	Phe	Ser	Gln 790	Ile	Leu	Pro	Asp	Pro 795	Ser	Lys	Pro	Ser	Lys 800
Arg	Ser	Phe	Ile	Glu	Asp	Leu	Leu	Phe	Asn	Lys	Val	Thr	Leu	Ala	Asp
				805					810					815	

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Arg	Asp	Leu 835	Ile	Сув	Ala	Gln	Lys 840	Phe	Ası	n G	ly I	Leu	Thr 845	Va]	L Lei	ı Pro
Pro	Leu 850	Leu	Thr	Asp	Glu	Met 855	Ile	Ala	Glı	n T	yr '	Thr 360	Ser	Ala	a Lei	ı Leu
Ala 865	Gly	Thr	Ile	Thr	Ser 870	Gly	Trp	Thr	Ph	e G 8	ly 2 75	Ala	Gly	Ala	a Ala	a Leu 880
Gln	Ile	Pro	Phe	Ala 885	Met	Gln	Met	Ala	Ty: 890	r A	rg 1	Phe	Asn	ι Glγ	7 Il. 89!	e Gly 5
Val	Thr	Gln	Asn 900	Val	Leu	Tyr	Glu	Asn 905	Glı	n Lj	ys 1	Leu	Ile	e Ala 91(a Ası)	n Gln
Phe	Asn	Ser 915	Ala	Ile	Gly	Lys	Ile 920	Gln	Asj	p S	er 1	Leu	Ser 925	Sei	Th:	r Ala
Ser	Ala 930	Leu	Gly	Lya	Leu	Gln 935	Asp	Val	Va	1 A	sn (31n 940	Asn	ı Ala	a Gli	n Ala
Leu 945	Asn	Thr	Leu	Val	Lys 950	Gln	Leu	Ser	Se:	r A 9	sn 1 55	Phe	Gly	Ala	a Ile	e Ser 960
Ser	Val	Leu	Asn	Asp 965	Ile	Leu	Ser	Arg	Le: 97(и А С	ab j	ŗλa	Val	. Glu	1 Ala 97!	a Glu 5
Val	Gln	Ile	Asp 980	Arg	Leu	Ile	Thr	Gly 985	Arg	gĿ	eu (Gln	Ser	Leu 99(ı Glı)	n Thr
Tyr	Val	Thr 995	Gln	Gln	Leu	Ile	Arg 100	Al.	a A	la	Glu	Ile	e Ar 10	g 1 105	Ala :	Ser Ala
Asn	Leu 101(Ala)	ı Ala	a Thr	: Lуғ	Met 101	: S 15	er G	lu (Cys	Va	l L.	eu 020	Gly	Gln	Ser
Lys	Arg 1029	Va]	. Asj	p Phe	e Cya	6 Gly 103	7 L <u>.</u> 30	γs G	ly '	Гуr	Hi	5 Le 10	eu 035	Met	Ser	Phe
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Val	Pro 1055	Ala 5	Glı	n Glu	ι Lуε	Ası 106	n Pl 50	ne Ti	hr '	Thr	Ala	a P: 10	ro 065	Ala	Ile	Сүз
His	Asp 1070	Gl _y	и Гла	s Ala	a His	9 Phe 107	e P: 75	ro A	rg (Glu	Gl	y Va 10	al 080	Phe	Val	Ser
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Gln	Ile 1100	Ile)	e Th:	r Thr	: Asp) Asr 11(n Tl 05	nr Pi	he '	Val	Se:	r G: 1:	ly 110	Asn	Суз	Asp
Val	Val 1119	Ile	e Gly	y Il€	e Val	. Asr 112	n A: 20	sn Ti	hr '	Val	ту:	r A: 1:	sp 125	Pro	Leu	Gln
Pro	Glu 1130	Leu)	ı Asj	o Ser	: Phe	e Lys 113	3 G 35	lu G	lu 1	Leu	Asj	p Ly 13	ys 140	Tyr	Phe	Lys
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Leu	Gly 1190	Lys)	ту:	r Glu	ı Glr	n Tyj 119	r I 95	le L	γs '	Γrp	Pro	> H: 1:	is 200	His	His	His
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Thr Lys Leu Asn Asp Leu Cys Phe Thr Asn Val Tyr Ala Asp Ser Phe

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ГЛЗ	Ile	Ala	Asp 420	Tyr	Asn	Tyr	Lys	Leu 425	Pro	Asp	Asp	Phe	Thr 430	Gly	Суз
Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	Lys	Val 445	Gly	Gly	Asn
Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	Lys	Ser	Asn 460	Leu	Lys	Pro	Phe
Glu 465	Arg	Aap	Ile	Ser	Thr 470	Glu	Ile	Tyr	Gln	Ala 475	Gly	Ser	Thr	Pro	Cys 480
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Phe	Gln	Pro	Thr	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val
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Гла	Ser	Thr	Asn	Leu	Val	Lys	Asn	Lys	Суз	Val	Asn	Phe	Asn	Phe	Asn
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Ala	Val	595 Leu	Tyr	Gln	Asp	Val	600 Asn	Суз	Thr	Glu	Val	605 Pro	Val	Ala	Ile
His	6⊥0 Ala	Asp	Gln	Leu	Thr	ь15 Pro	Thr	Trp	Arg	Val	620 Tyr	Ser	Thr	Gly	Ser
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Ser	Tyr	Gln	660 Thr	Gln	Thr	Asn	Ser	665 Pro	Gln	Gln	Ala	Gln	670 Ser	Val	Ala
Leu	Gly	675 Ala	Glu	Asn	Ser	Val	680 Ala	Tyr	Ser	Asn	Asn	685 Ser	Ile	Ala	Ile
Pro	690 Thr	Asn	Phe	Thr	Ile	695 Ser	Val	- Thr	Thr	Glu	700 Ile	Leu	Pro	Val	Ser
705 Met	Thr	INC	Thr	Sor	710 Vəl	Dor	Cue	Thr		715 Tur	 T1-	Cve	Glv	Aan	720 Ser
met	TULL.	цув	1111	5er 725	va1	чар	сув	1111	730	ıyr	тте	сув	GTÀ	дэр 735	261
Thr	Glu	Сүз	Ser 740	Asn	Leu	Leu	Leu	Gln 745	Tyr	Gly	Ser	Phe	Cys 750	Thr	Gln
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Gln	Glu 770	Val	Phe	Ala	Gln	Val 775	Lys	Gln	Ile	Tyr	Lys 780	Thr	Pro	Pro	Ile
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Asp	Ile	Ala 835	Ala	Arg	Asp	Leu	Ile 840	Суз	Ala	Gln	Lys	Phe 845	Asn	Gly	Leu
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Leu	Met 1040	Ser	Phe	e Pro	Gln	Sei 104	2 A. 15	la P	ro H	is G	ly Va 10	al ' 050	Val	Phe	Leu
His	Val 1055	Thr	тут	Val	. Pro	Ala 106	a G: 50	ln G	lu Ly	ys A:	sn Pl 1(ne 065	Thr	Thr	Ala
Pro	Ala 1070	Il∈)	е Суз	His	a Asp	Gl ₃ 107	/ Ly 75	ys A	la H	is Pl	ne Pi 10	ro . 080	Arg	Glu	Gly
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Phe	Tyr 1100	Glu)	l Pro) Glr	n Ile	Ile 11(e T1)5	nr Ti	hr A	ab Ya	sn Tl 1:	nr L10	Phe '	Val	Ser
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Asp	Leu 1190	Glr	ı Glu	ı Lev	ı Gly	Ly: 119	3 T <u>3</u> 95	yr G	lu G	ln Ty	yr I. 12	Le : 200	Lys	Trp	Pro
Trp	Tyr 1205	Il∈	e Trp) Leu	ı Gly	Phe 121	e I: LO	le A	la G	ly Le	eu II 12	le . 215	Ala	Ile	Val

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Me	t V 1	al 220	Thr	: Ile	e Mei	t Leı	1 Cys 122	ε C _λ 25	∕s Me	et Tl	nr S	er Cy 1	ув 230	Суз	Ser	СЛа
Le	u L 1	ys 235	Gly	r Cys	э Су	s Sei	r Cy: 124	3 G] 10	Ly Se	∍r C	ya C	ys Lj 1:	ув 245	Phe	Asp	Glu
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Se	er V	al	Leu 35	His	Ser	Thr	Gln	Asp 40	Leu	Phe	Leu	Pro	Phe 45	Phe	Ser	Asn
Va	1 T 5	hr 0	Trp	Phe	His	Ala	Ile 55	His	Val	Ser	Gly	Thr 60	Asn	Gly	Thr	Lys
Ar 65	g F	he	Asp	Asn	Pro	Val 70	Leu	Pro	Phe	Asn	Asp 75	Gly	Val	Tyr	Phe	Ala 80
Se	er I	'hr	Glu	Lys	Ser 85	Asn	Ile	Ile	Arg	Gly 90	Trp	Ile	Phe	Gly	Thr 95	Thr
Le	eu A	ab	Ser	Lys 100	Thr	Gln	Ser	Leu	Leu 105	Ile	Val	Asn	Asn	Ala 110	Thr	Asn
Va	ιlV	al	Ile 115	Lys	Val	Сүз	Glu	Phe 120	Gln	Phe	Сүз	Asn	Asp 125	Pro	Phe	Leu
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Ar 14	g V	al	Tyr	Ser	Ser	Ala 150	Asn	Asn	Суз	Thr	Phe 155	Glu	Tyr	Val	Ser	Gln 160
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Ly	rs H	lis	Thr 195	Pro	Ile	Asn	Leu	Val 200	Arg	Asp	Leu	Pro	Gln 205	Gly	Phe	Ser
Al	.a L 2	eu 10	Glu	Pro	Leu	Val	Asp 215	Leu	Pro	Ile	Gly	Ile 220	Asn	Ile	Thr	Arg
Ph 22	ue G :5	ln	Thr	Leu	Leu	Ala 230	Leu	His	Arg	Ser	Tyr 235	Leu	Thr	Prc	Gly	Asp 240
Se	r S	er	Ser	Gly	Trp 245	Thr	Ala	Gly	Ala	Ala 250	Ala	Tyr	Tyr	Val	Gly 255	Tyr
Le	eu G	ln	Pro	Arg 260	Thr	Phe	Leu	Leu	Lys 265	Tyr	Asn	Glu	Asn	Gly 270	Thr	Ile
Th	ır A	ab	Ala 275	Val	Asp	Суа	Ala	Leu 280	Asp	Pro	Leu	Ser	Glu 285	Thr	. TÀa	Суа
Th	ır L	eu	Lys	Ser	Phe	Thr	Val	Glu	ГЛа	Gly	Ile	Tyr	Gln	Thr	Ser	Asn
Ph 30	ie A	rg	Val	Gln	Pro	Thr 310	Glu	Ser	Ile	Val	Arg 315	Phe	Pro	Asn	Ile	Thr 320

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Asn	Leu	Суз	Pro	Phe 325	Gly	Glu	Val	Phe	Asn 330	Ala	Thr	Arg	Phe	Ala 335	Ser
Val	Tyr	Ala	Trp 340	Asn	Arg	Lys	Arg	Ile 345	Ser	Asn	Суз	Val	Ala 350	Asp	Tyr
Ser	Val	Leu 355	Tyr	Asn	Ser	Ala	Ser 360	Phe	Ser	Thr	Phe	Lys 365	Cys	Tyr	Gly
Val	Ser 370	Pro	Thr	Lys	Leu	Asn 375	Asp	Leu	Cys	Phe	Thr 380	Asn	Val	Tyr	Ala
Asp 385	Ser	Phe	Val	Ile	Arg 390	Gly	Asp	Glu	Val	Arg 395	Gln	Ile	Ala	Pro	Gly 400
Gln	Thr	Gly	Lys	Ile 405	Ala	Asp	Tyr	Asn	Tyr 410	Lys	Leu	Pro	Asp	Asp 415	Phe
Thr	Gly	Суз	Val 420	Ile	Ala	Trp	Asn	Ser 425	Asn	Asn	Leu	Asp	Ser 430	Lys	Val
Gly	Gly	Asn 435	Tyr	Asn	Tyr	Leu	Tyr 440	Arg	Leu	Phe	Arg	Lys 445	Ser	Asn	Leu
ГЛа	Pro 450	Phe	Glu	Arg	Asp	Ile 455	Ser	Thr	Glu	Ile	Tyr 460	Gln	Ala	Gly	Ser
Thr 465	Pro	Суз	Asn	Gly	Val 470	Glu	Gly	Phe	Asn	Cys 475	Tyr	Phe	Pro	Leu	Gln 480
Ser	Tyr	Gly	Phe	Gln 485	Pro	Thr	Asn	Gly	Val 490	Gly	Tyr	Gln	Pro	Tyr 495	Arg
Val	Val	Val	Leu 500	Ser	Phe	Glu	Leu	Leu 505	His	Ala	Pro	Ala	Thr 510	Val	Сүз
Gly	Pro	Lys 515	Lys	Ser	Thr	Asn	Leu 520	Val	Lys	Asn	Lys	Сув 525	Val	Asn	Phe
Asn	Phe 530	Asn	Gly	Leu	Thr	Gly 535	Thr	Gly	Val	Leu	Thr 540	Glu	Ser	Asn	Lys
Lys 545	Phe	Leu	Pro	Phe	Gln 550	Gln	Phe	Gly	Arg	Asp 555	Ile	Ala	Asb	Thr	Thr 560
Asp	Ala	Val	Arg	Asp 565	Pro	Gln	Thr	Leu	Glu 570	Ile	Leu	Asp	Ile	Thr 575	Pro
Сүз	Ser	Phe	Gly 580	Gly	Val	Ser	Val	Ile 585	Thr	Pro	Gly	Thr	Asn 590	Thr	Ser
Asn	Gln	Val 595	Ala	Val	Leu	Tyr	Gln 600	Asp	Val	Asn	Суз	Thr 605	Glu	Val	Pro
Val	Ala 610	Ile	His	Ala	Asp	Gln 615	Leu	Thr	Pro	Thr	Trp 620	Arg	Val	Tyr	Ser
Thr 625	Gly	Ser	Asn	Val	Phe 630	Gln	Thr	Arg	Ala	Gly 635	Суз	Leu	Ile	Gly	Ala 640
Glu	His	Val	Asn	Asn 645	Ser	Tyr	Glu	Сув	Asp 650	Ile	Pro	Ile	Gly	Ala 655	Gly
Ile	Cys	Ala	Ser 660	Tyr	Gln	Thr	Gln	Thr 665	Asn	Ser	Pro	Gln	Gln 670	Ala	Gln
Ser	Val	Ala 675	Leu	Gly	Ala	Glu	Asn 680	Ser	Val	Ala	Tyr	Ser 685	Asn	Asn	Ser
Ile	Ala 690	Ile	Pro	Thr	Asn	Phe 695	Thr	Ile	Ser	Val	Thr 700	Thr	Glu	Ile	Leu
Pro 705	Val	Ser	Met	Thr	Lys 710	Thr	Ser	Val	Asp	Cys 715	Thr	Met	Tyr	Ile	Cys 720
Gly	Asp	Ser	Thr	Glu 725	СЛа	Ser	Asn	Leu	Leu 730	Leu	Gln	Tyr	Gly	Ser 735	Phe
Суз	Thr	Gln	Leu	Asn	Arg	Ala	Leu	Thr	Gly	Ile	Ala	Val	Glu	Gln	Asp

740 745 750 Lys Asn Thr Gin Glu Val Phe Ala Gin Val Lys Gin File Tyr Lys Thr 755 760 770 780 Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser Gin Ile Leu Pro 770 780 780 Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe 785 611 611 Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe 785 611 611 Cys Leu Gly Asp Ile Ala Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp 805 611 611 Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gln Lys Phe 825 611 611 Gin Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr Ser Gly Trp Thr 860 845 612 Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn 895 870 870 870 Gin Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln 900 905 811 812 Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Glu Leu Ser 930 925 940 Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 945 955 950 Lu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Arg Ala 990 990 975 Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ser Glu 955 950 Lu As																
Lys Asn Thr Gln Glu Val Phe Ala Gln Val Lys Gln Ile Tyr Lys Thr 760Pro Pro Ile Lys Asp Phe Gly Gly Phe Asn Phe Ser Gln Ile Leu Pro 775Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe 790Asp Pro Ser Lys Pro Ser Lys Arg Ser Phe Ile Glu Asp Leu Leu Phe 790Asn Lys Val Thr Leu Ala Asp Ala Gly Phe Ile Lys Gln Tyr Gly Asp 820Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala 835Gln Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr Ser Gly Trp Thr 650650Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala 855Gln Lys Leu The Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gly 850Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn 885Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Gln Leu Ser 900Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val 915Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 950Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 950Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ser Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ser Jasn Phe Gly Ala Ile Ser Asg Arg Set Ala Pro His Gly Val Val 970Ser Jasn Phe Gly Ala Ile Ser Asg Set Val Lau Asn Asp Ile Leu Ser Arg 950Ser Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ser Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ser Jash Phe Gly Ala Ile Ser Asg Gly Lys Asg Phe Cyc Gly Lys Gly 1010Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cyc Gly Lys Gly 1020Cys Val Leu Gly Gln Ser Lys Arg Val Asp Ph				740					745					750		
Pro Pro Pro Pro Ser Lys Arg Pro Ser Lys Arg Arg Pro Ser Lys Arg Arg Pro Ser Lys Arg Ser Lys Arg Ser Lys Arg A	Lys	Asn	Thr 755	Gln	Glu	Val	Phe	Ala 760	Gln	Val	Lys	Gln	Ile 765	Tyr	Lys	Thr
Asp 785ProSerLysArgSerPhe11eGluAspLeuAnd 810AsnLysValThrLeuAlaAlaAlgAspLeuFileLysGluTyGlyAspCysLeuGlyAspIAlaAlgAspLeuLeuThrAspGluMetIAlaAsnGlyLeuThrValLeuProProLeuThrAspGluMetIAlaGluTyrThrSerAlaLeuProProPheAlaGluMetAlaAlaSerGluThrThrAspAlaAlaAlaSerGluThrThrSerAlaAlaAspSerAlaAlaAlaSerAlaAlaAlaSerAlaAlaAlaSerAlaAlaAlaAlaSerAlaAlaAlaSerAlaAlaAlaSerAlaAlaSerAlaSerAlaIlaAlaAlaSerAlaIlaAlaAlaSerAlaIlaAlaAlaSerAlaIlaAlaAlaSerAlaIlaAlaAlaSerAlaIlaLeuAspAlaIlaAlaSerAlaIlaAlaAlaSerAlaIlaIlaAlaSerAlaIlaLeu<	Pro	Pro 770	Ile	Lys	Asp	Phe	Gly 775	Gly	Phe	Asn	Phe	Ser 780	Gln	Ile	Leu	Pro
Asn Lys Val Thr Leu Ala Asp Ala Gly Phe 1le Lys Gln Tyr Gly Asp 810Cys Leu Gly Asp Ile Ala Ala Arg Asp Leu Ile Cys Ala Gin Lys Phe 820Asn Gly Leu Thr Val Leu Pro Pro Leu Leu Thr Asp Glu Met Ile Ala 835Gin Tyr Thr Ser Ala Leu Leu Ala Gly Thr Ile Thr Ser Gly Trp Thr 860Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met 883Gin Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln 905Gin Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln 910Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val 915Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser 930Yar Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly 965Yar Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ser Asn Phe Gly Ala Ile Ser Lys Arg Val Asp Asp 985Yar Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Yar J Leu Gly Gln Ser Lys Arg Val Asp Phe Cys 	Asp 785	Pro	Ser	Lys	Pro	Ser 790	Гла	Arg	Ser	Phe	Ile 795	Glu	Asp	Leu	Leu	Phe 800
CysLeuGlyAspIteAlaArgArgAppLeuTheCysAlaGlnLysPheAsnGlyLeuThrValLeuProProLeuThrAspGluMetIteAlaSoftSoftAlaGlyAlaAlaLeuProProLeuThrTheThrSoftPheGlyAlaGlyAlaAlaAlaLeuGluAlaGluThrTheTheSoftTyrArgPheAsnGlyIteGlnAsnGlnAsnSoftSoftSoftSoftGlnLysLeuIteAlaAsnGlnPheAsnSoft </td <td>Asn</td> <td>Lys</td> <td>Val</td> <td>Thr</td> <td>Leu 805</td> <td>Ala</td> <td>Asp</td> <td>Ala</td> <td>Gly</td> <td>Phe 810</td> <td>Ile</td> <td>Lys</td> <td>Gln</td> <td>Tyr</td> <td>Gly 815</td> <td>Asp</td>	Asn	Lys	Val	Thr	Leu 805	Ala	Asp	Ala	Gly	Phe 810	Ile	Lys	Gln	Tyr	Gly 815	Asp
Asn Giy Leu Thr Val Leu Pro 840Pro Leu Leu Thr Asp Glu Met 11e Ala 845Gin Tyr Thr Ser Ala Leu Leu Ala Giy Thr IIe Thr Ser Giy Trp Thr 855Phe Giy Ala Giy Ala Ala Leu Gin IIe Pro Phe Ala Met Gin Met Ala 875Tyr Arg Phe Asn Giy IIe Giy Val Thr Gin Asn Val Leu Tyr Giu Asn 885Gin Lys Leu IIe Ala Asn Gin Phe Asn Ser Ala IIe Giy Lys IIe Gin 900Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Giy Lys Leu Gin Asp Val 935Val Asn Gin Asn Ala Gin Ala Leu Asn Thr Leu Val Lys Gin Leu Ser 945Ser Asn Phe Giy Ala 11e Ser Ser Val Leu Asn Asp IIe Leu Ser Arg 955Ser Asn Phe Giy Ala 11e Ser Ser Val Leu Asn Asp IIe Leu Ser Arg 955Arg Leu Gin Ser Leu Gin Thr Tyr Val Thr Gin Gin Leu IIe Thr Giv 965Arg Leu Gin Ser Leu Gin Thr Tyr Val Thr Gin Gin Leu Iie Arg Ala 980Ala Giu IIe Arg Ala Ser Ala Asn Leu Ala Arn Lys Met Ser Giu 1005Cyr Val 1025Leu His Val Thr Tyr Val Thr Gin Gin Lui Jie Arg Ala 985Phe Leu His Val Thr Tyr Val Pro Ala Gin Giu Lys Asn Phe Thr 1035Cin Giy Ala IIe Cyr His Asp Giy Lys Ala His Phe Pro Arg 1060Giu Giy Val Phe Val Ser Asp Giy Thr His Trp Phe 1065Ciu Giy Ser Chu Gin Pro Gin IIe IIe Thr Thr Asp Asn Thr Phe 1060Cin Giy Asn Cys Asp Val Sul Thr Gin Cin Leu Val Asp Asn Thr Phe 1095Val Ser Giy Asn Cys Asp Val Sul Thr Gin Cin Leu Asp Asp The Tyr Giu Giu 1120Leu Asp Pro Leu Gin Pro 1105Ciu Giy Sir Fry Fine Lys Asn Shar Thr Phe 1060Ciu Giy Asn Cys Asp Val Sul Thr His Trp Phe 1065Ciu Giy Asn Cys Asp Val Sul Thr Eine Thr Thr Asp 	Суз	Leu	Gly	Asp 820	Ile	Ala	Ala	Arg	Asp 825	Leu	Ile	Суз	Ala	Gln 830	Lys	Phe
GlnTyrThrSerAlaLeuAlaGlyThrIThrSecGlyThrThrPheGlyAlaGlyAlaAlaLeuGlnIleProPheAlaMetGlnMetAlaSecGlyAlaGlyAlaAlaLeuGlnIleProPheAlaMetGlnMetAlaSecLeuIleAlaAsnGlnPheAsnSerAlaIleGlyLeuGlyLysIleGlnAspSerLeuSerSerAsnGlnAlaSerAlaLeuGlyLysIleGlnAspSerLeuSerSerAsnAsnGlnAlaLeuAsnThrGlnAspVal930SerLeuSerSerAsnPheGlyAlaLeuSerAspYalSer44AsnClnAsnAsnAlaGluAlaLeuAsnAspYalSerSe	Asn	Gly	Leu 835	Thr	Val	Leu	Pro	Pro 840	Leu	Leu	Thr	Asp	Glu 845	Met	Ile	Ala
Phe Gly Ala Gly Ala Ala Leu Gln Ile Pro Phe Ala Met Gln Met Ala 870Tyr Arg Phe Asn Gly Ile Gly Val Thr Gln Asn Val Leu Tyr Glu Asn 885Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln 900Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val 915Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser 930Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 950Pat Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly 965Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu 1000Asp Lys Val Gln Ser Lys Arg Val Asp Phe Cys 995Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys 1015Cys Val Leu Het Ser Phe Pro 1020Tyr His Leu Met Ser Phe Pro 1030Cha Phe Asn Phe Tyr Glu Pro Ala Gln Glu Lys Asn Phe Thr 1045Cha Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln 1055Cha Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln 1055Cha Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln 1055Cha Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr 1100Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr 	Gln	Tyr 850	Thr	Ser	Ala	Leu	Leu 855	Ala	Gly	Thr	Ile	Thr 860	Ser	Gly	Trp	Thr
TyrArgPheAsnGlyIleGlyValThrGlnAsnValLeuTyrGluAsnGlnLysLeuIleAlaAsnGlnPheAsnSerAlaIleGlyLysIleGlnAspSerLeuSerSerThrAlaSerAlaLeuGlyLysLeuGlnAspVal910SerLeuSerAsnGlnAlaGlnAlaLeuAsnThrLeuValSerSerAsnGlnAsnAlaGlnAlaSerSerSerAsnPheGlyAlaIleSerSerValAsnAsnGlnLeuAspYalSerSerSerAsnPheGlySerSerSerSerPheClySerAsnPheClySer <td< td=""><td>Phe 865</td><td>Gly</td><td>Ala</td><td>Gly</td><td>Ala</td><td>Ala 870</td><td>Leu</td><td>Gln</td><td>Ile</td><td>Pro</td><td>Phe 875</td><td>Ala</td><td>Met</td><td>Gln</td><td>Met</td><td>Ala 880</td></td<>	Phe 865	Gly	Ala	Gly	Ala	Ala 870	Leu	Gln	Ile	Pro	Phe 875	Ala	Met	Gln	Met	Ala 880
Gln Lys Leu Ile Ala Asn Gln Phe Asn Ser Ala Ile Gly Lys Ile Gln 910Asp Ser Leu Ser Ser Thr Ala Ser Ala Leu Gly Lys Leu Gln Asp Val 915Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser 930Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 945Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 965Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly 965Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 980Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu 1000Cys Val Leu Met Ser Phe Pro Gln Ser Ala Pro His 1025Thr Ala Pro Ala Ile Cys His 1055Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp 1056Asn Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp 1056Asn Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp 1025Asn Asn Phe Tyr Glu Pro Gln Leu Asp Asp Phe Lys Glu Glu 1057Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp 1058Asn Phe Tyr Glu Pro Gln Leu Asp Ser Phe 1026Asp Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp 1026Asp Pro Leu Gln Pro 1105Val Ser Gly Asn Cys Asp Val 1122Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp 1130Leu Asp 1130Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp 	Tyr	Arg	Phe	Asn	Gly 885	Ile	Gly	Val	Thr	Gln 890	Asn	Val	Leu	Tyr	Glu 895	Asn
AspSerLeuSerSerThrAlaSerAlaLeuGlyLysLeuGlnAspValValAsnGlnAsnAlaGlnAlaLeuAsnThrLeuValLysGlnLeuSerSerAsnPheGlyAlaIleSerSerValLeuAsnAspIleLeuSerArg945SerAsnPheGlyAlaGluValGlnIleAspAspIleLeuSerArgArgSerArgLeuIleThrGly955ArgLeuGlnSerLeuGlnThrTyrValThrGlnGlnLeuIleArgAla960SerLeuGlnSerArgValThrTyrValThrGlnGlnLeuIleArgAla970970970970970970970970975ArgAlaGlyArgAlaGlyArgAlaGlyArgAlaGlyArgAlaGlyArgAlaGlyArgAlaGly970975ArgArgAlaGlyArgAlaGlyArgAlaGlyAlaAlaAlaArgAlaAlaArgAlaAlaArgAlaAlaArgAlaAlaAlaAlaAla	Gln	Lys	Leu	Ile 900	Ala	Asn	Gln	Phe	Asn 905	Ser	Ala	Ile	Gly	Lys 910	Ile	Gln
 Val Asn Gln Asn Ala Gln Ala Leu Asn Thr Leu Val Lys Gln Leu Ser 930 Ser Asn Phe Gly Ala Ile Ser Ser Val Leu Asn Asp Ile Leu Ser Arg 955 Leu Asp Lys Val Glu Ala Glu Val Gln Ile Asp Arg Leu Ile Thr Gly 965 Arg Leu Gln Ser Leu Gln Thr Tyr Val Thr Gln Gln Leu Ile Arg Ala 985 Ala Glu Ile Arg Ala Ser Ala Asn Leu Ala Ala Thr Lys Met Ser Glu 1000 Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly 1010 Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly Val Val 1025 Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn Phe Thr 1040 Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe Pro Arg 1055 Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln 1075 Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr 1100 Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr 1110 Val Sup Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu 1135 Leu Asp Lys Tyr Phe Lys Asn Ala Ser Val Val Asn Ile Gln Lys 	Asp	Ser	Leu 915	Ser	Ser	Thr	Ala	Ser 920	Ala	Leu	Gly	Lys	Leu 925	Gln	Asp	Val
Ser 945Asn PheGly AlaIle 950Ser 950Val 201Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 205Leu 205Asp 	Val	Asn 930	Gln	Asn	Ala	Gln	Ala 935	Leu	Asn	Thr	Leu	Val 940	Lys	Gln	Leu	Ser
LeuAspLysValGluAlaGluValGlnJespArgLeuGlnSerLeuGlnThrTyrValThrGlnGlnLeuIleArgAla980SerLeuGlnSerAlaAsnLeuAlaAlaThrLysMetSerGluAlaGluJleArgAlaSerAlaAsnLeuAlaThrLysMetSerGlu995ValLeuGlyGlnSerLysArgValAspPheCysGlyLysGly1010LeuGlyGlnSerLysArgValAspPheCysGlyLysGly1010LeuGlyGlnSerPheProAlaFroAlaFroCysGlyValVal1025CuMetSerPheProAlaGlnSerAspPheCysGlyValVal1025CuMetSerPheProAlaGlnFroAlaGlnLysAsnPheTroTroTroTroTroTroTroTroTroTroTroTroTroAlaHisCysAsnPhoArgAsnPhoArgAsnPhoArgAsnPhoArgAsnAsnTroTroTroTroTroTroTroTroTroTroTroTroTroTroTroTroTroTr	Ser 945	Asn	Phe	Gly	Ala	Ile 950	Ser	Ser	Val	Leu	Asn 955	Asp	Ile	Leu	Ser	Arg 960
ArgLeuGlnSerLeuGlnThrTyrValThrGlnLeuIleArgAlaAlaGluIleArgAlaSerAlaAsnLeuAlaAnrLysMetSerGluCysValLeuGlyGlnSerLysArgValAspPheCysGlyLysGlyGlyTyrHisLeuMetSerPheProAlaGlnSerAlaProHisGlyValValPheLeuHisValThrTyrValProAlaGlnGluLysAsnPheThr1040ThrTyrValThrTyrValProAlaGluLysAsnPheThr1040ThrTyrValThrTyrValProAlaGluLysAsnPheThr1040ThrTyrValThrTyrValProAlaGluLysAsnPheThr1040ThrTyrValProAlaGluLysAsnPheThrThrThr1045ProAlaGluSerGlyLysAsnThr	Leu	Asp	Lys	Val	Glu 965	Ala	Glu	Val	Gln	Ile 970	Asp	Arg	Leu	Ile	Thr 975	Gly
AlaGluIle Arg Ala Ser Ala Asn 1000Leu Ala AlaThrLysMet Ser GluCysValLeu GlyGln SerLysArgValAspPheCys 1020GlyLysGlyTyrHisLeu MetSerPhePro 1030Gln SerAlaProHis 1035GlyValValPheLeuHisValThrTyrVal 1045ProAlaGluLysAsnPheThrThrAlaPro 1055AlaIleCysHis 1045AspGlyLysAlaHis 1050PhoArgGluGlyValPheValSerAsnGlyLysAlaHis 1065PhoArgArgAsnPheTyrGluProGlnIleThrHisTrpPheValSerGlyAsnCysAspValValThrHisTrpPheValSerGlyAsnCysAspValValIleGlyIleValAsnThrPheValSerGlyAsnCysAspValValIleGlyIleValAsnThrHisIntoGlyAsnCysAspValValIleGlyIleValAsnThrHisInfIleIleIleIleIleIleIleIle <td>Arg</td> <td>Leu</td> <td>Gln</td> <td>Ser 980</td> <td>Leu</td> <td>Gln</td> <td>Thr</td> <td>Tyr</td> <td>Val 985</td> <td>Thr</td> <td>Gln</td> <td>Gln</td> <td>Leu</td> <td>Ile 990</td> <td>Arg</td> <td>Ala</td>	Arg	Leu	Gln	Ser 980	Leu	Gln	Thr	Tyr	Val 985	Thr	Gln	Gln	Leu	Ile 990	Arg	Ala
CysVal 1010Leu Gly Gln SerLys 1015Arg Val Asp PheCys 1020Gly Lys GlyTyrHis 1025Leu MetSer PhePro 1030Gln Ser Ala Pro 1036His 1035Gly Val Val Val 1035PheLeu 1040His ValThr TyrYal 	Ala	Glu	Ile 995	Arg	Ala	Ser	Ala	Asn 100(Le [:] 0	u Al	a Al	a Th	r Ly 10	s M 05	et S	er G
TyrHis 1025Leu MetSerPhePro 1030GlnSerAlaPro AlaGlyValValValPheLeu 1040HisValThrTyrVal 1045ProAlaGlnGluLys 1050AsnPheThrThrAla 1055ProAlaIleCysHis 1060AspGlyLysAlaHis 1055PheProArgGluGly 1070ValPheValSer 1075AsnGlyThrHis 1075TrpPhe 1080ValThrGlnArg 1085Asn 1085PheTyrGluPro 	Сүз	Val 1010	Lei	ı Gly	y Glı	n Sei	r Ly: 10:	s Ai 15	rg V	al A	ap P	he C 1	уз 020	Gly	Lys	Gly
PheLeuHisValThrTyrValProAlaGluGluLysAsnPheThrThrAlaProAlaIleCysHisAspGlyLysAlaHisPheProArgGluGlyValPheValSerAsnGlyThrHisTrpPheValThrGlnGluGlyValPheValSerAsnGlyThrHisTrpPheValThrGlnArgAsnPheTyrGluProGlnIleThrThrAspAsnThrPheYalAsnPheTyrGluProGluLeuAspSerPheTyrAspThrPhoYalTyrAspProLeuGluProAspYalYalYalYalYalYalYalYalYalAspProLeuGluProAspYal <td< td=""><td>Tyr</td><td>His 1025</td><td>Lei 5</td><td>ı Met</td><td>t Se:</td><td>r Phe</td><td>e Pro 103</td><td>5 GI 30</td><td>ln S</td><td>er A</td><td>la P</td><td>ro H 1</td><td>is 035</td><td>Gly</td><td>Val</td><td>Val</td></td<>	Tyr	His 1025	Lei 5	ı Met	t Se:	r Phe	e Pro 103	5 GI 30	ln S	er A	la P	ro H 1	is 035	Gly	Val	Val
ThrAlaProAlaIleCysHisAspGlyLysAlaHisPheProArgGluGlyValPheValSerAsnGlyThrHisTrpPheValThrGlnArgAsnPheTyrGluProGlnIleIleThrHisTrpPheValThrGlnArgAsnPheTyrGluProGlnIleIleThrThrAspAsnThrPheValSerGlyAsnCysAspValValIleGlyIleValAsnAsnThrPheValTyrAspProLeuGluLeuAspSerProAspIleGluLeuAspSerProAspLeuAspLeuAspIleGluLeuAspIleGluAspLeuAspIleGluLeuAspIleGluLeuAspIleIleGluLeuAspIle </td <td>Phe</td> <td>Leu 1040</td> <td>Hi:</td> <td>e Val</td> <td>l Th:</td> <td>r Tyj</td> <td>r Va 104</td> <td>1 Pi 45</td> <td>ro A</td> <td>la G</td> <td>ln G</td> <td>lu L 1</td> <td>уа 050</td> <td>Asn</td> <td>Phe</td> <td>Thr</td>	Phe	Leu 1040	Hi:	e Val	l Th:	r Tyj	r Va 104	1 Pi 45	ro A	la G	ln G	lu L 1	уа 050	Asn	Phe	Thr
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 Val Ser Gly Asn Cys Asp Val Val Ile Gly Ile Val Asn Asn Thr 1100 Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu 1120 Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp 1140 Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys 	Arg	Asn 1085	Phe 5	e Ty:	r Glı	ı Pro	5 Gli 109	n II 90	le I	le T	hr T	hr A 1	sp 095	Asn	Thr	Phe
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Leu Asp Lys Tyr Phe Lys Asn His Thr Ser Pro Asp Val Asp Leu 1130 1135 1140 Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys	Val	Tyr	Asl	o Pro	o Lei	ı Glr	n Pro	5 GI 20	lu L	eu A	ap S	er P	he 125	Lys	Glu	Glu
Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys	Leu	Asp	Ly	з Ту:	r Phe	∋ Ly:	s Asi	л Н: 25	is T	hr S	er P	ro A	.sp	Val	Asp	Leu
	Gly	Yab TT3(, Ile	e Se:	r Gly	y Il€	11: e Asi	35 n Al	la S	er V	al V	1 al A	140 .sn	Ile	Gln	Гла

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Leu	Ile 1175	Asp) Lei	ı Glr	n Glu	Leu 118	. G: 0	Ly L	ys	Tyr	G]	Lu G 1	ln 185	Tyr	Ile	Lys
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Ser	Cys 1220	Leu	ц Буя	s Gly	y Cys	Cys 122	S€ 5	er C	уa	Gly	Se	er C 1	уя 230	Сүз	Lys	Phe
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His	Val 1055	Th:	т Туз	r Val	L Pro	> Ala 106	a G1 50	ln G	lu Ly	/s A:	sn Pl 10	ne 1 065	Thr 1	Thr A	Ala
Pro	Ala 1070	Ile)	е Су:	3 Hi:	a yał	9 Gly 107	/ L3 75	/s Al	la Hi	ls Pl	ne P: 10	ro 2 080	Arg (Glu (Gly
Val	Phe	Va]	l Sei	Ası	n Gly	/ Thi	: H:	is Tı	rp Pł	ne Va	al Tl	nr (Gln A	Arg A	Asn

	_	_			_	_	_		_	_	_	_	_	_	_	_	
-	_	1085	_	_	_	_	109	0	_		_	_	_	1095	_	_	
:	Phe	Tyr 1100	Glu	ı Pro	o Glr	n Ile	e Ile 110	e Tl)5	hr '	「hr	Asp) As	sn	Thr 1110	Phe	Val	Ser
(Gly	Asn 1115	Суз	a yal	p Val	L Val	. Ile 112	e Gi 20	ly :	Ile	Val	. As	en i	Asn 1125	Thr	Val	Tyr
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1	Asp	Asp 1250	Ser	: Glu	ı Pro	> Val	. Leu 125	1 L <u>1</u> 55	γs (Gly	Val	. Цу	75	Leu 1260	His	Tyr	Thr
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Gly	Pro	Lys 515	Lys	Ser	Thr	Asn	Leu 520	Val	Lys	Asn	LÀa	Суя 525	Val	Asn	Phe
Asn	Phe 530	Asn	Gly	Leu	Thr	Gly 535	Thr	Gly	Val	Leu	Thr 540	Glu	Ser	Asn	Lya
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Thr 625	Gly	Ser	Asn	Val	Phe 630	Gln	Thr	Arg	Ala	Gly 635	Сув	Leu	Ile	Gly	Ala 640
Glu	His	Val	Asn	Asn 645	Ser	Tyr	Glu	Cys	Asp 650	Ile	Pro	Ile	Gly	Ala 655	Gly
Ile	Cys	Ala	Ser 660	Tyr	Gln	Thr	Gln	Thr 665	Asn	Ser	Pro	Gln	Gln 670	Ala	Gln
Ser	Val	Ala 675	Ser	Gln	Ser	Ile	Ile 680	Ala	Tyr	Thr	Met	Ser 685	Leu	Gly	Ala
Glu	Asn 690	Ser	Val	Ala	Tyr	Ser 695	Asn	Asn	Ser	Ile	Ala 700	Ile	Glu	Ile	Leu
Pro 705	Val	Ser	Met	Thr	Lys 710	Thr	Ser	Val	Aab	Cys 715	Thr	Met	Tyr	Ile	Cys 720
Gly	Aab	Ser	Thr	Glu 725	CAa	Ser	Asn	Leu	Leu 730	Leu	Gln	Tyr	Gly	Ser 735	Phe
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Gln	Tyr 850	Thr	Ser	Ala	Leu	Leu 855	Ala	Gly	Thr	Ile	Thr 860	Ser	Gly	Trp	Thr
Phe 865	Gly	Ala	Gly	Ala	Ala 870	Leu	Gln	Ile	Pro	Phe 875	Ala	Met	Gln	Met	Ala 880
Tyr	Arg	Phe	Asn	Gly 885	Ile	Gly	Val	Thr	Gln 890	Asn	Val	Leu	Tyr	Glu 895	Asn
Gln	ГЛа	Leu	Ile 900	Ala	Asn	Gln	Phe	Asn 905	Ser	Ala	Ile	Gly	Lys 910	Ile	Gln
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Cys Val Leu Gly Gln Ser Lys Arg Val Asp Phe Cys Gly Lys Gly 1010 1015 1020

Tyr His Leu Met Ser Phe Pro Gln Ser Ala Pro His Gly Val Val 1025 1030 1035
Phe Leu His Val Thr Tyr Val Pro Ala Gln Glu Lys Asn Phe Thr 1040 1045 1050
Thr Ala Pro Ala Ile Cys His Asp Gly Lys Ala His Phe Pro Arg 1055 1060 1065
Glu Gly Val Phe Val Ser Asn Gly Thr His Trp Phe Val Thr Gln 1070 1075 1080
Arg Asn Phe Tyr Glu Pro Gln Ile Ile Thr Thr Asp Asn Thr Phe
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Val Tyr Asp Pro Leu Gln Pro Glu Leu Asp Ser Phe Lys Glu Glu
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1130 1135 1140 Gly Asp Ile Ser Gly Ile Asn Ala Ser Val Val Asn Ile Gln Lys
1145 1150 1155 Glu Ile Asp Arg Leu Asp Glu Val Ala Lys Asp Leu Asp Glu Ser
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Leu He Asp Leu Gin Giu Leu Giy Lys Tyr Giu Gin Tyr Ile Lys 1175 1180 1185
Trp Pro Trp Tyr Ile Trp Leu Gly Phe Ile Ala Gly Leu Ile Ala 1190 1195 1200
Ile Val Met Val Thr Ile Met Leu Cys Cys Met Thr Ser Cys Cys 1205 1210 1215
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Lys Ser Asn Ile Ile Arg Gly Trp Ile Phe Gly Thr Thr Leu Asp Ser 100 105 110

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Val	Phe	Lys 195	Asn	Ile	Asp	Gly	Tyr 200	Phe	Lys	Ile	Tyr	Ser 205	Lys	His	Thr	
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His	Val 1055	Thi	Tyr	Val	Pro	Ala 1060	Gln	Glu	Lys	Asn	Phe 1065	Thr	Thr	Ala
Pro	Ala 1070	Ile)	е Сує	His	Asp	Gly 1075	Lys	Ala	His	Phe	Pro 1080	Arg	Glu	Gly
Val	Phe 1085	Va]	. Ser	Asr	Gly	Thr 1090	His	Trp	Phe	Val	Thr 1095	Gln	Arg	Asn
Phe	Tyr 1100	Glu)	ı Pro	Glr	lle	Ile 1105	Thr	Thr	Aap	Asn	Thr 1110	Phe	Val	Ser
Gly	Asn 1115	Cya	a yab	Val	Val	Ile 1120	Gly	Ile	Val	Asn	Asn 1125	Thr	Val	Tyr
Aap	Pro 1130	Leu)	ı Glr	Pro	Glu	Leu 1135	Asp	Ser	Phe	Lys	Glu 1140	Glu	Leu	Asp
Lys	Tyr 1145	Phe	е Lуа	Asr	His	Thr 1150	Ser	Pro	Asp	Val	Asp 1155	Leu	Gly	Asp
Ile	Ser 1160	Gl}	⁄ Il∈	Asr.	Ala	Ser 1165	Val	Val	Asn	Ile	Gln 1170	Lys	Glu	Ile
Asp	Arg 1175	Leu	ı Asr	Glu	. Val	Ala 1180	Lys	Asn	Leu	Asn	Glu 1185	Ser	Leu	Ile
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Leu	Lys 1235	Gly	и Суа	Суз	Ser	Cys 1240	Gly	Ser	Суз	Сүз	Lys 1245	Phe	Asp	Glu
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Ser	Val	Leu 35	His	Ser	Thr	Gln A	зр L. Э	eu P	he L	eu Pi	ro Phe 45	Phe	e Ser	Asn

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Val	Val	Ile 115	Lys	Val	CAa	Glu	Phe 120	Gln	Phe	Сүз	Asn	Asp 125	Pro	Phe	Leu
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ГЛа	Arg	Ser	Phe	Ile 805	Ala	Asp	Ala	Gly	Phe 810	Ile	Lys	Gln	Tyr	Gly 815	Asp
Сүз	Leu	Gly	Asp 820	Ile	Ala	Ala	Arg	Asp 825	Leu	Ile	Сүз	Ala	Gln 830	Lys	Phe
Asn	Gly	Leu 835	Thr	Val	Leu	Pro	Pro 840	Leu	Leu	Thr	Asp	Glu 845	Met	Ile	Ala
Gln	Tyr 850	Thr	Ser	Ala	Leu	Leu 855	Ala	Gly	Thr	Ile	Thr 860	Ser	Gly	Trp	Thr
Phe 865	Gly	Ala	Gly	Ala	Ala 870	Leu	Gln	Ile	Pro	Phe 875	Ala	Met	Gln	Met	Ala 880
Tyr	Arg	Phe	Asn	Gly	Ile	Gly	Val	Thr	Gln	Asn	Val	Leu	Tyr	Glu	Asn

-continued

										_		_				_	
				885					89	0					89	95	
Gln	Lys	Leu	Ile 900	Ala	Asn	Gln	Phe	Asn 905	Se	rΑ	la	11	e Gl	у Ly 91	s I] 0	Le	Gln
Asp	Ser	Leu 915	Ser	Ser	Thr	Ala	Ser 920	Ala	Le	u G	ly	Ьγ	s Lei 92!	ı Gl 5	n As	p	Val
Val	Asn 930	Gln	Asn	Ala	Gln	Ala 935	Leu	Asn	Th	r L	eu	Va 94	l Ly: 0	s Gl	n Le	eu	Ser
Ser 945	Asn	Phe	Gly	Ala	Ile 950	Ser	Ser	Val	Le	u A 9	sn 55	Asj	p Ile	e Le	u Se	er	Arg 960
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Arg	Leu	Gln	Ser 980	Leu	Gln	Thr	Tyr	Val 985	Th	r G	ln	Gl	n Lei	ı Il 99	е А1 0	g	Ala
Ala	Glu	Ile 995	Arg	Ala	Ser	Ala	Asn 1000	Le)	u A	la	Ala	i Tl	hr Ly 10	ខ្ទ 205	Met	Se	er Glu
Суз	Val 1010	Leu	Gly	/ Glr	ı Ser	: Lys 101	3 A: .5	rg V	al .	Asp	Ph	ne i	Cys 1020	Gly	Lys	3 (Gly
Tyr	His 1025	Leu	. Met	: Ser	Phe	e Pro 103	5 G. 80	ln S	er.	Ala	. Pr	:o 1	His 1035	Gly	Va]	LT	Val
Phe	Leu 1040	His	Va]	l Thr	Туг	: Va] 104	L P:	ro A	la	Gln	Gl	.u	Lys 1050	Asn	Ph€	è !	Thr
Thr	Ala 1055	Pro	Ala	a Ile	e Cya	8 His 106	3 A: 50	∃p G	ly	Lys	Al	.a I	His 1065	Phe	Pro	Ż	Arg
Glu	Gly 1070	Val	Phe	e Val	. Ser	: Asr 107	n G: 75	ly T	hr	His	Tr	р	Phe 1080	Val	Thi	c (Gln
Arg	Asn 1085	Phe	ту1	r Glu	l Pro	Glr 109	n I: 90	le I	le	Thr	Th	ır .	Asp 1095	Asn	Thi	: 1	Phe
Val	Ser 1100	Gly	Asr	n Cya	Asp) Va] 110	L Va 05	al I	le	Gly	· 11	.e `	Val 1110	Asn	Asr	1 '	Thr
Val	Tyr 1115	Asp	Pro) Leu	ı Glr	n Pro 112	G: 20	lu L	eu .	Asp	s∈	er i	Phe 1125	Lys	Glu	1 (Glu
Leu	Asp 1130	Lys	Туг	: Phe	е Буз	s Asr 113	n H: 85	is T	hr	Ser	Pr	:o	Asp 1140	Val	Asp	5 1	Leu
Gly	Asp 1145	Ile	sei	c Gly	′ Il€	e Asr 115	n A: 50	la S	er	Val	. V <i>e</i>	11	Asn 1155	Ile	Glr	ı 1	Lys
Glu	Ile 1160	Asp	Arg	g Leu	ı Asr	1 Glu 116	1 Va 55	al A	la	Lys	As	n	Leu 1170	Asn	Glu	1 :	Ser
Leu	Ile 1175	Asp) Leu	ı Glr	ı Glu	1 Leu 118	1 G. 30	ly L	Уз	Tyr	Gl	.u	Gln 1185	Tyr	Ile	e]	ГЛа
Trp	Pro 1190	Trp	ту1	r Ile	e Tr <u>p</u>) Leu 119	1 G. 95	ly P	he	Ile	e A1	.a	Gly 1200	Leu	Ile	e i	Ala
Ile	Val 1205	Met	Va]	l Thr	Il€	e Met 121	: Le .0	∋u C	Уa	Cya	M∈	et	Thr 1215	Ser	Суя	; (Суз
Ser	Cys 1220	Leu	L Lys	s Gly	r Cys	су: 122	3 Se 25	∍r C	Ув -	Gly	s∈	r	Cys 1230	Суз	Lys	3]	Phe
Asp	Glu 1235	Asp) Ast) Ser	Glu	1 Pro 124	> V∂	al L	eu	Lys	G1	-y	Val 1245	Lys	Leu	11	His
Tyr	Thr 1250																

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US 10,953,089 B1

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Thr Phe Lys Cys Tyr Gly Val Ser Pro Thr Lys Leu Asn Asp Leu Cys 50 55 60
Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val 65 70 75 80
Arg Gln Ile Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr 85 90 95
Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn 100 105 110
Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu 115 120 125
Phe Arg Lys Ser Asn Leu Lys Pro Phe Glu Arg Asp Ile Ser Thr Glu 130 135 140
Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn 145 150 155 160
Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val 165 170 175
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coronavirus <400> SEQUENCE: 71

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Ala Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser

Thr Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val

Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala

Asn Asp Thr Lys	Ile Ala Ser Gln L	u Gly Asn Cys Val	. Glu Tyr
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20	2		30
Phe Ala Ser Val	Tyr Ala Trp Asn A	g Lys Arg Ile Ser	Asn Cys Val
35	40	45	
Ala Asp Tyr Ser	Val Leu Tyr Asn S	r Ala Ser Phe Ser	Thr Phe Lys
50	55	60	
Cys Tyr Gly Val	Ser Pro Thr Lys L	u Asn Asp Leu Cys	9 Phe Thr Asn
65	70	75	80
Val Tyr Ala Asp	Ser Phe Val Ile A	g Gly Asp Glu Val	. Arg Gln Ile
	85	90	95
Ala Pro Gly Gln	Thr Gly Lys Ile A	a Asp Tyr Asn Tyr	Lys Leu Pro
100	1	5	110
Asp Asp Phe Thr	Gly Cys Val Ile A	a Trp Asn Ser Asn	n Asn Leu Asp
115	120	125	5
Ser Lys Val Gly	Gly Asn Tyr Asn T	r Leu Tyr Arg Leu	l Phe Arg Lys
130	135	140	
Ser Asn Leu Lys	Pro Phe Glu Arg A	p Ile Ser Thr Glu	1 Ile Tyr Gln
145	150	155	160
Ala Gly Ser Thr	Pro Cys Asn Gly V	l Glu Gly Phe Asn	n Cys Tyr Phe
	165	170	175
Pro Leu Gln Ser	Tyr Gly Phe Gln P	o Thr Asn Gly Val	. Gly Tyr Gln
180	1	5	190
Pro Tyr Arg Val	Val Val Leu Ser P	e Glu Leu Leu His	a Ala Pro Ala
195	200	205	5
Thr Val Cys Gly	Pro Lys Lys Ser T	r Asn Leu Val Lys	s Asn Lys Cys
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Val Asn Phe Asn	Phe Asn Gly Leu T	r Gly Thr Gly Val	. Leu Thr Glu
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Ser Asn Lys Lys	Phe Leu Pro Phe G	n Gln Phe Gly Arg	; Asp Ile Ala
	245	250	255
Asp Thr Thr Asp	Ala Val Arg Asp P	o Gln Thr Leu Glu	1 Ile Leu Asp
260	2	5	270
Ile Thr Pro Cys	Ser Phe Gly Gly V	l Ser Val Ile Thr	Pro Gly Thr
275	280	285	
Asn Thr Ser Asn	Gln Val Ala Val L	u Tyr Gln Asp Val	. Asn Cys Thr
290	295	300	
Glu Arg Phe Pro	Asn Ile Thr Asn L	u Cys Pro Phe Gly	7 Glu Val Phe
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Asn Ala Thr Arg	Phe Ala Ser Val T	r Ala Trp Asn Arg	1 Lys Arg Ile
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Ser Asn Cys Val	Ala Asp Tyr Ser V	l Leu Tyr Asn Ser	Ala Ser Phe
340	3	5	350

Ser Cve	Thr														
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CYD	Phe 370	Thr	Asn	Val	Tyr	Ala 375	Asp	Ser	Phe	Val	Ile 380	Arg	Gly	Asp	Glu
Val 385	Arg	Gln	Ile	Ala	Pro 390	Gly	Gln	Thr	Gly	Lys 395	Ile	Ala	Asp	Tyr	Asn 400
Tyr	Lys	Leu	Pro	Asp 405	Asp	Phe	Thr	Gly	Cys 410	Val	Ile	Ala	Trp	Asn 415	Ser
Asn	Asn	Leu	Asp 420	Ser	Гла	Val	Gly	Gly 425	Asn	Tyr	Asn	Tyr	Leu 430	Tyr	Arg
Leu	Phe	Arg 435	Lys	Ser	Asn	Leu	Lys 440	Pro	Phe	Glu	Arg	Asp 445	Ile	Ser	Thr
Glu	Ile 450	Tyr	Gln	Ala	Gly	Ser 455	Thr	Pro	Суз	Asn	Gly 460	Val	Glu	Gly	Phe
Asn 465	Суз	Tyr	Phe	Pro	Leu 470	Gln	Ser	Tyr	Gly	Phe 475	Gln	Pro	Thr	Asn	Gly 480
Val	Gly	Tyr	Gln	Pro 485	Tyr	Arg	Val	Val	Val 490	Leu	Ser	Phe	Glu	Leu 495	Leu
His	Ala	Pro	Ala	Thr	Val	Суз	Gly	Pro	Гуз	Lys	Ser	Ala	Ile	Gly	Gly
Tyr	Ile	Pro	Glu	Ala	Pro	Arg	Asp	Gly	Gln	Ala	Tyr	Val	Arg	Lys	Asp
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Asn	Ivs	195 Cvs	Val	Asn	Phe	Asn	200 Phe	Asn	Glv	Leu	Thr	205 Glv	Thr	Glv	Val	
11011	210	сyы	Tar	11011	T IIC	215	1 IIC	11011	Gry	ЦСu	220	ULY		Gry	Var	
Leu 225	Thr	Glu	Ser	Asn	Lys 230	Lys	Phe	Leu	Pro	Phe 235	Gln	Gln	Phe	Gly	Arg 240	
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Asp 385	Tyr	Asn	Tyr	Гла	Leu 390	Pro	Asp	Asp	Phe	Thr 395	Gly	Сүз	Val	Ile	Ala 400	
Trp	Asn	Ser	Asn	Asn 405	Leu	Asp	Ser	Lys	Val 410	Gly	Gly	Asn	Tyr	Asn 415	Tyr	
Leu	Tyr	Arg	Leu	Phe	Arg	Lys	Ser	Asn	Leu	Lys	Pro	Phe	Glu	Arg	Asp	
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Glu	Gly 450	Phe	Asn	Суз	Tyr	Phe 455	Pro	Leu	Gln	Ser	Tyr 460	Gly	Phe	Gln	Pro	
Thr 465	Asn	Gly	Val	Gly	Tyr 470	Gln	Pro	Tyr	Arg	Val 475	Val	Val	Leu	Ser	Phe 480	
Glu	Leu	Leu	His	Ala	Pro	Ala	Thr	Val	Cys	Gly	Pro	Гла	Lys	Ser	Ala	
TIA	Glv	Glv	ዋህም	485 Tle	Pro	Glu	∠ا⊳	Pro	490 Arc	Agn	Glv	Glr	دا۵	495 Tvr	Val	
- 1G	зту	Сту	500	- <u>-</u> - E	110	JIU	лта	505	тy	чар	сту	111	510	тут	vai	
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Phe	Ala	Ser 35	Val	Tyr	Ala	Trp	Asn 40	Arg	Lys	Arg	Ile	Ser 45	Asn	Cys	Val
Ala	Asp 50	Tyr	Ser	Val	Leu	Tyr 55	Asn	Ser	Ala	Ser	Phe 60	Ser	Thr	Phe	Lys
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Val 225	Asn	Phe	Asn	Phe	Asn 230	Gly	Leu	Thr	Gly	Thr 235	Gly	Val	Leu	Thr	Glu 240
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Val 385	Arg	Gln	Ile	Ala	Pro 390	Gly	Gln	Thr	Gly	Lys 395	Ile	Ala	Asp	Tyr	Asn 400
Tyr	Lys	Leu	Pro	Asp 405	Asp	Phe	Thr	Gly	Cys 410	Val	Ile	Ala	Trp	Asn 415	Ser
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Tyr	Ile	Pro 515	Glu	Ala	Pro	Arg	Asp 520	Gly	Gln	Ala	Tyr	Val 525	Arg	Lys	Asp
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Arg	Gln	Ile	Ala	Pro 85	Gly	Gln	Thr	Gly	Lys 90	Ile	Ala	Asp	Tyr	Asn 95	Tyr
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Gly	Tyr	Gln	Pro 180	Tyr	Arg	Val	Val	Val 185	Leu	Ser	Phe	Glu	Leu 190	Leu	His
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Glu 305	Val	Phe	Asn	Ala	Thr 310	Arg	Phe	Ala	Ser	Val 315	Tyr	Ala	Trp	Asn	Arg 320
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Ala	Ser	Phe	Ser 340	Thr	Phe	Lys	Cys	Tyr 345	Gly	Val	Ser	Pro	Thr 350	Lys	Leu
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Phe	Ala	Ser 35	Val	Tyr	Ala	Trp	Asn 40	Arg	Lys	Arg	Ile	Ser 45	Asn	Сув	Val
Ala	Asp 50	Tyr	Ser	Val	Leu	Tyr 55	Asn	Ser	Ala	Ser	Phe 60	Ser	Thr	Phe	Lys
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Pro	Tyr	Arg 195	Val	Val	Val	Leu	Ser 200	Phe	Glu	Leu	Leu	His 205	Ala	Pro	Ala
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Leu	Ser	Ala 435	Ile	Gly	Gly	Tyr	Ile 440	Pro	Glu	Ala	Pro	Arg 445	Asp	Gly	Gln
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255

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 75
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Thr 225	Asn	Leu	Суз	Pro	Phe 230	Gly	Glu	Val	Phe	Asn 235	Ala	Thr	Lys	Phe	Pro 240
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Ser	Thr	Gly	Asn 340	Tyr	Asn	Tyr	Lys	Tyr 345	Arg	Tyr	Leu	Arg	His 350	Gly	ГЛа
Leu	Arg	Pro 355	Phe	Glu	Arg	Asp	Ile 360	Ser	Asn	Val	Pro	Phe 365	Ser	Pro	Asp
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Суя 65	Tyr	Gly	Val	Ser	Pro 70	Thr	Lys	Leu	Asn	Asp 75	Leu	Сүз	Phe	Thr	Asn 80
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Ala Pro Gly Gln Thr Gly Lys Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Thr Gly Cys Val Ile Ala Trp Asn Ser Asn Asn Leu Asp Ser Lys Val Gly Gly Asn Tyr Asn Tyr Leu Tyr Arg Leu Phe Arg Lys Ser Asn Leu Lys Pro Phe Glu Arg Asp Ile Ser Thr Glu Ile Tyr Gln Ala Gly Ser Thr Pro Cys Asn Gly Val Glu Gly Phe Asn Cys Tyr Phe Pro Leu Gln Ser Tyr Gly Phe Gln Pro Thr Asn Gly Val Gly Tyr Gln Pro Tyr Arg Val Val Val Leu Ser Phe Glu Leu Leu His Ala Pro Ala Thr Val Cys Gly Pro Lys Lys Ser Gly Gly Gly Ser Gly Gly Gly Ser 210 215 Gly Gly Gly Ser Gly Gly Gly Ser Phe Glu Ala Lys Pro Ser Gly Ser Val Val Ala Glu Gly Val Glu Cys Asp Phe Ser Pro Leu Leu Ser Gly Thr Pro Pro Gln Val Tyr Asn Phe Lys Arg Leu Val Phe Thr Asn Cys Asn Tyr Asn Leu Thr Lys Leu Leu Ser Leu Phe Ser Val Asn Asp Phe Thr Cys Ser Gln Ile Ser Pro Ala Ala Ile Ala Ser Asn Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys Phe Pro Ser Val Tyr

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Leu	Tyr 530	Asn	Ser	Thr	Phe	Phe 535	Ser	Thr	Phe	Lys	Cys 540	Tyr	Gly	Val	Ser
Ala 545	Thr	Lys	Leu	Asn	Asp 550	Leu	Сүз	Phe	Ser	Asn 555	Val	Tyr	Ala	Asb	Ser 560
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Gly	Val	Ile	Ala 580	Asp	Tyr	Asn	Tyr	Lys 585	Leu	Pro	Asp	Asp	Phe 590	Met	Gly
СЛа	Val	Leu 595	Ala	Trp	Asn	Thr	Arg 600	Asn	Ile	Asp	Ala	Thr 605	Ser	Thr	Gly
Asn	Tyr 610	Asn	Tyr	Lya	Tyr	Arg 615	Tyr	Leu	Arg	His	Gly 620	Lya	Leu	Arg	Pro
Phe 625	Glu	Arg	Asp	Ile	Ser 630	Asn	Val	Pro	Phe	Ser 635	Pro	Asp	Gly	Lys	Pro 640
Суз	Thr	Pro	Pro	Ala 645	Leu	Asn	Суз	Tyr	Trp 650	Pro	Leu	Asn	Asp	Tyr 655	Gly
Phe	Tyr	Thr	Thr 660	Thr	Gly	Ile	Gly	Tyr 665	Gln	Pro	Tyr	Arg	Val 670	Val	Val
Leu	Ser	Phe 675	Glu	Leu	Leu	Asn	Ala 680	Pro	Ala	Thr	Val	Cys 685	Gly	Pro	Lys
Leu	Ser	Ala	Ile	Gly	Gly	Tyr	Ile	Pro	Glu	Ala	Pro	Arg	Asp	Gly	Gln
Ala	Tyr	Val	Arg	Lys	Asp	Gly	Glu	Trp	Val	Leu	Leu	Ser	Thr	Phe	Leu
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Phe	Ala	Ser	20 Val	Tyr	Ala	Trp	Asn	25 Arg	Lys	Arg	Ile	Ser	30 Asn	Cys	Val
Ala	Asp	35 Tyr	Ser	Val	Leu	Tyr	40 Asn	Ser	Ala	Ser	Phe	45 Ser	Thr	Phe	Lys
Crea	50	ci	Vol	Cor	Dro	55 Thr	Tura	Lou	Aan	Acro	60 L 011	Crea	Dho	The	lan
Сув 65	IYL	GIY	vai	ser	70	TUL	цув	Leu	ASII	Авр 75	Leu	сув	Pne	IIII	80 80
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Ser	Lys 130	Val	Gly	Gly	Asn	Tyr 135	Asn	Tyr	Leu	Tyr	Arg 140	Leu	Phe	Arg	Lys

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Pro	Leu	Gln	Ser 180	Tyr	Gly	Phe	Gln	Pro 185	Thr	Asn	Gly	Val	Gly 190	Tyr	Gln
Pro	Tyr	Arg 195	Val	Val	Val	Leu	Ser 200	Phe	Glu	Leu	Leu	His 205	Ala	Pro	Ala
Thr	Val 210	Суз	Gly	Pro	Lys	Lys 215	Ser	Gly	Gly	Gly	Ser 220	Gly	Gly	Gly	Ser
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Asn	Tyr	Asn 275	Leu	Thr	Lys	Leu	Leu 280	Ser	Leu	Phe	Ser	Val 285	Asn	Asp	Phe
Thr	Cys 290	Ser	Gln	Ile	Ser	Pro 295	Ala	Ala	Ile	Ala	Ser 300	Asn	Cys	Tyr	Ser
Ser 305	Leu	Ile	Leu	Asp	Tyr 310	Phe	Ser	Tyr	Pro	Leu 315	Ser	Met	Lys	Ser	Asp 320
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Ser	Arg 370	Leu	Leu	Ser	Asb	Asp 375	Arg	Thr	Glu	Val	Pro 380	Gln	Leu	Val	Asn
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Ala	Trp	Glu 515	Arg	Lys	Lys	Ile	Ser 520	Asn	Суз	Val	Ala	Asp 525	Tyr	Ser	Val
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Ala 545	Thr	Lys	Leu	Asn	Asp 550	Leu	Суз	Phe	Ser	Asn 555	Val	Tyr	Ala	Aap	Ser 560
Phe	Val	Val	Lys	Gly	Asp	Asp	Val	Arg	Gln	Ile	Ala	Pro	Gly	Gln	Thr

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Asn	Tyr 610	Asn	Tyr	Lys	Tyr	Arg 615	Tyr	Leu	Arg	His	Gly 620	Lys	Leu	Arg	Pro
Phe 625	Glu	Arg	Asp	Ile	Ser 630	Asn	Val	Pro	Phe	Ser 635	Pro	Asp	Gly	Lys	Pro 640
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Leu	Ser	Phe 675	Glu	Leu	Leu	Asn	Ala 680	Pro	Ala	Thr	Val	Суз 685	Gly	Pro	Lys
Leu	Ser 690	Ala	Ile	Gly	Gly	Tyr 695	Ile	Pro	Glu	Ala	Pro 700	Arg	Asp	Gly	Gln
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1	Thr	Ara	Dhe	5 219	Cor	Vəl	Tur	- 219	10 Trp	Agn	Ara	Lug	Ara	15 Tle	Cor
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Arg	Gln	Ile	Ala	Pro 85	Gly	Gln	Thr	Gly	Lуз 90	Ile	Ala	Asp	Tyr	Asn 95	Tyr
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Суз	Tyr	Phe	Pro	Leu 165	Gln	Ser	Tyr	Gly	Phe 170	Gln	Pro	Thr	Asn	Gly 175	Val
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Lys 305	Ser	Asp	Leu	Ser	Val 310	Ser	Ser	Ala	Gly	Pro 315	Ile	Ser	Gln	Phe	Asn 320
Tyr	Lys	Gln	Ser	Phe 325	Ser	Asn	Pro	Thr	Сув 330	Leu	Ile	Leu	Ala	Thr 335	Val
Pro	His	Asn	Leu 340	Thr	Thr	Ile	Thr	Lys 345	Pro	Leu	Lys	Tyr	Ser 350	Tyr	Ile
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Thr	Asn	Leu	Суз	Pro 485	Phe	Gly	Glu	Val	Phe 490	Asn	Ala	Thr	Lys	Phe 495	Pro
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 Phe Thr Asn Val Tyr Ala Asp Ser Phe Val Ile Arg Gly Asp Glu Val

 65
 70
 75
 80
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Cys Tyr Ser Ser Leu Ile Leu Asp Tyr Phe Ser Tyr Pro Leu Ser Met Lys Ser Asp Leu Ser Val Ser Ser Ala Gly Pro Ile Ser Gln Phe Asn Tyr Lys Gln Ser Phe Ser Asn Pro Thr Cys Leu Ile Leu Ala Thr Val Pro His Asn Leu Thr Thr Ile Thr Lys Pro Leu Lys Tyr Ser Tyr Ile Asn Lys Cys Ser Arg Leu Leu Ser Asp Asp Arg Thr Glu Val Pro Gln Leu Val Asn Ala Asn Gln Tyr Ser Pro Cys Val Ser Ile Val Pro Ser Thr Val Trp Glu Asp Gly Asp Tyr Tyr Arg Lys Gln Leu Ser Pro Leu Glu Gly Gly Gly Trp Leu Val Ala Ser Gly Ser Thr Val Ala Met Thr 405 410 415 Glu Gln Leu Gln Met Gly Phe Gly Ile Thr Val Gln Tyr Gly Thr Asp Thr Asn Ser Val Cys Pro Lys Leu Glu Phe Ala Asn Asp Thr Lys Ile Ala Ser Gln Leu Gly Asn Cys Val Glu Tyr Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Arg Phe Pro Asn Ile Thr Asn Leu Cys Pro Phe Gly Glu Val Phe Asn Ala Thr Lys Phe Pro Ser Val Tyr Ala Trp Glu Arg Lys Lys Ile Ser Asn Cys Val Ala Asp Tyr Ser Val Leu Tyr Asn Ser Thr Phe Phe Ser Thr Phe Lys Cys Tyr Gly Val Ser Ala Thr Lys Leu Asn Asp Leu Cys Phe Ser Asn Val Tyr Ala Asp Ser Phe Val Val Lys Gly Asp Asp Val Arg Gln Ile Ala Pro Gly Gln Thr Gly Val Ile Ala Asp Tyr Asn Tyr Lys Leu Pro Asp Asp Phe Met Gly Cys Val Leu Ala Trp Asn Thr Arg Asn Ile Asp Ala Thr Ser Thr Gly Asn Tyr Asn Tyr Lys Tyr Arg Tyr Leu Arg His Gly Lys Leu Arg Pro Phe Glu Arg Asp Ile Ser Asn Val Pro Phe Ser Pro Asp Gly Lys Pro Cys Thr Pro Pro Ala Leu Asn Cys Tyr Trp Pro Leu Asn Asp Tyr Gly Phe Tyr Thr Thr Thr Gly Ile Gly Tyr Gln Pro Tyr Arg Val Val Leu Ser Phe Glu Leu Leu Asn Ala Pro Ala Thr Val Cys Gly Pro Lys Leu Ser Ala Ile Gly Gly Tyr Ile Pro Glu Ala Pro Arg Asp Gly Gln Ala Tyr Val Arg Lys Asp Gly Glu Trp Val Leu Leu Ser

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Thr Phe Leu

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Val	Ile	Ala 435	Trp	Asn	Ser	Asn	Asn 440	Leu	Asp	Ser	ГЛа	Val 445	Gly	Gly	Asn	
Tyr	Asn 450	Tyr	Leu	Tyr	Arg	Leu 455	Phe	Arg	Lys	Ser	Asn 460	Leu	Lys	Pro	Phe	
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Phe	Gln	Pro	Thr 500	Asn	Gly	Val	Gly	Tyr 505	Gln	Pro	Tyr	Arg	Val 510	Val	Val	
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Lys	Ser 530	Thr	Asn	Leu	Val	Lys 535	Asn	Гла	Сүз	Val	Asn 540	Phe	Asn	Phe	Asn	
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Arg	Asp	Pro	Gln 580	Thr	Leu	Glu	Ile	Leu 585	Asp	Ile	Thr	Pro	Сув 590	Ser	Phe	
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Phe	Ile	Glu	Asp 820	Leu	Leu	Phe	Asn	Lys 825	Val	Thr	Leu	Ala	Asp 830	Ala	Gly
Phe	Ile	Lys 835	Gln	Tyr	Gly	Asp	Cys 840	Leu	Gly	Asp	Ile	Ala 845	Ala	Arg	Asp
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Leu 865	Thr	Asp	Glu	Met	Ile 870	Ala	Gln	Tyr	Thr	Ser 875	Ala	Leu	Leu	Ala	Gly 880
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Ser	Ala 930	Ile	Gly	Lys	Ile	Gln 935	Asp	Ser	Leu	Ser	Ser 940	Thr	Ala	Ser	Ala
Leu 945	Gly	Lys	Leu	Gln	Asp 950	Val	Val	Asn	Gln	Asn 955	Ala	Gln	Ala	Leu	Asn 960
Thr	Leu	Val	Lys	Gln 965	Leu	Ser	Ser	Asn	Phe 970	Gly	Ala	Ile	Ser	Ser 975	Val
Leu	Asn	Asp	Ile 980	Leu	Ser	Arg	Leu	Asp 985	Pro	Pro	Glu	Ala	Glu 990	Val	Gln
Ile	Asp	Arg 995	Leu	Ile	Thr	Gly	Arg 1000	Lei	ı Glı	n Sei	r Leı	1 Gl: 10	n T 05	hr T	yr Val
Thr	Gln 1010	Glr)	n Leu	ι Il€	e Arg	Ala 101	a Al .5	La GI	lu I	le An	rg A. 10	La)20	Ser	Ala	Asn
Leu	Ala 1025	Ala 5	a Thr	г Буа	3 Met	Sei 103	c GI 80	Lu Cy	ys Va	al Le	eu GI 10	Ly 035	Gln	Ser	Lys
Arg	Val 1040) Asř	⊳ Ph∈	е Суа	s Gly	r Lys 104	3 GI 15	∟у Ту	yr H	is Le	eu Me 10	et . 050	Ser	Phe	Pro
Gln	Ser 1055	Ala 5	a Pro) His	s Gly	7 Val 106	L Va 50	al Pł	ne Le	eu H:	is Va 1(al 065	Thr	Tyr	Val
Pro	Ala 1070	Glr)	n Glu	ι Буз	a Asr	107	e Tł 75	ır Tł	nr A	la Pi	ro Al 10	La 080	Ile	Суз	His
Asp	Gly 1085	Ly: 5	a Ala	ı His	9 Phe	Pro 109) A1	rg G	lu G	ly Va	al Ph 1(ne ')95	Val	Ser	Asn
Gly	Thr	TT 4 a	• Trr	- 1	e Val	The	- G	l an 70 a	~ ~	an Pl	ne Ta	/r	Glu	Pro	Gln
	1100)	, 11F) Phe		110)5	LII AJ	LY A		1	10			
Ile	1100 Ile 1115	Thi	r Thr	a Pre) Asr	110 110 112	: 0.)5 : Pł	ne Va	al Se	er G	1: 1: 1: 1: 1:	110 9n 125	Суа	Asp	Val
Ile Val	1100 Ile 1115 Ile 1130	Thi Gly	Thr	Asr Asr Val) Asr	110 110 112 112 13)5 7 Pł 20 1 Tł 35	ne Va nr Va	al Se al T	er Gi yr Af	1: 1: 1: 1: 3: 1:	110 5n 125 50	Cys Leu	Asp Gln	Val Pro
Ile Val Glu	1100 Ile 1115 Ile 1130 Leu 1145	Thi Gly Asp	Thr Thr Ile Ser	Asp Val) Asr. L Asr. e Lys	110 110 112 112 113 5 Glu 115	20 20 20 20 20 20 20 20 20 20 20 20 20 2	ne Va nr Va Lu Le	al So al T eu As	∍r G] yr As ap Ly	ly As ly As ly As l p Pi l: ys Ty l:	110 3n 125 ro 140 7r	Cys Leu Phe	Asp Gln Lys	Val Pro Asn
Ile Val Glu His	1100 Ile 1115 Ile 1130 Leu 1145 Thr 1160	Gly Asp Sen	Thr Thr Ser	> Phe Asp > Val > Phe > Asp) Asr L Asr E Lys Val	110 110 1112 112 113 6 Glu 115 . Asp 116	20 F Pl 20 Tl 35 1 G 50 Le 55	ne Va nr Va Lu Le	al So al T eu As	∍r G] γr As ∋p Ly ∋p I]	ly As ly As i sp Pi l: ys Ty le Se li	110 3n 125 140 7r 155 9r	Cys Leu Phe Gly	Asp Gln Lys Ile	Val Pro Asn Asn

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Thr	Leu 290	Lys	Ser	Phe	Thr	Val 295	Glu	Lys	Gly	Ile	Tyr 300	Gln	Thr	Ser	Asn
Phe 305	Arg	Val	Gln	Pro	Thr 310	Glu	Ser	Ile	Val	Arg 315	Phe	Pro	Asn	Ile	Thr 320
Asn	Leu	Cys	Pro	Phe 325	Gly	Glu	Val	Phe	Asn 330	Ala	Thr	Arg	Phe	Ala 335	Ser
Val	Tyr	Ala	Trp 340	Asn	Arg	Lys	Arg	Ile 345	Ser	Asn	Суз	Val	Ala 350	Asp	Tyr
Ser	Val	Leu 355	Tyr	Asn	Ser	Ala	Ser 360	Phe	Ser	Thr	Phe	Lys 365	Суз	Tyr	Gly
Val	Ser 370	Pro	Thr	Lys	Leu	Asn 375	Asp	Leu	Сув	Phe	Thr 380	Asn	Val	Tyr	Ala
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Lys	Pro 450	Phe	Glu	Arg	Aab	Ile 455	Ser	Thr	Glu	Ile	Tyr 460	Gln	Ala	Gly	Ser
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Thr	Ser	Val	Asp	Cys 725	Thr	Met	Tyr	Ile	Cys 730	Gly	Asp	Ser	Thr	Glu 735	Суз
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Ala	Leu	Thr 755	Gly	Ile	Ala	Val	Glu 760	Gln	Asp	Lys	Asn	Thr 765	Gln	Glu	Val
Phe	Ala 770	Gln	Val	Lys	Gln	Ile 775	Tyr	Lys	Thr	Pro	Pro 780	Ile	Lys	Asp	Phe
Gly 785	Gly	Phe	Asn	Phe	Ser 790	Gln	Ile	Leu	Pro	Asp 795	Pro	Ser	Lys	Pro	Ser 800
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Asp	Ala	Gly	Phe 820	Ile	ГЛа	Gln	Tyr	Gly 825	Asp	Сүз	Leu	Gly	Aap 830	Ile	Ala
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Leu 865	Ala	Gly	Thr	Ile	Thr 870	Ser	Gly	Trp	Thr	Phe 875	Gly	Ala	Gly	Ala	Ala 880
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Gln	Phe	Asn 915	Ser	Ala	Ile	Gly	Lys 920	Ile	Gln	Asp	Ser	Leu 925	Ser	Ser	Thr
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Ala	Asn 1010	Leu)	ı Ala	a Alá	a Thr	Ly: 101	3 M€ L5	et Se	∍r G	lu Cy	ys V 1	al : 020	Leu (Gly (Gln
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Phe	Pro 1040	Glr	n Sei	r Ala	a Prc	Hi: 104	9 GI 15	Ly Va	al Va	al Pl	ne L 1	eu : 050	His '	Val '	Thr
Tyr	Val 1055	Pro	> Ala	a Glr	ı Glu	. Ly: 106	50 As	sn Pl	ne Tł	nr Tl	nr A 1	la 065	Pro 2	Ala :	Ile
Cys	His 1070) Ast	Gly	/ Ly:	3 Ala	. His 107	s Pł 75	ne Pi	ro Ai	rg Gi	lu G 1	ly ' 080	Val :	Phe V	Val
Ser	Asn 1085	Gly	7 Thi	r Hif	s Trp	Phe 109	e Va ∂0	al Tł	nr G	ln A:	rg A 1	sn 095	Phe '	Tyr (Glu
Pro	Gln	Ile	e Ile	e Thi	r Thr	Ast	D As	an Th	nr Pl	ne Va	al S	er	Gly 3	Asn (Cys

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Gln	Pro 1130	Glu	. Leu	ı Asp	Sei	: Phe 113	e Ly 85	/s G	lu	Glu	Leu	As 11	sp .40	Lys	Tyr	Phe
Lys	Asn 1145	His	Thr	: Sei	r Pro	Asp 115	o Va 50	al A	ab	Leu	Gly	As 11	sp .55	Ile	Ser	Gly
Ile	Asn 1160	Ala	Sei	: Val	l Val	l Asr 116	n I] 55	Le G	ln	Lys	Glu	I] 11	.e .70	Asp	Arg	Leu
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Glu	Leu 1190	Gly	Ъуа	з Туз	c Glu	ı Glr 119	1 Τ <u>λ</u> 95	yr I	le	Lys	Trp	Pr 12	:0 200	Trp	Tyr	Ile
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Ile	Met 1220	Leu	. Суз	в Суя	s Met	: Thr 122	: S€ 25	er C	ys	CÀa	Ser	Су 12	/s 230	Leu	Lys	Gly
Суз	Cys 1235	Ser	Суа	β Gl _λ	/ Sei	с Суя 124	з С <u>у</u> 10	/s L	ya	Phe	Asp	G1 12	.u 245	Asp	Asp	Ser
Glu	Pro 1250	Val	Leu	ı Lys	β Glγ	/ Val	L L ₃	/s L	eu	His	Tyr	Th 12	nr 260			
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Thr	Arg	Gly 35	Val	Tyr	Tyr	Pro	Asp 40	Lys	Va	l Pł	ne A	rg	Ser 45	: Sei	: Val	l Le
His	Ser 50	Thr	Gln	Asp	Leu	Phe 55	Leu	Pro	Ph	e Pł	ne S 6	er 0	Asr	n Val	. Thi	r Tr
Phe 65	His	Ala	Ile	His	Val 70	Ser	Gly	Thr	As	n G 79	Lу Т 5	hr	Lys	a Arg	J Ph€	e As 80
Asn	Pro	Val	Leu	Pro 85	Phe	Asn	Asp	Gly	. Va 90	1 T ₃	yr P	he	Ala	. Sei	: Thi 95	r Gl
Lys	Ser	Asn	Ile 100	Ile	Arg	Gly	Trp	Ile 105	Ph	e G	LуТ	hr	Thr	: Leu 11(ı Ası	ș Se
Lys	Thr	Gln 115	Ser	Leu	Leu	Ile	Val 120	Asn	. As	n Al	la T	hr	Asr 125	n Val	. Val	1 11
Lys	Val 130	Cys	Glu	Phe	Gln	Phe 135	Суз	Asn	As	p Pı	ro P 1	he 40	Leu	ι Gl <u>γ</u>	v Val	L Ty
Tyr 145	His	Lys	Asn	Asn	Lys 150	Ser	Trp	Met	Gl	u Se 15	er G 55	lu	Phe	e Arç	g Val	L Ty 16
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Met	Asp	Leu	Glu 180	Gly	Lys	Gln	Gly	Asn 185	Ph	e L <u>3</u>	ys A	sn	Leu	ι Arg 190	g Glu)	ı Ph
Val	Phe	Lvs	Asn	Tle	Asp	Glv	Tvr	Phe	Laz	а Т ⁻	IA T	vr	Cor	- T.J.C	. ui (a Th

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Pro 225	Leu	Val	Asp	Leu	Pro 230	Ile	Gly	Ile	Asn	Ile 235	Thr	Arg	Phe	Gln	Thr 240
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Ala	Val 610	Leu	Tyr	Gln	Asp	Val 615	Asn	Суз	Thr	Glu	Val 620	Pro	Val	Ala	Ile

His 625	Ala	Asp	Gln	Leu	Thr 630	Pro	Thr	Trp	Arg	Val 635	Tyr	Ser	Thr	Gly	Ser 640
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Leu	Ala 1029	Ala	a Thi	r Ly:	s Met	: Sei 103	c G] 80	lu Cγ	vs Va	al Le	eu GI	ly ()35	3ln S	Ger I	γya

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7	n	6
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C	Jly	Val 130	Tyr	Tyr	His	Lys	Asn 135	Asn	Lys	Ser	Trp	Met 140	Glu	Ser	Glu	Phe
7 1	Arg L45	Val	Tyr	Ser	Ser	Ala 150	Asn	Asn	Cys	Thr	Phe 155	Glu	Tyr	Val	Ser	Gln 160
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Ι	Jya	His	Thr 195	Pro	Ile	Asn	Leu	Val 200	Arg	Asp	Leu	Pro	Gln 205	Gly	Phe	Ser
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Ι	Jeu	Gln	Pro	Arg 260	Thr	Phe	Leu	Leu	Lys 265	Tyr	Asn	Glu	Asn	Gly 270	Thr	Ile
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H C	Phe 805	Arg	Val	Gln	Pro	Thr 310	Glu	Ser	Ile	Val	Arg 315	Phe	Pro	Asn	Ile	Thr 320
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Ser	Ser	Val	Leu	Asn 965	Asp	Ile Le	eu S	er A: 9'	rg Le 70	∋u As	sp Pro) Pro	975 Glu	ı Ala 5
Glu	Val	Gln	Ile 980	Asp	Arg	Leu II	le T 9	hr G: 85	ly A:	rg Le	∋u Glr	1 Sei 990	r Leu)	ı Gln
Thr	Tyr '	Val 995	Thr	Gln	Gln	Leu II 10	le . 200	Arg 2	Ala i	Ala (Glu I] 10	.e 2 005	Arg A	Ala Ser
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Tyr	Val 1055	Pro	Ala	ı Glr	ı Glu	. Lys 1060	Asn	Phe	Thr	Thr	Ala 1065	Pro	Ala	Ile
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Thr	Arg	Gly 35	Val	Tyr	Tyr	Pro As 40	sp Lj D	ys Va	al Pl	ne Ai	rg Sei 45	: Sei	r Val	L Leu

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Lys	Ser 530	Thr	Asn	Leu	Val	Lys 535	Asn	ГЛа	Суз	Val	Asn 540	Phe	Asn	Phe	Asn
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				885					890						895	5	
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Ala	Leu	Thr 755	Gly	Ile	Ala	Val	Glu 760	Gln	Asp	Ly	s A	sn	Thr 765	Gln	Glu	Val
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Суз	Leu	Gly	Asp 820	Ile	Ala	Ala	Arg	Asp 825	Leu	11	e C	ya	Ala	Gln 830	Lys	Phe
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Gln	Tyr 850	Thr	Ser	Ala	Leu	Leu 855	Ala	Gly	Thr	11	e T 8	'hr 60	Ser	Gly	Trp	Thr
Phe 865	Gly	Ala	Gly	Ala	Ala 870	Leu	Gln	Ile	Pro	Ph 87	е А 5	la	Met	Gln	Met	Ala 880
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Tyr	His 1025	Leu	ı Met	t Se:	r Phe	e Pro 103	5 G 30	ln S	er A	la	Pro) Hi	is 035	Gly '	Val	Val
Phe	Leu 104(His)	g Val	l Th:	r Tyj	r Va 104	l P: 15	ro A	la G	ln	Glu	ι Lγ 1(/ទ)50	Asn i	Phe	Thr
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Glu	Gly 1070	Va]	L Phe	e Val	l Sei	r Ası 10'	n G 75	ly Tl	hr H	is	Trp	• Pł 10	ne 080	Val '	Thr	Gln
Arg	Asn 1085	Phe	е Туз	r Glı	u Pro	5 Gli 104	n I 90	le I	le T	hr	Thr	A:	3p 095	Asn '	Thr	Phe
Val	Ser	Gl	/ Ası	n Cyr	a Asl	• Va:	- 1 V.	al I	le G	ly	Ile	va va	al	Asn J	Asn	Thr
Val	Tyr	Asī) Pro	o Lei	u Glr	1 Pro	, , G	lu L	eu A	.sp	Ser	Pł	ne	Lys (Glu	Glu
Leu	1119 Asp	LY:	а Туз	r Phe	e Ly:	112 3 Ası	20 1 H	is Tl	nr S	er	Pro	11 • As	125 ∋p	Val 2	Asp	Leu
Gly	1130 Asp) Ile	e Sei	r Gly	y Ile	113 e Ası	35 n A	la Se	er V	al	Val	11 . As	140 ∋n	Ile (Gln	Lys
-	-			-												

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Leu	Ile 1175	Asr	p Lei	ı Glı	n Glu	1 Lei 118	u G: 80	ly Ly	ys T	yr G	lu G 1	ln 185	Tyr	Ile	Lys
Trp	Pro 1190	Tr <u>p</u>)	р Ту:	r Ile	e Trp	2 Le: 119	u G: 95	ly Pl	he I	le A	la G 1	ly 200	Leu	Ile	Ala
Ile	Val 1205	Met 5	: Vai	l Th:	r Ile	e Met 12:	t Le 10	eu C	ys C	ys M	et T 1	'hr 215	Ser	Сүз	Сув
Ser	Cys 1220	Leu)	і Бу	a Gly	у Суғ	9 Cy: 122	s Se 25	er C	ys G	ly S	er C 1	уя 230	Суз	Lys	Phe
Asp	Glu 1235	Yař	o Aal	p Se:	r Glu	1 Pro 124	o Va 40	al L	eu L	ya G	ly V 1	al 245	ràa	Leu	His
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Lys	Thr	Gln 115	Ser	Leu	Leu	Ile	Val 120	Asn	Asn	Ala	Thr	Asn 125	Val	Val	Ile
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Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
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Pro Phe Leu Met Asp Leu Glu Gly Lys Gln Gly Asn Phe Lys Asn Leu 165 170 175

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Glu	Asn 690	Ser	Val	Ala	Tyr	Ser 695	Asn	Asn	Ser	Ile	Ala 700	Ile	Pro	Thr	Asn
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Сүз	Leu	Gly	Asp 820	Ile	Ala	Ala	Arg	Asp 825	Leu	Ile	Суз	Ala	Gln 830	Гла	Phe
Asn	Gly	Leu 835	Thr	Val	Leu	Pro	Pro 840	Leu	Leu	Thr	Asp	Glu 845	Met	Ile	Ala
Gln	Tyr 850	Thr	Ser	Ala	Leu	Leu 855	Ala	Gly	Thr	Ile	Thr 860	Ser	Gly	Trp	Thr
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Суз	Val 1010	Lei	ı Gly	y Glı	n Sei	r Ly: 101	3 A1 15	rg Va	al As	sp Pl	ne Cy 10	ys ()20	Gly I	jàs (Gly

Tyr	His 1025	Leu	Met	Ser	Phe	Pro 1030	Gli	n Se	er A	Ala	Pro	His 1039	G]	Ly	Val	Val
Phe	Leu 1040	His	Val	Thr	Tyr	Val 1045	Pro	0 A.	La G	Jn	Glu	Lys 1050	As)	sn	Phe	Thr
Thr	Ala 1055	Pro	Ala	Ile	Сув	His 1060	Asj	p GI	Ly I	ya	Ala	His 1069	Pł	ıe	Pro	Arg
Glu	Gly 1070	Val	Phe	Val	Ser	Asn 1075	Gl	y Tł	nr H	lis	Trp	Phe 1080	Va)	al	Thr	Gln
Arg	Asn 1085	Phe	Tyr	Glu	Pro	Gln 1090	11	e II	le 1	[hr	Thr	Asp 1095	As 5	₹n	Thr	Phe
Val	Ser 1100	Gly	Asn	Cys	Asp	Val 1105	Va	1 1	Le G	ly	Ile	Val 1110	As)	n	Asn	Thr
Val	Tyr 1115	Asp	Pro	Leu	Gln	Pro 1120	Gl	u Le	eu A	/ab	Ser	Phe 1129	г?	/s	Glu	Glu
Leu	Asp 1130	Lys	Tyr	Phe	Lys	Asn 1135	Hi	s Tł	ır S	Ser	Pro	Asp 114(Va)	al	Asp	Leu
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Glu	Ile 1160	Asp	Arg	Leu	Asn	Glu 1165	Va	1 A.	La I	yya	Asn	Leu 1170	As)	₹n	Glu	Ser
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Ser	Сув 1220	Leu	ГЛЗ	Gly	Суз	Cys 1225	Se:	r Cj	/s G	Jy	Ser	Cys 1230) C7	/8	Lys	Phe
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Asn	Leu	Thr	Thr 20	Arg	Thr (Gln L	eu :	Pro 25	Pro	Al	a Ty	yr Tł	nr A S	4sn 30	Sei	Phe
Thr	Arg	Gly 35	Val	Tyr	Tyr 1	Pro A 4	o ap	Lys	Val	L Ph	ne Ar	rg Se 45	er S	Ser	Val	. Leu
His	Ser 50	Thr	Gln	Asp	Leu 1	Phe L 55	ieu :	Pro	Phe	e Ph	ie Se 60	er As O	an V	/al	Thi	Trp
Phe 65	His .	Ala	Ile	His '	Val : 70	Ser G	ly '	Thr	Asr	n Gl 75	y Tł	hr Lj	/s A	Arg	Phe	e Asp 80
Asn	Pro '	Val	Leu	Pro 1 85	Phe i	Asn A	ab (Gly	Val 90	LТу	r Pl	he Al	la S	Ser	Thi 95	r Glu
ГЛа	Ser .	Asn	Ile 100	Ile .	Arg (Gly T	rp	Ile 105	Phe	e Gl	y Tł	hr Tł	nr I 1	Leu	Asp) Ser

Lys	Thr	Gln 115	Ser	Leu	Leu	Ile	Val 120	Asn	Asn	Ala	Thr	Asn 125	Val	Val	Ile
Lys	Val 130	Cys	Glu	Phe	Gln	Phe 135	Суз	Asn	Asp	Pro	Phe 140	Leu	Gly	Val	Tyr
Tyr 145	His	Lys	Asn	Asn	Lys 150	Ser	Trp	Met	Glu	Ser 155	Glu	Phe	Arg	Val	Tyr 160
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Pro	Ile 210	Asn	Leu	Val	Arg	Asp 215	Leu	Pro	Gln	Gly	Phe 220	Ser	Ala	Leu	Glu
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Ser	Tyr	Gln 675	Thr	Gln	Thr	Asn	Ser 680	Pro	Gly	Ser	Ala	Ser 685	Ser	Val	Ala
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945					950					ç	955					96	50
Thr	Leu	Val	Lys	Gln 965	Leu	Ser	Ser	As:	n P: 9	he (70	3ly .	Ala	a Ile	e Sei	r Se 97	r Vá 5	al
Leu	Asn	Asp	Ile 980	Leu	Ser	Arg	Leu	As 98	рР: 5	ro H	Pro 1	Glu	ı Ala	a Glu 990	ı Va D	1 G	ln
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Leu	Ala 1029	Ala 5	a Thi	r Lys	; Met	: Sei 103	c G 80	lu	Cys	Va]	L Le	u (1	∃ly L035	Gln	Ser	LY	3
Arg	Val 1040) Yař) Phe	е Суа	; Gly	7 Lys 104	3 G 15	ly	Tyr	His	: Le	u M 1	4et 1050	Ser	Phe	Pro	þ
Gln	Ser 1059	Ala 5	a Pro) His	; Gly	7 Va] 106	L V 50	al :	Phe	Leu	ı Hi	s / 1	/al L065	Thr	Tyr	Va:	L
Pro	Ala 1070	Glr)	n Glu	і Lys	s Asr	n Phe 107	е Т 75	hr '	Thr	Ala	a Pr	0 <i>P</i> 1	Ala 1080	Ile	Суз	Hi	3
Asp	Gly 1089	Ly: 5	s Ala	a His	9 Phe	e Pro 109	> A 90	rg	Glu	Glγ	7 Va	1 H 1	Phe L095	Val	Ser	Ası	ı
Gly	Thr 1100	Hi:	a Tr <u>p</u>	> Phe	e Val	l Thi 110	c G)5	ln 2	Arg	Asr	n Ph	e 1 1	fyr L110	Glu	Pro	Glı	ı
Ile	Ile 1119	Thi 5	r Thi	r Asp) Asr	n Thi 112	2 P 20	he '	Val	Sei	Gl;	y P 1	Asn L125	Cys	Asp	Va:	L
Val	Ile 1130	Gl ₃	/ Ile	e Val	. Asr	n Asr 113	n T 35	hr '	Val	Туі	: Asj	p I 1	Pro 1140	Leu	Gln	Pro	þ
Glu	Leu 1149	Aar) Sei	r Phe	e Lys	3 Glu 115	1 G	lu i	Leu	Asr	р Бу	s] 1	[yr L155	Phe	Lys	Ası	ı
His	Thr 1160	Sei	r Pro	o Asp) Val	l Asp 116	р L 55	eu (Gly	Asp	, Il	e S 1	Ger L170	Gly	Ile	Ası	ı
Ala	Ser 1175	Va]	L Val	l Asr	n Ile	e Glr 118	n L 30	ys (Glu	Ile	e Asj	р <i>I</i> 1	Arg L185	Leu	Asn	Glı	ı
Val	Ala 1190	Ly:	a Asr	n Leu	ı Asr	n Glu 119	1 S 95	er i	Leu	Ile	e As	p I 1	Leu L200	Gln	Glu	Lei	ı
Gly	Lys 1209	Туз	c Glu	ı Glr	ı Tyr	: Ile 121	e L LO	ys ′	Trp	Pro	o Tr	p 1 1	[yr 1215	Ile	Trp	Lei	ı
Gly	Phe 1220	Ile)	e Ala	a Gly	r Leu	ı Ile 122	e A 25	la	Ile	Val	L Me	t \ 1	/al L230	Thr	Ile	Met	5
Leu	Cys 1235	Cys 5	s Met	: Thr	: Ser	с Суя 124	; C 10	ys :	Ser	Cys	s Le	u I 1	уя L245	Gly	Суз	Су	3
Ser	Cys 1250	Gl ₃	/ Sei	r Cys	cys	5 Lys 125	≇ P. 55	he .	Asp	Glu	ı Asj	р <i>7</i> 1	4ap 1260	Ser	Glu	Pro	þ
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Thr	Leu 290	Lys	Ser	Phe	Thr	Val 295	Glu	Lys	Gly	Ile	Tyr 300	Gln	Thr	Ser	Asn
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Thr	Gly	Cys	Val 420	Ile	Ala	Trp	Asn	Ser 425	Asn	Asn	Leu	Asp	Ser 430	Lys	Val
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Ser	Tyr	Gly	Phe	Gln 485	Pro	Thr	Asn	Gly	Val 490	Gly	Tyr	Gln	Pro	Tyr 495	Arg
Val	Val	Val	Leu 500	Ser	Phe	Glu	Leu	Leu 505	His	Ala	Pro	Ala	Thr 510	Val	Сүз
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Lys 545	Phe	Leu	Pro	Phe	Gln 550	Gln	Phe	Gly	Arg	Asp 555	Ile	Ala	Asp	Thr	Thr 560
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Glu	Asn 690	Ser	Val	Ala	Tyr	Ser 695	Asn	Asn	Ser	Ile	Ala 700	Ile	Pro	Thr	Asn
Phe 705	Thr	Ile	Ser	Val	Thr 710	Thr	Glu	Ile	Leu	Pro 715	Val	Ser	Met	Thr	Lys 720
Thr	Ser	Val	Asp	Cys 725	Thr	Met	Tyr	Ile	Cys 730	Gly	Asp	Ser	Thr	Glu 735	Сүз
Ser	Asn	Leu	Leu 740	Leu	Gln	Tyr	Gly	Ser 745	Phe	Суз	Thr	Gln	Leu 750	Asn	Arg
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Ala	Arg	Asp 835	Leu	Ile	Суз	Ala	Gln 840	Lya	Phe	Asn	Gly	Leu 845	Thr	Val	Leu
Pro	Pro 850	Leu	Leu	Thr	Asp	Glu 855	Met	Ile	Ala	Gln	Tyr 860	Thr	Ser	Ala	Leu

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Leu 865	Ala	Gly	Thr	Ile	Thr 870	Ser G	ly 1	rp T	hr P 8	he G 75	ly Al	a Gly	y Ala	a Ala 880
Leu	Gln	Ile	Pro	Phe 885	Ala	Met G	ln M	let A 8	la T 90	yr A	rg Ph	e Ası	n Gly 895	7 Ile 5
Gly	Val	Thr	Gln 900	Asn	Val	Leu T	yr G	lu A 05	sn G	ln L	ys Le	u Il. 910	e Ala D	a Asn
Gln	Phe	Asn 915	Ser	Ala	Ile	Gly L 9	ys I 20	le G	ln A	sp S	er Le 92	u Se: 5	r Sei	r Thr
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Phe	Pro 1040	Gln	ı Sei	r Ala	a Prc	His 1045	Gly	Val	Val	Phe	Leu 1050	His	Val	Thr
Tyr	Val 1055	Pro	> Ala	a Glr	n Glu	Lys 1060	Asr	Phe	Thr	Thr	Ala 1065	Pro	Ala	Ile
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Ser	Asn 1085	Gly	7 Thi	r His	s Trp	• Phe 1090	Val	Thr	Gln	Arg	Asn 1095	Phe	Tyr	Glu
Pro	Gln 1100	Ile	e Ile	e Thr	Thr	Asp 1105	Asr	Thr	Phe	Val	Ser 1110	Gly	Asn	Суз
Asp	Val 1115	Val	. Ile	e Gly	/ Ile	• Val 1120	Asr	Asn	Thr	Val	Tyr 1125	Asp	Pro	Leu
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ГЛЗ	Asn 1145	His	5 Thi	s Ser	Prc	Asp 1150	Val	Asp	Leu	Gly	Asp 1155	Ile	Ser	Gly
Ile	Asn 1160	Ala	ı Sei	r Val	. Val	. Asn 1165	Ile	Gln	Гла	Glu	Ile 1170	Asp	Arg	Leu
Asn	Glu 1175	Val	. Ala	a Lys	s Asn	1180 Leu	Asr	Glu	Ser	Leu	Ile 1185	Asp	Leu	Gln
Glu	Leu 1190	Gly	у Буз	з Тут	Glu	l Gln 1195	Tyr	Ile	Lys	Trp	Pro 1200	Trp	Tyr	Ile
Trp	Leu 1205	Gly	7 Phe	e Ile	e Ala	Gly 1210	Leu	. Ile	Ala	Ile	Val 1215	Met	Val	Thr
Ile	Met 1220	Leu	ι Суя	в Суа	8 Met	Thr 1225	Ser	Сув	Суз	Ser	Cys 1230	Leu	Гла	Gly
Суз	Cys 1235	Ser	с Суа	; Gly	⁄ Ser	Cys 1240	Cys	Lys	Phe	Asp	Glu 1245	Asp	Asp	Ser
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What is claimed is:

1. An immunogenic composition comprising:

(i) a nanoparticle comprising a coronavirus S (CoV S) glycoprotein having the amino acid sequence of SEQ

ID NO: 87, and a non-ionic detergent core; (ii) a pharmaceutically acceptable buffer, and

(iii) a saponin adjuvant.

2. The immunogenic composition of claim 1, comprising between about 5 μ g and about 25 μ g of CoV S glycoprotein.

3. The immunogenic composition of claim 2, comprising about 5 μ g of CoV S glycoprotein.

4. The immunogenic composition of claim **1**, wherein the ²⁵ saponin adjuvant comprises at least two iscom particles, wherein:

- the first iscom particle comprises fraction A of *Quillaja* saponaria Molina and not fraction C of *Quillaja* saponaria Molina; and
- the second iscom particle comprises fraction C of *Quillaja* saponaria Molina and not fraction A of *Quillaja* saponaria Molina.

5. The immunogenic composition of claim **4**, wherein fraction A of *Quillaja saponaria* Molina accounts for ³⁵ 50-96% by weight and fraction C of *Quillaja saponaria* Molina accounts for the remainder, respectively, of the sum of the weights of fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina in the adjuvant.

6. The immunogenic composition of claim **4**, wherein ⁴⁰ fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina account for about 85% by weight and about 15% by weight, respectively, of the sum of the weights of fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina in the adjuvant. ⁴⁵

7. The immunogenic composition of claim 1, comprising about 50 μ g of saponin adjuvant.

8. The immunogenic composition of claim **1**, wherein the non-ionic detergent core is selected from the group consisting of polysorbate-20 (PS20), polysorbate-40 (PS40), poly- ⁵⁰ sorbate-60 (PS60), polysorbate-65 (PS65), and polysorbate-80 (PS80).

9. A method of stimulating an immune response against SARS-CoV-2 in a subject comprising administering the immunogenic composition of claim **1**.

10. The method of claim 9, comprising between about 5 μ g and about 25 μ g of CoV S glycoprotein.

11. The method of claim 10, comprising 5 μ g of CoV S glycoprotein.

- **12**. The method of claim **9**, wherein the saponin adjuvant comprises at least two iscom particles, wherein:
- the first iscom particle comprises fraction A of *Quillaja* saponaria Molina and not fraction C of *Quillaja* saponaria Molina; and
- the second iscom particle comprises fraction C of *Quillaja* saponaria Molina and not fraction A of *Quillaja* saponaria Molina.

13. The method of claim **12**, wherein fraction A of *Quillaja saponaria* Molina accounts for 50-96% by weight and fraction C of *Quillaja saponaria* Molina accounts for the remainder, respectively, of the sum of the weights of fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina in the adjuvant.

14. The method of claim 12, wherein fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina account for about 85% by weight and about 15% by weight, respectively, of the sum of the weights of fraction A of *Quillaja saponaria* Molina and fraction C of *Quillaja saponaria* Molina in the adjuvant.

15. The method of claim 9, comprising about 50 μ g of saponin adjuvant.

16. The method of claim **9**, wherein the non-ionic detergent core is selected from the group consisting of polysorbate-20 (PS20), polysorbate-40 (PS40), polysorbate-60 (PS60), polysorbate-65 (PS65), and polysorbate-80 (PS80).

17. The method of claim **9**, wherein the subject is administered a first dose at day 0 and a boost dose at day 21.

18. The method of claim **9**, wherein a single dose of the immunogenic composition is administered.

19. The method of claim **9**, comprising administering a second immunogenic composition different from the first immunogenic composition.

20. The method of claim **19** wherein the second immunogenic composition comprises an mRNA encoding a SARS-Cov-2 Spike glycoprotein, a plasmid DNA encoding a SARS-Cov-2 Spike glycoprotein, an viral vector encoding a SARS-Cov-2 Spike glycoprotein, or an inactivated SARS-CoV-2 virus.

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