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(54) Title: BETACORONAVIRUS PROPHYLAXIS AND THERAPY

Fig. 1

SEQ ID NO: 230

MFVFLVLLPLVSSQCVNLTTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFD
NPVLPFNDGVYFASTEKSNIRGWIFGTTLDSTQSLIVNNATNVVIVKCEFCNDPFLGVYHKNKNSWMESEFRVYS
SANNCTFEYVSQPFLLMDLEGKQGNFKNLREFVFNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLAL
HRSYLTPLGDSSSGWTAGAAAYVGYLQPRFTLLKYNENGTITDAVDCALDPLSETKCTLSFTVEKGIYQTSNFRVQPT
SIVRFPNITNLCPPFGEVFNATRFASVYAWNKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGD
EVRQIAPGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGNNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEG
FNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNENGLTGTGVLTESNKKFLPFQQ
FGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQT
RAGCLIGAEHVNSYECDIPIGAGICASYQTQTNPRRARSVASQSIAYTMSLGAENSVAYSNNISIAIPTNFTISVTEILPV
SMTKTSVDCTMYICGDSTECNSLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPS
KPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDIAARDLCAQKFNGLTVLPLLTDEMIAQYTSALLAGTITSGWTFGAGAA
LQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAIS
SVLNDILSRDLKVEAEVQIDRLITGRQLSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLSFPQS
APHGVVFLHVTYVPAQEKNFTTAPAIGHDGKAHFPREGVVFVSNGTHWFVTQRNFYEPQIITDNTFVSGNCDVVIGVNN
VYDPLQPELDSFKEELDKYFKNHTSPDVLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWL
GFIAGLIAIVMTIMLCCMTSCCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

(57) **Abrégé/Abstract:**

Disclosed is a vaccine comprising an immunologically effective amount of a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope. The vaccine is ideal for pandemic and epidemics as it can induce rapid, strong immune response with lower/fewer doses because the antigen is targeted to antigen presenting cells and the antigen is produced in the body.

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Abstract:

Disclosed is a vaccine comprising an immunologically effective amount of a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope. The vaccine is ideal for pandemic and epidemics as it can induce rapid, strong immune response with lower/fewer doses because the antigen is targeted to antigen presenting cells and the antigen is produced in the body.

Betacoronavirus prophylaxis and therapy

Technical field

The present invention relates to therapeutic and prophylactic vaccines against betacoronavirus, such as vaccines against corona virus disease 2019 (COVID-19).

5 Summary

The present invention relates to a vaccine comprising a vaccibody construct ideal for fighting pandemics and epidemics as it can induce rapid, strong immune response with lower/fewer doses compared to typical vaccines because the antigen is targeted to antigen presenting cells and the antigen preferably is produced in the body. This
10 vaccibody construct is designed to induce an antigenic effect through the full length or a part of the spike protein; or selected T cell epitopes, e.g. those which are conserved between different betacoronaviruses (such as SARS-CoV and SARS-CoV2); or through combinations thereof.

By targeting these antigenic epitopes in the body through e.g. anti-pan HLA class II or
15 MIP-1 α , an immune response will be raised through B cells and/or T cells, such that the vaccine can be used in a prophylactic setting and a therapeutic setting.

Description of Drawings

Figure 1:

Full-length spike protein of SARS-CoV-2 (SEQ ID NO: 230)

20 Figure 2:

A: Exemplary sequence of RBD of spike protein of SARS-CoV-2 (SEQ ID NO: 231)

B: The RBD sequence of spike protein of SARS-CoV-2 of the Wuhan strain used in the VB10.COVS2 constructs of the Examples (SEQ ID NO: 802)

C: The RBD sequence of spike protein of SARS-CoV-2 South African variant B.1.351
25 used in the VB10.COVS2 constructs of the Examples (SEQ ID NO: 803)

D: The RBD sequence of spike protein of SARS-CoV-2 UK variant B.1.1.7 used in the VB10.COVS2 constructs of the Examples (SEQ ID NO: 804)

E: The RBD sequence of spike protein of SARS-CoV-2 Californian variant B.1.427
used in the VB10.COVS2 constructs of the Examples (SEQ ID NO: 805)

Figure 3:

HR2 domain of spike protein of SARS-CoV-2 and SARS-CoV (SEQ ID NO: 232)

Figure 4:

5 Amino acid sequence of signal peptide and mature peptide of hMIP1 α (LD78b), human hinge region 1 from IgG3, human hinge region 4 from IgG3, glycine-serine linker, human CH3 domain of IgG3 and glycine-leucine linker (SEQ ID NO: 233).
The sequence is split up by " | " to help distinguish the various parts of the sequence

Figure 5:

10 C-C motif chemokine 3-like 1 precursor including signal peptide (amino acids 1-23) and mature peptide (hMIP1 α /LD78-beta, amino acids 24-93) (SEQ ID NO: 234)

Figure 6:

Signal peptide (SEQ ID NO: 235)

Figure 7:

Signal peptide (SEQ ID NO: 236)

15 Figure 8:

Amino acid sequence of the antigenic unit of VB2040 (SEQ ID NO: 237)

Figure 9:

Amino acid sequence of the antigenic unit of VB2041 (SEQ ID NO: 238)

Figure 10:

20 Amino acid sequence of the antigenic unit of VB2042 (SEQ ID NO: 239)

Figure 11:

Amino acid sequence of the antigenic unit of VB2043 (SEQ ID NO: 240)

Figure 12:

Amino acid sequence of the antigenic unit of VB2044 (SEQ ID NO: 241)

Figure 13:

Amino acid sequence of the antigenic unit of VB2045 (SEQ ID NO: 242)

Figure 14:

Amino acid sequence of the antigenic unit of VB2046 (SEQ ID NO: 243)

5 Figure 15:

Amino acid sequence of the antigenic unit of VB2047 (SEQ ID NO: 244)

Figure 16:

Amino acid sequence of the antigenic unit of VB2048 (SEQ ID NO: 245).

Figure 17:

10 Amino acid sequence of the antigenic unit of VB2049 (SEQ ID NO: 246)

Figure 18:

Amino acid sequence of the antigenic unit of VB2050 (SEQ ID NO: 247)

Figure 19:

Amino acid sequence of the antigenic unit of VB2051 (SEQ ID NO: 248)

15 Figure 20:

Alternative HR2 domain of spike protein of SARS-CoV-2 and SARS-CoV (SEQ ID NO: 249)

Figure 21:

Amino acid sequence of the antigenic unit of VB2053 (SEQ ID NO: 250)

20 Figure 22:

Amino acid sequence of the antigenic unit of VB2054 (SEQ ID NO: 251)

Figure 23:

A. Nucleotide sequence of VB2049 (SEQ ID NO: 252)

B. Amino acid sequence of VB2049 (SEQ ID NO: 253)

The nucleotide sequence encodes the VB2049 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and the short RBD domain.

Figure 24:

5 A. Nucleotide sequence of VB2060 (SEQ ID NO: 254)

B. Amino acid sequence of VB2060 (SEQ ID NO: 255)

The nucleotide sequence encodes the VB2060 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and the long RBD domain.

10 Figure 25:

A. Nucleotide sequence of VB2065 (SEQ ID NO: 256)

B. Amino acid sequence of VB2065 (SEQ ID NO: 257)

The capitalised nucleotide sequence encodes the VB2065 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and the spike domain.

15

Figure 26:

A. Nucleotide sequence of VB2048 (SEQ ID NO: 258)

B. Amino acid sequence of VB2048 (SEQ ID NO: 259)

The nucleotide sequence encodes the VB2048 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and 20 predicted T cell epitopes.

20

Figure 27:

A. Nucleotide sequence of VB2059 (SEQ ID NO: 260)

B. Amino acid sequence of VB2059 (SEQ ID NO: 261)

The nucleotide sequence encodes the VB2059 protein with its targeting unit anti-mouse MHCII scFv, the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and the long RBD domain.

25

Figure 28:

A. Nucleotide sequence of VB2071 (SEQ ID NO: 262)

B. Amino acid sequence of VB2071 (SEQ ID NO: 263)

30

The nucleotide sequence encodes the VB2071 protein with its targeting unit anti-mouse MHCII scFv, the dimerisation unit comprising h1 and h4 and the CH3 domain of hlgG3, and the spike protein.

Figure 29:

5 A. Nucleotide sequence of VB2081 (SEQ ID NO: 264)

B. Amino acid sequence of VB2081 (SEQ ID NO: 265)

The nucleotide sequence encodes the VB2081 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hlgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep08) and the long RBD domain
10 linked with a (GGGGS)₂ linker.

Figure 30:

A. Nucleotide sequence of VB2082 (SEQ ID NO: 266)

B. Amino acid sequence of VB2082 (SEQ ID NO: 267)

The nucleotide sequence encodes the VB2082 protein with its targeting unit hMIP-1 α ,
15 the dimerisation unit comprising h1 and h4 and the CH3 domain of hlgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep18) and the long RBD domain linked with a (GGGGS)₂ linker.

Figure 31:

A. Nucleotide sequence of VB2083 (SEQ ID NO: 268)

20 B. Amino acid sequence of VB2083 (SEQ ID NO: 269)

The nucleotide sequence encodes the VB2083 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hlgG3, and an antigenic unit comprising 2 predicted T cell epitopes (pep08 + pep18 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a (GGGGS)₂ linker.

25 Figure 32:

A. Nucleotide sequence of VB2084 (SEQ ID NO: 270)

B. Amino acid sequence of VB2084 (SEQ ID NO: 271)

The nucleotide sequence encodes the VB2084 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hlgG3, and an
30 antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 + pep25 with a

(GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a (GGGGS)₂ linker.

Figure 33:

A. Nucleotide sequence of VB2085 (SEQ ID NO: 272)

5 B. Amino acid sequence of VB2085 (SEQ ID NO: 273)

The nucleotide sequence encodes the VB2085 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep08) and the long RBD domain, linked with a GLGGL linker.

10 Figure 34:

A. Nucleotide sequence of VB2086 (SEQ ID NO: 274)

B. Amino acid sequence of VB2086 (SEQ ID NO: 275)

The nucleotide sequence encodes the VB2086 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an
15 antigenic unit comprising 1 predicted T cell epitope (pep08) and the long RBD domain, linked with a (GLGGL)₂ linker.

Figure 35:

A. Nucleotide sequence of VB2087 (SEQ ID NO: 276)

B. Amino acid sequence of VB2087 (SEQ ID NO: 277)

20 The nucleotide sequence encodes the VB2087 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep18) and the long RBD domain, linked with a GLGGL linker.

Figure 36:

25 A. Nucleotide sequence of VB2088 (SEQ ID NO: 278)

B. Amino acid sequence of VB2088 (SEQ ID NO: 279)

The nucleotide sequence encodes the VB2088 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 2 predicted T cell epitopes (pep08 + pep18 with a (GGGGS)₂
30 linker in between epitopes) and the long RBD domain, linked with a GLGGL linker.

Figure 37:

A. Nucleotide sequence of VB2089 (SEQ ID NO: 280)

B. Amino acid sequence of VB2089 (SEQ ID NO: 281)

5 The nucleotide sequence encodes the VB2089 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a GLGGL linker.

Figure 38:

10 A. Nucleotide sequence of VB2091 (SEQ ID NO: 282)

B. Amino acid sequence of VB2091 (SEQ ID NO: 283)

The nucleotide sequence encodes the VB2091 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep08) and the long RBD domain,
15 linked with a TQKSLSLSPGKGLGGL linker.

Figure 39:

A. Nucleotide sequence of VB2092 (SEQ ID NO: 284)

B. Amino acid sequence of VB2092 (SEQ ID NO: 285)

20 The nucleotide sequence encodes the VB2092 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a TQKSLSLSPGKGLGGL linker.

Figure 40:

25 A. Nucleotide sequence of VB2094 (SEQ ID NO: 286)

B. Amino acid sequence of VB2094 (SEQ ID NO: 287)

The nucleotide sequence encodes the VB2094 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 1 predicted T cell epitope (pep08) and the long RBD domain,
30 linked with a SLSLSPGKGLGGL linker.

Figure 41:

A. Nucleotide sequence of VB2095 (SEQ ID NO: 288)

B. Amino acid sequence of VB2095 (SEQ ID NO: 289)

- 5 The nucleotide sequence encodes the VB2095 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a SLSLSPGKGLGGL linker.

10 Figure 42:

A. Nucleotide sequence of VB2097 (SEQ ID NO: 290)

B. Amino acid sequence of VB2097 (SEQ ID NO: 291)

- 15 The nucleotide sequence encodes the VB2097 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a GSAT linker.

Figure 43:

A. Nucleotide sequence of VB2099 (SEQ ID NO: 292)

- 20 B. Amino acid sequence of VB2099 (SEQ ID NO: 293)

- 25 The nucleotide sequence encodes the VB2099 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and the long RBD domain, linked with a SEG linker.

Figure 44:

A. Nucleotide sequence of VB2129 (SEQ ID NO: 294)

B. Amino acid sequence of VB2129 (SEQ ID NO: 295)

- 30 The nucleotide sequence encodes the VB2129 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising the long RBD domain with 3 mutations characterised in the South African variant B.1.351.

Figure 45:

Amino acid sequence of VB2131 (SEQ ID NO: 296)

5 The VB2131 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the Wuhan strain and the South African variant B.1.351) linked with a SEG linker.

Figure 46:

Amino acid sequence of VB2132 (SEQ ID NO: 297)

10 The VB2132 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the Wuhan strain and the South African variant B.1.351) linked with a GSAT linker.

Figure 47:

Amino acid sequence of VB2133 (SEQ ID NO: 298)

15 The VB2133 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the Wuhan strain and the South African variant B.1.351) linked with a TQKSLSLSPGKGLGGL linker.

Figure 48:

20 Amino acid sequence of VB2134 (SEQ ID NO: 299)

The VB2134 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the Wuhan strain and the South African variant B.1.351) linked with a SLSLSPGKGLGGL linker.

Figure 49:

25 Amino acid sequence of VB2135 (SEQ ID NO: 300)

30 The VB2135 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the South African variant B.1.351 and the UK variant B.1.1.7) linked with a SEG linker.

Figure 50:

Amino acid sequence of VB2136 (SEQ ID NO: 301)

The VB2136 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the South African variant B.1.351 and the UK variant B.1.1.7) linked with a GSAT linker.

Figure 51:

Amino acid sequence of VB2137 (SEQ ID NO: 302)

The VB2137 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the South African variant B.1.351 and the Californian variant B.1.427) linked with a SEG linker.

Figure 52:

Amino acid sequence of VB2138 (SEQ ID NO: 303)

The VB2138 protein with its targeting unit hMIP-1 α , the dimerisation unit comprising h1 and h4 and the CH3 domain of hIgG3, and an antigenic unit comprising two long RBD domains (RBD from the South African variant B.1.351 and the Californian variant B.1.427) linked with a GSAT linker.

Figure 53:

Overview of protein formats of the VB10.COVID constructs used in the non-clinical development:

A: VB2049, VB2060, VB2065 and VB2048.

B: VB2059 and VB2071.

C: VB2081-VB2099.

D: VB2129.

E: VB2131-VB2138.

Figure 54:

VB10.COVID vaccibody proteins VB2049, VB2060 and VB2065 were produced and secreted as functional homodimers 3 days after transfection of HEK293 cells.

Conformational integrity of the proteins was confirmed by binding to antibodies

detecting human MIP-1 α (targeting unit), human IgG CH3 domain (dimerisation unit) (as capture antibody), the RBD domain or the spike protein (antigenic unit) in ELISA.

Figure 55:

- A: VB2048 vaccibody protein were produced and secreted as a functional homodimer 3 days after transfection of HEK293 cells. Conformational integrity of the proteins was confirmed by binding to antibodies detecting human MIP-1 α (targeting unit) and antibodies capturing human IgG CH3 domain (dimerisation unit).
- B: VB10.COVID2 vaccibody proteins VB2059 and VB2071 were produced and secreted as functional homodimers 3 days after transfection of HEK293 cells. Conformational integrity of the proteins was confirmed by binding to antibodies detecting human IgG CH3 domain (dimerisation unit), the RBD domain or the spike protein (antigenic unit) in ELISA.
- C: VB10.COVID2 vaccibody proteins VB2081 - VB2099 were produced and secreted as functional homodimers 6 days after transfection of HEK293 cells. Conformational integrity of the proteins was confirmed by binding to antibodies capturing human IgG CH3 domain (dimerisation unit) and detecting the RBD domain (antigenic unit) protein in ELISA.
- D: VB10.COVID2 vaccibody proteins VB2129 and VB2060 were produced and secreted as functional homodimers 3 days after transfection of HEK293 cells. Conformational integrity of the proteins was confirmed by binding to antibodies detecting human MIP-1 α (targeting unit), human IgG CH3 domain (dimerisation unit, as capture antibody) and the RBD domain protein (antigenic unit) in ELISA.
- E: ELISA carried out on supernatants harvested on day 3 post transient transfection from HEK293 cells which had been co-transfected with VB2048 and VB2049. Conformational integrity of the proteins was confirmed by binding to antibodies detecting human IgG CH3 domain (dimerisation unit) (as capture antibody) and human MIP-1 α (targeting unit), or the RBD domain protein (antigenic unit) in ELISA. Expression of both plasmids are confirmed by these results in combination with data showing an immune response *in vivo* in mice against VB2048 (response against T cell epitopes) and VB2049 (response against RBD domain) (for example fig. 76).

Figure 56:

SDS-PAGE and western blot analysis of VB10.COVID2 vaccibody protein VB2060. (A) Supernatant harvested from VB2060-transfected HEK293 cells under reducing (SDS +

reducing agent) or non-reducing (SDS) conditions. Supernatant was harvested 6 days after transient transfection and up-concentrated about 4-times before loaded onto gels. Arrows indicate possible bands.

Figure 57:

- 5 A: Anti-RBD IgG immune response in mice vaccinated with VB2049 or VB2060 DNA vaccine according to the invention (bar chart and line chart). Mice were vaccinated by intramuscular administration of DNA immediately followed by electroporation of the injection site. Vaccine, administration days, dose number and dose levels are indicated. Mean of 2 independent experiments are shown.
- 10 B: Anti-RBD IgG immune response in mice vaccinated with 2 doses of 50 µg of one of three VB10.COVS2 DNA vaccines (VB2049, VB2060, VB2065 and VB2071). Mice were vaccinated by intramuscular administration of DNA on days 0 and 21, immediately followed by electroporation of the injection site. Type of vaccine and controls (PBS) are indicated. Sera obtained at days 7, 14 and 28 post first vaccination were tested for anti-
- 15 RBD IgG antibodies binding the RBD protein. Mean of up to 5 mice per group is shown. C: Anti-RBD IgG immune response in mice vaccinated with 1 or 2 doses of either 3, 6, 12.5 or 25 µg of VB2060 DNA vaccine. Mice were vaccinated by intramuscular administration of DNA on day(s) 0 (and 21), immediately followed by electroporation of the injection site. Sera obtained at days 7, 14 and 21 and 28 post first vaccination and
- 20 at day 7 post boost vaccination at day 21 were tested for anti-RBD IgG antibodies binding the RBD protein. Mean of 4- 5 mice per group is shown. D: Anti-RBD IgG measured in bronchoalveolar lavage (BAL) of mice vaccinated with either 1 dose or 2 doses of 3, 6.25, 12.5 or 25 µg of VB2060 DNA vaccine. Mice were vaccinated by intramuscular administration of DNA on either on day 0, or day 0 and 21,
- 25 immediately followed by electroporation of the injection site. BAL fluid obtained at days 14, 21 and 28 post first vaccination and day 7 post boost vaccination at day 21 was tested for anti-RBD. E: Anti-RBD IgG immune response in mice vaccinated with VB2059 DNA vaccine according to the invention. Mice were vaccinated by intramuscular administration of
- 30 DNA immediately followed by electroporation of the injection site. Vaccine, administration days, dose number and dose levels are indicated. Mean of 2 independent experiments are shown. F: Anti-RBD IgG immune response in mice vaccinated with 1 dose of 25 µg of the indicated vaccine candidates. Mice were vaccinated by intramuscular administration of

DNA on day 0, immediately followed by electroporation of the injection site. Sera obtained at day 14 post vaccination were tested for anti-RBD IgG antibodies binding the RBD protein. Mean of 2- 5 mice per group is shown.

- 5 G: Anti-RBD IgG immune response in mice vaccinated with 1 or 2 doses of either 1, 6.25, 12.5 or 25 µg of VB2129 and VB2060 DNA vaccine. Mice were vaccinated by intramuscular administration of DNA on day(s) 0 (and 21), immediately followed by electroporation of the injection site. Sera obtained at days 7, 14 and 21 and 28 post first vaccination and at day 7 post boost vaccination at day 21 were tested for anti-RBD IgG antibodies binding the RBD protein. Mean of 4- 5 mice per group is shown.
- 10 H: Anti-RBD IgG immune response in mice vaccinated with a vaccine comprising DNA plasmids VB2048 and VB2049. 1 dose of 12.5 µg of each plasmid combined in one pharmaceutically acceptable carrier was administered intramuscularly to mice on day 0, immediately followed by electroporation of the injection site. Sera obtained at days 7 and 14 post vaccination were tested for anti-RBD IgG antibodies binding the RBD
- 15 protein. Mean of 3- 5 mice per group is shown.

Figure 58:

- A: VB10.COVS DNA vaccines VB2049, VB2060 and VB2065 elicit robust neutralizing antibody responses. Mice were vaccinated intramuscularly at day 0, 21 and 89 with 2.5 µg, 25 µg or 50 µg of VB2049, VB2060 or VB2065 (groups tested are indicated). Sera
- 20 were collected and assessed for neutralizing antibodies against homotypic SARS-CoV-2 live virus strain Australia/VIC01/2020 isolate 44. Sera from PBS vaccinated mice served as a negative control and NIBSC 20/130 served as a positive control. Dotted line indicates the assay limit of detection.

- B: VB10.COVS DNA vaccine VB2060 elicits robust neutralizing antibody responses.
- 25 Mice were vaccinated intramuscularly at day (s) 0 (and 21) with either 3, 6, 12.5 or 25 µg of VB2060 (groups tested are indicated). Sera were collected and assessed for neutralizing antibodies against homotypic SARS-CoV-2 live virus strain Australia/VIC01/2020 isolate 44. Sera from PBS vaccinated mice served as a negative control and NIBSC 20/130 served as a positive control. Dotted line indicates the assay
- 30 limit of detection.

Figure 59:

T cell response induced with different doses and number of doses of VB10.COVS DNA vaccine VB2049. Total number of IFN-γ positive spots/1x10⁶ splenocytes from mice (5

mice/group) vaccinated intramuscularly with 2.5 µg or 25 µg VB2049 DNA plasmid after re-stimulation with overlapping RBD peptide pools. Splenocytes were harvested at day 14 post first vaccination and at day 7 post boost vaccination at day 21.

Figure 60:

- 5 Induction of CD4+ and CD8+ RBD specific immune responses and T cell epitope mapping after intramuscular vaccination of mice. CD4 and CD8 cell populations were stimulated for 24 hours with 61 individual RBD peptides (15-mer peptides overlapping by 12 amino acid from SARS-COV2 RBD domain) and number of IFN-γ positive spots/1x10⁶ splenocytes were detected in an ELISpot assay
- 10 A. Vaccination of mice (5 animals/group) with 2 x 25 µg of VB2049 on day 0 and 21 (boost vaccination) and ELISpot assay performed on day 28 (7 days post boost vaccination).
- B. Vaccination of mice (2-3 animals/group) with 3 x 50 µg of VB2060 on day 0, 21 and 89 and ELISpot assay performed on day 99 (10 days post last boost vaccination).
- 15 C. Map of the SARS-COV2 RBD domain and identification of immunodominant peptides in BALB/c mice.

Figure 61:

- A. Kinetics of T cells responses in mice vaccinated with 25 µg of VB2060. Mice were vaccinated with 1 or 2 doses (days 0 and 7) and the splenocytes were harvested at day 4, day 7, day 11, day 14, day 18 and day 21 5-6 animals/group, except day 21 (2 animals/group) for single immunization group.
- 20 B. T cell response induced comparing three VB10.COVID DNA vaccines, VB2049, VB2059 and VB2060. Total number of IFN-γ positive spots/1x10⁶ splenocytes from mice (4-5 mice/group) vaccinated intramuscularly with 2 x 2.5 µg of three VB10.COVID DNA plasmids after re-stimulation with overlapping RBD peptide pools. Splenocytes
- 25 were harvested at day 28 (7 days post boost vaccination at day 21).

Figure 62:

- T cell response induced with different doses and number of doses of VB2060. Total number of IFN-γ positive spots/1x10⁶ splenocytes from mice (2-3 animals/group)
- 30 vaccinated intramuscularly with 25 µg or 50 µg VB2060 DNA plasmid after re-stimulation with overlapping RBD peptide pools. Splenocytes were harvested either at day 90 post first vaccination or 10 days after the boost vaccination at day 89.

Figure 63:

A: Induction of CD4+ and CD8+ spike specific immune responses elicited by vaccination with VB2065 or VB2071 DNA vaccine. Total number of IFN- γ positive spots/ 1×10^6 splenocytes from mice (5-6 animals/group) vaccinated intramuscularly with two doses of 50 μ g VB2065 DNA plasmid (day 0 and 21) after re-stimulation with spike peptide pools. Splenocytes were harvested at day 28 (7 days post boost vaccination at day 21).

B T cell response induced by the DNA vaccine VB2129. Total number of IFN- γ positive spots/ 1×10^6 splenocytes from mice (5 mice/group) vaccinated intramuscularly with 1 x 1.0, 6.25, 12.5 or 25 μ g after re-stimulation with overlapping RBD peptide pools. Splenocytes were harvested at day 7 and 14 days post vaccination.

Figure 64:

A and B:

Th1/Th2 cytokine profile indicative of RBD specific Th1 responses. Cytokine concentration in supernatant of splenocytes cell culture from mice vaccinated intramuscularly with VB10.COVID DNA vaccines (A) VB2060, VB2049 or VB2059 and (B) VB2065 or VB2071 and control group (PBS).

Figure 65:

Gating strategy for identification of T cells: A. All cells were examined using side scatter (SSC) and forward scatter (FSC) parameters. Lymphocyte gate was set based on the relative size (FSC) of the cells. B. Lymphocytes were analyzed for presence of doublets, and a gate was set to include only single cells in further analysis. C. Dead cells were identified using viability dye and a gate was set to include live cells in further analysis. D. In the population of live cells all CD3+ cells were gated for future analysis. E. T cells were defined as CD3+ and $\gamma\delta$ TCR T cells were excluded from the analysis. F. All T cells were analyzed for expression of CD4 and CD8 markers.

Figure 66:

Detection of RBD specific multifunctional T cell responses in VB2060 (A and B) or VB2049 (C and D) vaccinated mice 28 days post first vaccination. A/C. Percent of CD4+ and CD8+ T cells responding to RBD stimulation. Percent of cells expressing each marker (or combinations of markers) is shown as total of each respective

population. B/D. Graphical presentation of response type based on the expression of cytokines. CD4 and CD8 graphs were made using SPICE software.

Figure 67:

5 Detection of RBD specific multifunctional CD4⁺ T cell responses in VB2060 vaccinated mice 90 days post first vaccination. A. Percent of CD4⁺ T cells responding to RBD stimulation. Graph shows production of cytokines in three groups – twice vaccinated with medium dose (VB2060 2x25 µg), once vaccinated with high dose (VB2060 1x50 µg) and twice vaccinated with high dose (VB2060 2x50 µg). B. Graphical presentation of response type based on the expression of cytokines. CD4 and CD8 graphs were
10 made using SPICE software.

Figure 68:

Detection of RBD specific multifunctional CD8⁺ T cell responses in VB2060 vaccinated mice 90 days post initial vaccination. A. Percent of CD8⁺ T cells responding to RBD stimulation. Graph shows production of cytokines in three groups – twice vaccinated
15 with medium dose (VB2060 2x25 µg), once vaccinated with high dose (VB2060 1x50 µg) and twice vaccinated with high dose (VB2060 2x50 µg). B. Graphical presentation of response type based on the expression of cytokines. Pie charts were made using SPICE software.

Figure 69:

20 Detection of RBD specific multifunctional CD4⁺ T cell responses in VB2060 vaccinated mice 100 days post initial vaccination. A. Percent of CD4⁺ T cells responding to RBD stimulation. Graph shows production of cytokines in three groups – thrice vaccinated with medium dose (VB2060 3x25 µg), twice vaccinated with high dose (VB2060 2x50 µg) and thrice vaccinated with high dose (VB2060 3x50 µg). B. Graphical presentation
25 of response type based on the expression of cytokines. Pie charts were made using SPICE software.

Figure 70:

Detection of RBD specific multifunctional CD8⁺ T cell responses in VB2060 vaccinated mice 100 days post initial vaccination. A. Percent of CD8⁺ T cells responding to RBD
30 stimulation. Graph shows production of cytokines in three groups – 3x vaccinated with medium dose (VB2060 3x 25µg), 2x vaccinated with high dose (VB2060 2x50 µg) and

3x vaccinated with high dose (VB2060 3x50 µg) B. Graphical presentation of response type based on the expression of cytokines. CD4 and CD8 Graphs were made using SPICE software.

Figure 71:

5 T cell responses in lymph node 7 days post vaccination and 7 days post boost. Mice were vaccinated on day 0 and on day 21 with VB2060 DNA vaccine, and T cell responses were analyzed in draining lymph nodes on day 28. The cells were stimulated with RBD peptides for 16 hours, and analyzed using multiparameter flow cytometry. T cells were gated as described in Figure 65. CD4⁺ and CD8⁺ T cells were
10 examined for expression of TNF- α , IFN- γ , IL-2 and granzyme B. Percentages of positive cells are displayed in bar graphs in panels A, B, D and E. The Trm cells as shown in figure 72 were also examined for expression of TNF- α , IFN- γ , IL-2 and granzyme B, and percentages of positive cells are displayed in panel C and F.

15 Figure 72:

CD8⁺ positive T cells in figure 71 were analyzed for expression of CD103 and CD69 to define tissue resident memory T cells (Trm).

Figure 73:

20 T cell response induced with different doses and number of doses of VB10.COVID DNA vaccine VB2048. Total number of IFN- γ positive spots/1x10⁶ splenocytes from mice (5 animals/group) vaccinated intramuscularly on day(s) 0 (and day 21) with 2.5 µg or 25 µg VB2048 DNA plasmid after re-stimulation with 20 predicted T cell epitopes. Splenocytes were harvested at day 14 post first vaccination and at day 28 (7 days post boost vaccination at day 21).

25 Figure 74:

Induction of CD4⁺ and CD8⁺ peptide specific immune responses in mice (5 animals/group) after intramuscular vaccination with 2 x 25 µg of VB2048 DNA plasmid at days 0 and 21. CD4 and CD8 cell populations were stimulated for 24 hours with 20 predicted peptides and number of IFN- γ positive spots/1x10⁶ splenocytes were
30 detected in an ELISpot assay 7 days post boost vaccination on day 21.

Figure 75:

T cell response induced by VB10.COVID constructs with an antigenic unit comprising both predicted T cell epitopes and the RBD domain. Mice (5 animals/group) were vaccinated intramuscularly on day 0 with 25 µg of the indicated VB10.COVID DNA plasmids. On day 14 post vaccination, the spleens were harvested and splenocytes re-stimulation with either 1-3 predicted T cell epitopes or RBD pools. The figure represents the total number of IFN-γ positive spots/1x10⁶ splenocytes.

Figure 76:

T cell response induced by single plasmid vaccine compared to a vaccine comprising 2 plasmids. The VB10.COVID constructs VB2048 (20 T cell epitopes) and VB2049 (RBD) were used for vaccination either as a stand-alone vaccine or a vaccine comprising both VB2048 and VB2049 in a pharmaceutically acceptable carrier (combination vaccine). Mice (5 animals/group) were vaccinated intramuscularly on day 0 with either 25 µg of VB2048 or VB2049 as stand-alone vaccines or the combination vaccine comprising 12.5 µg of each VB2048 and VB2049. On day 14 post vaccination, the spleens were harvested and splenocytes were re-stimulated with either 20 predicted T cell epitopes and/or RBD pools. The figure represents the total number of IFN-γ positive spots/1x10⁶ splenocytes.

Figure 77:

Amino acid sequence of the signal peptide and anti-pan HLA class II targeting unit. The sequence is split up by " | " to help distinguish the following various parts of the sequence: Ig VH signal peptide | anti-pan HLA class II VL | linker | anti-pan HLA class II VH.

Figure 78

VB10.COVID DNA vaccine VB2060 stability data. VB2060 was stored at 37°C for up to 4 weeks and % supercoil DNA content was determined by HPLC as a stability indicating parameter after week 1 (T1), week 2 (T2), week 3 (T3) and week 4 (T4).

Detailed description

One aspect of the invention relates to a vaccine comprising an immunologically effective amount of:

- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope; or
- (ii) a polypeptide encoded by the polynucleotide as defined in (i); or
- 5 (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.

In general, a vaccibody construct comprises, in sequence, a targeting unit, a dimerization unit, and an antigenic unit. The vaccine induces a rapid, strong immune response, e.g. with few low doses. This makes it ideal for epidemic and pandemic situations.

Herein, a vaccine is capable of eliciting an immune response in a human individual to which it has been administered. In one embodiment, the immune response is a humoral immune response through generation of antibodies by B cells. In another embodiment, the immune response is a cellular immune response through generation of T cells. In yet another embodiment, the immune response is a humoral and cellular immune response.

The human individual may be a healthy human individual and the vaccine is used to provide a prophylactic treatment to said individual, i.e. rendering the individual a certain protection against an infection with a betacoronavirus. Alternatively, the human individual may be an individual who has been infected with a betacoronavirus and the vaccine is used to provide a therapeutic treatment to said individual, i.e. alleviating the symptoms of or curing the infection.

Betacoronaviruses denotes a genus in the subfamily Orthocoronaviridae. Betacoronaviruses are enveloped, positive-sense single-stranded RNA viruses. Within the genus, four lineages are commonly recognized: lineage A (subgenus Embecovirus), lineage B (subgenus Sarbecovirus), lineage C (Merbecovirus) and lineage D (Nobecovirus). Betacoronaviruses include the following viruses which caused/cause epidemics/pandemics in humans or can infect humans: SARS-CoV, which causes severe acute respiratory syndrome (SARS), MERS-CoV, which causes Middle East respiratory syndrome (MERS), SARS-CoV-2, which causes coronavirus disease 2019 (Covid-19), HCoV-OC43 and HCoV-HKU1. SARS-CoV and SARS-CoV-2

belong to the lineage B (subgenus Sarbecovirus), MERS-CoV belongs to the lineage C (Merbecovirus) and HCoV-OC43 and HCoV-HKU1 belong to the lineage A (subgenus Embecovirus).

5 Thus, in a further embodiment the human individual may be an individual who is at risk to be infected or has been infected with a betacoronavirus belonging to the lineage B (subgenus Sarbecovirus). Alternatively, the human individual may be an individual who is at risk to be infected or has been infected with SARS-CoV or SARS-CoV-2.

10 It is a common belief, that viral infections should be avoided by raising neutralizing antibodies against the virus. However, an aspect of the present invention relates to a vaccine that, once administered to a human individual, elicits only a T cell response or both a T cell response and a B cell response. The polynucleotides/polypeptides/dimeric proteins presented herein are able to raise cytotoxic T cells. Raised CD8⁺ T cells will kill virus-infected cells and eliminate the virus, thus curing the/protecting from disease
15 or at least alleviate the severity of the disease, both in a prophylactic and therapeutic setting. The antigenic unit of the vaccine according to the invention may comprise T cell epitopes only or T cell epitopes which are comprised in a betacoronavirus protein, which also comprises B cell epitopes - for example the spike protein, as shown herein. For an antigenic unit comprising T cell epitopes only, these can be from essential
20 intracellular viral proteins that are more conserved than viral surface proteins. Hereby is obtained a vaccine that can be used both for ongoing and future pandemics/epidemics caused by a similar betacoronavirus. For T cell epitopes comprised in a betacoronavirus surface protein, the surface protein can also comprise B cell epitopes that can induce an antibody response, i.e. antibodies binding to the viral
25 surface protein when the virus is in circulation and neutralizing the virus by inhibiting it from entering the host cell. The aforementioned vaccine can be used as a therapeutic vaccine or as a prophylactic vaccine.

In one aspect a human individual suffers from a betacoronavirus infection and the vaccine is a therapeutic vaccine. Then the vaccine is administered to an individual that
30 has been exposed to and may be affected by a betacoronavirus virus to eliminate infected cells and thus minimize the severity of the disease and to produce neutralizing antibodies against infection of further cells.

In another aspect of the invention, a human individual is a healthy individual and the vaccine is a prophylactic vaccine. Typically, this will be used to induce immunity to people where it is desired to raise neutralizing antibodies against the betacoronavirus in a prophylactic setting, e.g. to prevent an infection.

One aspect of the invention relates to a vaccine, wherein the antigenic unit comprises at least one betacoronavirus epitope which is a full-length viral surface protein of a betacoronavirus or a part of such a protein. As such, in one embodiment, the at least one betacoronavirus epitope is a full-length protein or a part thereof, wherein the protein is selected from the group consisting of envelope protein, spike protein, membrane protein and, if the betacoronavirus is an Embecovirus, spike-like protein hemagglutinin esterase.

In one embodiment, the antigenic unit comprises at least a B cell epitope comprised in a full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins and preferably comprises several B cell epitopes comprised in a full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins.

The term "several" herein is used interchangeably with the term "multiple" and "more than one".

The B cell epitope may be a linear or a conformational B cell epitope.

Thus, in one aspect, the invention relates to a vaccine comprising an immunologically effective amount of:

(i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a full-length viral surface protein of a betacoronavirus or a part thereof, preferably a protein selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase, or

(ii) a polypeptide encoded by the polynucleotide as defined in (i), or

(iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and

a pharmaceutically acceptable carrier.

Once administered, a vaccine as described above, i.e. comprising an antigenic unit, wherein the antigenic unit comprises a full-length viral surface protein of a betacoronavirus or a part thereof, elicits a B cell response and T cell response and can
5 be used as a prophylactic or therapeutic vaccine. In one embodiment, the aforementioned vaccine is used a prophylactic vaccine.

One aspect of the invention relates to a vaccine, wherein the at least one betacoronavirus epitope is the full-length spike protein of a betacoronavirus. The spike
10 protein is one of the virus' structural proteins and forms, together with the envelope and membrane proteins, the viral envelope. The interaction between viral spike protein and angiotensin-converting enzyme 2 (ACE2) on host cell surface allows the virus to attach to and fuse with the membrane of the host cell, enter the cell and thus initiates the infection process. The spike protein is a major antigen inducing neutralizing antibodies,
15 and thus it is considered as an antigen for vaccine design. The spike protein is prone to mutation and as such several variants exist of the spike protein and the RBD domain comprised in the spike protein (Fig 2.)

In another embodiment the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of
20 SEQ ID NO: 230, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

25 In a preferred embodiment, the at least one betacoronavirus epitope is a part of the spike protein, i.e. the receptor binding domain (RBD) of the spike protein or a part of the RBD. The RBD has been found to contain multiple conformation-dependent epitopes relevant for inducing highly potent neutralizing antibodies. In another embodiment, the at least one betacoronavirus epitope comprises an amino acid
30 sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such

as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In another embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 802, such as at least 75%, such as at least 77%, such as at least 80%,
5 such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

10 In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of SEQ ID NO: 802.

In yet another embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 803, such as at least 75%, such as at least 77%, such as at
15 least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

20 In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of SEQ ID NO: 803.

In yet another embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 804, such as at least 75%, such as at least 77%, such as at
25 least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of SEQ ID NO: 804.

In yet another embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as
5 at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of SEQ ID NO: 805.

10 In a preferred embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such
15 as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of SEQ ID NO: 246.

20 In another preferred embodiment, the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of amino acids 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%,
25 such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the at least one betacoronavirus epitope has the amino acid sequence of amino acids 243 to 465 of SEQ ID NO: 255.

In a further embodiment, the antigenic unit comprises multiple copies of the RBD and/or parts thereof, e.g. 2, 3, 4 or 5 copies, wherein the copies are not identical and
30 comprise mutations, e.g. 1, 2, 3, 4, 5 or more mutations.

As an example, the antigenic unit may comprise two RBDs or parts thereof, e.g. the RBD of the spike protein of the Wuhan strain of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the South African variant B.1.351 of SARS-CoV-2 or a part thereof. As a further example, the antigenic unit may the RBD of the spike protein of the South African variant B.1.351 of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the UK variant B.1.1.7 of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the Californian variant B.1.427 of SARS-CoV-2 or a part thereof. In a preferred embodiment, the copies are separated by linkers.

In another embodiment, the at least one betacoronavirus epitope is a variant causing significantly reduced neutralizing titer of prototype sera from patients or vaccines compared to the new variant strain. In one embodiment, the variant is causing a 2-4 fold or more reduced neutralizing titer, i.e. calculated by serum titer of prototype strain divided by titer against new variant strain. In another embodiment this may be all variants with RBD mutation in E484 (e.g. B.1.351, P.1, B.1.429 etc. in Greaney et al.), L452 (Cherian et al. 2021) and Q498 (Zahradnik et al 2021, and PHE, 22 April 2021 VOC Tech briefing).

In another embodiment, the at least one betacoronavirus epitope is a part of the spike protein, i.e. the heptad repeat 1 (HR1) or heptad repeat 2 (HR2) domain of the spike protein. After binding of the spike protein on the virion to the ACE2 receptor on the host cell, the HR1 and HR2 domain interact with each other to form a six-helix bundle (6-HB) fusion core, bringing viral and cellular membranes into close proximity for fusion and infection. In one embodiment, the at least one betacoronavirus epitope is the HR1 domain of the spike protein, in another embodiment, the at least one betacoronavirus epitope is the HR2 domain of the spike protein.

In another embodiment the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 232 such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In yet another embodiment the at least one betacoronavirus epitope comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 249 such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as
5 at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In another embodiment, the at least one betacoronavirus epitope comprises at least a part of the spike protein, preferably at least a B cell epitope comprised in the spike
10 protein or more preferably several of such B cell epitopes.

Thus, in one aspect, the invention relates to a vaccine comprising an immunologically effective amount of:

- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises the
15 full-length spike protein or at least a part of the full-length spike protein of a betacoronavirus or at least a B cell epitope comprised in the spike protein; or
- (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
- (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
20 a pharmaceutically acceptable carrier.

In a preferred embodiment, the at least one part of the spike protein is the receptor binding domain (RBD). In another preferred embodiment, the at least one part of the spike protein is the HR1 domain or the HR2 domain. In yet another preferred embodiment, the at least one part of the spike protein is the HR2 domain.

25 In another preferred embodiment, the antigenic unit comprises at least a B cell epitope comprised in the spike protein of a betacoronavirus, preferably comprises several B cell epitopes comprised in the spike protein of a betacoronavirus or a part thereof, e.g. the receptor binding domain, the HR1 domain or the HR2 domain.

Antibody response is more important in a prophylactic than therapeutic setting since it can block the virus and prevent that the virus infects host cells. For SARS-CoV and CoV-2, infection of human cells can occur through binding of the spike protein of the virus to the ACE2 receptor on human lung epithelia.

5 Another approach is a vaccine, wherein the at least one betacoronavirus epitope is a betacoronavirus T cell epitope. The present disclosure reveals that conserved parts of the genome among betacoronaviruses comprise T cell epitopes capable of initiating an immune response. Thus, one aspect of the invention relates to a vaccine comprising at
10 least one T cell epitope, preferably at least one T cell epitope that is conserved between several species or strains of betacoronaviruses, e.g. conserved between SARS-Cov2 and SARS-CoV.

The T cell epitopes may be comprised in any of the virus' proteins, i.e. in viral surface proteins but also in the nucleocapsid protein or replicase polyproteins or in other
15 structural and non-structural proteins.

Several of the T cell epitopes that have been found to be reactive in humans are also in the non-structural proteins and open reading frames, where functions may not have been fully elucidated but could still have a critical function for the virus (see e.g. Tarke et al 2021 Table in Suppl where genes and epitopes are listed).

20 Thus, in another aspect, the invention relates to a vaccine comprising an immunologically effective amount of:

- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one T cell epitope of a betacoronavirus; or
 - 25 (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.

In a preferred embodiment, the antigenic unit comprises several T cell epitopes of a
30 betacoronavirus, preferably several T cell epitopes that are conserved between several

species or strains of betacoronaviruses. In one embodiment, the antigenic unit comprises 2 to 50 T cell epitopes, e.g. 3 to 45 T cell epitopes, e.g. 4 to 40 T cell epitopes, e.g. 5 to 35 T cell epitopes, e.g. 6 to 30 T cell epitopes, e.g. 7 to 25 T cell epitopes, such as 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25
5 T cell epitopes.

A vaccine comprising T cell epitopes from conserved regions of betacoronaviruses will provide protection against several species/strains of betacoronaviruses, e.g. against several strains of SARS-CoV, e.g. against SARS-CoV and SARS-CoV-2. Such a vaccine will also provide protection against multiple variants of a betacoronavirus, e.g.
10 variants of the SARS-CoV virus or variants of the SARS-CoV-2 virus, which is important for the efficacy of such a vaccine against future mutated viruses. Viruses are known to mutate, e.g. undergo viral antigen drift or antigen shift. The finding of conserved regions across the betacoronavirus genus makes it likely that these conserved regions are needed to maintain essential structures or functions, thus it is
15 anticipated that future mutations will take place in the less-conserved regions. By raising an immune response against the conserved regions, the vaccinated individual will be protected also against mutated (and thus novel) strains of the future.

In one embodiment of the present invention, the vaccine is therefore designed to evoke a cell-mediated immune response through activation of T cells against betacoronavirus epitopes. T cells recognize epitopes when they have been processed and presented
20 complexed to an MHC molecule.

There are two primary classes of major histocompatibility complex (MHC) molecules, MHC I and MHC II. The terms MHC (class) I and MHC (class) II are interchangeably used herein with HLA (class) I and HLA (class) II. Human leukocyte antigen (HLA) is a
25 major histocompatibility complex in humans.

The T cell epitope comprised in the antigenic unit of a vaccine of the invention which only comprises T cell epitopes or in the antigenic unit of a vaccine of the invention which comprises T cell epitopes but further comprises at least one betacoronavirus epitope which is a full-length viral surface protein or a part thereof, the T cell epitope
30 has a length of from 7 to about 200 amino acids, with the longer T cell epitopes possibly including hotspots of minimal epitopes. A hotspots of minimal epitopes is a region that contains several minimal epitopes (e.g. having a length of from 8-15 amino

acids) that are predicted to be presented by different HLA alleles to cover a broad range of world population

In one embodiment, the antigenic unit of such a vaccine comprises T cell epitopes with a length of from 7 to 150 amino acids, preferably of from 7 to 100 amino acids, e.g.
5 from about 10 to about 100 amino acids or from about 15 to about 100 amino acids or from about 20 to about 75 amino acids or from about 25 to about 50 amino acids.

In a preferred embodiment, the antigenic unit of such a vaccine comprises T cell epitopes having a length suitable for specific presentation on MHC I or MHC II. In one embodiment, the T cell epitope has a length of from 7 to 11 amino acids for MHC I
10 presentation. In another embodiment, the T cell epitope sequence has a length of from 9 – 60 amino acids, such as from 9 to 30 amino acids, such as 15 – 60 amino acids, such as 15- 30 for MHC II presentation. In a preferred embodiment the T cell epitope has a length of 15 amino acids for MHC II presentation.

In another preferred embodiment, the T cell epitope is selected based on the predicted
15 ability to bind to HLA class I/II alleles. In yet another embodiment, the T cell epitope is known to be immunogenic, e.g. its immunogenicity has been confirmed by appropriate methods and the results have been published, e.g. in a scientific publication.

In another embodiment of the invention the antigenic unit includes multiple T cell epitopes that are known to be immunogenic or predicted to bind to HLA class I/II
20 alleles. The latter T cell epitopes are selected *in silico* on the basis of predictive HLA-binding algorithms. After having identified all relevant epitopes, the epitopes are ranked according to their ability to bind to HLA class I/II alleles and the epitopes that are predicted to bind best are selected to be included in the antigenic unit.

Any suitable HLA-binding algorithm may be used, such as one of the following:

25 Available software analysis of peptide-MHC binding (IEDB, NetMHCpan and NetMHCIIpan) may be downloaded or used online from the following websites:

<http://www.iedb.org/>

<https://services.healthtech.dtu.dk/service.php?NetMHCpan-4.0>

<https://services.healthtech.dtu.dk/service.php?NetMHCIIpan-3.2>

Commercially available advanced software to predict optimal sequences for vaccine design are found here:

<http://www.oncoimmunity.com/>

<https://omictools.com/t-cell-epitopes-category>

5 <https://github.com/griffithlab/pVAC-Seq>

<http://crdd.osdd.net/raghava/cancertope/help.php>

<http://www.epivax.com/tag/neoantigen/>

10 In another embodiment, each T cell epitope is ranked with respect to its predicted binding affinity and/or antigenicity, and the predicted most antigenic epitopes are selected and preferably optimally arranged in the antigenic unit.

15 In an embodiment of the present invention, the T cell epitope sequence is a part of the sequence of the spike protein or the membrane protein or the envelope protein or the nucleocapsid protein or the ORF1a/b or ORF3a protein. In another embodiment, the T cell epitope sequence is part of the following genes/proteins: NCAP, AP3A, spike, ORF1a/b, ORF3a, VME1 and VEMP.

One embodiment of the invention relates to a method of identifying T cell epitopes that are conserved between betacoronaviruses, e.g. between betacoronaviruses of the same subgenus, e.g. between SARS-CoV-2 and SARS-CoV comprising:

- 20 • Identification of sets of HLA class I and II alleles that are specific for a specific population or a specific ethnic group or a specific geographic region
- Identification of genomic regions in the conserved viral sequence of SARS-CoV-2 that contain hotspots of minimal epitopes, i.e. minimal epitopes predicted to be presented by different HLA class I and II alleles to cover a broad range of the world's population
- 25 • Selection of SARS-CoV-2 T cell epitopes in the hotspots that cover the highest number of different HLA class I and II alleles
- From the selected T cell epitopes, identifying those that are conserved between SARS-CoV and SARS-CoV-2

- Checking the selected T cell epitopes for similarity to sequences found in the normal human proteome and removing those T cell epitopes with a high number of matches to such sequences
- From the remaining selected T cell epitopes, identifying those that match or have a high similarity to minimal epitopes already described to be immunogenic

In another embodiment the invention relates to a method of identifying T cell epitopes that are conserved between betacoronaviruses, e.g. between betacoronaviruses of the same subgenus, e.g. between SARS-CoV-2 and SARS-CoV comprising:

- Identification of sets of HLA class I and II alleles that are specific for a specific population or a specific ethnic group or a specific geographic region
- Identification of genomic regions in the viral sequence of SARS-CoV-2 that contain hotspots of minimal epitopes
- Selection of the optimal set of hotspots that covers the highest number of SARS-CoV and SARS-CoV-2 variants, as well as the highest number of different HLA class I and II alleles
- Checking the selected T cell epitopes for similarity to sequences found in the normal human proteome and removing those T cell epitopes with a high number of matches to such sequences
- From the remaining selected T cell epitopes, identifying those that match or have a high similarity to minimal epitopes already described to be immunogenic

In this method, the selection of the optimal set of hotspots is implemented as an optimization algorithm (maximum set coverage) so both HLA coverage and pathogen conservation are optimized at the same time.

Specific T cell epitopes have been identified by the disclosed procedure. In an embodiment of the present invention the T cell epitope is selected from the epitopes listed in Example 1. In a preferred embodiment, the T cell epitope is selected from the list consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30,

SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35,
SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40,
SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45,
SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50,
5 SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55,
SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60,
SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65,
SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70,
SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75,
10 SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80,
SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85,
SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90,
SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95,
SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100,
15 SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO:
105, SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID
NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ
ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119,
SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO:
20 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID
NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ
ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138,
SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO:
143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID
25 NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152, SEQ
ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID NO: 157,
SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO:
162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID
NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ
30 ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176,
SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO:
181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID
NO: 186, SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ
ID NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195,
35 SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO:

200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223, SEQ ID NO: 224, SEQ ID NO: 225, SEQ ID NO: 226, SEQ ID NO: 227, SEQ ID NO: 228, SEQ ID NO: 229 and SEQ ID NOs: 322 – 444.

In preferred embodiment, the T cell epitope is selected from the list consisting of: SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87, SEQ ID NO: 62, SEQ ID NO: 39, SEQ ID NO: 59, SEQ ID NO: 26, SEQ ID NO: 53, SEQ ID NO: 32, SEQ ID NO: 38, SEQ ID NO: 30, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 35, SEQ ID NO: 71, SEQ ID NO: 9, SEQ ID NO: 21, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ ID NO: 20.

In another embodiment, the T cell epitope is selected from the list consisting of: SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87 and SEQ ID NO: 62.

In yet another embodiment, the T cell epitopes is selected from the list consisting of pep1 – pep20 disclosed in Table 1 and SEQ ID NO: 75. In yet another embodiment, the T cell epitope is one that has been confirmed to be immunogenic in a clinical trial or is validated in human patients having had an infection with a betacoronavirus.

In yet another aspect the invention relates to a vaccine comprising an immunologically effective amount of:

(i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a) a full-length viral surface protein of a betacoronavirus or a part thereof and b) at least one betacoronavirus T cell epitope; or

(ii) a polypeptide encoded by the polynucleotide as defined in (i), or

(iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and

a pharmaceutically acceptable carrier.

In one embodiment, the full-length protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.

- 5 In another embodiment, the antigenic unit comprises at least a B cell epitope comprised in such full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins and preferably comprises several B cell epitopes comprised in such full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins.
- 10 In yet another aspect the invention relates to a vaccine comprising an immunologically effective amount of:
- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a)
15 betacoronavirus B cell epitope comprised in the spike protein and b) at least one betacoronavirus T cell epitope; or
 - (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- 20 a pharmaceutically acceptable carrier.
- In one embodiment, the antigenic unit comprises the full-length spike protein. As such, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 230, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such
25 as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.
- In one embodiment, the antigenic unit of the aforementioned vaccine comprises a) the receptor binding domain of the spike protein of a betacoronavirus and b) at least one
30 betacoronavirus T cell epitope.

In one embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%,
5 such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 231.

In another embodiment, the antigenic unit comprises an amino acid sequence
10 comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 802, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at
15 least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 802.

In yet another embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 803,
20 such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID
25 NO: 803.

In yet another embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 804,
such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at
30 least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 804.

In yet another embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 805.

In a preferred embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246 , such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 246.

In another preferred embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of amino acids 243 to 455 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of amino acids 243 to 455 of SEQ ID NO: 255.

In a further embodiment, the antigenic unit comprises multiple copies of the RBD and/or parts thereof, e.g. 2, 3, 4 or 5 copies, wherein the copies are not identical and comprise mutations, e.g. 1, 2, 3, 4, 5 or more mutations.

As an example, the antigenic unit may comprise two RBDs or parts thereof, e.g. the RBD of the spike protein of the Wuhan strain of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the South African variant B.1.351 of SARS-CoV-2 or a part thereof domains. As a further example, the antigenic unit may the RBD of the spike
5 protein of the South African variant B.1.351 of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the UK variant B.1.1.7 of SARS-CoV-2 or a part thereof and the RBD of the spike protein of the Californian variant B.1.427 of SARS-CoV-2 or a part thereof.

In another embodiment, the antigenic unit of the aforementioned vaccine comprises a)
10 the HR1 domain or HR2 domain of the spike protein of a betacoronavirus and b) at least one betacoronavirus T cell epitope. In yet another embodiment, the antigenic unit of the aforementioned vaccine comprises a) the HR2 domain of the spike protein of a betacoronavirus and b) at least one betacoronavirus T cell epitope.

In a preferred embodiment, the at least one T cell epitope is selected from the list
15 consisting of SEQ ID NO: 1 - SEQ ID NO: 444, preferably at least one T cell epitope selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87, SEQ ID NO: 62, SEQ ID NO: 39, SEQ ID NO: 59, SEQ ID NO: 26, SEQ ID NO: 53, SEQ ID NO: 32, SEQ ID NO: 38, SEQ ID NO: 30, SEQ ID NO: 40,
20 SEQ ID NO: 42, SEQ ID NO: 35, SEQ ID NO: 71, SEQ ID NO: 9, SEQ ID NO: 21, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ ID NO: 20, more preferably at least one T cell epitope selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87 and
25 SEQ ID NO: 62.

The length of the antigenic unit is primarily determined by the length of the epitope sequences comprised therein as well as their numbers. In one embodiment, the epitopes are separated from each other by linkers, which also contribute to the length of the antigenic unit.

30 In one embodiment, the antigenic unit comprises up to 3500 amino acids, such as from 21 to 3500 amino acids, preferably from about 30 amino acids to about 2000 amino acids such as from about 50 to about 1500 amino acids, more preferably from about

100 to about 1500 amino acids, such as from about 100 to about 1000 amino acids or from about 100 to about 500 amino acids or from about 100 to about 300 amino acids.

Although it is possible to obtain a relevant immune response if the betacoronavirus epitopes are randomly arranged in the antigenic unit, it is preferred to follow at least one of the following methods for arranging T cell epitopes and/or B cell epitopes, preferably linear B cell epitopes (in the following denoted "epitopes") in the antigenic unit in order to enhance the immune response.

The antigenic unit can be described as a polypeptide having an N-terminal start and a C-terminal end. The antigenic unit is connected to the dimerization unit, preferably via a unit linker. The antigenic unit is either located at the COOH-terminal end or the NH₂-terminal end of the polypeptide/dimeric protein. It is preferred that the antigenic unit is in the COOH-terminal end of the polypeptide/dimeric protein.

In one embodiment, the epitopes are arranged in the order of from most antigenic to least antigenic in the direction from the dimerization unit towards the end of the antigenic unit, i.e. the terminal epitope.

In another embodiment, in particular if the hydrophilicity/hydrophobicity varies greatly among the epitopes, it is preferred that the most hydrophobic epitope(s) is/are positioned substantially in the middle of the antigenic unit and the most hydrophilic epitope(s) is/are positioned at the beginning and/or end of the antigenic unit.

Since a true positioning in the middle of the antigenic unit is only possible if the antigenic unit comprises an odd number of epitopes, the term "substantially" in this context refers to antigenic units comprising an even number of epitopes, wherein the most hydrophobic epitopes are positioned as closed to the middle as possible.

By way of example, an antigenic unit comprises 5 epitopes which are arranged as follows: 1-2-3*-4-5; with 1, 2, 3*, 4 and 5 each being an epitope and * indicates the most hydrophobic epitope, which is positioned in the middle of the antigenic unit.

In another example, an antigenic unit comprises 6 epitopes which are arranged as follows: 1-2-3*-4-5-6 or, alternatively, as follows: 1-2-4-3*-5-6; with 1, 2, 3*, 4, 5 and 6 each being an epitope and * indicates the most hydrophobic epitope, which is positioned substantially in the middle of the antigenic unit.

Alternatively, the epitopes may be arranged alternating between a hydrophilic and a hydrophobic antigen sequence.

Furthermore, GC rich epitopes should not be arranged adjacent to each other to avoid GC clusters. In a preferred embodiment, one GC rich epitope is followed by at least one non-GC rich epitope before a second GC rich epitope follows.

In one embodiment, the vaccine according to the invention comprises an antigenic unit which comprises 1 to 50 epitopes. In a preferred embodiment, said epitopes are T cell epitopes.

In one embodiment from 3 to 50 epitopes are included in the antigenic unit, such as from 3 to 30 epitopes, such as from 3 to 20 epitopes, such as from 3 to 15 epitopes, or such as from 3 to 10 epitopes. In a preferred embodiment, said epitopes are T cell epitopes.

In another embodiment 5 to 50 epitopes are included in the antigenic unit, such as from 5 to 30 epitopes, such as for example from 5 to 25 epitopes, such as from 5 to 20 epitopes, such as from 5 to 15 epitopes or such as from 5 to 10 epitopes. In a preferred embodiment, said epitopes are T cell epitopes.

In a further embodiment 10 to 50 epitopes are included in the antigenic unit, such as from 10 to 40 epitopes, such as from 10 to 30 epitopes, such as from 10 to 25 epitopes, such as from 10 to 20 epitopes or such as from 10 to 15 epitopes. In a preferred embodiment, said epitopes are T cell epitopes.

In a preferred embodiment the antigenic unit consists of 10, 20, 30 or 50 epitopes. In a preferred embodiment, said epitopes are T cell epitopes.

The antigenic unit may further comprise one or more linkers, which separate one epitope or several epitopes from one other epitopes or several other epitopes and a linker, which connects the antigenic unit to the dimerization unit (hereinafter called the unit linker). The one or more linkers ensure that the epitopes are presented in an optimal way to the immune system, which increases the vaccine's efficacy. For vaccines wherein the antigenic unit comprises a full-length protein of the betacoronavirus or a part of such protein, the presence of a linker may also ensure that the protein is folding correctly.

The one or more linkers are preferably designed to be non-immunogenic and are preferably also flexible. In a vaccine comprising a full-length viral surface protein or a part thereof, e.g. the spike protein or parts thereof, the linkers allow for the protein to fold correctly and thus optimize presentation of the included B cell epitopes to B cells.

5 In addition, the linkers allow effective secretion of a functional vaccine protein that is effectively delivered to antigen presenting cells and thus increases presentation of T cell epitopes to T cells, even if the antigenic unit comprises a high number of epitopes. Preferably, the length of the one or more linkers is from 4 to 20 amino acids to secure flexibility. In another preferred embodiment, the length of the one or more linkers is

10 from 8 to 20 amino acids, such as from 8 to 15 amino acids, for example 8 to 12 amino acids or such as for example from 10 to 15 amino acids. In a particular embodiment, the length of the one or more linkers is 10 amino acids.

The one or more linkers have preferably all the same nucleotide or amino acid sequence. If, however, one or more of the epitopes comprise an amino acid motif

15 similar to the linker, it may be an advantage to substitute the neighboring linkers of that epitope with linker of a different sequence. Further, if an epitope/linker junction is predicted to constitute an epitope in itself, then a linker of a different sequence might be used.

The one or more linkers are preferably serine (S)-glycine (G) linkers which comprise several serine and/or several glycine residues. Preferred examples are GGGGS (SEQ ID NO: 806), GGGSS (SEQ ID NO: 807), GGGSG (SEQ ID NO: 808), GGGGS or multiple variants thereof such as GGGGSGGGGS (SEQ ID NO: 809) or (GGGGS)_m, (GGGSS)_m, (GGGSG)_m, where m is an integer from 1 to 5, from 1 to 4 or from 1 to 3. In a preferred embodiment, m is 2.

20

25 In a preferred embodiment, the serine-glycine linker further comprises at least one leucine (L) residue, such as at least 2 or at least 3 leucines. The serine-glycine linker may for example comprise 1, 2, 3 or 4 leucine. Preferably, the serine-glycine linker comprises 1 leucine or 2 leucines.

In one embodiment, the one or more linkers comprise or consist of the sequence

30 LGGGS (SEQ ID NO: 810), GLGGS (SEQ ID NO: 811), GGLGS (SEQ ID NO: 812), GGGLS (SEQ ID NO: 813) or GGGGL (SEQ ID NO: 814). In another embodiment, the one or more linkers comprise or consist of the sequence LGGSG (SEQ ID NO: 815),

GLGSG (SEQ ID NO: 816), GGLSG (SEQ ID NO: 817), GGGLG (SEQ ID NO: 818) or GGGSL. In yet another embodiment, the one or more linkers comprise or consist of the sequence LGGSS (SEQ ID NO: 819), GLGSS (SEQ ID NO: 820), GGLSS (SEQ ID NO: 821), GGGLS or GGGSL (SEQ ID NO: 822).

- 5 In yet another embodiment, the one or more linkers comprise or consist of the sequence LGLGS (SEQ ID NO: 823), GLGLS (SEQ ID NO: 824), GLLGS (SEQ ID NO: 825), LGGLS (SEQ ID NO: 826) or GLGGL (SEQ ID NO: 827). In yet another embodiment, one or more linkers comprise or consist of the sequence LGLSG (SEQ ID NO: 828), GLLSG (SEQ ID NO: 829), GGLSL (SEQ ID NO: 830), GGLLG (SEQ ID NO: 831) or GLGSL (SEQ ID NO: 832). In yet another embodiment, the one or more linkers
10 comprise or consist of the sequence LGLSS (SEQ ID NO: 833), GLGLS, GGLLS (SEQ ID NO: 834), GLGSL or GLGSL.

In another embodiment, the one or more linkers are serine-glycine linkers that have a length of 10 amino acids and comprise 1 leucine or 2 leucines.

- 15 In one embodiment, the one or more linkers comprise or consist of the sequence LGGSGGGGS (SEQ ID NO: 835), GLGGSGGGGS (SEQ ID NO: 836), GGLSGGGGS (SEQ ID NO: 837), GGGLSGGGGS (SEQ ID NO: 838) or GGGGLGGGS (SEQ ID NO: 839). In another embodiment, the one or more linkers comprise or consist of the sequence LGGSGGGGSG (SEQ ID NO: 840),
20 GLGSGGGGSG (SEQ ID NO: 841), GGLSGGGGSG (SEQ ID NO: 842), GGGLGGGSG (SEQ ID NO: 843) or GGGSLGGGSG (SEQ ID NO: 844). In yet another embodiment, the one or more linkers comprise or consist of the sequence LGGSSGGGSS (SEQ ID NO: 845), GLGSSGGGSS (SEQ ID NO: 846), GGLSSGGGSS (SEQ ID NO: 847), GGGLSGGGSS (SEQ ID NO: 848) or
25 GGGSLGGGSS (SEQ ID NO: 849).

- In a further embodiment, the one or more linkers comprise or consist of the sequence LGGSLGGGS (SEQ ID NO: 850), GLGGSLGGS (SEQ ID NO: 851), GGLSGGLGS (SEQ ID NO: 852), GGGLSGGGLS (SEQ ID NO: 853) or GGGGLGGGGL (SEQ ID NO: 854). In another embodiment, the one or more linkers
30 comprise or consist of the sequence LGGSGLGGS (SEQ ID NO: 855), GLGSGGLGS (SEQ ID NO: 856), GGLSGGGLS (SEQ ID NO: 857), GGGLGGGLG (SEQ ID NO: 858) or GGGSLGGGSL (SEQ ID NO: 859). In yet

another embodiment, the one or more linkers comprise or consist of the sequence LGGSSLGGSS (SEQ ID NO: 860), GLGSSGLGSS (SEQ ID NO: 861), GGLSSGGLSS (SEQ ID NO: 862), GGGLSGGGLS or GGGSLGGGSL.

5 In further embodiments, the one or more linkers comprise or consist of the sequence TQKSLSLSPGKGLGGL (SEQ ID NO: 863). In another embodiment, the one or more linkers comprise or consist of the sequence SLSLSPGKGLGGL (SEQ ID NO: 864).

For a vaccine comprising an antigenic unit comprising a full-length protein of the betacoronavirus or a part of such protein and one or more T cell epitopes, in one embodiment, the linker separating the T cell epitopes and the protein has a length of
10 from 10 to 60 amino acids, e.g. from 11 to 50 amino acid or from 12 to 45 amino acids or from 13 to 40 amino acids.

Also such linkers are preferably non-immunogenic. Examples of such linkers are glycine-serine rich linkers or glycine-serine-leucine rich linkers as described above, GSAT (SEQ ID NO: 865) linkers comprising or consisting of the sequence
15 GGSAGGSGSGSSGGSSGASGTGTAGGTGSGSGTGSG (SEQ ID NO: 866). In another embodiment, such linkers are SEG linkers comprising or consisting of the sequence GGSAGGSGSGSSGGSSGASGTGTAGGTGSGSGTGSG (SEQ ID NO: 866). In another embodiment, such linkers are SEG linkers comprising or consisting of the sequence GGSAGGSGSGSSGGSSGASGTGTAGGTGSGSGTGSG (SEQ ID NO: 866). Further, protein modelling may be used to model 3D structures/conformations of the protein connected to the linker to determine, which length and amino acid
20 sequence promotes correct folding.

In one embodiment, the antigenic unit comprises from 10 to 20 or from 10 to 25 epitopes and a plurality of linkers, which separate each of the epitopes or separate several epitopes from several other epitopes. Preferably, said linkers have a length of 10 amino acids. The linkers may also have any length as defined herein above, such
25 as for example from 5 to 12 amino acids.

Alternatively, the one or more linkers may be selected from the group consisting of GSAT linkers, i.e. a linker comprising one or more glycine, serine, alanine and threonine residues, and SEG linkers, i.e. a linker comprising one or more serine, glutamic acid and glycine residues, or multiple variants thereof.

30 The antigenic unit and the dimerization unit are preferably connected by a unit linker. The unit linker may comprise a restriction site in order to facilitate the construction of

the polynucleotide. It is preferred that the unit linker is a GLGGL linker or a GLSGL (SEQ ID NO: 868) linker.

Examples of further sequences of linkers are disclosed in paragraphs [0098]-[0099] and in the recited sequences of WO 2020/176797A1, which is incorporated herein by
5 reference and in paragraphs [0135] to [0139] of US 2019/0022202A1, which is incorporated herein by reference.

The term "targeting unit" as used herein refers to a unit that delivers the polypeptide/dimeric protein (encoded by the polynucleotide as) comprised in the
10 vaccine with its antigenic unit to an antigen presenting cell.

Due to the targeting unit, the polypeptide/dimeric protein comprised in the vaccine of the invention attracts dendritic cells (DCs), neutrophils and other immune cells. Thus, the polypeptide/dimeric protein/vaccine comprising the targeting unit will not only target the antigenic unit comprised therein to specific cells, but in addition facilitates a
15 response-amplifying effect (adjuvant effect) by recruiting specific immune cells to the administration site of the vaccine. This unique mechanism is of great importance in a clinical setting where patients can receive the vaccine of the invention without any additional adjuvants since the vaccine itself provides the adjuvant effect.

The targeting unit is connected through the dimerization unit to the antigenic unit,
20 wherein the latter is in either the COOH-terminal or the NH₂-terminal end of the polypeptide/dimeric protein. It is preferred that the antigenic unit is in the COOH-terminal end of the polypeptide/dimeric protein.

The targeting unit is designed to target the polypeptide/dimeric protein/vaccine of the invention to surface molecules expressed on the APCs, such as molecules expressed
25 exclusively on subsets of DCs.

Examples of such surface molecules on APCs are HLA, cluster of differentiation 14 (CD14), cluster of differentiation 40 (CD40), chemokine receptors and Toll-like receptors (TLRs). Chemokine receptors include C-C motif chemokine receptor 1 (CCR1), C-C motif chemokine receptor 3 (CCR3) and C-C motif chemokine receptor 5
30 (CCR5) and XCR1. Toll-like receptors include TLR-2, TLR-4 and TLR-5.

The targeting unit is or comprises a moiety that interacts with surface molecules. Thus, the targeting unit comprises or consists of an antibody-binding region with specificity for HLA, CD14, CD40, or Toll- like receptors. In another embodiment, the targeting unit comprises or consists of a synthetic or natural ligand. Examples include soluble CD40
5 ligand, natural ligands like chemokines, e.g. chemokine ligand 5, also called C-C motif ligand 5 (CCL5 or RANTES), macrophage inflammatory protein alpha (CCL3 or MIP-1 α), chemokine motif ligand 1 or 2 (XCL1 or XCL2) and bacterial antigens like for example flagellin.

In one aspect of the invention the targeting unit comprises antibody binding regions
10 with specificity for surface receptors on antigen presenting cells, such as CD14, CD40, Toll- like receptors such as TLR-2, TLR-4 and/or TLR-5, chemokine receptors such as CCR1, CCR3, CCR5 or MHC class I and II proteins.

In another embodiment, the targeting unit has affinity for a surface molecule selected from the group consisting of CD40, TLR-2, TLR-4 and TLR-5. Thus, in one
15 embodiment the targeting unit comprises or consist of the antibody variable domains (VL and VH) with specificity for anti-CD40, anti-TLR-2, anti-TLR-4 or anti-TLR-5. In yet another embodiment, targeting unit comprises or consists of flagellin, which has affinity for TLR-5.

In one embodiment, the targeting unit has affinity for an MHC class II protein. Thus, in
20 one embodiment, the targeting unit comprises or consists of the antibody variable domains (VL and VH) with specificity for MHC class II proteins selected from the group consisting of anti-HLA-DP, anti-HLA-DR and anti-pan HLA class II.

In a preferred embodiment of the invention, the targeting unit has affinity for a chemokine receptor selected from CCR1, CCR3 and CCR5, preferably for a
25 chemokine receptor selected from CCR1 and CCR5. In another preferred embodiment of the invention, the targeting unit has an affinity for MHC class II proteins, preferably MHC class II proteins, selected from the group consisting of anti-HLA-DP, anti-HLA-DR and anti-pan HLA class II. More specifically in one embodiment the targeting unit comprises anti-pan HLA class II and MIP-1 α .

30 In one embodiment the binding of the targeting unit to its cognate receptors leads to internalization of the polypeptide/dimeric protein/vaccine into the APC and degradation thereof into small peptides that are loaded onto MHC molecules and presented to

CD4+ and CD8+ T cells to induce specific immune responses. Peptides loaded onto MHC II molecules can be recognized by antigen-specific CD4+ T helper cells, whereas peptides loaded on MHC I molecules can be recognized by antigen-specific CD8+ T cells, leading to proliferation and activation of cytotoxic function. Presentation of internalized antigens on MHC I molecules is a process termed cross-presentation. Once stimulated, and with help from activated CD4+ T cells, CD8+ T cells will target and kill cells expressing the same antigens.

In one aspect of the invention, the targeting unit comprises or is MIP-1 α , preferably human MIP-1 α (h MIP-1 α , also called LD78 β). Not only does MIP-1 α attract APC to the vaccine through its chemotactic ability, it also causes internalisation of the polypeptide/dimeric protein vaccine construct through both the classical and cross-presentation pathway, whereby the epitopes are processed by enzymes and presented on the cell surface to raise the T cell response, particularly Th1 CD4+ responses and CD8+ T cell responses. MIP-1 α is also capable of supporting the induction of antibody responses, in particular IgG2a, which is important for protection against betacoronavirus infection.

In one embodiment of the present invention, the targeting unit comprises an amino acid sequence having at least 80% sequence identity to the amino acid sequence 24-93 of SEQ ID NO: 234. In a preferred embodiment, the targeting unit comprises an amino acid sequence having at least 85% sequence identity to the amino acid sequence 24-93 of SEQ ID NO: 234, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity. In yet another preferred embodiment, the targeting unit comprises the amino acid sequence 24-93 of SEQ ID NO: 234.

In a more preferred embodiment the targeting unit consists of an amino acid sequence having at least 80% sequence identity to the amino acid sequence 24-93 of SEQ ID NO:1, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%,

such as at least 100% sequence identity to the amino acid sequence 24-93 of SEQ ID NO: 234.

5 In one embodiment the targeting unit comprises or is anti-pan HLA class II. This targeting unit induces rapid and strong antibody responses with mixed IgG1 and IgG2a antibodies. Moreover, this targeting unit induces a significant cellular response (CD4 +and CD8+ type T cells).

10 One aspect of the invention relates to a vaccine that comprises an immunologically effective amount of:

(i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit comprising anti-pan HLA class II, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a full-length viral surface protein of a betacoronavirus or a part thereof, preferably a protein selected from the group consisting of envelope
15 protein, spike protein, membrane protein and hemagglutinin esterase; or

(ii) a polypeptide encoded by the polynucleotide as defined in (i), or

(iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and

a pharmaceutically acceptable carrier.

20 In one embodiment, the antigenic unit of the above-mentioned vaccine comprises at least a B cell epitope comprised in a full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins and preferably comprises several B cell epitopes comprised in a full-length viral surface protein of a betacoronavirus, e.g. comprised in any of the aforementioned proteins.

25 One other aspect of the invention relates to a vaccine that comprises an immunologically effective amount of:

(i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit comprising anti-pan HLA class II, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises the full-length spike protein of a betacoronavirus or a part
30 thereof or at least a B cell epitope comprised in the spike protein or part thereof; or

- (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.
- 5 One further aspect of the invention relates to a vaccine that comprises an immunologically effective amount of:
- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit comprising hMIP-1 α , a dimerization unit and an antigenic unit, wherein the antigenic unit comprises the full-length spike protein of a betacoronavirus or a part thereof or at least a B cell epitope comprised in the spike protein or part thereof; or
 - 10 (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.
- 15 In one embodiment, the antigenic unit of the above-mentioned vaccine comprises the receptor binding domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR1 domain or HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In yet another embodiment, the
- 20 antigenic unit of the above-mentioned vaccine comprises the HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein.
- Once administered, this vaccine elicits a strong humoral response and potentially also a cellular response.
- 25 Another aspect of the invention relates to a vaccine that comprises an immunologically effective amount of:
- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit comprising hMIP-1 α , a dimerization unit and an antigenic unit, wherein the

antigenic unit comprises at least one betacoronavirus T cell epitope, preferably several T cell epitopes that are conserved among betacoronaviruses; or

(ii) a polypeptide encoded by the polynucleotide as defined in (i), or

(iii) a dimeric protein consisting of two polypeptides encoded by the
5 polynucleotide as defined in (i); and

a pharmaceutically acceptable carrier.

This vaccine, once administered, elicits a T cell response, i.e. a strong cellular response, which is particularly important in a therapeutic setting, as the CD8+ T cells can kill virus-infected cells and thus eliminate the virus. If the vaccine comprises T cell
10 epitopes that are conserved among betacoronaviruses, it could provide protection against multiple variants betacoronaviruses, e.g. multiple variants of SARS-CoV viruses, which is important for potential efficacy also against future betacoronavirus variants wherein mutations occur in the non-conserved regions.

15 A particular aspect relates to a vaccine that comprises an immunologically effective amount of:

(i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a)
the full-length spike protein or of a betacoronavirus or a part thereof or at least one B
20 cell epitope comprised in the spike protein or part thereof and b) at least one betacoronavirus T cell epitope; or

(ii) a polypeptide encoded by the polynucleotide as defined in (i), or

(iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and

25 a pharmaceutically acceptable carrier.

In one embodiment, the antigenic unit of the above-mentioned vaccine comprises the receptor binding domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR1 domain or HR2 domain of the spike protein or a part

thereof or at least a B cell epitope comprised therein. In yet another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein.

Such a vaccine will, once administered, elicit a T cell response and a B cell response.

- 5 In a pandemic or an epidemic situation, it is not time efficient to first diagnose an individual to determine if he or she needs primarily a B or T cell response, neither whether prophylactic or therapeutic treatment is the highest medical need. Less so, as the determination of whether or not an individual is infected can be difficult due to lack of (sufficient) applicable tests. Thus, being able to protect and cure at the same time is
- 10 important. By combining the full-length or part of the spike protein or several B cell epitopes present in the spike protein and the conserved T cell epitopes, both a strong humoral and cellular response is elicited once the vaccine is administered. The response can be more humoral or more cellular, depending on the selected targeting unit.
- 15 The vaccine above preferably comprises a targeting unit comprising MIP-1 α or anti-pan HLA class II.

Thus, one aspect of the present invention relates to a vaccine that comprises an immunologically effective amount of:

- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting
- 20 unit comprising MIP-1 α , a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a) the full-length spike protein of a betacoronavirus or a part thereof or at least one B cell epitope comprised in the spike protein or part thereof and b) at least one betacoronavirus T cell epitope; or
- (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
- 25 (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.

- In one embodiment, the antigenic unit of the above-mentioned vaccine comprises the receptor binding domain of the spike protein or a part thereof or at least a B cell epitope
- 30 comprised therein. In another embodiment, the antigenic unit of the above-mentioned

vaccine comprises the HR1 domain or HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In yet another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein.

- 5 In another embodiment the targeting unit comprises anti-pan HLA class II. This targeting unit induce rapid and strong antibody responses with mixed IgG1 and IgG2a antibodies. Moreover, this targeting unit induces a significant cellular response (CD4+ and CD8+ type T cells).

10 Thus, one embodiment of the present invention discloses a vaccine that comprises an immunologically effective amount of:

- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit comprising anti-pan HLA class II, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises a) the full-length spike protein of a betacoronavirus or a part thereof or at least one B cell epitope comprised in the spike protein or part thereof and b) at least one betacoronavirus T cell epitope; or
- 15

- (ii) a polypeptide encoded by the polynucleotide as defined in (i), or

- (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and

a pharmaceutically acceptable carrier.

- 20 In one embodiment, the antigenic unit of the above-mentioned vaccine comprises the receptor binding domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR1 domain or HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein. In yet another embodiment, the antigenic unit of the above-mentioned vaccine comprises the HR2 domain of the spike protein or a part thereof or at least a B cell epitope comprised therein.
- 25

- In further embodiments of the present invention, the antigenic unit comprises sets of 10, 14, 20, 24 and 30 T cell epitopes and the RBD and linkers between the epitopes. In one embodiment the antigenic unit comprises 10 T cell epitopes and the RBD and 10 T cell epitopes. In another embodiment the antigenic unit comprises the RBD and 20
- 30

epitopes. In a further embodiment the antigenic unit comprises 20 T cell epitopes and RBD with no linkers. In another embodiment the antigenic unit comprises 20 T cell epitopes.

5 In further embodiments of the present invention, the antigenic unit comprises sets of 10, 14, 20, 24 and 30 T cell epitopes and the HR1 domain or HR2 domain, preferably the HR2 domain, and linkers between the epitopes. In one embodiment the antigenic unit comprises 10 T cell epitopes and the HR1 domain or HR2 domain, preferably the HR2 domain and 10 T cell epitopes. In another embodiment the antigenic unit comprises the HR1 domain or HR2 domain, preferably the HR2 domain and 20
10 epitopes. In a further embodiment the antigenic unit comprises 20 T cell epitopes and HR1 domain or HR2 domain, preferably the HR2 domain with no linkers.

In yet another embodiment, the antigenic unit comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 T cell epitopes and the full-length of the spike protein or a part thereof, preferably the RBD or a part thereof. In yet another embodiment, the 2-10 T cell epitopes are
15 separated from each other by linkers and the full-length of the spike protein or a part thereof, preferably the RBD or a part thereof, is separated from the final T cell epitope by a linker. In yet another embodiment, the antigenic unit comprises 1-3 T cell epitopes and the full-length of the spike protein or a part thereof, preferably the RBD or a part thereof. In yet another embodiment, the 2 or 3 T cell epitopes are separated from each
20 other by linkers and the full-length of the spike protein or a part thereof, preferably the RBD or a part thereof, is separated from the one or the final T cell epitope by a linker.

In one embodiment, the antigenic unit comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 265 or SEQ ID NO: 267 or SEQ ID NO: 269 or SEQ ID NO: 271 or SEQ ID NO: 273 or SEQ ID NO: 275 or SEQ ID NO: 277 or SEQ ID NO: 279 or SEQ ID NO: 281 or SEQ ID NO: 283 or SEQ ID NO: 285 or SEQ ID NO: 287 or SEQ ID NO: 289 or SEQ ID NO: 291 or SEQ ID NO: 293, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%,
30 such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In one embodiment, the antigenic unit comprises the amino acid sequence of SEQ ID NO: 265 or SEQ ID NO: 267 or SEQ ID NO: 269 or SEQ ID NO: 271 or SEQ ID NO:

273 or SEQ ID NO: 275 or SEQ ID NO: 277 or SEQ ID NO: 279 or SEQ ID NO: 281 or
SEQ ID NO: 283 or SEQ ID NO: 285 or SEQ ID NO: 287 or SEQ ID NO: 289 or SEQ
ID NO: 291 or SEQ ID NO: 293.

5 In a preferred embodiment the 10, 14, 20, 24 and 30 T cell epitopes are selected from
the group consisting of: SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO:
57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87,
SEQ ID NO: 62, SEQ ID NO: 39, SEQ ID NO: 59, SEQ ID NO: 26, SEQ ID NO: 53,
SEQ ID NO: 32, SEQ ID NO: 38, SEQ ID NO: 30, SEQ ID NO: 40, SEQ ID NO: 42,
SEQ ID NO: 35, SEQ ID NO: 71, SEQ ID NO: 9, SEQ ID NO: 21, SEQ ID NO: 85, SEQ
10 ID NO: 75, SEQ ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ
ID NO: 20.

In a another preferred embodiment of the present invention, the antigenic unit is
selected from the group consisting of: SEQ ID NO: 237, SEQ ID NO: 238, SEQ ID NO:
15 239, SEQ ID NO: 240, SEQ ID NO: 241, SEQ ID NO: 242, SEQ ID NO: 243, SEQ ID
NO: 244, SEQ ID NO: 245, SEQ ID NO: 246, SEQ ID NO: 247, SEQ ID NO: 248. SEQ
ID NO: 249, SEQ ID NO: 250 and SEQ ID NO: 251.

The vaccine of the invention comprises a dimerization unit. The term "dimerization unit"
as used herein, refers to a sequence of nucleotides or amino acids between the
20 antigenic unit and the targeting unit. Thus, the dimerization unit serves to connect the
antigenic unit and the targeting unit and facilitates dimerization of two monomeric
polypeptides into a dimeric protein. Furthermore, the dimerization unit also provides the
flexibility in the polypeptide/dimeric protein to allow optimal binding of the targeting unit
to the surface molecules on the APCs, even if they are located at variable distances.
25 The dimerization unit may be any unit that fulfils these requirements.

Accordingly, in one embodiment dimerization unit comprises a hinge region. In another
embodiment, the dimerization unit comprises a hinge region and another domain that
facilitates dimerization. In one embodiment, the hinge region and the other domain are
connected through a linker, i.e. a dimerization unit linker. In yet another embodiment,
30 the dimerization unit comprises a hinge region, a dimerization unit linker and another
domain that facilitates dimerization, wherein the dimerization unit linker is located
between the hinge region and the other domain that facilitates dimerization.

The term "hinge region" refers to an amino acid sequence comprised in the dimeric protein that contributes to joining two polypeptides, i.e. contributes to the formation of a dimeric protein. Moreover, the hinge region functions as a flexible spacer between the polypeptides, allowing the two targeting units of the dimeric protein to bind simultaneously to two surface molecules on APCs, even if they are expressed with variable distances. The hinge region may be Ig derived, such as derived from IgG3. The hinge region may contribute to the dimerization through the formation of covalent bond(s), e.g. disulfide bridge(s) between cysteines. Thus, in one embodiment the hinge region has the ability to form one or more covalent bonds. Preferably, the covalent bond is a disulfide bridge.

In one embodiment, the dimerization unit comprises a hinge exon h1 and hinge exon h4 (human hinge region 1 and human hinge region 4) having an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 94-120 of SEQ ID NO: 233.

In a preferred embodiment, the dimerization unit comprises a hinge exon h1 and hinge exon h4 with an amino acid sequence having at least 85% sequence identity to the amino acid sequence 94-120 of SEQ ID NO: 233, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

In a preferred embodiment, the dimerization unit comprises a hinge exon h1 and hinge exon h4 with the amino acid sequence 94-120 of SEQ ID NO: 233.

In one embodiment, the dimerization unit comprises another domain that facilitates dimerization, said other domain is an immunoglobulin domain, such as an immunoglobulin constant domain (C domain), such as a carboxyterminal C domain (i.e. a CH3 domain), a CH1 domain or a CH2 domain, or a sequence that is substantially identical to the C domain or a variant thereof. Preferably, the other domain that facilitates dimerization is a carboxyterminal C domain derived from IgG. More preferably, the other domain that facilitates dimerization is a carboxyterminal C domain derived from IgG3.

The immunoglobulin domain contributes to dimerization through non-covalent interactions, e.g. hydrophobic interactions. For example, the immunoglobulin domain has the ability to form dimers via noncovalent interactions. Thus, in one embodiment, the immunoglobulin domain has the ability to form dimers via noncovalent interactions.

5 Preferably, the noncovalent interactions are hydrophobic interactions.

It is preferred that if the dimerization unit comprises a CH3 domain, it does not comprise a CH2 domain. Further, it is preferred that if the dimerization unit comprises a CH2 domain, it does not comprise a CH3 domain.

In one embodiment, the dimerization unit comprises a carboxyterminal C domain derived from IgG3 with an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 131-237 of SEQ ID NO: 233.

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In a preferred embodiment, the dimerization unit comprises a carboxyterminal C domain derived from IgG3 with an amino acid sequence having at least 85% sequence identity to the amino acid sequence 131-237 of SEQ ID NO: 233, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity.

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In a preferred embodiment, the dimerization unit comprises a carboxyterminal C domain derived from IgG3 with the amino acid sequence 131-237 of SEQ ID NO: 233.

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In a preferred embodiment, the dimerization unit comprises a hinge exon h1, a hinge exon h4, a dimerization unit linker and a CH3 domain of human IgG3. In a further preferred embodiment, the dimerization unit comprises a polypeptide consisting of hinge exon h1, hinge exon h4, a dimerization unit linker and a CH3 domain of human IgG3.

25

In another preferred embodiment, the dimerization unit consists of hinge exon h1 and hinge exon h4 connected through a dimerization unit linker to a CH3 domain of human IgG3.

In one embodiment of the present invention, the dimerization unit comprises an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 94-

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237 of SEQ ID NO: 233. In a preferred embodiment, the dimerization unit comprises an amino acid sequence having at least 85% sequence identity to the amino acid sequence 94-237 of SEQ ID NO: 233, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% sequence identity.

In one embodiment of the present invention, the dimerization unit comprises the amino acid sequence 94-237 of SEQ ID NO: 233

In a more preferred embodiment the dimerization unit consists of an amino acid sequence having at least 80% sequence identity to the amino acid sequence 94-237 of SEQ ID NO: 233, such as at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence 94-237 of SEQ ID NO: 233. In an even more preferred embodiment, the dimerization unit consists of the amino acid sequence 94-237 of SEQ ID NO: 233.

In one embodiment the dimerization unit linker, i.e. linker connecting the hinge region to the other domain, is present in the dimerization unit. In another embodiment, the linker is present and is a glycine-serine rich linker, preferably G3S2G3SG linker (GGGSSGGGSG).

The dimerization unit has any orientation with respect to antigenic unit and targeting unit. In one embodiment, the antigenic unit is in the COOH- terminal end of the dimerization unit with the targeting unit in the N-terminal end of the dimerization unit. As such, the antigenic unit is connected to the C-terminal end of the dimerization unit (e.g. via a unit linker) with the targeting unit being connected to the N-terminal end of the dimerization unit. In another embodiment, the antigenic unit is in the N-terminal end of the dimerization unit with the targeting unit in the COOH-terminal end of the dimerization unit. As such, the antigenic unit is connected to the N-terminal end of the dimerization unit (e.g. via a unit linker) with the targeting unit being connected to the C-terminal end of the dimerization unit. It is preferred that the antigenic unit is in the

COOH end of the dimerization unit, i.e. the antigenic unit is connected to the C-terminal end of the dimerization unit, preferably via the unit linker, and the targeting unit is connected to the N-terminal end of the dimerization unit.

5 In a preferred embodiment, the antigenic unit is connected to the dimerization unit by a unit linker. Thus, in one embodiment, the polynucleotide/polypeptide/dimeric protein comprises a nucleotide sequence encoding a unit linker or an amino acid sequence being the unit linker that connects the antigenic unit to the dimerization unit.

The unit linker may comprise a restriction site in order to facilitate the construction of the polynucleotide. In a preferred embodiment, unit linker is GLGGL or GLSGL.

10 In a preferred embodiment, the vaccine of the invention comprises a polynucleotide of which further comprises a nucleotide sequence encoding a signal peptide. The signal peptide is either located at the N-terminal end of the targeting unit or the C-terminal end of the targeting unit, depending on the orientation of the targeting unit in the
15 polypeptide. The signal peptide is designed and constructed to allow secretion of the polypeptide encoded by the polynucleotide in the cells transfected with said polynucleotide.

Any suitable signal peptide may be used. Examples of suitable peptides are a human Ig VH signal peptide, such as a signal peptide comprising an amino acid sequence
20 having at least 80 % sequence identity to the amino acid sequence of SEQ ID NO: 235, a human TPA signal peptide, such as SEQ ID NO: 236 and a signal peptide comprising an amino acid sequence having at least 80 % sequence identity to the amino acid sequence 1-23 of SEQ ID NO: 234, i.e. a human MIP1- α signal peptide.

25 In a preferred embodiment, the polynucleotide comprises a targeting unit which is hMIP1- α and a nucleic acid sequence which encodes for a human MIP1- α signal peptide.

In another preferred embodiment, the polynucleotide comprises a targeting unit which is human anti-pan HLA class II and a nucleic acid sequence which encodes for an Ig VH signal peptide.

30 In a preferred embodiment, the signal peptide comprises an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%,

such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence of SEQ ID NO: 235.

- 5 In a more preferred embodiment, the signal peptide consists of an amino acid sequence having at least 80%, preferably at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence of SEQ ID NO: 235.

- 15 In a preferred embodiment, the signal peptide comprises an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence 1-23 of SEQ ID NO: 234.

- 20 In a more preferred embodiment, the signal peptide consists of an amino acid sequence having at least 80%, preferably at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99%, such as 100% sequence identity to the amino acid sequence 1-23 of SEQ ID NO: 234.

- 25 Sequence identity may be determined as follows: A high level of sequence identity indicates likelihood that a second sequence is derived from a first sequence. Amino acid sequence identity requires identical amino acid sequences between two aligned sequences. Thus, a candidate sequence sharing 70% amino acid identity with a reference sequence requires that, following alignment, 70% of the amino acids in the candidate sequence are identical to the corresponding amino acids in the reference sequence. Identity may be determined by aid of computer analysis, such as, without limitations, the ClustalW computer alignment program (Higgins D., Thompson J.,
- 30

Gibson T., Thompson J.D., Higgins D.G., Gibson T.J., 1994. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. *Nucleic Acids Res.* 22:4673-4680), and the default parameters suggested therein. Using this program with its
5 default settings, the mature (bioactive) part of a query and a reference polypeptide are aligned. The number of fully conserved residues is counted and divided by the length of the reference polypeptide. In doing so, any tags or fusion protein sequences, which form part of the query sequence, are disregarded in the alignment and subsequent determination of sequence identity.

10 The ClustalW algorithm may similarly be used to align nucleotide sequences. Sequence identities may be calculated in a similar way as indicated for amino acid sequences.

Another preferred mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated
15 into the ALIGN program (version 2.0) which is part of the FASTA sequence alignment software package (Pearson WR, *Methods Mol Biol*, 2000, 132:185-219). Align calculates sequence identities based on a global alignment. Align0 does not penalize to gaps in the end of the sequences. When utilizing the ALIGN and Align0 program for comparing amino acid sequences, a BLOSUM50 substitution matrix with gap
20 opening/extension penalties of -12/-2 is preferably used.

Another preferred mathematical algorithm utilized for the comparison of sequences is the implementation of local pairwise alignment algorithm of BioPython called "Smith-Waterman algorithm".

25 One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 253, construct VB2049, or a polynucleotide encoding same, which comprises a humanMIP-1 α targeting unit and an antigenic unit comprising a short form of the SARS-CoV-2 RBD ("RBD short", amino acids 331-524, i.e. 193 amino acids). This construct is capable of raising anti-RBD IgG antibodies with neutralizing effects. It
30 is also capable of inducing strong T cell responses against epitopes comprised in the RBD.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 255, construct VB2060, or a polynucleotide encoding same, which

comprises a human MIP-1 α as targeting unit and an antigenic unit comprising a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids). It is capable of raising neutralizing anti-RBD IgG antibodies, which are even found in the lungs. This construct is capable of inducing strong T cell responses
5 against RBD within 7 days after vaccination that are long lasting.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 257, construct VB2065, or a polynucleotide encoding same, which comprises a human MIP-1 α targeting unit and an antigenic unit comprising the full-length spike protein from SARS-CoV2 strain Wuhan Hu-1. It is capable of raising
10 neutralizing anti-RBD IgG antibodies. The construct is capable of inducing broad and strong T cells responses.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 259, construct VB2048, or a polynucleotide encoding same, comprising a human MIP-1 α targeting unit and an antigenic unit comprising 20 immunogenic T cell
15 epitopes (see Table 1) from multiple SARS-CoV2 strains. It is capable of inducing strong T cell responses even when co-administered with other constructs, e.g. VB2049.

One aspect of the invention relates to a polypeptide or a polynucleotide encoding same, comprising a human anti-pan HLA class II targeting unit and an antigenic unit comprising the longer version of the SARS-CoV-2 RBD ("RBD long" amino acids 319-
20 542 i.e. 223 amino acids). The corresponding mouse construct, construct VB2059, comprising an anti-mouse MHCII scFv as targeting unit is capable of raising antibodies against RBD and of inducing a T cell response against RBD.

One aspect of the invention relates to a polypeptide or a polynucleotide encoding same, comprising a human anti-pan HLA class II targeting unit and an antigenic unit
25 comprising the full-length spike protein from SARS-CoV2 strain Wuhan Hu-1. The corresponding mouse construct, construct VB2071, comprising an anti-mouse MHCII scFv as targeting unit is able to induce anti-RBD IgG antibodies and induces broad and strong T cell responses.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 265, construct VB2081, or a polynucleotide encoding same, comprising a
30 humanMIP-1 α targeting unit and an antigenic unit comprising one predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD linked to the T cell

epitope with a (GGGGS)₂ linker. This construct raises IgG antibodies against RBD and induces T cell responses against RBD, to the included one T cell epitope.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 267, construct VB2082, or a polynucleotide encoding same, which
5 comprises a human MIP-1 α targeting unit and an antigenic unit comprising one predicted T cell epitope (pep18) and a longer version of the SARS-CoV-2 RBD linked to the T cell epitope with a (GGGGS)₂ linker. This construct is able to raise IgG responses against RBD, and to induce T cell response against the included one T cell epitope.

10 One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 271, construct VB2084, or a polynucleotide encoding same, which comprises a human MIP-1 α targeting unit. It has an antigenic unit comprising three predicted T cell epitopes (pep08, pep18, pep25) and the longer version of the SARS-CoV-2 RBD all linked with a (GGGGS)₂ linker. This construct is capable of inducing T
15 cell response against epitopes in the RBD, as well as against the included three T cell epitopes.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 293, construct VB2097, or a polynucleotide encoding same, which
20 comprises a human MIP-1 α targeting unit. The antigenic unit comprises three predicted T cell epitopes (pep08, pep18 and pep25) separated from each other with a (GGGGS)₂ linker and the "RBD long", which is separated from the T cell epitope by a GSAT linker. Not only did the construct raise IgG antibodies against RBD; it also showed a remarkable strong T cell responses against the RBD and the included T cell epitopes.

One aspect of the invention relates to a polypeptide with the amino acid sequence of
25 SEQ ID NO: 297, construct VB2099, or a polynucleotide encoding same, which comprises a human MIP-1 α targeting unit. The antigenic unit comprises 3 predicted T cell epitopes (pep08, pep18 and pep25), separated from each other with a (GGGGS)₂ linker and a longer version of the SARS-CoV-2 RBD ("RBD long", 223 amino acids) which is connected to the T cell epitope by a SEG linker. It is capable of raising IgG
30 antibodies against RBD. In addition, it is capable of inducing T cell responses against RBD and against the included T cell epitopes.

One aspect of the invention relates to a polypeptide with the amino acid sequence of SEQ ID NO: 295, construct VB2129, or a polypeptide encoding same, which comprises a human MIP-1 α targeting unit and an antigenic unit comprising the South African RBD (with 3 mutations characterised in the South African variant B.1.351) in. It is capable of raising IgG responses against RBD and of inducing T cell responses.

In one embodiment of the present invention the targeting unit, dimerization unit and antigenic unit in said polypeptide or dimeric protein are in the N-terminal to C-terminal order of targeting unit, dimerization unit and antigenic unit.

The vaccine of the invention comprises a pharmaceutically acceptable carrier , including but not limited to saline, buffered saline, such as PBS, dextrose, water, glycerol, ethanol, sterile isotonic aqueous buffers, and combinations thereof.

The vaccine may further comprise an adjuvant. Particularly for vaccines comprising polypeptides/proteins, pharmaceutically acceptable adjuvants include, but are not limited to poly-ICLC, 1018 ISS, aluminum salts, Amplivax, AS 15, BCG, CP-870,893, CpG7909, CyaA, dSLIM, GM-CSF, IC30, IC31, Imiquimod, ImuFact EV1 P321, IS Patch, ISS, ISCOMATRIX, JuvImmune, LipoVac, MF59, monophosphoryl lipid A, Montanide IMS 1312, Montanide ISA 206, Montanide ISA 50V, Montanide ISA-51, OK-432, OM-174, OM-197-MP-EC, ONTAK, PLGA microparticles, resiquimod, SRL172, virosomes and other virus-like particles, YF-17D, VEGF trap, R848, beta-glucan, Pam3Cys, Aquila's QS21 stimulon, vadimezan, and/or AsA404 (DMXAA).

For vaccines comprising polynucleotides, the vaccines may comprise molecules that ease transfection of cells and/or adjuvants in the form of plasmids comprising nucleotide sequences encoding chemokines or cytokines in order to enhance the immune response.

The vaccine may be formulated into any way suitable administration to a subject, e.g. human individual, e.g. such as a liquid formulation for injection, e.g. for intradermal or intramuscular injection.

The vaccine of the invention may be administered in any way suitable for administration to a subject, e.g. human individual, of either a polypeptide/protein vaccine or a polynucleotide vaccine, such as administered by intradermal, intramuscular, intranodal or subcutaneous injection, or by mucosal or epithelial

application, such as intranasal, oral, enteral or intravesicular (to the bladder) administration.

In a preferred embodiment, the vaccine comprises a polynucleotide, and is administered by intramuscular or intradermal injection.

- 5 The vaccine may comprise one polynucleotide, e.g. in the form of a DNA plasmid or may comprise more than one polynucleotide, e.g. in the form of more than one DNA plasmids. In one embodiment, the vaccine comprises 2 DNA plasmids, one comprising a polynucleotide comprising a nucleotide encoding for an antigenic unit that comprises a full-length surface protein of betacoronavirus or a part thereof, e.g. the RBD and the
- 10 other comprising a polynucleotide comprising a nucleotide encoding for an antigenic unit that comprises T cell epitopes, preferably conservative T cell epitopes. Due to the “T cell epitope plasmid”, the vaccine will provide protection against several species/strains of betacoronaviruses, e.g. against several strains of SARS-CoV, e.g. against SARS-CoV and SARS-CoV-2. Such a vaccine will also provide protection
- 15 against multiple variants of a betacoronavirus, e.g. variants of the SARS-CoV virus or variants of the SARS-CoV-2 virus, which is important for the efficacy of such a vaccine against future mutated viruses.

In one embodiment, when the virus mutates, the plasmid comprising a polynucleotide comprising a nucleotide encoding for an antigenic unit that comprises a full-length

20 surface protein of betacoronavirus or a part thereof may be engineered such that it comprise the mutations, while the plasmid comprising a polynucleotide comprising a nucleotide encoding for an antigenic unit that comprises T cell epitopes may be kept as is.

The vaccine of the invention comprises an immunologically effective amount of the

25 polynucleotide/polypeptide or dimeric protein. The term “immunologically effective amount” means an amount inducing an immunoprotective response (for a prophylactic vaccine) or an immunotherapeutic response (for a therapeutic vaccine) in the individual vaccinated with such vaccine, wherein such response is induced by either a single vaccination or several vaccinations, e.g. an initial vaccination and one or several

30 booster vaccinations, adequately spaced in time. Such amount may vary depending upon which specific polynucleotide/polypeptide/dimeric protein is employed. It may also vary depending on whether the vaccine is administered for prophylaxis or treatment,

the severity of the disease in individuals infected with betacoronavirus, the age, weight, medical history and pre-existing conditions.

5 The immunologically effective amount may be an amount effective to reduce or to prevent the incidence of signs/symptoms, to reduce the severity of the incidence of signs/symptoms, to eliminate the incidence of signs/symptoms, to slow the development of the incidence of signs/symptoms, to prevent the development of the incidence of signs/symptoms, and/or effect prophylaxis of the incidence of signs/symptoms.

10 An immunologically effective amount for a prophylaxis may be an amount effective for prophylaxis of a disease caused by betacoronavirus or prevention of the reoccurrence of such a disease, is sufficient to effect such prophylaxis for the disease or reoccurrence. It may be an amount effective to prevent the incidence of signs and/or symptoms of a betacoronavirus infection.

15 An immunologically effective amount for a treatment may be an amount effective for arresting, or reducing the development of a disease caused by a betacoronavirus or its clinical symptoms, and/or alleviating or relieving the disease, causing regression of the disease or its clinical symptoms.

20 The vaccine of the invention typically comprises the polynucleotide in a range of from 0.1 to 10 mg, e.g. about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 or 1 mg or e.g. 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg. The vaccine of the invention typically comprises the polypeptide/dimeric protein in the range of from 5 µg to 5 mg.

25 The invention also relates to a polynucleotide as described above. The polynucleotide may comprise a DNA nucleotide sequence or an RNA nucleotide sequence, such as genomic DNA, cDNA, and RNA sequences, either double stranded or single stranded.

It is preferred that the polynucleotide is optimized to the species of the subject to which it is administered. For administration to a human, it is preferred that the polynucleotide sequence is human codon optimized.

30 In a preferred embodiment, the vaccine is a DNA vaccine, i.e. the polynucleotide is a DNA.

The invention further relates to a polypeptide encoded by the polynucleotide sequence as defined above. The polypeptide may be expressed *in vitro* for production of the vaccine according to the invention, or the polypeptide may be expressed *in vivo* as a
5 result of administration of the polynucleotide to a subject, such as a human individual.

Due to the presence of the dimerization unit, dimeric proteins are formed when the polypeptide is expressed. The dimeric protein may be a homodimer, i.e. wherein the two polypeptide chains are identical and consequently comprise identical
10 betacoronavirus epitopes, or the dimeric protein may be a heterodimer comprising two different monomeric polypeptides encoded in the antigenic units. The latter may be relevant if e.g. the number of betacoronavirus epitopes and thus the number of amino acids exceeds the upper limit for inclusion into the antigenic unit. It is however preferred that the dimeric protein is a homodimeric protein.

15 Furthermore, the invention relates to a vector comprising a polynucleotide sequence (e.g. in the form of a DNA) comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope.

The vector is for transfecting a host cell and expression of a polypeptide/dimeric protein encoded by the polynucleotide described above, i.e. an expression vector, preferably a
20 DNA plasmid.

It is preferred that the vector allows for easy exchange of the various units described above, particularly the antigenic unit. In one embodiment, the expression vector may be pUMVC4a vector or a vector comprising NTC9385R vector backbones. The
25 antigenic unit may be exchanged with an antigenic unit cassette restricted by the SfiI restriction enzyme cassette where the 5' site is incorporated in the GLGGL/GLSGL linker and the 3' site is included after the stop codon in the vector.

The invention also relates to a host cell comprising a polynucleotide comprising a
30 nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope or comprising a vector comprising a polynucleotide sequence comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope.

Suitable host cells include prokaryotes, yeast, insect or higher eukaryotic cells. In a preferred embodiment, the host cell is a human cell, preferably the cell of a human individual in need of the vaccine of the invention.

5 In one aspect, the invention relates to the use of the polynucleotide, the polypeptide or the dimeric protein described above as a medicament.

In a specific embodiment of the present invention the polynucleotide or the polypeptide or the dimeric protein are for use in the treatment of an infection with a betacoronavirus. In a preferred embodiment the betacoronavirus is SARS-CoV-2.

10 Suitable methods for preparing the vaccine according to the invention are disclosed in WO 2004/076489A1, WO 2011/161244A1, WO 2013/092875A1 and WO 2017/118695A1, which are incorporated herein by reference.

15 In one aspect, the invention relates to a method for preparing the vaccine comprising an immunologically effective amount of the dimeric protein, or the polypeptide as defined above by producing the polypeptides in vitro. The in vitro synthesis of the polypeptides and proteins may be carried out by any suitable method known to the person skilled in the art, such as through peptide synthesis or expression of the polypeptide in any of a variety of expression systems followed by purification.

20 Accordingly, in one embodiment the invention provides a method for preparing a vaccine comprising

- (i) a dimeric protein consisting of two polypeptides encoded by a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit
25 comprises at least one betacoronavirus epitope; or
- (ii) a polypeptide encoded by a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope by producing the dimeric protein or polypeptide in vitro, the method
30 comprises

- a) transfecting cells with the polynucleotide;
- b) culturing the cells;

- c) collecting and purifying the dimeric protein or the polypeptide expressed from the cells; and
- d) mixing the dimeric protein or polypeptide obtained from step c) with the pharmaceutically acceptable carrier.

5 In a preferred embodiment, the dimeric protein or polypeptide obtained from step c) is dissolved in said pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier is one of the aforementioned pharmaceutically acceptable carriers, e.g. an aqueous pharmaceutically acceptable carrier, such as water or a buffer. In one embodiment, the vaccine comprises further an adjuvant.

10 Purification may be carried out according to any suitable method, such as chromatography, centrifugation, or differential solubility.

In another aspect the invention relates to a method for preparing the vaccine according to the invention comprising an immunologically effective amount of the polynucleotide as defined above.

15 Thus, in one embodiment the invention provides a method for preparing a vaccine comprising an immunologically effective amount of a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope, the method comprises

- 20 a) preparing the polynucleotide;
- b) optionally cloning the polynucleotide into an expression vector; and
- c) mixing the polynucleotide obtained from step a) or the vector obtained from step b) with the pharmaceutically acceptable carrier.

25 The polynucleotide may be prepared by any suitable method known to the skilled person. For example, the polynucleotide may be prepared by chemical synthesis using an oligonucleotide synthesizer.

In particular, smaller nucleotide sequences, such as for example nucleotide sequences encoding the targeting unit, the dimerization unit and/or the subunits of the antigenic unit may be synthesized individually and then ligated to produce the final
30 polynucleotide into the vector backbone.

Examples

Example 1: Selection of T cell epitopes:

The predicted immunogenic epitopes from conserved regions of SARS CoV viruses were identified as follows:

5 In a first step, the worldwide population of HLA class I and II alleles were identified. For HLA class I, the allele frequency database available at <http://www.allelefrequencies.net> was used and the identification of the most frequent HLA alleles was conducted in the following manner: a separate search for each locus: A, B and C and a separate search for following regions: Europe, South-East Asia (focus on China) and North America
10 (focus on US) was carried out. The population standard was set to "Gold" to obtain only the high-quality studies. The level of resolution was set to at least 4 digits, for instance: HLA-A*01:01. The sampling year was set to 2005 and later. The top 4 frequent alleles for each study was collected. Among all top 4 for all studies, the top 4 - 5 frequent alleles for each region (Europe/South-East Asia/North America) was selected. Due to
15 overlap between the regions, the number of the final selected alleles was 10, 10 and 11 for A, B and C, respectively. These 31 HLA class I alleles cover 99.4% of the world population, as estimated by IEDB population coverage estimation tool (<http://tools.iedb.org/population/>). The coverage in detail was as follows: Europe: 99.9%; North America: 99.2%; South America: 92.7%; East Asia: 98.5%; Southeast
20 Asia: 98.1%; Northeast Asia: 97.4%; South Asia: 93.1%; Southwest Asia: 93.3%; Central Africa: 94.3%; East Africa: 92.3%; North Africa: 96.2%; South Africa: 91.2% and West Africa: 94.3%.

For HLA class II, although not done in this Example 1, the allele frequency may be collected in a similar manner as for HLA class I.

25 The next step was to identify T cell epitopes for SARS-CoV-2. This was done by obtaining the high-quality SARS-CoV-2 reference amino-acid sequence. The annotated (annotation score 5/5) Uniprot Wuhan strain was downloaded from Uniprot, query SARS-CoV-2 ([https://www.uniprot.org/uniprot/?query=sars-cov-2&fil=organism%3A%22Severe%20acute%20respiratory%20syndrome%20coronaviruss%20%20\(2019-nCoV\)%20\(SARS-CoV-2\)%20%5B2697049%5D%22&columns=id%2Centry%20name%2Creviewed%2Cprotein%20names%2Cgenes%2Corganism%2Clength&sort=score](https://www.uniprot.org/uniprot/?query=sars-cov-2&fil=organism%3A%22Severe%20acute%20respiratory%20syndrome%20coronaviruss%20%20(2019-nCoV)%20(SARS-CoV-2)%20%5B2697049%5D%22&columns=id%2Centry%20name%2Creviewed%2Cprotein%20names%2Cgenes%2Corganism%2Clength&sort=score)). Six proteins were
30

selected: four structural proteins: the spike protein, the envelope protein, the membrane protein, and the nucleocapsid protein and two non-structural proteins: ORF1a/b and ORF3a. A search was carried out for hotspot genomic areas of epitopes predicted to bind to HLA class I alleles in the six protein sequences using NetMHCpan 4.0 (<https://services.healthtech.dtu.dk/service.php?NetMHCpan-4.0>) and the HLA class I alleles as defined in the initial step. In total 13236 epitopes predicted to bind to at least one HLA class I allele were found. To identify the hotspot areas, filtering was applied to keep only those epitopes that bind to more than 10 different HLA class I alleles and to at least 1 allele from each locus (A/B/C). The remaining high quality 604 epitopes were further processed by merging the overlapping or adjacent epitopes (within 3 amino acids apart) to obtain hotspot epitope regions. The epitopes shorter than 15 amino acids were extended to 15 amino acids. The binding to HLA I and HLA II alleles was predicted using NetMHCpan 4.0 and NetMHCIIpan 3.2 (<https://services.healthtech.dtu.dk/service.php?NetMHCIIpan-3.2>), respectively, on the final list of merged epitopes.

Up-to-date high-quality annotated sequences from NCBI virus database for SARS-CoV2 and SARS-CoV were then obtained. The homology to these sequences by global alignment (%identity between the strain and epitope sequence) was determined. Up-to-date high-quality annotated human reference protein sequences were obtained from <https://www.uniprot.org/proteomes/UP000005640>. A summary of all identical matches between the epitopes and the human proteome using 6, 7, 8 and 9 amino acid short sequences was created and a search for substring matches between the epitopes and all epitopes deposited in the Immune Epitope Database (IEDB) shown to elicit T/B cell response or binding to MHC class I was carried out. The final prioritization of epitopes was made based on the collected information:

- Maximizing the global population coverage by prioritizing epitopes covering a large set of distinct MHC class I and II alleles
- Conservation within > 200 different SARS CoV-2 strains worldwide from up-to-date NCBI virus database
- Conservation within different SARS CoV strains and betacoronaviruses in general

- No/minimal numbers of exact match of 6 amino acids to any protein in the human proteome
- Identity with an immunodominant SARS-CoV epitope deposited in the Immune Epitope Database (IEDB)

5 The epitopes with the SEQ ID NO: 1-229 were identified:

Peptide ID	Amino Acid Sequence	Sequence Number
orf1ab_6411-6454	HANEYRLYLDAYNMMISAGFSLWVYKQFDTYNL WNTFTRLQSL	SEQ ID NO: 1
orf1ab_2844-2905	YTNDKACPLIAAVITREVGFVVPGLPGTILRTTNGD FLHFLPRVFSAVGNICYTPSKLIEY	SEQ ID NO: 2
orf1ab_2936-2969	NVLEGSVAYESLRPDTRYVLM DGSIIQFPNTYL	SEQ ID NO: 3
orf1ab_5266-5307	QEYADV FHLYLQYIRKLHDEL TGHMLDMYSVMLT NDNTSRY	SEQ ID NO: 4
SPIKE_864-906	LTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFA MQMAYRF	SEQ ID NO: 5
orf1ab_1413-1448	GVVDYGARFYFYTSKTTVASLINTLNDLNETLV TM	SEQ ID NO: 6
orf1ab_3097-3123	YSFLPGVYSVIYLYLTFYLTNDVSFL	SEQ ID NO: 7
orf1ab_3182-3217	FLLNKEMY LKL RSDVLLPLTQYNRYLALYNKYKYF	SEQ ID NO: 8
orf1ab_2371-2400	VQMAPISAMVRMYIFFASFYYVWKS YVHV	SEQ ID NO: 9
orf1ab_1535-1560	YYTSNPTTFHLDGEVITFDNLKTLL	SEQ ID NO: 10
orf1ab_1565-1599	RTIKVFTTVDNINLHTQVVDM SMTYGQQFGPTYL	SEQ ID NO: 11
orf1ab_4751-4781	NLHSSRLSFKELLVYAADPAMHAASGNLLL	SEQ ID NO: 12
orf1ab_3068-3092	RAFGEYSHV VAFNTLLFLMSFTVL	SEQ ID NO: 13
orf1ab_2331-2365	ILFTRFFYVLGLAAIMQLFFSYFAVHFISNSWLM	SEQ ID NO: 14

orf1ab_1169-1193	RTNVYLAVFDKNLYDKLVSSFLEM	SEQ ID NO: 15
SPIKE_257-277	WTAGAAAYYVGYLQPRTFLL	SEQ ID NO: 16
orf1ab_3932-3957	EMLDNRATLQAIASEFSSLPSYAAF	SEQ ID NO: 17
orf1ab_1261-1286	NLHPDSATLVSDIDITFLKKDAPYI	SEQ ID NO: 18
orf1ab_5973-5998	MTYRRLISMMGFKMNYQVNGYPNMF	SEQ ID NO: 19
SPIKE_703-726	SVAYSNNSIAIPTNFTISVTTEI	SEQ ID NO: 20
orf1ab_6481-6507	TVYTKVDGVDVELFENKTTLPVNVAF	SEQ ID NO: 21
orf1ab_5613-5638	HFAIGLALYYPSARIVYTACSHAAV	SEQ ID NO: 22
orf1ab_1797-1816	VQQESPFBMMSAPPAQYEL	SEQ ID NO: 23
orf1ab_5462-5489	KATEETFKLSYGIATVREVLSDRELHL	SEQ ID NO: 24
orf1ab_3619-3647	AMSAFAMMFVKHKHAFCLCLLPSLATV	SEQ ID NO: 25
orf1ab_5072-5100	SSGDATTAYANSVFNICQAVTANVNALL	SEQ ID NO: 26
orf1ab_2771-2796	QLIKVTLVFLFVAAIFYLITPVHVM	SEQ ID NO: 27
orf1ab_3682-3701	VMYASAVVLLILMTARTVY	SEQ ID NO: 28
orf1ab_999-1023	TTIQTIVEVQPQLEMELTPVVQTI	SEQ ID NO: 29
orf1ab_5168-5186	ASIKNFKSVLYYQNNVFM	SEQ ID NO: 30
VEMP_3-21	FVSEETGTLIVNSVLLFL	SEQ ID NO: 31

orf1ab_6093-6117	MLSDTLKNLSDRVVFLWAHGFEL	SEQ ID NO: 32
orf1ab_676-709	TFFKLVNKFLALCADSIIIGGAKLKALNLGETF	SEQ ID NO: 33
orf1ab_2588-2604	KMFDAYVNTFSSTFNV	SEQ ID NO: 34
VME1_36-51	FAYANRNRFLYIIKL	SEQ ID NO: 35
orf1ab_824-849	FGDDTVIEVQGYKSVNITFELDERI	SEQ ID NO: 36
orf1ab_3604-3619	FLYENAFLPFAMGII	SEQ ID NO: 37
orf1ab_3355-3375	TANPKTPKYKFVRIQPGQTF	SEQ ID NO: 38
NCAP_304-320	AQFAPSASAFFGMSRI	SEQ ID NO: 39
orf1ab_5132-5148	FVNEFYAYLRKHFSMM	SEQ ID NO: 40
orf1ab_2166-2181	NYMPYFFTLLLQLCT	SEQ ID NO: 41
orf1ab_3706-3721	RVWTLMNVLTLVYKV	SEQ ID NO: 42
orf1ab_2241-2262	SLIYSTAALGVLMNSNLGMPSY	SEQ ID NO: 43
orf1ab_2611-2633	LVATAEAEALAKNVSLDNVLSTF	SEQ ID NO: 44
orf1ab_1760-1776	TLKGVEAVMYMGTLSTY	SEQ ID NO: 45
orf1ab_3905-3921	EAFEKMOVSLLSVLLSM	SEQ ID NO: 46
orf1ab_1466-1486	RSLKVPATVSVSPDAVTAY	SEQ ID NO: 47
AP3A_88-107	TVYSHLLLVAAGLEAPFLY	SEQ ID NO: 48

SPIKE_49-70	STQDLFLPFFSNVTWFHAIHV	SEQ ID NO: 49
orf1ab_3651-3666	MVYMPASVWMRIMTW	SEQ ID NO: 50
orf1ab_76-92	RTAPHGHVMVELVAEL	SEQ ID NO: 51
orf1ab_3038-3055	GALDISASIVAGGIVAI	SEQ ID NO: 52
orf1ab_5356-5373	HVISTSHKLVLVSNPYV	SEQ ID NO: 53
AP3A_53-68	AVFQSASKIITLKKR	SEQ ID NO: 54
orf1ab_3481-3498	FLNRFTTTLNDFNLVAM	SEQ ID NO: 55
AP3A_203-218	HSYFTSDYYQLYSTQ	SEQ ID NO: 56
orf1ab_5015-5030	RAMPNMLRIMASLVL	SEQ ID NO: 57
SPIKE_686-701	VASQSIIAYTMSLGA	SEQ ID NO: 58
orf1ab_5770-5785	EIVDTVSAVYDNKL	SEQ ID NO: 59
SPIKE_191-210	FVFKNIDGYFKIYSKHTPI	SEQ ID NO: 60
orf1ab_4023-4038	KVTSAMQTMLFTMLR	SEQ ID NO: 61
orf1ab_6850-6865	YLNTLTLAVPYNMRV	SEQ ID NO: 62
SPIKE_108-127	TLDSKTQSLIVNNATNVV	SEQ ID NO: 63
orf1ab_4824-4842	SSVELKHFFFAQDGNAAI	SEQ ID NO: 64
orf1ab_478-493	SFSASTSAFVETVKG	SEQ ID NO: 65

orf1ab_1674-1689	YLATALLTLQQIELK	SEQ ID NO: 66
SPIKE_814-829	RSFIEDLLFNKVTLA	SEQ ID NO: 67
orf1ab_527-544	SILSPLYAFASEAARVV	SEQ ID NO: 68
orf1ab_3129-3144	VMFTPLVPFWITIAY	SEQ ID NO: 69
orf1ab_6748-6763	LLLDDFVEIIKSQDL	SEQ ID NO: 70
orf1ab_4630-4645	SLLMPILTLTRALTA	SEQ ID NO: 71
VME1_94-109	YFIASFRLFARTRSM	SEQ ID NO: 72
orf1ab_7039-7054	YSLFDMSKFPLKLRG	SEQ ID NO: 73
orf1ab_6283-6298	KAYKIEELFYSYATH	SEQ ID NO: 74
VEMP_50-65	LVKPSFYVYSRVKNL	SEQ ID NO: 75
orf1ab_4086-4101	TTFTYASALWEIQQV	SEQ ID NO: 76
SPIKE_633-648	RVYSTGSNVFQTRAG	SEQ ID NO: 77
orf1ab_5245-5260	LMIERFVSLAIDAYP	SEQ ID NO: 78
orf1ab_6153-6168	HSIGFDYVYNPFMID	SEQ ID NO: 79
orf1ab_3541-3557	RTILGSALLEDEFTPF	SEQ ID NO: 80
orf1ab_5532-5547	VVYRGTTTTYKLNVD	SEQ ID NO: 81
orf1ab_7063-7078	QINDMILSLLSKGRL	SEQ ID NO: 82

AP3A_222-237	TGVEHVTFFIYNKIV	SEQ ID NO: 83
VEMP_28-43	VTLAILTALRLCAYC	SEQ ID NO: 84
orf1ab_859-874	YTVELGTEVNEFACV	SEQ ID NO: 85
orf1ab_3573-3591	RTIKGTHHWLLLTLTSL	SEQ ID NO: 86
orf1ab_4228-4243	YFIKGLNNLNRMVL	SEQ ID NO: 87
orf1ab_5380-5405	VTDVTQLYLGGMSYYCKSHKPPISF	SEQ ID NO: 88
orf1ab_6799-6815	SQAWQPGVAMPNLYKM	SEQ ID NO: 89
SPIKE_1053-1068	QSAPHGVVFLHVTYV	SEQ ID NO: 90
orf1ab_5719-5736	YVYIGDPAQLPAPRTLL	SEQ ID NO: 91
orf1ab_4513-4528	YTMADLVYALRHFDE	SEQ ID NO: 92
SPIKE_494-513	YGFQPTNGVGYPYRVVVL	SEQ ID NO: 93
orf1ab_4725-4740	FVDGVPFVVSTGYHF	SEQ ID NO: 94
orf1ab_6873-6892	KGVAPGTAVLRQWLPTGTL	SEQ ID NO: 95
orf1ab_904-919	YYLFDESGEFKLASH	SEQ ID NO: 96
orf1ab_4113-4130	ISMDNSPNLAWPLIVTA	SEQ ID NO: 97
orf1ab_1633-1650	YYHTTDPSFLGRYMSAL	SEQ ID NO: 98
orf1ab_873-889	VVADAVIKTLQPVSEL	SEQ ID NO: 99

SPIKE_77-92	RFDNPVLPFNDGVYF	SEQ ID NO: 100
orf1ab_4064-4080	TTAAKLMVVIPDYNTY	SEQ ID NO: 101
orf1ab_561-576	LQKAAITILDGISQY	SEQ ID NO: 102
AP3A_32-47	ATIPIQASLPFGWLI	SEQ ID NO: 103
orf1ab_5212-5229	KQGDDYVYLPYPDPSRI	SEQ ID NO: 104
orf1ab_4709-4724	STVFPPTSFGPLVRK	SEQ ID NO: 105
orf1ab_2425-2444	IVNGVRRSFYVYANGGKGF	SEQ ID NO: 106
orf1ab_2298-2314	DTYPSLETIQITISSF	SEQ ID NO: 107
orf1ab_105-120	VLVPHVGEIPVAYRK	SEQ ID NO: 108
orf1ab_250-266	LQTPFEIKLAKKFDTF	SEQ ID NO: 109
orf1ab_4925-4940	NVIPTITQMNLKYAI	SEQ ID NO: 110
SPIKE_365-380	SVLYNSASFSTFKCY	SEQ ID NO: 111
orf1ab_6831-6846	ATLPKGIMMNVAKYT	SEQ ID NO: 112
orf1ab_4002-4017	KMADQAMTQMYKQAR	SEQ ID NO: 113
orf1ab_6605-6620	SVGPKQASLNGVTLI	SEQ ID NO: 114
SPIKE_432-452	VIAWNSNNLDSKVGGNYNYL	SEQ ID NO: 115
SPIKE_1219-1234	FIAGLIAIVMVTIML	SEQ ID NO: 116

NCAP_330-346	LTYTGAIKLDDKDPNF	SEQ ID NO: 117
orf1ab_1618-1633	YVLPNDDTLRVEAFE	SEQ ID NO: 118
orf1ab_6668-6683	AMDEFIERYKLEGYA	SEQ ID NO: 119
orf1ab_804-819	NMMVTNNTFTLKGGA	SEQ ID NO: 120
orf1ab_5555-5570	VMPLSAPTLVPQEHY	SEQ ID NO: 121
orf1ab_4672-4687	KLFDRYFKYWDQTYH	SEQ ID NO: 122
orf1ab_2269-2284	YLNSTNVTIATYCTG	SEQ ID NO: 123
orf1ab_4997-5012	YSDVENPHLMGWDYP	SEQ ID NO: 124
orf1ab_4904-4919	RLYYDSMSYEDQDAL	SEQ ID NO: 125
SPIKE_220-235	SALEPLVDLPIGINI	SEQ ID NO: 126
orf1ab_2098-2113	YVDNSSLTIKKPNEI	SEQ ID NO: 127
SPIKE_325-340	IVRFPNITNLCPFGE	SEQ ID NO: 128
orf1ab_3751-3766	MFLARGIVFMCVEYC	SEQ ID NO: 129
SPIKE_1135-1150	TVYDPLQPELDSFKE	SEQ ID NO: 130
SPIKE_27-42	YTNSFTRGVYYPDKV	SEQ ID NO: 131
orf1ab_1336-1351	YTVEEAKTVLKKCKS	SEQ ID NO: 132
orf1ab_5314-5329	AMYTPHTVLQAVGAC	SEQ ID NO: 133

orf1ab_6632-6647	KVDGVVQQLPETYFT	SEQ ID NO: 134
orf1ab_4977-4993	TVVIGTSKFYGGWHNM	SEQ ID NO: 135
orf1ab_2140-2156	YAKPFLNKVVSTTTNI	SEQ ID NO: 136
AP3A_5-20	RIFTIGTVTLKQGEI	SEQ ID NO: 137
AP3A_246-263	HTIDGSSGVVNPVMEPI	SEQ ID NO: 138
orf1ab_618-633	TVYEKLKPVLDWLEE	SEQ ID NO: 139
orf1ab_1247-1262	FLTENLLLYIDINGN	SEQ ID NO: 140
orf1ab_6342-6357	SLYVNBKHAFTPAFD	SEQ ID NO: 141
orf1ab_733-748	KAPKEIIFLEGETLP	SEQ ID NO: 142
orf1ab_37-53	VLSEARQHLKDGTGCL	SEQ ID NO: 143
orf1ab_6708-6723	RFKESPFELEDFIPM	SEQ ID NO: 144
SPIKE_936-951	SLSSTASALGKLQDV	SEQ ID NO: 145
orf1ab_6694-6709	SQLGGLHLLIGLAKR	SEQ ID NO: 146
orf1ab_5843-5858	AVASKILGLPTQTVD	SEQ ID NO: 147
orf1ab_1153-1168	FGADPIHSLRVCVDT	SEQ ID NO: 148
orf1ab_272-287	FVFPLNSIIKTIQPR	SEQ ID NO: 149
SPIKE_1094-1109	FVSNGTHWFTVQRNF	SEQ ID NO: 150

VME1_190-205	SGFAAYSRYRIGNYK	SEQ ID NO: 151
orf1ab_6900-6915	FVSDADSTLIGDCAT	SEQ ID NO: 152
orf1ab_5923-5938	LQAENVTLGLFKDCSK	SEQ ID NO: 153
VME1_169-184	VATSRTLSYYKLGAS	SEQ ID NO: 154
orf1ab_2216-2233	YLKSPNFSKLINIIWF	SEQ ID NO: 155
orf1ab_4862-4877	FVVEVVDKYFDCYDG	SEQ ID NO: 156
orf1ab_2075-2090	ILKPANNSLKITEEV	SEQ ID NO: 157
NCAP_158-173	LQLPQGTTLPKGFYA	SEQ ID NO: 158
AP3A_138-153	LLYDANYFLCWHTNC	SEQ ID NO: 159
orf1ab_6763-6778	SVVSKVVKVTIDYTE	SEQ ID NO: 160
SPIKE_914-929	VLYENQKLIANQFNS	SEQ ID NO: 161
SPIKE_950-966	VVNQNAQALNTLVKQL	SEQ ID NO: 162
orf1ab_6245-6260	LLADKFPVLHDIGNP	SEQ ID NO: 163
orf1ab_5515-5530	KVQIGEYTFEKG DYG	SEQ ID NO: 164
AP3A_70-85	LALSKGVHFVCNLLL	SEQ ID NO: 165
orf1ab_3311-3326	MLNPNYEDLLIRKSN	SEQ ID NO: 166
orf1ab_3966-3981	AVANGDSEVV LK LK	SEQ ID NO: 167

SPIKE_1184-1199	RLNEVAKNLNESLID	SEQ ID NO: 168
orf1ab_2552-2567	SAKSASVYYSQLMCQ	SEQ ID NO: 169
orf1ab_4418-4433	STDVVYRAFDIYNDK	SEQ ID NO: 170
SPIKE_780-795	VFAQVKQIYKTPPIK	SEQ ID NO: 171
SPIKE_975-990	VLNDILSRLDKVEAE	SEQ ID NO: 172
orf1ab_640-655	FLRDGWEIVKFISTC	SEQ ID NO: 173
orf1ab_444-459	GLNDNLLEILQKEKV	SEQ ID NO: 174
SPIKE_416-431	KIADYNYKLPDDFTG	SEQ ID NO: 175
NCAP_221-236	LLLDRLNQLESKMSG	SEQ ID NO: 176
orf1ab_2749-2764	VVNVVTTKIALKGGK	SEQ ID NO: 177
orf1ab_5110-5125	YVRNLQHRLYECLYR	SEQ ID NO: 178
orf1ab_4162-4177	CTDDNALAYYNTTKG	SEQ ID NO: 179
orf1ab_3163-3178	RVVFNGVSFSTFEEA	SEQ ID NO: 180
orf1ab_5945-5960	TQAPTHLSVDTKFKT	SEQ ID NO: 181
orf1ab_1056-1071	VVNAANVYLKHGGGV	SEQ ID NO: 182
orf1ab_6681-6696	YAFEHIVYGDFSHSQ	SEQ ID NO: 183
orf1ab_4846-4861	YYRYNLPTMCDIRQL	SEQ ID NO: 184

orf1ab_2488-2503	YIVDSVTVKNGSIHL	SEQ ID NO: 185
orf1ab_12-27	HVQLSLPVLQVRDVL	SEQ ID NO: 186
SPIKE_583-598	ILDITPCSFGGVSVI	SEQ ID NO: 187
orf1ab_5057-5072	MVMCGGSLYVKPGGT	SEQ ID NO: 188
orf1ab_5571-5586	RITGLYPTLNISDEF	SEQ ID NO: 189
orf1ab_358-373	YLPQNAVVKIYCPAC	SEQ ID NO: 190
orf1ab_5655-5670	RIIPARARVECFDKF	SEQ ID NO: 191
orf1ab_1922-1937	ASFDNFKFVCDNIKF	SEQ ID NO: 192
orf1ab_1875-1890	TIKPVTYKLDGVVCT	SEQ ID NO: 193
orf1ab_2468-2483	VARDLSLQFKRPINP	SEQ ID NO: 194
orf1ab_4282-4297	YLASGGQPITNCVKM	SEQ ID NO: 195
orf1ab_3240-3255	FSNSGSDVLYQPPQT	SEQ ID NO: 196
NCAP_265-280	KAYNVTQAFGRRGPE	SEQ ID NO: 197
NCAP_47-62	NTASWFTALTQHGKE	SEQ ID NO: 198
orf1ab_6577-6592	RVDGQVDLFRNARNG	SEQ ID NO: 199
orf1ab_1350-1365	SAFYILPSIISNEKQ	SEQ ID NO: 200
orf1ab_2534-2549	SLPINVIVFDGKSKC	SEQ ID NO: 201

orf1ab_599-614	YITGGVVQLTSQWLT	SEQ ID NO: 202
orf1ab_7019-7034	YVMHANYIFWRNTNP	SEQ ID NO: 203
orf1ab_4356-4371	ANDPVGFTLKNTVCT	SEQ ID NO: 204
orf1ab_4251-4266	LQAGNATEVPANSTV	SEQ ID NO: 205
VME1_147-162	HLRIAGHHLGRCDIK	SEQ ID NO: 206
orf1ab_2515-2530	HSLSHFVNLDNLRAN	SEQ ID NO: 207
orf1ab_5803-5818	ITHDVSSAINRPQIG	SEQ ID NO: 208
orf1ab_140-155	KSFDLGDELGTDPYE	SEQ ID NO: 209
orf1ab_2121-2136	LATHGLAAVNSVPWD	SEQ ID NO: 210
orf1ab_5753-5768	KTIGPDMFLGTCRRC	SEQ ID NO: 211
orf1ab_6958-6973	LALGGSVAIKITEHS	SEQ ID NO: 212
orf1ab_6212-6227	KRVDWTIEYPIIGDE	SEQ ID NO: 213
orf1ab_4197-4212	KSDGTGTIYTELEPP	SEQ ID NO: 214
orf1ab_5678-5693	YVFCTVNALPETTAD	SEQ ID NO: 215
orf1ab_2674-2689	LTYNKVENMTPRDLG	SEQ ID NO: 216
orf1ab_3329-3344	LVQAGNVQLRVIGHS	SEQ ID NO: 217
SPIKE_393-408	NVYADSFVIRGDEVR	SEQ ID NO: 218

orf1ab_4460-4475	YFVVKRHTFSNYQHE	SEQ ID NO: 219
VME1_64-79	FVLAAYRINWITGG	SEQ ID NO: 220
orf1ab_6048-6063	YVDTPNNTDFSRVSA	SEQ ID NO: 221
orf1ab_3767-3782	IFFITGNTLQCIMLV	SEQ ID NO: 222
orf1ab_5880-5895	NVNRFNVAITRAKVG	SEQ ID NO: 223
orf1ab_4532-4547	TLKEILVTYNCCDDD	SEQ ID NO: 224
orf1ab_1213-1228	FITESKPSVEQRKQD	SEQ ID NO: 225
SPIKE_603-618	TSNQVAVLYQDVNCT	SEQ ID NO: 226
orf1ab_1733-1748	YLFQHANLDSCKRVL	SEQ ID NO: 227
orf1ab_5437-5452	WTNAGDYILANTCTE	SEQ ID NO: 228
orf1ab_5038-5053	SLSHRFYRLANECAQ	SEQ ID NO: 229

Other T cell epitopes were predicted by methods based on the above-described method (similar or identical). The following T cell epitopes were identified:

Name	Sequence	SED ID NO:
AP3A_1_21	DLFMRIFTIGTVTLKQGEIK	322
AP3A_33_73	TIPIQASLPFGWLIVGVALLAVFQSASKIITLKKRWQLAL	323
AP3A_96_120	VAAGLEAPFLYLYALVYFLQSINF	324
AP3A_157_192	IPYNSVTSSIVITSGDGTTSPISEHDYQIGGYTEK	325
AP3A_201_219	VLHSYFTSDYYQLYSTQL	326
AP3A_219_235	STDTGVEHVTFFIYNK	327
NCAP_44_74	LPNNTASWFTALTQHGKEDLKFPRGQGVPI	328
NCAP_99_113	KMKDLSPRWYFYFL	329
NCAP_153_172	NAAIVLQLPQGTTLPKGFY	330
NCAP_215_230	DAALALLLLDRLNQL	331
NCAP_248_274	KSAAEASKKPRQKRTATKAYNVTQAF	332

NCAP_296_333	DYKHWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTY	333
NCAP_337_353	KLDDKDPNFKDQVILL	334
NCAP_344_370	NFKDQVILLNKHIDAYKTFPPTEPKK	335
NCAP_378_411	TQALPQRQKKQQTVTLLPAADLDDFSKQLQQSM	336
orf1ab_728_742	LLMPLKAPKEIIFL	337
orf1ab_824_843	FGDDTVIEVQGYKSVNITF	338
orf1ab_1172_1197	VYLAVFDKNLYDKLVSSFLEMKSEK	339
orf1ab_1605_1634	KIKPHNSHEGKTFYVLPNDDTLRVEAFEY	340
orf1ab_2067_2086	TTEVVGDIILKPANNSLKI	341
orf1ab_2165_2177	TNYMPYFFTLLL	342
orf1ab_2370_2394	LVQMAPISAMVRMYIFFASFYYVW	343
orf1ab_2478_2511	RPINPTDQSSYIVDSVT	344
orf1ab_2581_2613	DSAEVAVKMFDAYVNTFSSTFNVPMEKLKTLV	345
orf1ab_2880_2909	FLHFLPRVFSAVGNICYTPSKLIEYTDFA	346
orf1ab_2944_2975	YESLRPDTRYVLMDGSIQFPNTYLEGSRV	347
orf1ab_3387_3404	VYQCAMRPNFTIKGSFL	348
orf1ab_4195_4215	FPKSDGTGTIYTELEPPCRF	349
orf1ab_4498_4516	DGDMVPHISRQRLTKYTM	350
orf1ab_4647_4667	HVDTDLTKPYIKWDLKLYDF	351
orf1ab_5014_5037	DRAMPNMLRIMASLVLARKHTTC	352
orf1ab_5244_5292	TLMIERFVSLAIDAYPLTKHPNQEYADVFLYLQYIRKLHDELTGHML	353
orf1ab_5452_5481	RLKLFAAETLKATEETFKLSYGIATVREV	354
orf1ab_5556_5577	MPLSAPTLVPQEHYVRITGLY	355
orf1ab_5726_5741	AQLPAPRTLTKGTL	356
orf1ab_5813_5830	RPQIGVVREFLTRNPAW	357
orf1ab_6498_6509	TTLPVNVAFEL	358
orf1ab_6632_6655	KVDGVVQQLPETYFTQSRNLQEF	359
orf1ab_6792_6828	FYPKLQSSQAWQPGVAMPNLYKMQRMLLEKCDLQNY	360
orf1ab_6856_6874	LAVPYNMRVIHFGAGSDK	361

SPIKE_108_119	TLDSKTQSLLI	362
SPIKE_191_212	FVFKNIDGYFKIYSKHTPINL	363
SPIKE_264_279	YYVGYLQPRTFLLKY	364
SPIKE_291_320	ALDPLSETKCTLKSFTVEKGIYQTSNFRV	365
SPIKE_319_338	VQPTESIVRFPNITNLCPF	366
SPIKE_341_357	FNATRFASVYAWNRKR	367
SPIKE_358_380	SNCVADYSVLYNSASFSTFKCY	368
SPIKE_407_425	RQIAPGQTGKIADYNYKL	369
SPIKE_525_565	GPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQF	370
SPIKE_624_636	HADQLTPTWRVY	371
SPIKE_711_741	IAIPTNFTISVTTEILPVSMTKTSVDCTMY	372
SPIKE_778_797	QEVFAQVKQIYKTPPIKDF	373
SPIKE_814_841	RSFIEDLLFNKVTLADAGFIKQYGDCL	374
SPIKE_891_933	AALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGK	375
SPIKE_955_970	AQALNTLVKQLSSNF	376
SPIKE_974_991	SVLNDILSRLDKVEAEV	377
SPIKE_995_1008	LITGRLQSLQTYV	378
SPIKE_1046_1075	YHLMSFPQSAPHGVVFLHVTYVPAQEKNF	379
SPIKE_1136_1148	VYDPLQPELDSF	380
VEMP_48_69	VSLVKPSFYVYSRVKNLNSSR	381
VME1_2_23	DSNGTITVEELKKLLEQWNLV	382
VME1_36_54	FAYANRNRFLYIIKLIFL	383
VME1_88_116	GLMWLSYFIASFRLFARTRSMWSFNPET	384
VME1_147_180	HLRIAGHHLGRCDIKDLPKEITVATSRTLSTYYK	385

SPIKE 8_110: (SEQ ID NO: 386)

PLVSSQCVNLTTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFH
AIHVSGTNGTKRFDNPVLPFNDGVYFASTKSNIRGWIFGTTL

5 SPIKE_286_395 (SEQ ID NO: 387)

DAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNAT
RFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNV

SPIKE_483_552 (SEQ ID NO: 388)

EGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSELLHAPATVCGPKKSTNLVKNKCVN
10 FNFNGLTGTGVL

- NCAP_288_387 (SEQ ID NO: 389)
QELIRQGT DYKHWPQIAQFAPSASAFFGMSRIGMEVTPSGTWLTYTGAIKLDDKDPNF
KDQVILLNKHIDAYKTFPPTPEPKDKKKKADETQALPQRQK
- SPIKE_671_750 (SEQ ID NO: 390)
- 5 ASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNNSIAIPTNFTISVTTEILPVSM
TKTSVDCTMYICGDSTECS
- SPIKE_1036_1090 (SEQ ID NO: 391)
SKRVDFCGKGYHLMSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHDGKAHFP
- SPIKE_252_295 (SEQ ID NO: 392)
- 10 DSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDP
- SPIKE_805_853 (SEQ ID NO: 393)
LPDPSKPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDIAARDLICAQ
- SPIKE_1180_1232 (SEQ ID NO: 394)
KEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWLGFIAGLIAIVMVTI
- 15 NCAP_49_129 (SEQ ID NO: 395)
ASWFTALTQHGKEDLKFRGQGVPINTNSSPDDQIGYYRRATRRIRGGDGKMKDLSP
RWYFYLLGTGPEAGLPYGANKDG
- SPIKE_438_479 (SEQ ID NO: 396)
NNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTP
- 20 VME1_153_212 (SEQ ID NO: 397)
HHLGRCDIKDLPKEITVATSRTLSYYKLGASQRVAGDSGFAAYSRYRIGNYKLNTDHS
S
- AP3A_164_233 (SEQ ID NO: 398)
SSIVITSGDGTTSPISEHDYQIGGYTEKWESGVKDCVVLHSYFTSDYYQLYSTQLSTDT
- 25 GVEHVTFFIY
- AP3A_84_132 (SEQ ID NO: 399)
LLFVTVYSHLLLVAAGLEAPFLYLYALVYFLQSINFVRIIMRLWLCWK
- SPIKE_126_185 (SEQ ID NO: 400)
VIKVCEFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYVSQPFLMDLEGK
- 30 QGN
- SPIKE_880_941 (SEQ ID NO: 401)
TITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLS
ST
- VEMP_18_67 (SEQ ID NO: 402)
- 35 LFLAFVVFLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVKNLNS

AP3A_0_33 (SEQ ID NO: 403) MDLFMRIFTIGTVTLKQGEIKDATPSDFVRATA

Name/SEQ ID NO:	Sequence
SPIKE_187_218/404	NLREFVFKNIDGYFKIYSKHTPINLVRDLPQ
SPIKE_1085_1115/405	KAHFPREGVFVSNGTHWFVTQRNFYEPQII
NCAP_243_285/406	QTVTKKSAAEASKKPRQKRTATKAYNVTQAFGRRGPEQTQGN
SPIKE_619_651/407	VPVAIHADQLTPTWRVYSTGSNVFQTRAGCLI
SPIKE_849_890/408	ICAQKFNGLTVLPPLLDEMIQYTSALLAGTITSGWTFGA
SPIKE_398_435/409	SFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIA
AP3A_41_85/410	PFGWLIVGVALLAVFQSASKIITLKKRWQLALSKGVHFVCNLLL
SPIKE_771_805/411	VEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQI
VME1_85_120/412	CLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL
NCAP_206_242/413	PARMAGNGGDAALALLLDRLNQLESKMSGKGQQQQ
VME1_0_32/414	MADSNGTITVEELKKLLEQWNLVIGFLFTWI
VME1_30_63/415	WICLLQFAYANRNRFLYIIKLIFLWLLWPVTLA

<u>Name/ SEQ ID NO:</u>	<u>Sequence</u>
<u>NCAP 304-320/416</u>	<u>AQFAPSASAFFGMSRI</u>
<u>orf1ab 824-849/417</u>	<u>FGDDTVIEVQGYKSVNITFELDERI</u>
<u>orf1ab 859-874/418</u>	<u>YTVELGTEVNEFACV</u>
<u>orf1ab 1797-1816/419</u>	<u>VQQESPFVMMSAPPAQYEL</u>
<u>orf1ab 2371-2400/420</u>	<u>VQMAPISAMVRMYIFFASFYYVWKSYPVHV</u>
<u>orf1ab 2588-2604/421</u>	<u>KMFDAYVNTFSSTFNV</u>
<u>orf1ab 3355-3375/422</u>	<u>TANPKTPKYKFVRIQPGQTF</u>
<u>orf1ab 3481-3498/423</u>	<u>FLNRFTTTLNDFNLVAM</u>
<u>orf1ab 3651-3666/424</u>	<u>MVYMPASWVMRIMTW</u>
<u>orf1ab 3706-3721/425</u>	<u>RVWTLNMNVLTLYYKV</u>
<u>orf1ab 4228-4243/426</u>	<u>YFIKGLNNLNRMVNL</u>
<u>orf1ab 4630-4645/427</u>	<u>SLLMPILTTLTRALTA</u>
<u>orf1ab 4824-4842/428</u>	<u>SSVELKHFFFAQDGNAAI</u>
<u>orf1ab 5015-5030/429</u>	<u>RAMPNMLRIMASLVL</u>
<u>orf1ab 5072-5100/430</u>	<u>SSGDATTAYANSVFNICQAVTANVNALL</u>
<u>orf1ab 5132-5148/431</u>	<u>FVNEFYAYLRKHFSMM</u>
<u>orf1ab 5168-5186/432</u>	<u>ASIKNFKSVLYYQNNVFM</u>
<u>orf1ab 5245-5260/433</u>	<u>LMIERFVSLAIDAYP</u>
<u>orf1ab 5356-5373/434</u>	<u>HVISTSHKLVLVSVNPYV</u>

<u>orf1ab 5613-5638/435</u>	<u>HFAIGLALYYPSARIVYTACSHAAV</u>
<u>orf1ab 5770-5785/436</u>	<u>EIVDTVSAALVYDNKL</u>
<u>orf1ab 5973-5998/437</u>	<u>MTYRRLISMMGFKMNYQVNGYPNMF</u>
<u>orf1ab 6093-6117/438</u>	<u>MLSDTLKNLSDRVVFVLWAHGFEL</u>
<u>orf1ab 6481-6507/439</u>	<u>TVYTKVDGVDVELFENKTTLPVNVAE</u>
<u>orf1ab 6850-6865/440</u>	<u>YLNTLTLAVPYNMRV</u>
<u>SPIKE 633-648/441</u>	<u>RVYSTGSNVFQTRAG</u>
<u>SPIKE 703-726/442</u>	<u>SVAYSNNIAIPTNFTISVTTEI</u>
<u>VEMP 50-65/443</u>	<u>RSFIEDLLFNKVTLA</u>
<u>VME1 36-51/444</u>	<u>LVKPSFYVYSRVKNL</u>

Example 2: Construction and expression of the vaccines

5 All gene sequences of tested constructs (VB10.COVS2) were ordered from Genscript (860 Centennial Ave., Piscataway, NJ 08854, USA) and cloned into the expression vector pUMVC4a.

All constructs were transfected into HEK293 cells and verified expression of intact vaccibody proteins were performed by sandwich ELISA of the supernatant. In addition, western blot analysis was performed with some constructs to verify conformation and size of vaccibody proteins.

10 Example 3a: Design, production and characterisation of various DNA and protein vaccibody vaccines (called VB10.COVS2)

Multiple VB10.COVS2 DNA vaccines were designed (Fig. 53):

VB2049 (SEQ ID NO: 252, Fig. 23A), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising a short form of the SARS-CoV-2 RBD ("RBD short", amino acids 331-524, i.e. 193 amino acids).

15

VB2060 (SEQ ID NO: 254, Fig. 24A), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids)

5 VB2065 (SEQ ID NO: 256, Fig. 25A), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising the spike protein (codon optimized to enable the expression of a full-length prefusion stabilized spike protein, removing the polybasic cleavage site recognized by furin, and adding stabilizing mutations, see Wrapp et al., Science 367, (2020), 1260-1263) from SARS-CoV2 strain Wuhan Hu-1.

10 VB2048 (SEQ ID NO: 258, Fig. 26A), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising 20 immunogenic T cell epitopes (see Table 1 below) from multiple SARS-CoV2 strains designed to induce protective immunity and predicted as described in Example 1.

Table 1: T cell epitopes VB2048

	Sequence		Sequence
pep1	RSFIEDLLFNKVTLA	pep11	AQFAPSASAFFGMSRI
pep2	MTYRRLLISMMGFKMNYQVNG YPNMF	pep12	EIVDTVSAALVYDNKL
pep3	LMIERFVSLAIDAYP	pep13	SSGDATTAYANSVFNICQAVT ANVNALL
pep4	RAMPNMLRIMASLVL	pep14	HVISTSHKLVLVSNPYV
pep5	MVYMPASWVMRIMTW	pep15	MLSDTLKNLSRVVFLWAHG FEL
pep6	FLNRFTTTLNDFNLVAM	pep16	TANPKTPKYKFVRIQPGQTF
pep7	SSVELKHFFFAQDGNAAI	pep17	ASIKNFKSVLYYQNNVFM
pep8	HFAIGLALYYPSARIVYTACSHA AV	pep18	FVNEFYAYLRKHFSMM
pep9	YFIKGLNNLNRMVL	pep19	RVWTLNMVLTLYYKV
pep10	YLNTLTLAVPYNMRV	pep20	FAYANRNRFLYIIKL

15 VB2059 (SEQ ID NO: 260, Fig. 27), encoding an anti-mouse MHCII scFv targeting unit, a dimerization unit and an antigenic unit comprising a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids).

20 VB2071 (SEQ ID NO: 262, Fig. 28), encoding an anti-mouse MHCII scFv targeting unit, a dimerization unit and an antigenic unit comprising the spike protein (codon optimized to enable the expression of a full-length prefusion stabilized spike protein, removing the polybasic cleavage site recognized by furin, and adding stabilizing mutations, see Wrapp et al., Science 367, (2020), 1260-1263) from SARS-CoV2 strain Wuhan Hu-1.

The predicted T cell epitopes pep08 and pep18 included in the below-described constructs VB2081-VB2099 are identical to the corresponding epitopes in table 1. pep25 has the amino acid sequence of SEQ ID NO: 75 identified in Example 1.

5 VB2081 (SEQ ID NO: 264, Fig. 29), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a (GGGGS)₂ linker.

10 VB2082 (SEQ ID NO: 266, Fig. 30), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep18) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a (GGGGS)₂ linker.

15 VB2083 (SEQ ID NO: 268, Fig. 31), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 2 predicted T cell epitopes (pep08 + pep18 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a (GGGGS)₂ linker.

20 VB2084 (SEQ ID NO: 270, Fig. 32), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 + pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a (GGGGS)₂ linker.

25 VB2085 (SEQ ID NO: 272, Fig. 33), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a GLGGL linker.

VB2086 (SEQ ID NO: 274, Fig. 34), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a (GLGGL)₂ linker.

- VB2087 (SEQ ID NO: 276, Fig. 35), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep18) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a GLGGL linker.
- 5 VB2088 (SEQ ID NO: 278, Fig. 36), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 2 predicted T cell epitopes (pep08 + pep18 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a GLGGL linker.
- 10 VB2089 (SEQ ID NO: 280, Fig. 37), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 + pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a GLGGL linker.
- 15 VB2091 (SEQ ID NO: 282, Fig. 38), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a TQKSLSLSPGKGLGGL linker.
- 20 VB2092 (SEQ ID NO: 284, Fig. 39), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a TQKSLSLSPGKGLGGL linker.
- 25 VB2094 (SEQ ID NO: 286, Fig. 40), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 1 predicted T cell epitope (pep08) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a SLSLSPGKGLGGL linker.
- 30 VB2095 (SEQ ID NO: 288, Fig. 41), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a SLSLSPGKGLGGL linker.

5 VB2097 (SEQ ID NO: 290, Fig. 42), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a GSAT linker.

10 VB2099 (SEQ ID NO: 292, Fig. 43), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit consisting of 3 predicted T cell epitopes (pep08, pep18 and pep25 with a (GGGGS)₂ linker in between epitopes) and a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids), linked with a SEG linker.

VB2129 (SEQ ID NO: 294, Fig. 44), encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising a longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) with 3 mutations characterised in the South African variant B.1.351.

15 VB2131, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the Wuhan strain and the South African variant B.1.351, linked with a SEG linker (amino acid sequence: SEQ ID NO: 296, Fig. 45).

20 VB2132, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the Wuhan strain and the South African variant B.1.351, linked with a GSAT linker (amino acid sequence: SEQ ID NO: 297, Fig. 46).

25 VB2133, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the Wuhan strain and the South African variant B.1.351, linked with a TQKSLSLSPGKGLGGL linker (amino acid sequence: SEQ ID NO: 298, Fig. 47).

30 VB2134, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the Wuhan strain and the South African variant B.1.351,

linked with a SLSLSPGKGLGGL linker (amino acid sequence: SEQ ID NO: 299, Fig. 48).

5 VB2135, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the South African variant B.1.351 and the UK variant B.1.1.7, linked with a SEG linker (amino acid sequence: SEQ ID NO: 300, Fig. 49).

10 VB2136, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the South African variant B.1.351 and the UK variant B.1.1.7, linked with a GSAT linker (amino acid sequence: SEQ ID NO: 301, Fig. 50).

15 VB2137, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the South African variant B.1.351 and the Californian variant B.1.427, linked with a SEG linker (amino acid sequence: SEQ ID NO: 302, Fig. 51).

20 VB2138, encoding a MIP-1 α targeting unit, a dimerization unit and an antigenic unit comprising of 2 longer version of the SARS-CoV-2 RBD ("RBD long", amino acids 319-542 i.e. 223 amino acids) from the South African variant B.1.351 and the Californian variant B.1.427, linked with a GSAT linker (amino acid sequence: SEQ ID NO: 303, Fig. 52).

Example 3b: In vitro characterization of the VB10.COVID protein expression level post transient transfection of mammalian cells with VB10.COVID DNA plasmids

25 The purpose of this study was to do an *in vitro* characterization of the VB10.COVID protein expression level post transient transfection of mammalian cells with the VB10.COVID DNA plasmids, by measuring the presence of functional VB10.COVID proteins in the cell supernatant by an ELISA assay using binding of specific antibodies to the targeting, dimerization and antigenic units of the protein. In addition, a western blot analysis was performed to verify conformation and size of the protein encoded by VB2060.

30 The VB10.COVID DNA constructs were synthesized, cloned and produced by Genscript. The resulting constructs encoded for homodimeric proteins with MIP-1 α and

other targeting units and RBD/spike and/or T cell epitopes as antigenic unit, connected via a dimerization unit consisting of human hinge exons h1 and h4 and CH3 domain of IgG3. Genscript also performed DNA plasmid preparation (0.5 – 1.0 mg).

5 HEK293 cells were obtained from ATCC. HEK293 cells were transiently transfected with VB10.COVS2 DNA plasmids. Briefly, 2×10^5 cells/well were plated in 24-well tissue culture plates with 10% FBS growth medium and transfected with 1 μ g VB10.COVS2 DNA plasmid using Lipofectamine® 2000 reagent under the conditions suggested by the manufacturer (Invitrogen, Thermo Fischer Scientific). The transfected cells were then maintained for up to 6 days at 37°C with 5% CO₂ and the cell supernatant was
10 harvested for characterization of the VB10.COVS2 protein.

ELISA was performed to verify the amount of VB10.COVS2 protein produced by the HEK293 cells and secreted into the cell supernatant. Briefly, MaxiSorp Nunc-immuno plates were coated with 1 μ g/ml of anti-CH3 (MCA878G, BioRad) in 1x PBS with 100 μ l/well and plates were incubated overnight at 4°C. The microtiter wells were blocked
15 by the addition of 200 μ l/well 4% BSA in 1x PBS. 100 μ l of cell supernatant from transfected HEK293 cells containing VB10.COVS2 proteins were added to the plates. For detection antibody, either anti-human MIP-1 α biotinylated (R&D Systems), anti-human IgG biotinylated (Thermo Fischer Scientific) or SARS-CoV-2/2019-nCoV spike/RBD Antibody (1:1000) (Sino Biologic) was added and incubated. Thereafter,
20 strep-HRP (1:3000) or anti-Rabbit IgG-HRP (1:5000) was added and incubated. Unless specified, all incubations were carried out at 37°C for 1 h, followed by 3x washing with PBS-Tween. Afterwards, 100 μ l/well of TMB solution was added and color development was stopped after 5-15 min adding 100 μ l/well of 1 M HCl. The optical density at 450 nm was determined on an automated plate reader (Thermo Scientific
25 Multiscan GO).

In addition, western blot analysis was performed to verify the amount of VB10.COVS2 protein produced by the HEK293 cells and secreted into the cell supernatant. Briefly, samples were prepared by mixing 24 μ l supernatant from transfected HEK293 cells with 8 μ l of Novex Bolt LDS sample buffer 4x (Invitrogen) with or without 3 μ l of reducing
30 agent added (Invitrogen). Samples (reduced or non-reduced) were boiled at 95°C for 4-5 minutes before added to 4%–12% Novex Tris-glycine precast gels (Invitrogen). SDS-PAGE was performed in Novex Bolt SDS running buffer with a SeeBlue Plus2 pre-stained standard (Invitrogen). Proteins were transferred to EtOH-activated PVDF

membranes by using the Tran-Blot Turbo system (Bio-Rad). PVDF membranes were blocked with 3 % BSA PBST, and proteins were detected with spike-RBD Rabbit pAb (Sino Biological) – Goat anti-rabbit-AP (Sigma). Bands were developed with BCIP/NBT-Purple Liquid substrate system for membranes until color development.

- 5 Figures 54, 55 and 56 show the successful expression and secretion of the following functional VB10.COVS2 proteins:

VB2049 (SEQ ID NO: 253, Fig. 23B), VB2060 (SEQ ID NO: 255, Fig. 24B), VB2065 (SEQ ID NO: 257, Fig. 25B), VB2048 (SEQ ID NO: 259, Fig. 26B), VB2059 (SEQ ID NO: 261, Figure 27B), VB2071 (SEQ ID NO: 263, Figure 28B), VB2081 (SEQ ID NO: 265, Figure 29B), VB2082 (SEQ ID NO: 267, Figure 30B), VB2083 (SEQ ID NO: 269, Figure 31B), VB2084 (SEQ ID NO: 271, Figure 32B), VB2085 (SEQ ID NO: 273, Figure 33B), VB2086 (SEQ ID NO: 275, Figure 34B), VB2087 (SEQ ID NO: 277, Figure 35B), VB2088 (SEQ ID NO: 279, Figure 36B), VB2089 (SEQ ID NO: 281, Figure 37B), VB2091 (SEQ ID NO: 283, Figure 38B), VB2092 (SEQ ID NO: 285, Figure 39B), VB2094 (SEQ ID NO: 287, Figure 40B), VB2095 (SEQ ID NO: 289, Figure 41B), VB2097 (SEQ ID NO: 291, Figure 42B), VB2099 (SEQ ID NO: 293, Figure 43B), VB2129 (SEQ ID NO: 295, Figure 44B), VB2131 (SEQ ID NO: 296, Figure 45), VB2132 (SEQ ID NO: 297, Figure 46), VB2133 (SEQ ID NO: 298, Figure 47), VB2134 (SEQ ID NO: 299, Figure 48), VB2135 (SEQ ID NO: 300, Figure 49), VB2136 (SEQ ID NO: 301, Figure 50), VB2137 (SEQ ID NO: 302, Figure 51) and VB2138 (SEQ ID NO: 303, Figure 52).

Conformational integrity of the VB10.COVS2 proteins was confirmed by binding to antibodies specific for anti hlgG (CH3 domain) (as capture antibody), hMIP-1 α , the RBD domain or spike protein in ELISA and western blot analysis.

- 25 In ELISA, the expression level was found to vary between high, medium and low expression between the various VB10.COVS2 constructs depending on the molecule structure.

The constructs containing the longer RBD domain (VB2059 and VB2060) were expressed at the highest levels compared to the construct with the short RBD domain (VB2049) (Fig. 54 and Fig. 55B). Introducing mutations into the longer RBD domain did slightly change the expression level, as observed when comparing VB2060 with VB2129 (Fig. 55D). The constructs containing the spike protein (VB2065 and VB2071)

were expressed at lower levels than the RBD constructs (Fig. 54 and Fig. 55B). The constructs containing the same antigenic unit (either the long RBD or the spike protein) but with different targeting units (human MIP1 α or anti-mouse MHCII scFv) had no significant differences in expression levels (Fig. 54 and Fig. 55B).

- 5 For the constructs containing the combination of predicted T cell epitopes and the long RBD domain in the antigenic unit, differences in expression level are observed dependent on the T cell epitopes and linkers included. The expression level was highest for constructs containing pep18 (VB2082 and VB2087) compared to constructs containing pep08 (VB2081). When constructs comprised 3 T cell epitopes (pep08,
10 pep18 and pep25), constructs with a SEG or GSAT linker were significantly better expressed compared to the constructs with other linkers between the last of the 3 T cell epitopes and the long RBD domain (Fig. 55C).

- When co-transfecting HEK293 cells with 2 plasmids, VB2048 and VB2049, the expression levels were similar as when they were transfected with one of the plasmids
15 alone (Fig. 55E and Fig. 54/55B).

- In western blot analysis (Fig. 56), a strong band was detected for VB2060 at approximately 95 kDa under non-reducing conditions, indicating the presence of VB2060 homodimeric proteins. No bands were detected at approximately half the size under non-reducing conditions, suggesting that the encoded VB2060 polypeptides expressed from HEK293E cells, form
20 homodimers in the supernatant. Under reducing conditions, a band at approximately 50 kDa was observed indicating the reduction of covalent disulfide bridges in the hinge region of VB2060, and formation of monomeric molecules. Lack of observed bands in the lipofectamine control lane indicates high specificity and low cross-reactivity of the detection antibody (Fig. 56A).

- 25 In conclusion, Example 3 shows that constructs that are expressed in HEK293 cells which may indicate that they could also be secreted at higher levels *in vivo*, i.e. from myocytes after intramuscular vaccination.

Example 4: Anti-RBD immune responses in mice immunized with VB10.COVID2
vaccibody DNA vaccines

- 30 For all experiments with mice (Examples 4-8), the following study design was applied:

Female, 6-8-week-old BALB/c mice were obtained from Janvier Labs (France). All animals were housed in the animal facility at the Radium Hospital (Oslo, Norway) or the University of Oslo (Norway). All animal protocols were approved by the Norwegian Food Safety Authority (Oslo, Norway). For the studies, the mice were vaccinated with the DNA vaccines as described in table 2 below. The vaccine was administrated to each tibialis anterior (TA) muscle by needle injection (25 μ l solution of vaccibody DNA plasmids in sterile PBS in each leg) followed by AgilePulse *in vivo* electroporation (EP) (BTX, U.S.). The AgilePulse EP delivery consists of 3 sets of pulses with 110-450 voltage. The first set, there are 1 50 μ s pulse with a 0.2ms delay; the second set is 1 50 μ s pulse with a 50ms delay and the third set is 8 pulses with 10ms pulse and 20ms delay. Sera samples, samples collected from the lungs by bronchoalveolar lavage (BAL) and spleens were collected as described in table 2 below.

Table 2: Mouse studies: vaccination, frequency and dose, samples collection, reference to Examples and Figures

Group	Conc.[μ g]	Vaccination on day	Termination on day	Sera on day	Spleen on day	Example and Figures
Experiment 1						
Low dose	2.5	0	14	NA	14	Ex. 9 Fig. 73
Low dose	2.5	0, 21	14, 28	0, 7, 14, 20, 28	14, 28	Ex. 4-8 Figs. 57A, 58, 59, 61, 64, 66
Medium dose 1	25	0	7	NA	7	Ex 6 Fig. 61A
Medium dose 2	25	0	14	NA	14	Ex. 9 Fig. 73
Medium dose 3	25	0, 21	14, 28, 90	0, 7, 14, 20, 28, 42, 56, 70, 90	14, 28, 90	Ex. 4-6, 8, 9 Figs. 57A, 58, 59, 62, 67, 68, 73-74
Medium dose 4	25	0, 21, 89	99	0, 7, 14, 20, 28, 42, 56, 70, 90, 99	99	Ex. 4-6, 8 Figs. 57A, 58-60, 62, 57A, 69-70
High dose 1	50	0	90, 99	0, 7, 14, 20, 28, 42, 56, 70, 90, 99	90/99	Ex. 4-6, 8 Figs. 57A, 58, 62, 57, 67-68
High dose 2	50	0, 21 (or 89)	28,90	0, 7, 14, 20, 28,	28, 90	Ex. 4-6, 8 Figs. 57A/B,

				42, 56, 70, 90		58, 62, 63, 57, 67-70
High dose 3	50	0, 21, 89	99	0, 7, 14, 20, 28, 42, 56, 70, 90, 99	99	Ex. 4-6, 8 Figs. 57A, 58, 62, 57, 69-70
Experiment 2						
Treatment 1	3.0	0, (21)	28 + BAL	0, 7, 14, 21, 28	NA	Figs. 57C/D
Treatment 2	6.25	0, (21)	28 + BAL	0, 7, 14, 21, 28	NA	Figs. 57C/D
Treatment 3	12.5	0, (21)	28 + BAL	0, 7, 14, 21, 28	NA	Figs. 57C/D
Treatment 4	25	0, (21)	28 + BAL	0, 7, 14, 21, 28	NA	Figs. 57C/D
Experiment 3						
Treatment 1	1.0	0	7 + 14	7 + 14	7 + 14	Ex. 6 Fig. 63
Treatment 2	6.25	0	7 + 14	7 + 14	7 + 14	Ex. 6 Fig. 63
Treatment 3	12.5	0	7 + 14	7 + 14	7 + 14	Ex. 6 Fig. 63
Treatment 4	25	0	7 + 14	7 + 14	7 + 14	Ex. 6 Fig. 63

The purpose of the study of Example 4 was to evaluate the humoral immune response induced in mice against RBD when vaccinated with VB10.COVS2 vaccibody DNA vaccines as a function of the dose and number of doses of DNA vaccine administered.

- 5 The humoral immune response was evaluated in sera collected from vaccinated mice by an ELISA assay detecting total IgG in the sera binding to RBD from SARS-CoV2. Nunc ELISA plates were coated with 1 µg/ml recombinant protein antigen in D-PBS overnight at 4°C. Plates were blocked with 4% BSA in D-PBS for 1 hour at RT. Plates were then incubated with serial dilutions of mouse sera and incubated for 2h at 37°C.
- 10 Plates were washed 3x and incubated with 1:50 000 dilution of HRP-anti-mouse IgG secondary antibody (Southern Biotech) and incubated for 1h at 37°C. After final wash plates were developed using TMB substrate (Merck, cat. CL07-1000). Plates were read at 450 nm wavelength within 30 min using a Multiscan GO (Thermo Fischer Scientific). Binding antibody endpoint titers were calculated. Binding antigens tested included
- 15 SARS-CoV-2 antigens: RBD (Sino Biological 40592-V08H).

The four DNA vaccines (VB2049, VB2060, VB2065 and VB2071) were compared for the ability to induce anti-RBD IgG, and VB2060 was superior compared to VB2049 (Fig. 57A/B, the two graphs in Figure 57A present the same data in different ways).

5 VB2060 demonstrated a consistent dose-response with specific anti-RBD IgG as early as day 7 post a single vaccination; even at the lowest doses (Figure 57A and 57C). The antibody levels peaked at day 28 (10^5 endpoint titer) after a single dose and persisted for at least 90 days (Figure 57A and 57B). For VB2060, the peak and durability of the response were further increased ($>10^6$ endpoint titer) following a two-dose regimen (days 0 and 21) compared to the single dose group. Limited added
10 benefit was observed at day 99 in mice that received a boost vaccination at day 89 (Figure 57A and 57B).

A second experiment confirmed a dose-dependent response in the range of 3.0, 6.25, 12.5 and 25 μg of VB2060 (Figure 57C), in particular on day 7, however already at day 14 levels reached $\sim 10^5$ endpoint titer at all doses.

15 Furthermore, the kinetics of RBD-specific IgG were tested in bronchoalveolar lavage (BAL) from mice having been vaccinated once or twice with different doses of VB2060 (Figure 57D). RBD-specific IgG in the lung which may contribute to local virus neutralization as a first line of protection against respiratory tract infection. RBD-specific IgG was found in BAL at the earliest time point tested (day 14) even with the
20 lowest dose. The levels increased with dose and over time.

VB2065 and VB2071 (spike protein) also induced strong IgG responses against RBD, however, these appeared to be weaker than the RBD-based construct VB2060 (Figure 57 B). This finding may probably be explained with the lower secretion of the vaccine protein (see Figure 54). VB2059 (long RBD) and VB2071 (spike protein) with anti-mouse MHCII scFv targeting also induced strong IgG responses against RBD.
25 However, these appeared weaker to be weaker than the MIP1 α targeted RBD-based construct VB2060 (Figure 57B and 57E). VB2059 demonstrated a consistent dose-response with specific anti-RBD IgG as early as day 7 post a single vaccination; even at the lowest doses (Fig. 57E). However, the antibody levels peaked at a later time point with a lower response in comparison to VB2060 (day 56, 10^5 endpoint titer) (Fig. 57A and 57E). This finding clearly shows that the MIP1 α targeting unit is superior
30 compared to the anti-mouse MHCII scFv targeting at eliciting rapid and long-lasting

high levels of anti-RBD antibodies with the VB10.COVID vaccines comprising such targeting unit.

For the constructs containing a combination of predicted T cell epitopes and the long RBD domain in the antigenic unit, constructs VB2097 (3 epitopes + GSAT linker) and VB2099 (3 epitopes + SEG linker) induced stronger IgG responses against RBD than the constructs comprising 3 epitopes with other linkers (Fig. 57F). As for the constructs with 1 epitope, VB2082 and VB2087 (including pep18) induced stronger anti-RBD IgG responses compared to constructs comprising the pep08 epitope (VB2081) (Fig. 57F). These findings may probably be explained with the lower secretion of the vaccine proteins (see Fig. 55C). The best constructs containing a combination of predicted T cell epitopes and the long RBD, VB2097 and VB2087 induce similar immune responses compared to VB2060, comprising only the long RBD (Fig. 57A and 57B).

The VB10.COVID DNA vaccine containing the long RBD domain with the 3 South African variant mutations, VB2129, demonstrated a specific anti-RBD IgG as early as day 7 post a single vaccination; even at a low dose (Figure 57G). The antibody levels further increased until day 14 (10^4 endpoint titer) at all doses.

When co-vaccinating mice with 2 plasmids, VB2048 and VB2049, in one combined DNA vaccine solution with 12.5 μ g of each plasmid, the data shows that a strong anti-RBD IgG response is elicited already at day 14 (Fig. 57H).

Example 5: VB10.COVID vaccibody DNA vaccines elicit strong neutralizing antibody responses in mice

The purpose of this study was to evaluate the extent of neutralizing antibody response induced in mice against live SARS-CoV-2 virus, when vaccinated with VB10.COVID vaccibody DNA constructs VB2049, VB2060 and VB2065 as a function of the dose and number of doses of DNA vaccine given to the mice.

Live virus microneutralization assays (MNA) were performed at Public Health England (Porton Down, UK) as described in Folegatti et al., Lancet 396 (10249), 2020, 467-478. Neutralising virus titers were measured in heat-inactivated (56°C for 30 min) serum samples. Diluted SARS-CoV-2 (Australia/VIC01/20202) was mixed 50:50 in 1% FCS/MEM with doubling serum dilutions in a 96-well V-bottomed plate and incubated at 37°C in a humidified box for 1 h. The virus/serum mixtures were then transferred to

washed Vero E6 (ECACC 85020206) cell monolayers in 96-well flat-bottomed plates, allowed to adsorb at 37°C for a further hour, before removal of the virus inoculum and replacement with overlay (1% w/v CMC in complete media). The box was resealed and incubated for 24 hours prior to fixing with 8% (w/v) formaldehyde solution in PBS.

- 5 Microplaques were detected using a SARS-CoV-2 antibody specific for the SARS-CoV-2 RBD spike protein and a rabbit HRP conjugate, infected foci were detected using TrueBlue™ substrate. Stained microplaques were counted using ImmunoSpot® S6 Ultra-V Analyzer and resulting counts analysed in SoftMax Pro v7.0 software. International Standard 20/130 (human anti-SARS-CoV-2 antibody from human
10 convalescent plasma, NIBSC, UK) was used for comparison as a positive control.

Sera from mice vaccinated with the VB10.COVID2 vaccibody DNA constructs VB2049, VB2060 and VB2065 were assessed the live virus neutralization assay and neutralizing antibody responses were seen for all the constructs.

- 15 A dose-dependent response was observed, with a low dose of VB2060 (2.5 µg) being sufficient to induce notable neutralizing activity at day 28. Also, a single high dose of VB2060 (50 µg) was able to induce neutralizing activity already at day 7, which peaked at day 28 with no signs of decline at day 90, comparable or higher to levels observed in convalescent plasma from recovered COVID-19 patients (NIBSC standard 20/130). Independent of the dose, the strongest response was observed at day 99 (after boost
20 at day 89), showing induction of long-lasting, neutralising antibody responses with VB2060.

Two and three doses of 25 or 50 µg VB2049 did induce modest levels of neutralizing antibody responses at days 90 and 99 as did two doses of 50 µg VB2065 at day 28.

- 25 A second experiment confirmed a dose-dependent response in the range of 3.0, 6.25, 12.5 and 25 µg of VB2060 (Fig. 58B), in particular on day 7, however already at day 14 levels reached $\sim 10^3$ endpoint titer at all doses. In this experiment, one vaccination with the highest dose of VB2060 (25 µg) was able to induce strong neutralizing activity already at day 7, which peaked at day 28 (no boost), comparable or higher to levels observed in convalescent plasma from recovered COVID-19 patients (NIBSC standard
30 20/130).

From the above results, VB2060 appears superior to VB2065 and VB2049 in inducing rapid and high levels of neutralizing antibodies even with only one dose. The results

show that VB2060 is a potent DNA vaccine which is capable of eliciting virus neutralizing activity already at day 7 after vaccination (Figure 58).

Example 6: Evaluation of the magnitude and specificity of T cell responses after vaccination with VB10.COVS2 vaccibody DNA vaccines.

5 The purpose of this study was to evaluate the cellular immune response against RBD/spike in splenocytes from mice vaccinated with VB10.COVS2 vaccibody DNA constructs, evaluated as a function of the dose and number of doses administered. Splenocytes from vaccinated mice were analyzed in IFN- γ ELISpot assay detecting RBD/spike specific cellular responses. Briefly, the animals were sacrificed at days
10 shown in Table 2 and the spleens were harvested aseptically. The spleens were mashed, cell suspensions were incubated with 1x ACK buffer, washed and re-suspended to a cell concentration of 6×10^6 cells. In some experiments, CD4+ or CD8+ T cell populations were depleted from the total splenocyte population using the Dynabead (catalog no. 11447D or 11445D; Thermo Fischer Scientific) magnetic bead
15 system according to the manufacturer's recommended procedures. Cells were then re-suspended in complete medium at 6×10^6 cells/ml for the ELISpot assay. Depletion was confirmed by flow cytometry analysis. Furthermore, the cells were plated in triplicates (6×10^5 cells/well) and stimulated with 2 μ g/ml of RBD/spike peptide pools (Tables 3 and 4 below) or individual peptides (15-mer peptides overlapping by 12
20 amino acids spanning the entire RBD, 61 peptides in total, or the entire spike protein, 296 peptides in total) for 24h. No-peptide-stimulation was used as negative control. The stimulated splenocytes were analysed for IFN- γ responses using the IFN- γ ELISpot Plus kit (Mabtech AB, Sweden). Spot-forming cells were measured in a CTL ELISpot reader, ImmunoSpot 5.0.3 from Cellular Technology. Results are shown as the
25 mean number of IFN- γ + spots/ 10^6 splenocytes. Tables 3: RBD pools and peptides

Pool ID	Composition
RBD pool 1	RBD 1, 2, 3, 4, 5, 6, 7, 8, 9,10
RBD pool 2	RBD 11, 12, 13, 14, 15, 16, 17, 18, 19, 24
RBD pool 3	RBD 20, 21, 22, 23, 25, 26, 27, 28, 29, 30
RBD pool 4	RBD 31, 32, 33, 34, 35, 36, 37, 38, 39, 40
RBD pool 5	RBD 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51
RBD pool 6	RBD 52, 53, 54, 55, 56, 57, 58, 59, 60, 61

RBD Peptide No. /SEQ ID NO:	Sequence	RBD Peptide No. /SEQ ID NO:	Sequence
1/445	NITNLCPFGEVFNAT	32/476	KLPDDFTGCVIAWNS
2/446	NLCPFGEVFNATRFA	33/477	DDFTGCVIAWNSNNL
3/447	PFGEVFNATRFASVY	34/478	TGCVIAWNSNNLDSK
4/448	EVFNATRFASVYAWN	35/479	VIAWNSNNLDSKVGG
5/449	NATRFASVYAWNRRKR	36/480	WNSNNLDSKVGGNYN
6/450	RFASVYAWNRRKRISN	37/481	NNLDSKVGGNYNYLY
7/451	SVYAWNRRKRISNCVA	38/482	DSKVGGNYNYLYRLF
8/452	AWNRRKRISNCVADYS	39/483	VGGNYNYLYRLFRRKS
9/453	RKRISNCVADYSVLY	40/484	NYNYLYRLFRRKSNLK
10/454	ISNCVADYSVLYNSA	41/485	YLYRLFRRKSNLKPFE
11/455	CVADYSVLYNSASF	42/486	RLFRKSNLKPFERDI
12/456	DYSVLYNSASFSTFK	43/487	RKSNLKPFERDISTE
13/457	VLYNSASFSTFKCYG	44/488	NLKPFERDISTEIQ
14/458	NSASFSTFKCYGVSP	45/489	PFERDISTEIQAGS
15/459	SFSTFKCYGVSPTKL	46/490	RDISTEIQAGSTPC
16/460	TFKCYGVSPTKLNDL	47/491	STEIQAGSTPCNGV
17/461	CYGVSPTKLNDLCFT	48/492	IYQAGSTPCNGVEGF
18/462	VSPTKLNDLCFTNVY	49/493	AGSTPCNGVEGFNCY
19/463	TKLNDLCFTNVYADS	50/494	TPCNGVEGFNCYFPL
20/464	NDLCFTNVYADSFVI	51/495	NGVEGFNCYFPLQSY
21/465	CFTNVYADSFVIRGD	52/496	EGFNCYFPLQSYGFQ
22/466	NVYADSFVIRGDEVR	53/497	NCYFPLQSYGFQPTN
23/467	ADSFVIRGDEVRQIA	54/498	FPLQSYGFQPTNGVG
24/468	FVIRGDEVRQIAPGQ	55/499	QSYGFQPTNGVGYQP
25/469	RGDEVRQIAPGQTGK	56/500	GFQPTNGVGYQPYRV
26/470	EVRQIAPGQTGKIAD	57/501	PTNGVGYQPYRVVVL
27/471	QIAPGQTGKIADYNY	58/502	GVGYQPYRVVLSFE
28/472	PGQTGKIADYNYKLP	59/503	YQPYRVVLSFELLH
29/473	TGKIADYNYKLPDDF	60/504	YRVVLSFELLHAPA
30/474	IADYNYKLPDDFTGC	61/505	VVLSFELLHAPAT
31/475	YNYKLPDDFTGCVIA		

Tables 4: Spike pools and peptides

Pool ID	Composition
Spike pool 1	Peptides 1 - 12
Spike pool 2	Peptides 13 - 24
Spike pool 3	Peptides 25 - 35, 37
Spike pool 4	Peptides 38 - 49

Spike pool 5	Peptides 50 - 61
Spike pool 6	Peptides 62 - 73
Spike pool 7	Peptides 74 - 80, 82 - 84, 87, 88
Spike pool 8	Peptides 85,86,89 - 93, 98 - 101, 108
Spike pool 9	Peptides 94 - 97, 102 - 105, 109 - 112
Spike pool 10	Peptides 106, 107, 113 - 122
Spike pool 11	Peptides 123 - 134
Spike pool 12	Peptides 135 - 146
Spike pool 13	Peptides 147 - 156, 159 - 161
Spike pool 14	Peptides 156 - 158, 162 - 169, 172
Spike pool 15	Peptides 170, 171, 173, 174, 177 - 180, 186, 188, 189, 191
Spike pool 16	Peptides 175, 176, 181, 182, 193 - 195, 197 - 200
Spike pool 17	Peptides 183 - 185, 187, 190, 192, 201 - 206
Spike pool 18	Peptides 196, 207 - 217
Spike pool 19	Peptides 218 - 230
Spike pool 20	Peptides 231 - 238, 240 - 242, 244, 245
Spike pool 21	Peptides 23, 243, 246 - 256
Spike pool 22	Peptides 257- 269
Spike pool 23	Peptides 270 - 276, 278, 280 - 283
Spike pool 24	Peptides 284 - 287, 289 - 296

Peptide no./SEQ ID NO:	Sequence	Peptide no./SEQ ID NO:	Sequence
1/506	VNLTTRTQLPPAYTN	149/654	VAVLYQDVNCTEVPV
2/507	TRTQLPPAYTNSFTR	150/655	YQDVNCTEVPVAIHA
3/508	LPPAYTNSFTRGVYY	151/656	NCTEVPVAIHADQLT
4/509	YTNSFTRGVYYPDKV	152/657	VPVAIHADQLTPTWR
5/510	FTRGVYYPDKVFRSS	153/658	IHADQLTPTWRVYST
6/511	VYYPDKVFRSSVLHS	154/659	QLTPTWRVYSTGSNV
7/512	DKVFRSSVLHSTQDL	155/660	TWRVYSTGSNVFQTR
8/513	RSSVLHSTQDLFLPF	156/661	YSTGSNVFQTRAGCL
9/514	LHSTQDLFLPFFSNV	157/662	SNVFQTRAGCLIGAE
10/515	QDLFLPFFSNVTWFH	158/663	QTRAGCLIGAEHVNN
11/516	LPFFSNVTWFHAIHV	159/664	GCLIGAEHVNNSEYEC
12/517	SNVTWFHAIHVSGTN	160/665	GAEHVNNSEYECDIPI
13/518	WFHAIHVSGTNGTKR	161/666	VNNSEYECDIPIGAGI
14/519	IHVSGTNGTKRFDNP	162/667	YECDIPIGAGICASY
15/520	GTNGTKRFDNPVLPF	163/668	IPIGAGICASYQTQT
16/521	TKRFDNPVLPFNDGV	164/669	AGICASYQTQTNSPR
17/522	DNPVLPFNDGVYFAS	165/670	ASYQTQTNSPRRARS
18/523	LPFNDGVYFASTEKS	166/671	TQTNSPRRARSVASQ
19/524	DGVYFASTEKSNIIR	167/672	SPRRARSVASQSIIA

20/525	FASTEKSNIIRGWIF	168/673	ARSVASQSIIAYTMS
21/526	EKSNIIRGWIFGTTL	169/674	ASQSIIAYTMSLGAE
22/527	IIRGWIFGTTLDSKT	170/675	IIAYTMSLGAENSV
23/528	WIFGTTLDSKTQSLL	171/676	TMSLGAENSVAYSNN
24/529	TTLDSKTQSLLIVNN	172/677	GAENSVAYSNNNSIAI
25/530	SKTQSLLIVNNATNV	173/678	SVAYSNNNSIAIPTNF
26/531	SLIVNNATNVVIKV	174/679	NNNSIAIPTNFTISV
27/532	VNNATNVVIKVCEFQ	175/680	IAIPTNFTISVTTEI
28/533	TNVVIKVCEFQFCND	176/681	TNFTISVTTEILPVS
29/534	IKVCEFQFCNDPFLG	177/682	ISVTTEILPVSMKT
30/535	EFQFCNDPFLGVYYH	178/683	TEILPVSMKTSDVC
31/536	CNDPFLGVYYHKNNK	179/684	PVSMKTSDVCTMYI
32/537	FLGVYYHKNNKSWME	180/685	TKTSDVCTMYICGDS
33/538	YYHKNNKSWMESEFR	181/686	VDCTMYICGDSTEC
34/539	NNKSWMESEFRVYSS	182/687	MYICGDSTECNLLL
35/540	WMESEFRVYSSANNC	183/688	GDSTECNLLLQYGS
36/541	EFRVYSSANNCTFEY	184/689	ECSNLLLQYGSFCTQ
37/542	YSSANNCTFEYVSQP	185/690	LLLQYGSFCTQLNRA
38/543	NNCTFEYVSQPFMD	186/691	YGSFCTQLNRALTGI
39/544	FEYVSQPFMDLEGK	187/692	CTQLNRALTGIAVEQ
40/545	SQPFMDLEGKQGNF	188/693	NRALTGIAVEQDKNT
41/546	LMDLEGKQGNFKNLR	189/694	TGIAVEQDKNTQEVF
42/547	EGKQGNFKNLRREFV	190/695	VEQDKNTQEVFAQVK
43/548	GNFKNLRREFVFNID	191/696	KNTQEVFAQVKQIYK
44/549	NLREFVFNIDGYFK	192/697	EVFAQVKQIYKTPPI
45/550	FVFNIDGYFKIYSK	193/698	QVKQIYKTPPIKDFG
46/551	NIDGYFKIYSKHTPI	194/699	IYKTPPIKDFGGFNF
47/552	YFKIYSKHTPINLVR	195/700	PPIKDFGGFNFSQIL
48/553	YSKHTPINLVRDLPQ	196/701	DFGGFNFSQILPDPS
49/554	TPINLVRDLPQGFS	197/702	FNFSQILPDPSKPSK
50/555	LVRDLPQGFSALEPL	198/703	QILPDPSKPSKRSFI
51/556	LPQGFSALEPLVDLP	199/704	DPSKPSKRSFIEDLL
52/557	FSALEPLVDLPIGIN	200/705	PSKRSFIEDLLFNKV
53/558	EPLVDLPIGINITRF	201/706	SFIEDLLFNKVTLAD
54/559	DLPIGINITRFQTLL	202/707	DLLFNKVTLADAGFI
55/560	GINITRFQTLLALHR	203/708	NKVTLADAGFIKQYG
56/561	TRFQTLLALHRSYLT	204/709	LADAGFIKQYGDCLG
57/562	TLLALHRSYLTGDS	205/710	GFIKQYGDCLGDIAA
58/563	LHRSYLTGDSSSSGW	206/711	QYGDCLGDIAARDLI
59/564	YLTPGDSSSGWTAGA	207/712	CLGDIAARDLICAQK
60/565	GDSSSGWTAGAAAYY	208/713	IAARDLICAQKFNGL
61/566	SGWTAGAAAYYVGYL	209/714	DLICAQKFNGLTVLP
62/567	AGAAAYYVGYLQPR	210/715	AQKFNGLTVLPPLLT
63/568	AYYVGYLQPRTFLLK	211/716	NGLTVLPPLLTDEMI

64/569	GYLQPRTFLLKYNNEN	212/717	VLPPLLTDemiaQYT
65/570	PRTFLLKYnengTIT	213/718	LLTDemiaQYTSALL
66/571	LLKYnengTITDAVD	214/719	EMIAQYTSALLAGTI
67/572	NengTITDAVDCALD	215/720	QYTSALLAGTITSGW
68/573	TITDAVDCALDPLSE	216/721	ALLAGTITSGWTFGA
69/574	AVDCALDPLSETKCT	217/722	GTITSGWTFGAGAAL
70/575	ALDPLSETKCTLKSF	218/723	SGWTFGAGAALQIPF
71/576	LSETKCTLKsFTVEK	219/724	FGAGAALQIPFAMQM
72/577	KCTLKsFTVEKGIYQ	220/725	AALQIPFAMQMAYRF
73/578	KSFTVEKGIYQTSNF	221/726	IPFAMQMAYRFNGIG
74/579	VEKGIYQTSNFRVQP	222/727	MQMAYRFNGIGVTQN
75/580	IYQTSNFRVQPTESI	223/728	YRFNGIGVTQNVLYE
76/581	SNFRVQPTESIVRFP	224/729	GIGVTQNVLYENQKL
77/582	VQPTESIVRFPNITN	225/730	TQNVLYENQKLIANQ
78/583	ESIVRFPNITNLCPF	226/731	LYENQKLIANQFNSA
79/584	RFPNITNLCPFGEVF	227/732	QKLIANQFNSAIGKI
80/585	ITNLCPFGEVFNATR	228/733	ANQFNSAIGKIQDSL
81/586	CPFGEVFNATRFASV	229/734	NSAIGKIQDSLSSTA
82/587	EVFNATRFASVYAWN	230/735	GKIQDSLSSTASALG
83/588	ATRFASVYAWNRKRI	231/736	DSLSSTASALGKLQD
84/589	ASVYAWNRKRISNCV	232/737	STASALGKLQDVVNQ
85/590	AWNRKRISNCVADYS	233/738	ALGKLQDVVNQNAQA
86/591	KRISNCVADYSVLYN	234/739	LQDVVNQNAQALNTL
87/592	NCVADYSVLYNSASF	235/740	VNQNAQALNTLVKQL
88/593	DYSVLYNSASFSTFK	236/741	AQALNTLVKQLSSNF
89/594	LYNSASFSTFKCYGV	237/742	NTLVKQLSSNFGAIS
90/595	ASFSTFKCYGVSPTK	238/743	KQLSSNFGAISSVLN
91/596	TFKCYGVSPTKLNDL	239/744	SNFGAISSVLNDILS
92/597	YGVSPTKLNDLCFTN	240/745	AISSVLNDILSRDK
93/598	PTKLNDLCFTNVYAD	241/746	VLNDILSRDKVEAE
94/599	NDLCFTNVYADSFVI	242/747	ILSRDKVEAEVQID
95/600	FTNVYADSFVIRGDE	243/748	LDKVEAEVQIDRLIT
96/601	YADSFVIRGDEVQR	244/749	EAEVQIDRLITGRLQ
97/602	FVIRGDEVQRQAPGQ	245/750	QIDRLITGRLQSLQT
98/603	GDEVQRQAPGQTGKI	246/751	LITGRLQSLQTYVTQ
99/604	RQAPGQTGKIADYN	247/752	RLQSLQTYVTQQLIR
100/605	PGQTGKIADYNYKLP	248/753	LQTYVTQQLIRAAEI
101/606	GKIADYNYKLDDFT	249/754	VTQQLIRAAEIRASA
102/607	DYNYKLDDFTGCVI	250/755	LIRAAEIRASANLAA
103/608	KLDDFTGCVIAWNS	251/756	AEIRASANLAATKMS
104/609	DFTGCVIAWNSNNLD	252/757	ASANLAATKMSECVL
105/610	CVIAWNSNNLDSKVG	253/758	LAATKMSECVLGQSK
106/611	WNSNNLDSKVGGNYN	254/759	KMSECVLGQSKRVDF
107/612	NLDSKVGGNYNLYR	255/760	CVLGQSKRVDFCGKG

108/613	KVGGNYNYLYRLFRK	256/761	QSKRVDFCGKGYHLM
109/614	NYNYLYRLFRKSNLK	257/762	VDFCGKGYHLMSFPQ
110/615	LYRLFRKSNLKPFER	258/763	GKGYHLMSFPQSAPH
111/616	FRKSNLKPFERDIST	259/764	HLMSFPQSAPHGVVF
112/617	NLKPFERDISTEIYQ	260/765	FPQSAPHGVVFLHVT
113/618	FERDISTEIYQAGST	261/766	APHGVVFLHVTVPA
114/619	ISTEIYQAGSTPCNG	262/767	VVFLHVTVVPAQKN
115/620	IYQAGSTPCNGVEGF	263/768	HVTYVPAQKNFTTA
116/621	GSTPCNGVEGFNCYF	264/769	VPAQKNFTTAPAIC
117/622	CNGVEGFNCYFPLQS	265/770	EKNFTTAPAICHGK
118/623	EGFNCYFPLQSYGFQ	266/771	TTAPAICHGKAHFP
119/624	CYFPLQSYGFQPTNG	267/772	AICHGKAHFPREGV
120/625	LQSYGFQPTNGVGYYQ	268/773	DGKAHFPREGVFVSN
121/626	GFQPTNGVGYYQPYRV	269/774	HFPREGVFVSNGTHW
122/627	TNGVGYYQPYRVVLS	270/775	EGVFVSNGTHWFVTQ
123/628	GYQPYRVVLSFELL	271/776	VSNGTHWFVTQRNFY
124/629	YRVVLSFELLHAPA	272/777	THWFVTQRNFYEPQI
125/630	VLSFELLHAPATVCG	273/778	VTQRNFYEPQIITTD
126/631	ELLHAPATVCGPKKS	274/779	NFYEPQIITTDNTFV
127/632	APATVCGPKKSTNLV	275/780	PQIITTDNTFVSGNC
128/633	VCGPKKSTNLVKNKC	276/781	TTDNTFVSGNCDVVI
129/634	KKSTNLVKNKCVNFN	277/782	TFVSGNCDVVIIVN
130/635	NLVKNKCVNFNFNGL	278/783	GNCDVVIIVNNTVY
131/636	NKCVNFNFNGLTGTG	279/784	VVIGIVNNTVYDPLQ
132/637	NFNFNGLTGTGVLTE	280/785	IVNNTVYDPLQPELD
133/638	NGLTGTGVLTESNKK	281/786	TVYDPLQPELDSFKE
134/639	GTGVLTESNKKFLPF	282/787	PLQPELDSFKEELDK
135/640	LTESNKKFLPFQQFG	283/788	ELDSFKEELDKYFKN
136/641	NKKFLPFQQFGRDIA	284/789	FKEELDKYFKNHTSP
137/642	LPFQQFGRDIADTTD	285/790	LDKYFKNHTSPDVL
138/643	QFGRDIADTTDAVRD	286/791	FKNHTSPDVLGDIS
139/644	DIADTTDAVRDPQTL	287/792	TSPDVLGDISGINA
140/645	TTDAVRDPQTLEILD	288/793	VDLGDISGINASVVN
141/646	VRDPQTLEILDITPC	289/794	DISGINASVVNIQKE
142/647	QTLEILDITPCSFEGG	290/795	INASVVNIQKEIDRL
143/648	ILDITPCSFEGGVSVI	291/796	VVNIQKEIDRLNEVA
144/649	TPCSFEGGVSVITPGT	292/797	QKEIDRLNEVAKNLN
145/650	FGGVSVITPGTNTSN	293/798	DRLNEVAKNLNESLI
146/651	SVITPGTNTSNQVAV	294/799	EVAKNLNESLIDLQE
147/652	PGTNTSNQVAVLYQD	295/800	NLNESLIDLQELGKY
148/653	TSNQVAVLYQDVNCT	296/801	SLIDLQELGKYEYI

Overall, the VB10.CO2 constructs all induced strong, dose-dependent T cell responses after vaccination, which increased over time. The responses were dominated by CD8⁺ T cells and accompanied by significant, but weaker CD4⁺ T cell responses.

- 5 Strong T cell responses against the RBD domain of SARS-CoV-2 were detected in spleens from mice vaccinated with one or two doses of both 2.5 µg or 25 µg VB2049 (Fig. 59). Depending on dose level and the number of doses, the response ranged from ~1800 to 6000 SFU per 10⁶ cells in splenocytes sampled 2 weeks after 1st dose or 1st week post-boost-vaccination at day 21 and stimulated separately with 6 peptide pools
10 spanning RBD. The response was strong already 14 days post 1st vaccination even with a low dose (2.5 µg DNA) and was boosted by day 28 in groups receiving a 2nd vaccination at day 21 (in a dose-dependent manner, Fig. 59).

- The epitopes recognized by the T cells by stimulating with individual 15-mers overlapping with 12 amino acids in splenocytes depleted for either CD4 or CD8 T cell
15 populations were characterised. Strong (up to ~4000 SFU/10⁶ cells) CD8⁺ T cell responses against 9 peptides were observed. RBD-specific CD4⁺ responses were also detected against 7 peptides, but of a lower magnitude and fewer epitopes (up to ~1000 SFU/10⁶ cells) (Figure 60A and 60B). The amino acid sequence of the overlapping peptides indicated a reactivity against 4 distinct MHC class I-restricted epitopes and 3
20 MHC class II-restricted epitopes (Figure 60C) in RBD.

- The kinetics of the early T cell responses induced by either 1 dose (day 0) or 2 rapid doses (day 0 + 7) of VB2060 was examined. Vaccination with 1 x 25 µg of VB2060 induced T cell responses as early as at day 7 (~550 spots per 10⁶ splenocytes) with a peak response at day 14 (~2750 spots per 10⁶ splenocytes). An additional boost
25 vaccination at day 7 did not increase the T cell responses compared to the single dose vaccine regime (Figure 61A). In a separate experiment, the T cell responses were still found to persist for at least 90 days after vaccination with 50 µg of VB2060 (~5000 SFU/10⁶ splenocytes), with a strong boost effect at day 99; 10 days after a booster dose at day 89 (~20 000 SFU/10⁶ splenocytes) (Figure 62). When comparing T cell
30 responses induced by two doses of 2.5 µg 7 days post boost vaccination at day 21 of either VB2060, VB2049 or VB2059, VB2049 induced stronger responses than VB2060 and significantly stronger than VB2059 (~3800 versus ~2600 SFU/10⁶ cells versus ~1000 SFU/10⁶ cells, respectively) (Figure 61B). This finding clearly shows that the

MIP1 α targeting unit (VB2049 and VB2060) is superior compared to the anti-mouse MHCII scFv targeting unit (VB2059) at eliciting high levels of RBD-specific T cell responses with the VB10.COVS2 vaccines comprising such targeting unit.

5 An IFN- γ ELISpot assay was performed on fresh splenocytes from mice vaccinated with VB2065 and VB2071 DNA vaccine containing the spike protein to evaluate the vaccine dose T cell response effect. As predicted, both VB2065 and VB2071 induced a broader, stronger total T cell response than VB2049, VB2060 and VB2059 due to the larger antigen (Figure 63). The animals were sacrificed on day 28, i.e. 7 days post boost-vaccination at day 21. The spleens were harvested and the splenocytes isolated
10 before stimulation with spike peptide pools. CD4 and CD8 cell populations were depleted in the splenocyte total cell population by using beads to evaluate the specific CD8+ and CD4+ RBD specific immune responses. Both VB2065 and VB2071 induced strong, CD8+ dominating T cell responses, accompanied by broad, weaker CD4+ responses.

15 A single vaccination and dose-dependent early T cell response kinetics induced by VB2129, containing the long RBD domain with the 3 mutations from the South African virus variant, was examined. Vaccination with 1 x 1.0, 6.25, 12.5 or 25 μ g of VB2129 induced T cell responses as early as at day 7 at a low dose ($\sim$ 500 spots per 10^6 splenocytes for 6.25 μ g dose) with a significant increase in the response by day 14
20 ($\sim$ 2750 spots per 10^6 splenocytes for 25 μ g dose) (Fig. 63B). The data in this experiment is comparable to the data for VB2060 in similar experiments (Fig. 61).

Example 7: VB10.COVS2 DNA vaccines induce predominantly Th1 response against RBD/spike protein in mice

25 The purpose of this study was to analyze the Th1/2 profile of the cellular response elicited in mice after two doses of VB10.COVS2 DNA vaccine.

The animals were vaccinated with two doses of 2.5 μ g of VB10.COVS2 vaccibody DNA constructs VB2049, VB2059 and VB2060 or two doses of 50 μ g VB2065 and VB2071 on days 0 and 21 and sacrificed 28 days post primary vaccination. The spleens were removed aseptically, mashed to obtain cell suspensions with splenocytes, and 1x ACK
30 buffer was used to remove erythrocytes. The splenocytes were then washed, plated (1.5×10^6 cells/well in 24 well plate) and stimulated for 24h with 2 μ g/ml of RBD peptide pools or selected spike peptide pools (Tables 3 and 4). Cell culture supernatant was

harvested and analysed for cytokine presence. In short, 50µl of the cell culture supernatant was used in using ProcartaPlex Immunoassay as described in the supplier's protocol (Thermo Fisher). Presence of IFN- γ , TNF- α and IL-12p70 in the supernatant defined Th1 response. The Th2 response was defined through production of IL-4 and IL-5 and partially through presence of IL-6.

Characterization of the Th1 (IFN γ , TNF α , IL-12) and Th2 (IL-4, IL-5) cytokines in cell culture supernatant of splenocytes from vaccinated mice re-stimulated with RBD or spike peptide pools showed that for VB2060, the response was IFN γ and TNF α dominated and minor quantities of IL-6, IL-12 p70, IL-4 or IL-5 were detected. This indicates that T cell responses showed strong Th1 bias when characterized one month after vaccination, while the Th2 responses were minimal. For VB2049 and VB2059, minor IL-6 responses were observed and no significant responses for IL-12 p70, IL-4 or IL-5 (Fig. 64A).

The same pattern was observed for VB2065 and VB2071 (spike), where IL-6 was to some extent detected for one of the pooled peptides (peptides 5 and 6) (Fig. 64B).

Overall, this is consistent with a Th1-biased response induced by the vaccines. A Th1-biased response is preferable to avoid potential vaccine-related enhancement of disease which has been observed for some SARS-CoV vaccines; likely involving a Th2-biased response. Example 8: RBD specific cell mediated immune response to VB10.COVS2 DNA vaccines

Example 8: RBD specific cell mediated immune response to VB10.COVS2 DNA vaccines

The purpose of this study was to evaluate T cell responses, on a single cell level, in mice vaccinated with two doses of VB10.COVS2 vaccibody DNA constructs. The multi flow cytometry was developed to assess T cell subsets in mice vaccinated with VB2049 or VB2060 DNA vaccines. The T cells were defined with CD3, CD4, CD8 and $\gamma\delta$ TCR lineage markers. The in-depth analysis of IFN- γ , TNF- α , IL-2, IL-4, IL-17 and FoxP3 expression allowed evaluation of T helper (Th) 1 and 2 type responses, Th17, and regulatory T cells (Treg).

BALB/c mice were vaccinated with either low (2.5 µg), medium (25 µg) or high (50 µg) dose VB2049 or VB2060 DNA vaccine one-, two- or three times as described in Table

2. Splenocytes from vaccinated mice were isolated as previously described. The splenocytes were then washed, plated (2×10^6 cells/well in 24 well plate) and stimulated for 16 h with 2 $\mu\text{g/ml}$ of RBD peptide. For detection of cytokines with flow cytometry 1x monensin and 1x brefeldin were added to the wells during the incubation.
- 5 Following stimulation with RBD peptide pools, cells were harvested, washed, and stained with viability dye, followed by staining with extracellular antibodies (anti-CD3, anti-CD4, anti-CD8 and gdTCR), fixed and permeabilized, and then stained for detection of $\text{TNF}\alpha$, $\text{IFN}\gamma$, IL-2 (if assessed), IL-4, IL-17 and FoxP3. The stained cells were run in BD FACSymphony A5 and analysed using FlowJo software.
- 10 The RBD stimulated mice splenocyte T cells were defined through exclusion of dead cells, doublets and CD3- non-T cells (Fig. 65A-D). CD3+ T cells were then analysed for presence of $\gamma\delta\text{TCR}$ T cells, and these cells were further removed from the analysis (Fig. 65E). The remainder of the T cells was then examined for CD4 and CD8 makers, thus defining CD4+ and CD8+ T cells (Fig. 65F). Both populations were examined for
- 15 individual expression of $\text{IFN-}\gamma$, $\text{TNF-}\alpha$, IL-2, IL-4, IL-17 or FoxP3 and gates were set to define positive cells. These positive cells were further analysed using Boolean gating algorithm in FlowJo software, calculating all possible combinations of cytokines produced by each cell, thus allowing analysis of multifunctional T cells on a single cell level.
- 20 Flow cytometry analysis of T cells in VB2060-vaccinated mice (low dose) showed responses by CD4+ T cells and CD8+ T cells to RBD stimulation (Fig. 66A and 66B). The CD4+ RBD specific T cells produced $\text{IFN-}\gamma$, $\text{TNF}\alpha$, or a combination of these cytokines, a cytokine profile typical for Th1 responses. Presence of other markers like IL-4 (Th2 polarization), IL-17 (Th17) and FoxP3 (Treg) was also seen in a population of
- 25 CD4+ T cells. Analysis of CD8+ T cells showed responses dominated by $\text{IFN-}\gamma$, $\text{TNF}\alpha$ or a combination of the 2. A minor population of CD8+ T cells also expressed IL-17 and FoxP3. IL-2 expression was not examined.
- The same analysis of RBD specific T cells in VB2049 vaccinated mice (low dose) showed responses of CD4+ T cells and CD8+ T cells (Fig. 66C and 66D). The CD4+ T
- 30 cells expressed $\text{IFN-}\gamma$, $\text{TNF-}\alpha$, or a combination of the two cytokines. A portion of CD4+ T cells also expressed IL-4, a Th2 cell cytokine and IL-17, a Th17 cytokine, thus, revealing a mixture of Th1, Th2, Th17 and a Treg responses. CD8+ T cell responses,

however, were dominated by combined production of IFN- γ and TNF- α while the remainder of RBD specific cells produced one of these cytokines.

Thus, analysis of RBD specific CD4⁺ T cells in VB10.COVID-2-vaccinated mice (low dose) showed Th1 responses (defined by combined IFN- γ /TNF α production), and a mixture of Th2, Th17 and Treg responses. The CD8⁺ T cell were dominated by IFN- γ and TNF α presence, indicating that VB10.COVID-2 induces a cytotoxic T cell response specific for SARS-CoV-2.

To examine durability of T cell responses in mice vaccinated with VB2060 (medium and high dose), splenocytes were analysed on day 90. A dose dependent response was observed which was dominated by polyfunctional CD4⁺ T cells that produced IFN- γ , TNF α , IL-2 or combination of these cytokines (Fig. 67). Only a minor population of CD4⁺ T cells produced IL-17. Similarly, CD8⁺ T cell responses were also dose dependent and dominated by IFN- γ , TNF α (Fig. 68). These results confirmed the initial findings in mice vaccinated with a low dose of VB2060, i.e. that vaccination with VB2060 DNA vaccine elicits a combination of Th1 and Th17 T cell responses, and a cytotoxic T cell response specific for SARS-CoV-2. The results show a dose depended effect on T cells which persists for 90 days after the initial vaccination.

The animals were boost vaccinated on day 89 and subsequent T cell responses were analyzed on day 99. The CD4⁺ T cells produced IFN- γ and TNF α as previously observed. These cells also produced increased amounts of IL-2 indicating T cell survival and proliferation. A portion of CD4⁺ T cells also produces IL-17 (Fig. 69). The CD8⁺ T cells responses, similarly to the previous findings, were dominated by IFN- γ and to some extent TNF α (Fig. 70). In conclusion these data show that VB2060 DNA vaccine induces durable, Th1, Th17 and cytotoxic T cell responses which last for at least 100 days.

In addition, the early T cell responses in draining lymph nodes were evaluated on day 7 and day 28 after the first vaccination, i.e. seven days following the vaccination and seven days following the boost vaccination. Cells from the draining lymph nodes were stimulated with RBD peptides and then analysed using multi-color flow cytometry. We evaluated CD4⁺ and CD8⁺ T cells and a subset of CD8⁺ T cells called resident memory T cells (T_{rm}). To evaluate activation status and type of response we analysed expression of TNF- α , IFN- γ , IL-2 and granzyme B (Fig. 71 and Fig. 72).

Seven days after the vaccination, we analysed mice vaccinated with 25 µg VB2060 and compared to the control group (PBS). We observed strong CD8 T cell responses defined by presence of granzyme B. The Trm subset of CD8 T cell mainly expressed IFN-γ alone or in combination with granzyme B, indicating cytotoxic responses to RBD peptide (Fig. 71 A-C). At the same time point, the CD4⁺ T cell produced IL-2, TNF-α, or a combination of the two cytokines.

Seven days post the boost vaccination, we evaluated T cell responses in mice vaccinated with 3.0 µg, 6.25 µg, 12.5 µg and 25 µg VB2060. This analysis revealed dose dependent strong CD8⁺ T cell responses accompanied by production of granzyme B, TNF-α IFN-γ or a combination of these. Similar results were observed for resident memory T cells (Fig. 71E and F); additionally, this subset was increased in lymph nodes after the boost vaccination (Fig. 72B). After the boost vaccination, CD4⁺ T cells produced TNF-α, IFN-γ, IL-2 or a combination of these cytokines in a dose dependent manner.

Taken together these data show strong dose dependent T cell response dominated by cytotoxic T cells and accompanied by the Th1 polarized CD4⁺ T cells.

Example 9: Induction of specific cellular responses to predicted T cell epitopes by VB2048 DNA vaccination

The purpose of this study was to evaluate the cellular immune response against predicted T cell epitopes in splenocytes from mice vaccinated with VB2048 DNA vaccine, evaluated as a function of the dose and number of doses administered.

Splenocytes from vaccinated mice were analyzed in IFN-γ ELISpot assay detecting predicted epitopes specific cellular responses. Briefly, the animals were sacrificed at day 14 or day 28 and the spleens were harvested aseptically. The spleens were mashed, cell suspensions were incubated with 1x ACK buffer, washed and re-suspended to a cell concentration of 6×10^5 cells. Furthermore, the cells were plated in triplicates (6×10^5 cells/well) and stimulated with 2 µg/ml of individual peptides (T cell epitopes included in VB2048) for 24 h. No-peptide-stimulation was used as negative control. The stimulated splenocytes were analysed for IFN-γ responses using the IFN-γ ELISpot Plus kit (Mabtech AB, Sweden). Spot-forming cells were measured in a CTL

ELISpot reader, ImmunoSpot 5.0.3 from Cellular Technology. Results are shown as the mean number of IFN- γ + spots/ 10^6 splenocytes.

Strong T cell responses against the predicted epitopes from multiple SARS-CoV-2 strains were detected in spleens from mice vaccinated with one or two doses of either
5 2.5 μ g or 25 μ g VB2048 DNA vaccine. Depending on dose level and number of doses, the response ranged from ~1500 to 2200 SFC per 10^6 cells in splenocytes sampled 2 weeks after the first dose or one week post boost-vaccination at day 21. The response was strong already 14 days post first dose, even with a low dose (2.5 μ g DNA) and was boosted at day 28 after a second vaccination at day 21 with the high dose (25 μ g) (Fig.
10 73).

In splenocytes depleted for either CD4 or CD8 cell populations, strong (up to ~2200 SFU/ 10^6 cells), CD8+ dominated T cell responses against one dominating peptide (pep08) is observed (Fig. 74). T cell epitope specific CD4+ responses were also detected against 2 predicted peptides (pep02 and pep18), but of a lower magnitude (up
15 to ~460 SFU/ 10^6 cells).

Example 10: Induction of specific cellular responses to both predicted T cell epitopes and RBD by DNA vaccination with constructs containing both T cell epitopes and the long RBD domain

The purpose of this study was to evaluate the cellular immune response against both
20 predicted T cell epitopes and the RBD domain in splenocytes from mice vaccinated with VB10.COVID2 DNA vaccine containing both T cell epitopes and the long RBD domain.

Splenocytes from vaccinated mice were analysed in IFN- γ ELISpot assay detecting predicted epitopes and RBD-specific cellular responses. Briefly, the animals were
25 sacrificed at day 14 and the spleens were harvested aseptically. The spleens were mashed, cell suspensions were incubated with 1x ACK buffer, washed and re-suspended to a cell concentration of 6×10^5 cells. Furthermore, the cells were plated in triplicates (6×10^5 cells/well) and stimulated with 2 μ g/ml of individual peptides (T cell epitopes included in the respective constructs) and 2 μ g/ml of RBD peptide pools
30 (Table 3) for 24 h. No-peptide-stimulation was used as negative control. The stimulated splenocytes were analysed for IFN- γ responses using the IFN- γ ELISpot Plus kit (Mabtech AB, Sweden). Spot-forming cells were measured in a CTL ELISpot reader,

ImmunoSpot 5.0.3 from Cellular Technology. Results are shown as the mean number of IFN- γ + spots/ 10^6 splenocytes.

Strong T cell responses against the predicted epitopes from multiple SARS-CoV-2 strains were detected in spleens at day 14 from mice vaccinated once with 25 μ g of constructs containing either one or three predicted T cell epitopes. VB2097 (3 epitopes + GSAT linker) induced a stronger T cell specific response (~1250 SFC per 10^6 cells) than the other constructs comprising 3 epitopes with other linkers. In addition, all constructs were also able to elicit a strong RBD-specific cellular response. VB2097 and VB2087 elicited the strongest responses against RBD at a similar level to VB2060 (Fig. 75).

Example 11: Induction of specific cellular responses to both predicted T cell epitopes and RBD by vaccination with a vaccine containing two VB10.COVID constructs

The purpose of this study was to evaluate the cellular immune response against both predicted T cell epitopes and the RBD domain in splenocytes from mice vaccinated with a VB10.COVID DNA vaccine comprising 2 plasmids, VB2048 (20 T cell epitopes) and VB2049 (short RBD domain), with 12.5 μ g of each plasmid.

Splenocytes from vaccinated mice were analysed in IFN- γ ELISpot assay detecting predicted epitopes and RBD-specific cellular responses. Briefly, the animals were sacrificed at day 14 and the spleens were harvested aseptically. The spleens were mashed, cell suspensions were incubated with 1x ACK buffer, washed and re-suspended to a cell concentration of 6×10^5 cells. Furthermore, the cells were plated in triplicates (6×10^5 cells/well) and stimulated with 2 μ g/ml of 20 individual peptides and 2 μ g/ml of RBD peptide pools (Table 3) for 24 h. No-peptide-stimulation was used as negative control. The stimulated splenocytes were analysed for IFN- γ responses using the IFN- γ ELISpot Plus kit (Mabtech AB, Sweden). Spot-forming cells were measured in a CTL ELISpot reader, ImmunoSpot 5.0.3 from Cellular Technology. Results are shown as the mean number of IFN- γ + spots/ 10^6 splenocytes.

Strong T cell responses against the predicted epitopes from multiple SARS-CoV-2 strains were detected in spleens at day 14 from mice vaccinated once with a vaccine comprising a pharmaceutically acceptable carrier and 12.5 μ g of each plasmid (VB2048 and VB2049). In addition, the vaccine was also able to elicit a strong RBD-specific cellular response. When vaccinating mice with the aforementioned vaccine, the

total immune responses against both the predicted T cell epitopes and the RBD domain were similar as when mice were vaccinated with a vaccine containing either of the constructs (i.e. either VB2048 or VCB2049) , taking the dose into consideration (Fig. 76).

5 Example 12: VB10.COVS2 DNA vaccine VB2060 stability data

The purpose of the study was to determine the % supercoil DNA content as a stability indicating parameter after storage of VB10.COVS2 DNA vaccine VB2060 at elevated temperature (37°C) for up to 4 weeks.

10 0.5 ml of a sterile solution of VB2060 plasmid (3 mg/ml formulated in D-PBS), was filled with into 2ml, clear type I glass vials (Adelphi/Schott, VCDIN2R), sealed with 13 mm FluroTec® injection stopper (Adelphi/West, 7001-8021/INJ13TB3WRS) and capped with 13mm white Flip-off overseals (Adelphi/West, 5921-9826/FOT13W5117). The vials were stored upright in an incubator at 37°C for 4 weeks. Vials were tested for plasmid topology forms by HPLC at the beginning of the study and every week throughout the study. The HPLC method was performed with column TSKgel DNA-NPR (Tosoh Bioscience/Y0064), mobile phase A; 2.4 TRIS-Bas in 1000 ml water and pH adjustment to pH 9 by HCl and mobile phase B; 29.22 g NaCl in 500 ml mobile phase A at flow of 0.75 ml/min. Column temperature was 5 °C and sample injection volume was 1.5 µl. Topology is known as the most sensitive stability indicating parameters for plasmid DNA.

15 The supercoiling degree of plasmid VB2060 at the start of the study was determined to be approximately 90%. After one week the supercoiling degree had decreased to approximately 80%. In the following weeks, the plasmid topology did not materially change and only showed a minor further degradation. This shows that the VB10.COVS2 DNA vaccine VB2060 is highly stable, even when stored at elevated temperatures.

20 Summary of the Examples:

25 Using VB2060 as an example, we show, that dimeric molecules are formed (Example 3b). We also show, using VB2060, VB2129 and VB2132 as examples, that monomeric proteins have a molecular weight expected from the size of their constructs, as we start to add several RBD units to the protein (Example 3b).

We show that with vaccibodies comprising an antigenic unit comprising a short form of the SARS-CoV-2 RBD (VB2049), a longer version of the SARS-CoV-2 RBD (VB2060), a longer version of the SARS-CoV-2 RBD with 3 mutations found in the South African variant B.1.351 (VB2129) and the spike protein (VB2065 and VB2071) we induce anti-RBD IgG formation (Example 4). We show, that this response is unchanged, when adding predicted T cell epitopes to the construct (VB2081, VB2082, VB2087, VB2097 and VB2099). Thus, the post-translational modifications to the RBD protein (such as glycosylation and its correct folding which is needed to induce humoral response are unaffected by the addition of further amino acids (Example 4). We show, that the antibodies raised by the vaccibodies are effective in the live virus microneutralization assays (Example 5).

In addition to the raised antibodies, we show, that a cytotoxic T cell response is elicited against the RBD protein by constructs containing the RBD unit, and the RBD unit with the 3 mutations from the South African SARS-CoV-2 virus variant. This response is early (after only seven days) and long lasting (Example 6). We also raise a cytotoxic T cell response against the spike protein (Example 6). The majority of the T cell response is Th1 mediated (Example 7).

Thus, with a single vaccine, we can not only induce the required B cell response to obtain immunity against an infection with a betacoronavirus, but we also obtain T cells to attack an existing infection and help the patient recover.

We have developed a method to predict T cell epitopes from the betacoronavirus, and present those in Example 1. We show, that they elicit a strong T cell response (Example 9). When plasmids of constructs comprising predicted T cell epitopes are co-administered with plasmids of constructs comprising an RBD unit, we see that the T cell responses are similar to those elicited by each plasmid alone (Example 11). When these predicted T cell epitopes are combined with the RBD unit in the same construct, they still raise T cell specific responses, while the T cell specific response of the RBD unit is maintained (Example 10).

Conclusion from the conducted experiments

As a conclusion from the Examples 3-12, as detected by ELISA, the expression level was found to vary between high, medium and low expression between the various VB10.CO2 constructs depending on the molecule structure.

The VB10.COVS2 vaccines induced rapid and dose-dependent RBD IgG antibody responses that persisted up to at least 3 months after a single dose of the vaccine in mice. For VB2060, neutralizing antibody titers against live virus were detected from day 7 after one dose. All tested dose regimens reached higher or comparable titers to sera from human convalescent COVID-19 patients from day 28. Strong T cell responses were established detected already at day 7 with VB2060 and VB2129, and were subsequently characterized for both VB2049 and VB2060 to be multifunctional CD8+ and Th1 dominated CD4+ T cells. Responses remained at sustained high levels until at least 3 months after a single vaccination, being further strongly boosted by a second vaccination at day 89.

The MIP1 α targeting was superior compared to the anti-mouse MHCII scFv targeting at eliciting both stronger anti-RBD IgG responses and higher levels of RBD-specific T cell responses with the VB10.COVS2 vaccines.

It has also been shown that eliciting both strong RBD-specific antibody and T cell responses in addition to specific T cell responses against predicted T cell epitopes from the SARS-COV2 genome is feasible with two different strategies. One successful strategy is to combine the predicted T cell epitopes with the RBD domain in the antigenic unit in one VB10.COVS2 construct while another successful strategy is to vaccinate with a combination of two separate plasmids (one plasmid containing predicted T cell epitopes and one plasmid containing the RBD domain in the antigenic unit) in one vaccine solution.

These findings, together with simple administration and storage stability even at elevated temperatures, suggest that the VB10.COVS2 DNA vaccines are promising future candidates to prevent and treat Covid-19.

Embodiments A

1. A vaccine comprising an immunologically effective amount of:
 - (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope; or
 - (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); anda pharmaceutically acceptable carrier.
2. The vaccine according to embodiment A1, wherein the vaccine once administered to a human individual elicits a humoral response through generation of antibodies by B cells.
3. The vaccine according to embodiment A1, wherein the vaccine once administered to a human individual elicits a cellular immune response through generation of T cells.
4. The vaccine according to embodiment A1, wherein the vaccine once administered to a human individual elicits a humoral and a cellular immune response.
5. The vaccine according to any of the preceding embodiment A2 to A4, wherein the human individual suffers from a betacoronavirus infection and the vaccine is a therapeutic vaccine.
6. The vaccine according to any of the preceding embodiment A2 to A4, wherein the human individual is a healthy individual and the vaccine is a prophylactic vaccine.
7. The vaccine according to any of the preceding embodiments, wherein the at least one betacoronavirus epitope is a full-length viral surface protein of a betacoronavirus or a part thereof.
8. The vaccine according to embodiment A7, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.

9. The vaccine according to any of embodiments A7 to A8, wherein the viral surface protein is the spike protein.
- 5 10. The vaccine according to any of embodiments A7 to A9, wherein the viral surface protein is the full-length spike protein.
11. The vaccine according to any of embodiments A7 to A10, wherein the viral surface protein is a part of the spike protein.
- 10 12. The vaccine according to any of embodiments A7 to A11, wherein the at least one betacoronavirus epitope is a part of the spike protein selected from the group consisting of receptor binding domain (RBD), heptad repeat 1 (HR1) domain and heptad repeat 2 (HR2) domain.
- 15 13. The vaccine according to any of embodiments A7 to A12, wherein the at least one betacoronavirus epitope is the RBD.
14. The vaccine according to any of embodiments A7 to A12, wherein the at least one betacoronavirus epitope is the HR1 domain or the HR2 domain, preferably the HR2 domain.
- 20 15. The vaccine according to any of embodiments A7 to A14, wherein the at least one betacoronavirus epitope is a B cell epitope comprised in the viral surface protein or part thereof.
- 25 16. The vaccine according to any of embodiments A7 to A15, wherein the antigenic unit comprises multiple B cell epitopes comprised in the viral surface protein or part thereof.
- 30 17. The vaccine according to any of embodiments A1 to A6, wherein the at least one betacoronavirus epitope is a T cell epitope.
18. The vaccine according to embodiment A17, wherein the T cell epitope is conserved between different species and/or different strains of betacoronaviruses.
- 35

19. The vaccine according to any of embodiments A17 or A18, wherein the T cell epitope is conserved between SARS-Cov2 and SARS-CoV.
20. The vaccine according to any of embodiments A17 to A19, wherein the T cell epitope has a length suitable for presentation by HLA class I/II alleles, preferably a length of from 7 to 30 amino acids.
21. The vaccine according to any of embodiments A17 to A20, wherein the T cell epitope is selected based on the predicted ability to bind to HLA class I/II alleles.
22. The vaccine according to any of embodiments A17 to A21, wherein the antigenic unit includes multiple T cell epitopes, preferably multiple T cell epitopes that are predicted to bind to HLA class I/II alleles.
23. The vaccine according to any of embodiments A17 to A22, wherein the T cell epitope is selected from the list consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO: 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO: 81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO: 86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO: 91, SEQ ID NO: 92, SEQ ID NO:

93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO: 96, SEQ ID NO: 97, SEQ ID NO:
98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID
NO: 103, SEQ ID NO: 104, SEQ ID NO: 105, SEQ ID NO: 106, SEQ ID NO: 107,
SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID NO: 110, SEQ ID NO: 111, SEQ ID
5 NO: 112, SEQ ID NO: 113, SEQ ID NO: 114, SEQ ID NO: 115, SEQ ID NO: 116,
SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID NO: 119, SEQ ID NO: 120, SEQ ID
NO: 121, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 124, SEQ ID NO: 125,
SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID
NO: 130, SEQ ID NO: 131, SEQ ID NO: 132, SEQ ID NO: 133, SEQ ID NO: 134,
10 SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID NO: 137, SEQ ID NO: 138, SEQ ID
NO: 139, SEQ ID NO: 140, SEQ ID NO: 141, SEQ ID NO: 142, SEQ ID NO: 143,
SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID NO: 146, SEQ ID NO: 147, SEQ ID
NO: 148, SEQ ID NO: 149, SEQ ID NO: 150, SEQ ID NO: 151, SEQ ID NO: 152,
SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID NO: 155, SEQ ID NO: 156, SEQ ID
15 NO: 157, SEQ ID NO: 158, SEQ ID NO: 159, SEQ ID NO: 160, SEQ ID NO: 161,
SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID NO: 164, SEQ ID NO: 165, SEQ ID
NO: 166, SEQ ID NO: 167, SEQ ID NO: 168, SEQ ID NO: 169, SEQ ID NO: 170,
SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID NO: 173, SEQ ID NO: 174, SEQ ID
NO: 175, SEQ ID NO: 176, SEQ ID NO: 177, SEQ ID NO: 178, SEQ ID NO: 179,
20 SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID NO: 182, SEQ ID NO: 183, SEQ ID
NO: 184, SEQ ID NO: 185, SEQ ID NO: 186, SEQ ID NO: 187, SEQ ID NO: 188,
SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID NO: 191, SEQ ID NO: 192, SEQ ID
NO: 193, SEQ ID NO: 194, SEQ ID NO: 195, SEQ ID NO: 196, SEQ ID NO: 197,
SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID NO: 200, SEQ ID NO: 201, SEQ ID
25 NO: 202, SEQ ID NO: 203, SEQ ID NO: 204, SEQ ID NO: 205, SEQ ID NO: 206,
SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID NO: 209, SEQ ID NO: 210, SEQ ID
NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215,
SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID
NO: 220, SEQ ID NO: 221, SEQ ID NO: 222, SEQ ID NO: 223.

30

24. The vaccine according to any of embodiments A17 to A23, wherein the T cell
epitope is selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ
ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ
ID NO: 22, SEQ ID NO: 87, SEQ ID NO: 62, SEQ ID NO: 39, SEQ ID NO: 59, SEQ
35 ID NO: 26, SEQ ID NO: 53, SEQ ID NO: 32, SEQ ID NO: 38, SEQ ID NO: 30, SEQ

ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 35, SEQ ID NO: 71, SEQ ID NO: 9, SEQ ID NO: 21, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ ID NO: 20.

- 5 25. The vaccine according to any of embodiments A17 to A24, wherein the T cell epitope is selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87 and SEQ ID NO: 62.
- 10 26. The vaccine according to any of preceding embodiments A17 to A25, wherein the antigenic unit comprises multiple T cell epitopes.
- 15 27. The vaccine according to any of embodiments A17 to A26, wherein said antigenic unit further comprises a full-length viral surface protein of a betacoronavirus or a part thereof.
- 20 28. The vaccine according to embodiment A27, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.
- 25 29. The vaccine according to any of embodiments A27 or A28, wherein the viral surface protein is the spike protein.
- 30 30. The vaccine according to any of embodiments A27 to A29, wherein the viral surface protein is the full-length spike protein.
- 35 31. The vaccine according to any of embodiments A27 to A30, wherein the viral surface protein is a part of the spike protein.
- 40 32. The vaccine according to any of embodiments A27 to A31, wherein said antigenic unit further comprises a part of the spike protein selected from the group consisting of receptor binding domain (RBD), heptad repeat 1 (HR1) domain and heptad repeat 2 (HR2) domain.

33. The vaccine according to any of embodiments A27 to A32, wherein said antigenic unit further comprises the RBD.
- 5 34. The vaccine according to any of embodiments A27 to A33, wherein said antigenic unit further comprises the HR1 domain or the HR2 domain, preferably the HR2 domain.
- 10 35. The vaccine according to any of embodiments A27 to A34, wherein said antigenic unit further comprises a B cell epitope comprised in the viral surface protein or part thereof.
36. The vaccine according to any of embodiments A27 to A35, wherein said antigenic unit further comprises multiple B cell epitopes comprised in the viral surface protein or part thereof.
- 15 37. The vaccine according to any of the preceding embodiments, wherein the antigenic unit comprises from 21 to 2000 amino acids, preferably from about 30 amino acids to about a 1500 amino acids, more preferably from about 50 to about 1000 amino acids, such as from about 100 to about 500 amino acids or from about 100 to about 400 amino acids or from about 100 to about 300 amino acids.
- 20 38. The vaccine according to any of the preceding embodiments, wherein the antigenic unit comprises one or more linkers, preferably one or more non-immunogenic and/or flexible linkers.
39. The vaccine according to any of the preceding embodiments, wherein the antigenic unit comprises 10, 20, 30 or 50 epitopes, preferably T cell epitopes.
- 25 40. The vaccine according to any of the preceding embodiments, wherein said targeting unit comprises antibody binding regions with specificity for surface receptors on antigen presenting cells (APCs), preferably CD14, CD40, Toll- like receptor, CCR1, CCR3, CCR5, MHC class I proteins or MHC class II proteins.
- 30 41. The vaccine according to any of the preceding embodiments, wherein the targeting unit has affinity for a chemokine receptor selected from CCR1, CCR3 and CCR5.

42. The vaccine according to any of the preceding embodiments, wherein said targeting unit has an affinity for MHC class II proteins, preferably MHC class II proteins, selected from the group consisting of anti-HLA-DP, anti-HLA-DR and anti-pan HLA class II.
- 5 43. The vaccine according to any of the preceding embodiments, wherein the targeting unit is selected from anti-pan HLA class II and MIP-1 α .
44. The vaccine according to any of the preceding embodiments, wherein the targeting unit is MIP-1 α .
- 10 45. The vaccine according to any of the preceding embodiments, wherein the targeting unit is anti-pan HLA class II.
46. The vaccine according to any of the preceding embodiments, wherein the dimerization unit comprises a hinge region and optionally another domain that facilitates dimerization, optionally connected through a linker.
- 15 47. The vaccine according to any of the preceding embodiments, wherein said polynucleotide further encodes a signal peptide.
48. The vaccine according to any of the preceding embodiments, wherein said targeting unit, dimerization unit and antigenic unit in said peptide are in the N-terminal to C-terminal order of targeting unit, dimerization unit and antigenic unit.
- 20 49. The vaccine according to any of the preceding embodiments, wherein said betacoronavirus is one selected from the group consisting of SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 and HCoV-HKU1, preferably selected from the group consisting of SARS-CoV and SARS-CoV2.
- 25 50. A polynucleotide as defined in any of the embodiments A1-A49.
51. A vector comprising the polynucleotide according to embodiment A50.
52. A host cell comprising the polynucleotide according to embodiment A50 or comprising the vector according to embodiment A51.

53. The polynucleotide according to embodiment A50 formulated for administration to a human individual.
54. A polypeptide encoded by the polynucleotide sequence according to embodiment A50.
- 5 55. A dimeric protein consisting of two polypeptides according to embodiment A54.
56. The dimeric protein according to embodiment A55, being a homodimeric protein.
57. The polynucleotide according to embodiment A50 or the polypeptide according to embodiment 53 or the dimeric protein according to any of embodiments A55 or A56 for use as a medicament.
- 10 58. The polynucleotide according to embodiment A50 or the polypeptide according to embodiment A54 or the dimeric protein according to any of embodiments A55 or A56 for use in the treatment of an infection with a betacoronavirus or for use in the prevention of a betacoronavirus infection.
- 15 59. The polynucleotide according to embodiment A50 or the polypeptide according to embodiment 54 or the dimeric protein according to any of embodiments 55 or 56 for use in the treatment of an infection or for use in the prevention of an infection with SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 or HCoV-HKU1, preferably SARS-CoV or SARS-CoV2.
- 20 60. A method of preparing a vaccine according to any one of the preceding embodiments A1 to A49, wherein said method comprises:
- a) transfecting cells with the polynucleotide as defined in any of the embodiments A1-A49;
 - b) culturing the cells;
 - c) collecting and purifying the dimeric protein or the polypeptide expressed from the cells; and
 - d) mixing the dimeric protein or polypeptide obtained from step c) with a pharmaceutically acceptable carrier.
- 25
- 30 61. A polypeptide comprising an amino acid sequence from the list consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID

NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO:
11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO:
16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO:
21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO:
5 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO:
31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO:
36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO:
41, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO:
46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO:
10 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO:
56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO:
61, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO:
66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO:
71, SEQ ID NO: 72, SEQ ID NO: 73, SEQ ID NO: 74, SEQ ID NO: 75, SEQ ID NO:
15 76, SEQ ID NO: 77, SEQ ID NO: 78, SEQ ID NO: 79, SEQ ID NO: 80, SEQ ID NO:
81, SEQ ID NO: 82, SEQ ID NO: 83, SEQ ID NO: 84, SEQ ID NO: 85, SEQ ID NO:
86, SEQ ID NO: 87, SEQ ID NO: 88, SEQ ID NO: 89, SEQ ID NO: 90, SEQ ID NO:
91, SEQ ID NO: 92, SEQ ID NO: 93, SEQ ID NO: 94, SEQ ID NO: 95, SEQ ID NO:
96, SEQ ID NO: 97, SEQ ID NO: 98, SEQ ID NO: 99, SEQ ID NO: 100, SEQ ID
20 NO: 101, SEQ ID NO: 102, SEQ ID NO: 103, SEQ ID NO: 104, SEQ ID NO: 105,
SEQ ID NO: 106, SEQ ID NO: 107, SEQ ID NO: 108, SEQ ID NO: 109, SEQ ID
NO: 110, SEQ ID NO: 111, SEQ ID NO: 112, SEQ ID NO: 113, SEQ ID NO: 114,
SEQ ID NO: 115, SEQ ID NO: 116, SEQ ID NO: 117, SEQ ID NO: 118, SEQ ID
NO: 119, SEQ ID NO: 120, SEQ ID NO: 121, SEQ ID NO: 122, SEQ ID NO: 123,
25 SEQ ID NO: 124, SEQ ID NO: 125, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID
NO: 128, SEQ ID NO: 129, SEQ ID NO: 130, SEQ ID NO: 131, SEQ ID NO: 132,
SEQ ID NO: 133, SEQ ID NO: 134, SEQ ID NO: 135, SEQ ID NO: 136, SEQ ID
NO: 137, SEQ ID NO: 138, SEQ ID NO: 139, SEQ ID NO: 140, SEQ ID NO: 141,
SEQ ID NO: 142, SEQ ID NO: 143, SEQ ID NO: 144, SEQ ID NO: 145, SEQ ID
30 NO: 146, SEQ ID NO: 147, SEQ ID NO: 148, SEQ ID NO: 149, SEQ ID NO: 150,
SEQ ID NO: 151, SEQ ID NO: 152, SEQ ID NO: 153, SEQ ID NO: 154, SEQ ID
NO: 155, SEQ ID NO: 156, SEQ ID NO: 157, SEQ ID NO: 158, SEQ ID NO: 159,
SEQ ID NO: 160, SEQ ID NO: 161, SEQ ID NO: 162, SEQ ID NO: 163, SEQ ID
NO: 164, SEQ ID NO: 165, SEQ ID NO: 166, SEQ ID NO: 167, SEQ ID NO: 168,
35 SEQ ID NO: 169, SEQ ID NO: 170, SEQ ID NO: 171, SEQ ID NO: 172, SEQ ID

NO: 173, SEQ ID NO: 174, SEQ ID NO: 175, SEQ ID NO: 176, SEQ ID NO: 177,
 SEQ ID NO: 178, SEQ ID NO: 179, SEQ ID NO: 180, SEQ ID NO: 181, SEQ ID
 NO: 182, SEQ ID NO: 183, SEQ ID NO: 184, SEQ ID NO: 185, SEQ ID NO: 186,
 SEQ ID NO: 187, SEQ ID NO: 188, SEQ ID NO: 189, SEQ ID NO: 190, SEQ ID
 5 NO: 191, SEQ ID NO: 192, SEQ ID NO: 193, SEQ ID NO: 194, SEQ ID NO: 195,
 SEQ ID NO: 196, SEQ ID NO: 197, SEQ ID NO: 198, SEQ ID NO: 199, SEQ ID
 NO: 200, SEQ ID NO: 201, SEQ ID NO: 202, SEQ ID NO: 203, SEQ ID NO: 204,
 SEQ ID NO: 205, SEQ ID NO: 206, SEQ ID NO: 207, SEQ ID NO: 208, SEQ ID
 NO: 209, SEQ ID NO: 210, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213,
 10 SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID
 NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 221, SEQ ID NO: 222,
 SEQ ID NO: 223.

62. A polypeptide comprising an amino acid sequence from the list consisting of SEQ
 15 ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ
 ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87, SEQ ID NO: 62, SEQ
 ID NO: 39, SEQ ID NO: 59, SEQ ID NO: 26, SEQ ID NO: 53, SEQ ID NO: 32, SEQ
 ID NO: 38, SEQ ID NO: 30, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 35, SEQ
 ID NO: 71, SEQ ID NO: 9, SEQ ID NO: 21, SEQ ID NO: 85, SEQ ID NO: 75, SEQ
 20 ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ ID NO: 20.

63. A polypeptide comprising an amino acid sequence from the list consisting of SEQ
 ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ
 ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87 and SEQ ID NO: 62.

Embodiments B

1. A vaccine comprising an immunologically effective amount of:
 - (iv) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope; or
 - (v) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (vi) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); anda pharmaceutically acceptable carrier.
2. The vaccine according to embodiment B1, wherein the at least one betacoronavirus epitope is a full-length viral surface protein of a betacoronavirus or a part thereof.
3. The vaccine according to embodiment B2, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.
4. The vaccine according to any of embodiments B2 to B3 wherein the at least one betacoronavirus epitope comprises or is the spike protein.
5. The vaccine according to any of embodiments B2 to B4, wherein the at least one betacoronavirus epitope comprises or is the full-length spike protein.
6. The vaccine according to embodiment B5, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 230, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
7. The vaccine according to embodiment B5, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 1437 of SEQ ID

5 NO: 275, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

8. The vaccine according to any of embodiments B2 to B4 wherein the at least one betacoronavirus epitope comprises or is a part of the spike protein.

10 9. The vaccine according to embodiment B8, wherein the part of the spike protein is one selected from the group consisting of receptor binding domain (RBD), heptad repeat 1 (HR1) domain and heptad repeat 2 (HR2) domain.

10. The vaccine according to embodiment B9, wherein the at least one betacoronavirus epitope comprises or is the RBD or part of the RBD.

15 11. The vaccine according to embodiment B10, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

25 12. The vaccine according to embodiment B10, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

30 13. The vaccine according to embodiment B10, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having

5 at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

14. The vaccine according to any of embodiments B10 to B13, wherein the antigenic unit comprises multiple copies of the RBD or parts thereof which copies are identical or differ in their amino acid sequences.

10 15. The vaccine according to embodiment B14, wherein the antigenic unit comprises of from 1 to 5 copies.

16. The vaccine according to embodiment B8, wherein the at least one betacoronavirus epitope comprises or is the HR1 domain or the HR2 domain, preferably the HR2 domain.

15 17. The vaccine according to any of embodiments B2 to B16, wherein the at least one betacoronavirus epitope is a B cell epitope comprised in the viral surface protein or a part thereof.

20 18. The vaccine according to any of embodiments B2 to B17, wherein the antigenic unit comprises multiple B cell epitopes comprised in the viral surface protein or a part thereof.

19. The vaccine according to embodiment B1, wherein the at least one betacoronavirus epitope is a T cell epitope.

25 20. The vaccine to embodiment B19, wherein the antigenic unit comprises multiple T cell epitopes.

21. The vaccine according to any of embodiments B19 to B20, wherein the T cell epitope is comprised in a structural protein or in a non-structural protein.

22. The according to any of embodiments B19 to B21 wherein the T cell epitope is comprised in a surface protein, in the nucleocapsid protein or in a replicase polyprotein.
- 5 23. The vaccine according to any of embodiments B19 to B22, wherein the T cell epitope is conserved between different genus and/or species and/or strains of betacoronaviruses.
- 10 24. The vaccine according to any of embodiments B19 to B23, wherein the T cell epitope is conserved between SARS-Cov2 and SARS-CoV.
- 15 25. The vaccine according to any of embodiments B19 to B24, wherein the T cell epitope has a length of from 7 to about 200 amino acids, preferably of from 7 to 100 amino acids or the T cell epitope has a length suitable for presentation by HLA class I/II alleles, preferably a length of from 7 to 30 amino acids, more preferably a length of from 8 to 15 amino acids.
- 20 26. The vaccine according to any of embodiments B19 to B25, wherein the T cell epitope is known to be immunogenic or is selected based on the predicted ability to bind to HLA class I/II alleles.
- 25 27. The vaccine according to any of embodiments B19 to B26, wherein the antigenic unit comprises multiple T cell epitopes that are known to be immunogenic or predicted to bind to HLA class I/II alleles.
- 30 28 The vaccine according to any of embodiments B19 to B27, wherein the T cell epitope is selected from epitopes having an amino acid sequence of any of SEQ ID NO: 1 to SEQ ID NO: 444.
- 35 29. The vaccine according to embodiment B28, wherein the T cell epitope is selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87, SEQ ID NO: 62, SEQ ID NO: 39, SEQ ID NO: 59, SEQ ID NO: 26, SEQ ID NO: 53, SEQ ID NO: 32, SEQ ID NO: 38, SEQ ID NO: 30, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 35, SEQ ID NO: 71, SEQ ID NO: 9, SEQ ID NO:

21, SEQ ID NO: 85, SEQ ID NO: 75, SEQ ID NO: 23, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 77 and SEQ ID NO: 20.

5 30. The vaccine according to embodiment B28, wherein the T cell epitope is selected from the list consisting of SEQ ID NO: 67, SEQ ID NO: 19, SEQ ID NO: 78, SEQ ID NO: 57, SEQ ID NO: 50, SEQ ID NO: 55, SEQ ID NO: 64, SEQ ID NO: 22, SEQ ID NO: 87 and SEQ ID NO: 62.

10 31. The vaccine according to any of embodiments B19 to B27, wherein the T cell epitope is selected from T cell epitopes that are comprised in the antigenic unit having an amino acid sequence of SEQ ID NO: 245, wherein the sequence GGGGSGGGGS is a linker and not a T cell epitope.

15 32. The vaccine according to any of embodiments B19 to B27, wherein the T cell epitope is selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWVMRIMTW, FLNRFTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYPSARIVYTACSHAAV, YFIKGLNNLNRMV, YLNTLT LAVPYNMRV, AQFAPSASAFFGMSRI, 20 EIVDTV SALVYDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVL SVNPYV, MLSDTLKNLS DRVVFVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV, FAYANRNRFLYIIKL and LVKPSFYVYSRVKNL.

25 33. The vaccine according to any of embodiments B19 to B27, wherein the antigenic unit comprises one or more T cell epitopes selected from the list consisting of RAMPNMLRIMASLVL, HVISTSHKLVL SVNPYV and LVKPSFYVYSRVKNL.

30 34. The vaccine according to any of embodiment B19 to B33, wherein the antigenic unit further comprises at least one betacoronavirus epitope which is a full-length viral surface protein of a betacoronavirus or a part thereof.

35. The vaccine according to embodiment B34, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.

5 36. The vaccine according to any of embodiments B34 to B35 wherein the at least one betacoronavirus epitope comprises or is the spike protein.

37. The vaccine according to any of embodiments B34 to B36, wherein the at least one betacoronavirus epitope comprises or is the full-length spike protein.

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38. The vaccine according to embodiment B37, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 230, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

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39. The vaccine according to embodiment B37, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 1437 of SEQ ID NO: 275, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

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40. The vaccine according to any of embodiments B34 to B36 wherein the at least one betacoronavirus epitope comprises or is a part of the spike protein.

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41. The vaccine according to embodiment B40, wherein the part of the spike protein is one selected from the group consisting of receptor binding domain (RBD), heptad repeat 1 (HR1) domain and heptad repeat 2 (HR2) domain.

35

42 The vaccine according to embodiment 41, wherein the at least one betacoronavirus epitope comprises or is the RBD.

5 43. The vaccine according to embodiment B42, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

15 44 The vaccine according to embodiment B42, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

25 45 The vaccine according to embodiment B42, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

35 46. The vaccine according to any of embodiments B42 to B45, wherein the antigenic unit comprises multiple copies of the RBD or parts thereof which copies are identical or differ in their amino acid sequences.

47. The vaccine according to embodiment B46, wherein the antigenic unit comprises of from 1 to 5 copies.

5 48. The vaccine according to embodiment B40, wherein the at least one betacoronavirus epitope comprises or is the HR1 domain or the HR2 domain, preferably the HR2 domain.

49. The vaccine according to any of embodiments B34 to B48, wherein the at least one betacoronavirus epitope is a B cell epitope comprised in the viral surface protein or a part thereof.

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50. The vaccine according to any of embodiments B34 to B49, wherein the antigenic unit comprises multiple B cell epitopes comprised in the viral surface protein or a part thereof.

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51. The vaccine according to embodiment B34, wherein the antigenic unit comprises a T cell epitope selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWVMRIMTW, FLNRFTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYPSARIVYTACSHAAV, YFIKGLNNLNRMV, YLNTLT LAVPYNMRV, AQFAPSASAFFGMSRI, EIVDTV SALVYDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVL SVN PYV, MLSDTLKNLS DRV FVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV, FAYANRNRFLYIIKL and LVKPSFYVYSRVKN and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

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52. The vaccine according to embodiment B34, wherein the antigenic unit comprises a T cell epitope selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWVMRIMTW, FLNRFTTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYP SARIVYTACSHAAV, YFIKGLNNLN RGMVL, YLNTLT LAVPYNMRV, AQFAPSASAFFGMSRI, EIVDTV SALVYDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVL SVNPYV, MLSDTLKNLS DRVVFVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV, FAYANRNRFLYIIKL and LVKPSFYVYSRVKN and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

53. The vaccine according to embodiment B34, wherein the antigenic unit comprises a T cell epitope selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWVMRIMTW, FLNRFTTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYP SARIVYTACSHAAV, YFIKGLNNLN RGMVL, YLNTLT LAVPYNMRV, AQFAPSASAFFGMSRI, EIVDTV SALVYDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVL SVNPYV, MLSDTLKNLS DRVVFVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV, FAYANRNRFLYIIKL and LVKPSFYVYSRVKN and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

54. The vaccine according to embodiment B34, wherein the antigenic unit comprises a T cell epitope selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWVMRIMTW, FLNRFTTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYP SARIVYTACSHAAV, YFIKGLNNLNRGMVL, YLNTLT LAVPYNMRV, AQFAPSASAFFGMSRI, EIVDTV SALVYDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVL SVNPYV, MLSDTLKNLS DRVVFVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV, FAYANRRNFLYIIKL and LVKPSFYVYSRVKN and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
55. The vaccine according to embodiment B34, wherein the antigenic unit comprises one or more T cell epitopes selected from the list consisting of RAMPNMLRIMASLVL, HVISTSHKLVL SVNPYV and LVKPSFYVYSRVKNL and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
56. The vaccine according to embodiment B34, wherein the antigenic unit comprises one or more T cell epitopes selected from the list consisting of RAMPNMLRIMASLVL, HVISTSHKLVL SVNPYV and LVKPSFYVYSRVKNL and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such

as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%,
such as at least 90%, such as at least 91%, such as at least 92%, such as at least
93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at
least 97%, such as at least 98% or such as at least 99% sequence identity or such
as 100% sequence identity.

57. The vaccine according to any of the preceding embodiments, wherein the
antigenic unit comprises up to 3500 amino acids, such as from 21 to 3500 amino
acids, preferably from about 30 amino acids to about 2000 amino acids such as
from about 50 to about 1500 amino acids, more preferably from about 100 to about
1500 amino acids, such as from about 100 to about 1000 amino acids or from
about 100 to about 500 amino acids or from about 100 to about 300 amino acids.

58. The vaccine according to any of the preceding embodiments, wherein the
antigenic unit comprises one or more linkers, preferably one or more non-
immunogenic and/or flexible linkers.

59. The vaccine according to embodiment B58, wherein the antigenic unit
comprises multiple T cell epitopes which are separated by a non-immunogenic
and/or flexible linker, preferably a linker consisting of from 4 to 20 amino acids, e.g.
from 5 to 20 amino acids or 5 to 15 amino acids or 8 to 20 amino acids or 8 to 15
amino acids 10 to 15 amino acids or 8 to 12 amino acids, more preferably a linker
selected from the group consisting of serine and/or glycine rich linker which
optionally comprises at least one leucine residue, GSAT liker and SEG linker.

60. The vaccine according to embodiment B58, wherein the antigenic unit
comprises at least one T cell epitope and a full-length protein of the
betacoronavirus, or a part thereof, the at least one T cell epitope and the full-length
protein of the betacoronavirus or the part thereof are separated by a non-
immunogenic and/or flexible linker, preferably a linker consisting of from 10 to 60
amino acids, e.g. from 11 to 50 amino acids or 20 to 50 amino acids or 25 to 45
amino acids or 12 to 45 amino acids or 13 to 40 amino acids or 30 to 40 amino
acids, more preferably a linker selected from the group consisting of serine and/or
glycine rich linker which optionally comprises at least one leucine residue,
TQKSLSLSPGKGLGGL, SLSLSPGKGLGGL, GSAT liker such as

GGSAGGSGSGSSGGSSGASGTGTAGGTGSGSGTGSG and SEG linker such as GGSGGGSEGGGSEGGGSEGGGSEGGGSEGGGSGGGS.

61. The vaccine according to any of the preceding embodiments, wherein the antigenic unit comprises 10, 20, 30, 40 or 50 epitopes, preferably T cell epitopes.

5 62. The vaccine according to any of the preceding embodiments, wherein said targeting unit comprises antibody binding regions with specificity for surface molecules or receptors on antigen presenting cells (APCs), preferably specificity for CD14, CD40, Toll- like receptor, CCR1, CCR3, CCR5, MHC class I proteins or MHC class II proteins.

10 63. The vaccine according to any of the preceding embodiments, wherein the targeting unit has affinity for a chemokine receptor selected from CCR1, CCR3 and CCR5.

64. The vaccine according to any of embodiments B62 to B63, wherein said targeting unit has affinity for MHC class II proteins, preferably MHC class II proteins selected from the group consisting of anti-HLA-DP, anti-HLA-DR and anti-pan HLA class II.

65. The vaccine according to any of the preceding embodiments, wherein the targeting unit is selected from anti-pan HLA class II and MIP-1 α and preferably selected from anti-pan HLA class II and human MIP-1 α .

66. The vaccine according to embodiment B65, wherein the targeting unit is MIP-1 α , preferably human MIP-1 α .

25 67. The vaccine according to embodiment B66, wherein the targeting unit comprises or consists of an amino acid sequence having at least 85% sequence identity to the amino acid sequence 24-93 of SEQ ID NO: 233, such as at least 86% or at least 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, at least 99% or 100% sequence identity.

68. The vaccine according to embodiment B65, wherein the targeting unit is anti-pan HLA class II.

- 5 69. The vaccine according to embodiment B68, wherein the targeting unit comprises an amino acid sequence having at least 85% sequence identity to the amino acid sequence 20-260 of SEQ ID NO: 321, such as at least 86% or at least 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, at least 99% or 100% sequence identity.
70. The vaccine according to any of the preceding embodiments, wherein the dimerization unit comprises a hinge region.
71. The vaccine according to embodiment B70, wherein the hinge region has the ability to form one or more covalent bonds.
- 10 72. The vaccine according to any of embodiments B70 to B71, wherein the hinge region is Ig derived.
73. The vaccine according to any of embodiments B70 to B72, wherein the dimerization unit further comprises another domain that facilitates dimerization.
- 15 74. The vaccine according to embodiment B73, wherein the other domain is an immunoglobulin domain, preferably an immunoglobulin constant domain.
75. The vaccine according to any of embodiments B73 and B74, wherein the other domain is a carboxyterminal C domain derived from IgG, preferably from IgG3.
76. The vaccine according to any of embodiments B70 to B75, wherein the dimerization unit further comprises a dimerization unit linker.
- 20 77. The vaccine according to embodiment B76, wherein the dimerization unit linker connects the hinge region and the other domain that facilitates dimerization.
78. The vaccine according to any of embodiments B70 to B77, wherein the dimerization unit comprises hinge exon h1 and hinge exon h4, a dimerization unit linker and a CH3 domain of human IgG3.
- 25 79. The vaccine according to embodiment B78, wherein the dimerization unit comprises or consists of an amino acid sequence having at least 85% sequence identity to the amino acid sequence 94 to 237 of SEQ ID NO: 233, such as at least

86% or at least 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, at least 99% or 100% sequence identity.

80. The vaccine according to any of the preceding embodiments, wherein the vaccine comprises the polynucleotide (i).

5 81. The vaccine according to embodiment B80, wherein the polynucleotide is an RNA or DNA, preferably a DNA.

82. The vaccine according to any of embodiments B80 to B81, wherein the polynucleotide further comprises a nucleotide sequence encoding a signal peptide.

10 83. The vaccine according to embodiment B82, wherein the signal peptide is an Ig VH signal peptide, a human TPA signal peptide or a human MIP1- α signal peptide.

84. The vaccine according to embodiment B83, wherein the signal peptide comprises or consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%,
15 such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, such as at least 99% or 100% sequence identity to the amino acid sequence 1-23 of SEQ ID NO: 233.

85. The vaccine according to embodiment B84, wherein the targeting unit is human MIP-1 α .

20 86. The vaccine according to embodiment B83, wherein the signal peptide comprises or consists of an amino acid sequence having at least 85%, such as at least 86%, such as at least 87%, such as at least 88%, such as at least 89%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least
25 97%, such as at least 98%, such as at least 99% or 100% sequence identity to the amino acid sequence 1-19 of SEQ ID NO: 321.

87. The vaccine according to embodiment B86, wherein the targeting unit is anti-pan HLA class II.

88. The vaccine according to any of the preceding embodiments, wherein the vaccine comprises the polypeptide or the dimeric protein and said targeting unit, dimerization unit and antigenic unit in said peptide or dimeric protein are in the N-terminal to C-terminal order of targeting unit, dimerization unit and antigenic unit.
- 5 89. The vaccine according to any of the preceding embodiments, wherein said betacoronavirus is one selected from the group consisting of SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 and HCoV-HKU1, preferably selected from the group consisting of SARS-CoV and SARS-CoV.
- 10 90. The vaccine according to embodiment B89, wherein said betacoronavirus is SARS-CoV-2.
91. The vaccine according to any of the preceding embodiments, wherein the pharmaceutically acceptable carrier is selected from the group consisting of saline, buffered saline, PBS, dextrose, water, glycerol, ethanol, sterile isotonic aqueous buffers, and combinations thereof.
- 15 92. A polynucleotide as defined in any of the embodiments B1 to B90.
93. A vector comprising the polynucleotide according to embodiment B92.
94. A host cell comprising the polynucleotide as defined in any of the embodiments B1 to B90 or comprising the vector according to embodiment B93.
95. A polypeptide encoded by the polynucleotide as defined in embodiment B92.
- 20 96. A dimeric protein consisting of two polypeptides as defined in embodiment B95.
97. The dimeric protein according to embodiment B96, wherein the dimeric protein is a homodimeric protein.
98. The polynucleotide according to embodiment B92 or the polypeptide according to embodiment B95 or the dimeric protein according to any of embodiments B96 or B97 for use as a medicament.
- 25 99. The polynucleotide according to embodiment B92 or the polypeptide according to embodiment B95 or the dimeric protein according to any of embodiments B96 or

B97 for use in the treatment of an infection with a betacoronavirus or for use in the prevention of a betacoronavirus infection.

100. The polynucleotide according to embodiment B92 or the polypeptide according to embodiment B95 or the dimeric protein according to any of
5 embodiments B96 or B97 for use in the treatment of an infection or for use in the prevention of an infection with SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 or HCoV-HKU1, preferably SARS-CoV or SARS-CoV, more preferably SARS-CoV-2.

101. A method of preparing the vaccine according to any one of the preceding
10 embodiments B1 to B79 and B88 to B91, wherein the vaccine comprises the polypeptide or the dimeric protein, wherein said method comprises:
a) transfecting cells with the polynucleotide as defined in any of the embodiments B1 to B90;
b) culturing the cells;
15 c) collecting and purifying the dimeric protein or the polypeptide expressed from the cells; and
d) mixing the dimeric protein or polypeptide obtained from step c) with the pharmaceutically acceptable carrier.

20 102. A method for preparing the vaccine according to any one of the preceding embodiments B1 to B87 and B89 to B91, wherein the vaccine comprises the polynucleotide, the method comprises:
a) preparing the polynucleotide;
b) optionally cloning the polynucleotide into an expression vector; and
25 c) mixing the polynucleotide obtained from step a) or the vector obtained from step b) with the pharmaceutically acceptable carrier.

103. A method for treating a subject having suffering from a betacoronavirus infection or being in need of prevention thereof, the method comprising
30 administering to the subject the vaccine as defined in any of embodiments B1 to B91.

104. A vaccine as defined in any of embodiments B1 to B91 for use in the treatment of an infection with a betacoronavirus or for use in the prevention of a betacoronavirus infection.

Claims

1. A vaccine comprising an immunologically effective amount of:
- (i) a polynucleotide comprising a nucleotide sequence encoding a targeting unit, a dimerization unit and an antigenic unit, wherein the antigenic unit comprises at least one betacoronavirus epitope; or
 - (ii) a polypeptide encoded by the polynucleotide as defined in (i), or
 - (iii) a dimeric protein consisting of two polypeptides encoded by the polynucleotide as defined in (i); and
- a pharmaceutically acceptable carrier.
2. The vaccine according to claim 1, wherein the at least one betacoronavirus epitope is a full-length viral surface protein of a betacoronavirus or a part thereof.
3. The vaccine according to claim 2, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.
4. The vaccine according to any of claims 2 to 3 wherein the at least one betacoronavirus epitope comprises or is the spike protein.
5. The vaccine according to any of claims 2 to 4, wherein the at least one betacoronavirus epitope comprises or is the full-length spike protein.
6. The vaccine according to claim 5, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 1437 of SEQ ID NO: 275, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
7. The vaccine according to any of claims 2 to 4, wherein the at least one betacoronavirus epitope comprises or is a part of the spike protein.

8. The vaccine according to claim 7, wherein the part of the spike protein is one selected from the group consisting of receptor binding domain (RBD), heptad repeat 1 (HR1) domain and heptad repeat 2 (HR2) domain.
9. The vaccine according to claim 8, wherein the at least one betacoronavirus epitope comprises or is the RBD or a part of the RBD.
10. The vaccine according to claim 9, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
11. The vaccine according to claim 9, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
12. The vaccine according to claim 9, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
13. The vaccine according to any of claims 9 to 12, wherein the antigenic unit comprises multiple copies of the RBD or parts thereof which copies are identical or differ in their amino acid sequences.

14. The vaccine according to any of claims 2 to 13, wherein the at least one betacoronavirus epitope is a B cell epitope comprised in the viral surface protein or a part thereof.
- 5 15. The vaccine according to any of claims 2 to 14, wherein the antigenic unit comprises multiple B cell epitopes comprised in the viral surface protein or a part thereof.
16. The vaccine according to claim 1, wherein the at least one betacoronavirus epitope is a T cell epitope.
- 10 17. The vaccine to claim 16, wherein the antigenic unit comprises multiple T cell epitopes.
18. The vaccine according to any of claims 16 to 17, wherein the T cell epitope is conserved between different genus and/or species and/or strains of betacoronaviruses, preferably between SARS-Cov2 and SARS-CoV.
- 15 19. The vaccine according to any of claims 16 to 18, wherein the T cell epitope has a length of from 7 to about 200 amino acids, preferably of from 7 to 100 amino acids or the T cell epitope has a length suitable for presentation by HLA class I/II alleles, preferably a length of from 7 to 30 amino acids, more preferably a length of from 8 to 15 amino acids..
- 20 20. The vaccine according to any of claims 16 to 19, wherein the T cell epitope is known to be immunogenic or is selected based on the predicted ability to bind to HLA class I/II alleles.
- 21 The vaccine according to any of claims 16 to 20, wherein the T cell epitope is selected from epitopes having an amino acid sequence of any of SEQ ID NO: 1 to SEQ ID NO: 444.
- 25 22. The vaccine according to any of claims 16 to 20, wherein the T cell epitope is selected from the list consisting of RSFIEDLLFNKVTLA, MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWWMRIMTW, FLNRFTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYPSARIVYTACSHAAV, YFIKGLNNLNRMVL, YLNTLT LAVPYNMRV, 30 AQFAPSASAFFGMSRI, EIVDTV SALVYDNKL,

SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVLVSVNPYV,
 MLSDTLKNLSDRVVFVLWAHGFEL, TANPKTPKYK FVRIQPGQTF,
 ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTL MNVLT LVYKV,
 FAYANRNRFLYIIKL and LVKPSFYVYSRVKNL.

- 5 23. The vaccine according to any of claims 16 to 20, wherein the T cell epitope is selected from the list consisting of RAMPNMLRIMASLVL, HVISTSHKLVLVSVNPYV and LVKPSFYVYSRVKNL.
- 10 24. The vaccine according to any of claim 16 to 23, wherein the antigenic unit further comprises at least one betacoronavirus epitope which is a full-length viral surface protein of a betacoronavirus or a part thereof.
- 15 25. The vaccine according to claim 24, wherein the viral surface protein is selected from the group consisting of envelope protein, spike protein, membrane protein and hemagglutinin esterase.
- 20 26. The vaccine according to any of claims 24 to 25, wherein the at least one betacoronavirus epitope comprises or is the spike protein.
- 25 27. The vaccine according to any of claims 24 to 26, wherein the at least one betacoronavirus epitope comprises or is the full-length spike protein.
- 30 28. The vaccine according to claim 27, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 1437 of SEQ ID NO: 275, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.
29. The vaccine according to any of claims 24 to 26, wherein the at least one betacoronavirus epitope comprises or is a part of the spike protein.

30 The vaccine according to claim 29, wherein the at least one betacoronavirus epitope comprises or is the RBD or a part thereof.

5 31. The vaccine according to claim 30, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

15 32 The vaccine according to claim 30, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

25 33 The vaccine according to claim 30, wherein the at least one betacoronavirus epitope comprises or consists of an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 246, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

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34. The vaccine according to any of claims 30 to 33, wherein the antigenic unit comprises multiple copies of the RBD or parts thereof which copies are identical or differ in their amino acid sequences.

35. The vaccine according to any of claims 24 to 34, wherein the at least one betacoronavirus epitope is a B cell epitope comprised in the viral surface protein or a part thereof.

5 36. The vaccine according to any of claims 24 to 35, wherein the antigenic unit comprises multiple B cell epitopes comprised in the viral surface protein or a part thereof.

37. The vaccine according to claim 24, wherein the antigenic unit comprises a T cell epitope selected from the list consisting of RSFIEDLLFNKVTLA,
 10 MTYRRLISMMGFKMNYQVNGYPNMF, LMIERFVSLAIDAYP, RAMPNMLRIMASLVL, MVYMPASWWMRIMTW, FLNRFTTTLNDFNLVAM, SSVELKHFFFAQDGNAAI, HFAIGLALYYPSARIVYTACSHAAV, YFIKGLNNLNRMVL, YLNTLTAVPYNMRV, AQFAPSASAFFGMSRI, EIVDTVSAVLVDNKL, SSGDATTAYANSVFNICQAVTANVNALL, HVISTSHKLVLSVNPYV,
 15 MLSDTLKNLSDRVVFVLWAHGFEL, TANPKTPKYKFVRIQPGQTF, ASIKNFKSVLYYQNNVFM, FVNEFYAYLRKHFSMM, RVWTLNMVLTLYYKV, FAYANRNRFLYIIKL and LVKPSFYVYSRVKN and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 231 or SEQ ID NO: 802, or SEQ ID NO: 803 or SEQ ID NO: 804 or SEQ ID NO: 805, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

25 38. The vaccine according to claim 24, wherein the antigenic unit comprises one or more T cell epitopes selected from the list consisting of RAMPNMLRIMASLVL, HVISTSHKLVLSVNPYV and LVKPSFYVYSRVKNL and wherein the antigenic unit further comprises an amino acid sequence having at least 70% sequence identity to the amino acid sequence 243 to 465 of SEQ ID NO: 255, such as at least 75%, such as at least 77%, such as at least 80%, such as at least 85%, such as at least 90%, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at

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least 98% or such as at least 99% sequence identity or such as 100% sequence identity.

- 5 39. The vaccine according to any of the preceding claims, wherein the antigenic unit comprises up to 3500 amino acids, such as from 21 to 3500 amino acids, preferably from about 30 amino acids to about 2000 amino acids such as from about 50 to about 1500 amino acids, more preferably from about 100 to about 1500 amino acids, such as from about 100 to about 1000 amino acids or from about 100 to about 500 amino acids or from about 100 to about 300 amino acids.
- 10 40. The vaccine according to any of the preceding claims, wherein the antigenic unit comprises one or more linkers, preferably one or more non-immunogenic and/or flexible linkers.
- 15 41. The vaccine according to any of the preceding claims, wherein the antigenic unit comprises 10, 20, 30, 40 or 50 epitopes, preferably T cell epitopes.
- 20 42. The vaccine according to any of the preceding claims, wherein said targeting unit comprises antibody binding regions with specificity for surface molecules or receptors on antigen presenting cells (APCs), preferably specificity for CD14, CD40, Toll- like receptor, CCR1, CCR3, CCR5, MHC class I proteins or MHC class II proteins.
- 25 43. The vaccine according to any of the preceding claims, wherein the targeting unit has affinity for a chemokine receptor selected from CCR1, CCR3 and CCR5.
44. The vaccine according to any of claims 42 to 43, wherein said targeting unit has affinity for MHC class II proteins, preferably MHC class II proteins selected from the group consisting of anti-HLA-DP, anti-HLA-DR and anti-pan HLA class II.
45. The vaccine according to any of the preceding claims, wherein the targeting unit is selected from anti-pan HLA class II and MIP-1 α and preferably selected from anti-pan HLA class II and human MIP-1 α .
- 30 46. The vaccine according to claim 45, wherein the targeting unit is MIP-1 α , preferably human MIP-1 α .

47. The vaccine according to claim 45, wherein the targeting unit is anti-pan HLA class II.
48. The vaccine according to any of the preceding claims, wherein the dimerization unit comprises a hinge region.
- 5 49. The vaccine according to any of claims 48, wherein the dimerization unit further comprises another domain that facilitates dimerization.
50. The vaccine according to claim 49, wherein the other domain is an immunoglobulin domain, preferably an immunoglobulin constant domain.
- 10 51. The vaccine according to any of claims 48 to 49, wherein the dimerization unit further comprises a dimerization unit linker, which connects the hinge region and the other domain that facilitates dimerization.
52. The vaccine according to any of the preceding claims, wherein the vaccine comprises the polynucleotide.
- 15 53. The vaccine according to claim 52, wherein the polynucleotide further comprises a nucleotide sequence encoding a signal peptide.
54. The vaccine according to any of the preceding claims, wherein the vaccine comprises the polypeptide or the dimeric protein and said targeting unit, dimerization unit and antigenic unit in said peptide or dimeric protein are in the N-terminal to C-terminal order of targeting unit, dimerization unit and antigenic unit.
- 20 55. The vaccine according to any of the preceding claims, wherein said betacoronavirus is one selected from the group consisting of SARS-CoV, MERS-CoV, SARS-CoV-2, HCoV-OC43 and HCoV-HKU1, preferably selected from the group consisting of SARS-CoV and SARS-CoV.
56. A polynucleotide as defined in any of the claims 1 to 53.
- 25 57. A vector comprising the polynucleotide according to claim 56.
58. A host cell comprising the polynucleotide as defined in any of the claims 1 to 53 or comprising the vector according to claim 57.

59. A polypeptide encoded by the polynucleotide as defined in any of claims 1 to 53.
60. A dimeric protein consisting of two polypeptides as defined in claim 59.
61. The dimeric protein according to claim 60, wherein the dimeric protein is a homodimeric protein.
- 5 62. The polynucleotide according to claim 56 or the polypeptide according to claim 59 or the dimeric protein according to any of claims 60 or 61 for use as a medicament.
63. A method of preparing the vaccine according to any one of the preceding claims 1 to 51 and 54 to 55, wherein the vaccine comprises the polypeptide or the dimeric protein and wherein said method comprises:
- 10 a) transfecting cells with the polynucleotide as defined in any of the claims 1 to 53;
 b) culturing the cells;
 c) collecting and purifying the dimeric protein or the polypeptide expressed from the cells; and
 d) mixing the dimeric protein or polypeptide obtained from step c) with the
- 15 pharmaceutically acceptable carrier.
64. A method for preparing the vaccine according to any one of the preceding claims 1 to 53 and 55, wherein the vaccine comprises the polynucleotide and wherein the method comprises:
- 20 a) preparing the polynucleotide;
 b) optionally cloning the polynucleotide into an expression vector; and
 c) mixing the polynucleotide obtained from step a) or the vector obtained from step b) with the pharmaceutically acceptable carrier.
- 25 65. A method for treating a subject having suffering from a betacoronavirus infection or being in need of prevention thereof, the method comprising administering to the subject the vaccine as defined in any of claims 1 to 55.
- 30 66. A vaccine as defined in any of claims 1 to 55 for use in the treatment of an infection with a betacoronavirus or for use in the prevention of a betacoronavirus infection.

Fig. 1

SEQ ID NO: 230

MFVFLVLLPLVSSQCVNLTTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFD
NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSTQSLIVNNATNVVIKVEFCQFCNDPFLGVYYHKNNKSWMESEFRVYS
SANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRLDPQGFSALEPLVDLPIGINITRFQTLLAL
HRSYLTPGDSSSGWTAGAAAYYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPTE
SIVRFPNITNLCPFGEVFNATRFASVYAWNRRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGD
EVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEG
FNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQ
FGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQT
RAGCLIGAEHVNNSYECDIPIGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNNSIAIPTNFTISVTTEILPV
SMTKTSVDCTMYICGDSTECSNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPS
KPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLTDEMIAQYTSALLAGTITSGWTFGAGAA
LQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSSASALGKLQDVVNQNAQALNTLVKQLSSNFGAIS
SVLNDILSRDLKVEAEVQIDRLITGRQLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQS
APHGVVFLHVTYVPAQEKNFTTAPAICHGDKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNT
VYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWL
GFIAGLIAIVMTIMLCCMTSCCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

Fig. 2**A:** SEQ ID NO: 231

NITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYADSFVIRGDEVQRQIA
 PGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFP
 LQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNGLTGTGVLTESNKKFLPFQQFGRDIA
 DTTDAVRDPQTLE

B: SEQ ID NO: 802

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYADS
 FVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIYQAGSTPC
 NGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

C: SEQ ID NO: 803

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYADS
 FVIRGDEVQRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIYQAGSTPC
 NGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

D: SEQ ID NO: 804

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYADS
 FVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIYQAGSTPC
 NGVEGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

E: SEQ ID NO: 805

RVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYADS
 FVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRYRLFRKSNLKPFERDISTEIYQAGSTPC
 NGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 3

SEQ ID NO: 232

DVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDL

Fig. 4

SEQ ID NO: 233

MQVSTAALAVLLCTMALCNQVLS |
 APLAADTPTACCFYSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEEWVQKYVSDLELSA |
 ELKTPLGDTTHT | EPKSCDTPPPCPRCP | GGGSSGGSG |
 GQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQ
 QGNIFSCSVMEALHNRFTQKSLSLSPGK | GLGGL |

Fig. 5

SEQ ID NO: 234

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCCKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSA

Fig. 6

SEQ ID NO: 235

MNFGLRLIFLVLTLKGVQC

Fig. 7

SEQ ID NO: 236

MDAMKRGLCCVLLLCGAVFVSP

Fig. 8

SEQ ID NO: 237

MTYRRLISMMGFKMNYQVNGYPNMFSGGGSGGGGSFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAIGGGSGG
GGSRSFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPNMLRIMASLVMVYMPASWVMRIMTWGGGG
GGGSHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSYFIKGLNNLNRGMVLYLNTLTLAVPYNMRVGGGGSGGG
GSNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEV
QIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGNGYNYLYRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNC
YFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 9

SEQ ID NO: 238

MTYRRLISMMGFKMNYQVNGYPNMFSGGGSGGGGSHVISTSHKLVLNVNPYVGGGGSGGGGSFLNRFTTTLNDFNLV
AMSSVELKHFFFAQDGNAAIGGGSGGGGSHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSRAMPNMLRIMASL
VLMVYMPASWVMRIMTWGGGGSGGGGSRSFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSAQFAPSASAFF
GMSRIEIVDTVSALVYDNKLSGGGGSGGGGYFIKGLNNLNRGMVLYLNTLTLAVPYNMRVSGGGSGGGGSSGDATTA
YANSVFNICQAVTANVNALLGGGGSGGGGSNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKC
YGVSPTKLNDLCFTNVYADSFVIRGDEVQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGNGYNYLYRLFRKS
NLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 10

SEQ ID NO: 239

MTYRRLISMGMGFKMNYQVNGYPNMFGGGGSGGGGSHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMGGGGSGG
 GGSYFIKGLNNLNRGMVLYLNTLTLAVPYNMRVGGGGSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGG
 HFAIGLALYPSARIVYTACSHAAVGGGGSGGGGSRFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPN
 MLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGGSRVWTL MNVLTLYVKVFAYANRNRFLYIIKLSGGGGSGGGGAQ
 FAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGGGGFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAISGGGG
 GGGSGSGDATTAYANSVFNICQAVTANVNALLSGGGSGGGGTANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMM
 GGGSGGGGSGNITNLC PFGEVFNATRFASVYAWNRRKISNCVADYSVLNSASFSTFKCYGVSP TKLNDLCFTNVYADS
 FVIRGDEV RQIAPGQTGKIADYNYKL PDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPC
 NGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 11

SEQ ID NO: 240

MTYRRLISMGMGFKMNYQVNGYPNMFGGGGSGGGGSHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMSSGGGGSG
 GGGSGDATTAYANSVFNICQAVTANVNALLSGGGSGGGGFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAIGGG
 GSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGGHFAIGLALYPSARIVYTACSHAAVGGGGSGGGGSR
 SFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPNMLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGG
 SVQMAPISAMVRMYIFFASFYYWKS YVHVGGGGSGGGGSRVWTL MNVLTLYVKVFAYANRNRFLYIIKLSGGGGSGG
 GGAQFAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGGGGSLMPILT LTRALTAYTVELGTEVNEFACVGGGGSG
 GGGSYFIKGLNNLNRGMVLYLNTLTLAVPYNMRVGGGGSGGGGSTVYTKVDGVDVELFENKTTLPVNVAFGGGGGSGG
 GSTANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMMGGGGSGGGGSGNITNLC PFGEVFNATRFASVYAWNRRKISNC
 VADYSVLNSASFSTFKCYGVSP TKLNDLCFTNVYADSFVIRGDEV RQIAPGQTGKIADYNYKL PDDFTGCVIAWNSNNL
 SKVGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPA
 T

Fig. 12

SEQ ID NO: 241

KMFDAYVNTFSSTFNVRVYSTGSNVFQTRAGGSSGGGSSGGSVAYSNN SIAIPTNFTISVTTEIGGGSGGGGSGSTANPK
 TP KYKFVRIQPGQTFFVNEFYAYLRKHFSMMGGGGSGGGGSTVYTKVDGVDVELFENKTTLPVNVAFGGGSGGGGS
 YFIKGLNNLNRGMVLYLNTLTLAVPYNMRVGGGGSGGGGSLVKPSFYVYSRVKNLVQQESPFVMM SAPP AQYELSGG
 GSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGGHFAIGLALYPSARIVYTACSHAAVGGGGSGGGGSR
 FIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPNMLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGGS
 VQMAPISAMVRMYIFFASFYYWKS YVHVGGGGSGGGGSRVWTL MNVLTLYVKVFAYANRNRFLYIIKLSGGGGSGG
 GAQFAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGGGGSLMPILT LTRALTAYTVELGTEVNEFACVGGGGSG
 GGSFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAISGGGGSGGGGSGSGDATTAYANSVFNICQAVTANVNALLSG
 GSGGGGSHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMGGGGSGGGGSM TYRRLISMGMGFKMNYQVNGYPNMF
 GGGSGGGGSGFDDTVIEVQGYKSVNITFELDERIGGGSGGGGSGNITNLC PFGEVFNATRFASVYAWNRRKISNCVAD
 YSVLYNSASFSTFKCYGVSP TKLNDLCFTNVYADSFVIRGDEV RQIAPGQTGKIADYNYKL PDDFTGCVIAWNSNNLDSK
 VGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 13

SEQ ID NO: 242

MTYRRLISMMGFKMNYQVNGYPNMFSGGGSGGGGSHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMGGGGSGG
 GGSYFIKGLNNLNRMVLYLNTLTLAVPYNMRVGGGGSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGG
 HFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSRSFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSGNITNLC
 PFGEVFNATRFASVYAWNRKRISNCVADYSVLNSASFSTFKCYGVSP TKLNDLCFTNVYADSFVIRGDEV RQIAPGQTG
 KIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYG
 FQPTNGVGYQPYRVVLSFELLHAPATGGGGSGGGGSRAMPNMLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGG
 SRVWTL MNVLT LVYKVFAYANRNRFLYIIKLSGGGGSGGGGAQFAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGG
 GGFLNRFTTTLND FNLVAMSSVELKHFFFAQDGNAAISGGGGSGGGSSGDATTAYANSVFNICQAVTANVNALLSGGG
 GSGGGGTANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMM

Fig. 14

SEQ ID NO: 243

NITNLC PFGEVFNATRFASVYAWNRKRISNCVADYSVLNSASFSTFKCYGVSP TKLNDLCFTNVYADSFVIRGDEV RQIA
 PGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFP
 LQSYGFQPTNGVGYQPYRVVLSFELLHAPATGGGGSGGGGSM TYRRLISMMGFKMNYQVNGYPNMFSGGGSGGGG
 SHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMGGGGSGGGGSGSYFIKGLNNLNRMVLYLNTLTLAVPYNMRVGGG
 GSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGGHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSR
 SFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPNMLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGG
 SRVWTL MNVLT LVYKVFAYANRNRFLYIIKLSGGGGSGGGGAQFAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGG
 GGFLNRFTTTLND FNLVAMSSVELKHFFFAQDGNAAISGGGGSGGGSSGDATTAYANSVFNICQAVTANVNALLSGGG
 GSGGGGTANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMM

Fig. 15

SEQ ID NO: 244

MTYRRLISMMGFKMNYQVNGYPNMFHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMYFIKGLNNLNRMVLYLNTL
 TLAVPYNMRVMSD LTKNLSDRVFVLWAHGFELHFAIGLALYYPSARIVYTACSHAAVRSFIEDLLFNKVTALMIERFVS
 LAIDAYPRAMPNMLRIMASLVL MVYMPASWVMRIMTW RVWTL MNVLT LVYKVFAYANRNRFLYIIKLAQFAPSASAFFGM
 SRIEIVDTV SALVYDNKFLNRFTTTLND FNLVAMSSVELKHFFFAQDGNAAISSGDATTAYANSVFNICQAVTANVNALLT
 ANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMMNITNLC PFGEVFNATRFASVYAWNRKRISNCVADYSVLNSASF S
 TFKCYGVSP TKLNDLCFTNVYADSFVIRGDEV RQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRL
 FRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 16

SEQ ID NO: 245

MTYRRLISMMGFKMNYQVNGYPNMFSGGGSGGGGSHVISTSHKLVL SVNPHYVASIKNFKSVLYYQNNVFMGGGGSGG
 GGSYFIKGLNNLNRMVLYLNTLTLAVPYNMRVGGGGSGGGGSM LSDLTKNLSDRVFVLWAHGFELSGGGSGGGG
 HFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSRSFIEDLLFNKVTALMIERFVSLAIDAYPGGGSGGGGSRAMPN
 MLRIMASLVL MVYMPASWVMRIMTWGGGGSGGGGSRVWTL MNVLT LVYKVFAYANRNRFLYIIKLSGGGGSGGGGAQ
 FAPSASAFFGMSRIEIVDTV SALVYDNKLSGGGGSGGGGFLNRFTTTLND FNLVAMSSVELKHFFFAQDGNAAISGGGG
 GGGGSSGDATTAYANSVFNICQAVTANVNALLSGGGSGGGGTANPKTPKYKFVRIQPGQTFFVNEFYAYLRKHFSMM

Fig. 17

SEQ ID NO: 246

NITNLCPFGEVFNATRFASVYAWNRRKRISNCVADYSVLVNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIA
 PGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFP
 LQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 18

SEQ ID NO: 247

KMFDAYVNTFSSTFNVRVYSTGNSVFQTRAGGSSGGGSSGGGSVAYSNNNSIAIPTNFTISVTTEIGGGGSGGGGSGSTANPK
 TPKYKFVRIQPGQTFFVNEFYAYLRKHFSMMGGGGSGGGGSTVYTKVDGVDVELFENKTTLPVNVAFGGGGSGGGGS
 YFIKGLNNLNRMVLYLNTLTAVPYNMRVGGGGSGGGGSLVKPSFYVYSRVKNLVQQESPFVMSAPPAQYELSGGS
 GSGGGGMLSDTLKNLSDRVVFLWAHGFELSGGGGSGGGGHFAIGLALYYPSARIVYTACSHAAGGGGGSGGGGSR
 FIEDLLFNKVTALMIERFVSLAIDAYPGGGGSGGGGSRAMPNMLRIMASLVLVMPASWVMRIMTWGGGGSGGGGS
 VQMAPISAMVRMYIFFASFYYVWKSYYVHVGGGGSGGGGSRVWTLNMVLTLYVKVFAYANRNRFLYIILKSGGGGSGGG
 GAQFAPSASAFFGMSRIEIVDTVSALVYDNKLSGGGGSGGGGSLMPILTTLTRALTAYTVELGTEVNEFACVGGGGSGGG
 GGSFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAISGGGGSGGGGSGSGDATTAYANSVFNICQAVTANVNALLSGG
 GSGGGGGHVVISTSHKLVLSVNPYVASIKNFKSVLYYQNNVFMGGGGSGGGGSGMTYRRLISMMGFKMNYQVNGYPNMF
 GGGGSGGGGSGFGDDTVIEVQGYKSVNITFELDERI

Fig. 19

SEQ ID NO: 248

MFVFLVLLPLVSSQCVNLTTTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWTFHAIHVSGTNGTKRFD
 NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSTQSLNINATNVVIVKCEFCNDPFLGVYHKNKSWMESEFRVYS
 SANNCFTFEYVSQPFMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPOGFSALEPLVDLPIGINITRFQTLAL
 HRSYLT PGDSSSGWTAGAAAYYVGYLQPRFTLLKYNENGTITDAVDCALDPLSETKCTLSFTVEKGIYQTSNFRVQPT
 SIVRFPNITNLCPFGEVFNATRFASVYAWNRRKRISNCVADYSVLVNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRG
 EVRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEG
 FNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQ
 FGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGNSV
 RAGCLIGAHEVNNSYECDIPIGAGICASYQTQTNPRRARSVASQSIAYTMSLGAENSVAYSNNNSIAIPTNFTISVTTEILPV
 SMTKTSVDCTMYICGDSTECNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDP
 KPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDIAARDLCAQKFNGLTVLPLLTDEMIAQYTSALLAGTITSGWTFGAGAA
 LQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNISAIGKIQDSLSTASALGKLQDVVNQNAQALNTLVKQLSSNFC
 SVLNDILSRDLKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQS
 APHGTVFLHVTYVPAQEKNTTAPAICHGDKAHFPREGVFSNGTHWFVTQRNFYEPQIITDNTFVSGNCDVVIGIVNNT
 VYDPLQPELDSFKEELDKYFKNHTSPDVLGDISGINASVYNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKWPWYIWL
 GFIAGLIAIVMTIMLCCMTSCCCLKGCCSCGSCCKFDEDDSEPVLKGVKLHYT

Fig. 20

SEQ ID NO: 249

DVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIK

Fig. 21

SEQ ID NO: 250

KMFDAYVNTFSSTFNVRVYSTGSNVFQTRAGGSSGGGSSGGSSVAYSNNNSIAIPTNFTISVTTEIGGGGSGGGGSGGGSTANPK
TPKYKFVRIQPGQTFFVNEFYAYLRKHFSMMGGGGSGGGGSTVYTKVDGVDVELFENKTTLPVNVAFGGGGSGGGGS
YFIKGLNNLNRGMVLYLNTLTAVPYNMRVGGGGSGGGGSLVKPSFYVYSRVKNLVQQESPFVMMMSAPPAQYELSGGG
GSGGGGMLSDTLKNLSDRVVFVLAHGFELSGGGGSGGGGHFAIGLALYPSARIVYTACSHAAGGGGGSGGGGSSRS
FIEDLLFNKVTLALMIERFVSLAIDAYPGGGGSGGGGSRAMPNMLRIMASLVLVMPASWVMRIMTWGGGGSGGGGS
VQMAPISAMVRMYIFFASFYYVWKSYYVHVGGGGSGGGGSRVWTLMNVLTLVYKVFAYANRNRFLYIIKLSGGGGSGGG
GAQFAPSASAFFGMSRIEIVDTVSALVYDNKLSGGGGSGGGGSLMPILTALTRALTAYTVELGTEVNEFACVGGGGSGG
GGGFLNRFTTTTLDNFNLVAMSSVELKHFFFAQDGNAAISGGGGSGGGGSSGDATTAYANSVFNICQAVTANVNALLSGG
GGSGGGGHVISTSHKLVLVSNPYVASIKNFKSVLYYQNNVFMGGGGSGGGGSMTYRRLISMMGFKMNYQVNGYPNMF
GGGGSGGGGSFGDDTVIEVQGYKSVNITFELDERIGGGGSGGGGSDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLI
DLQELGKYEQYIK

Fig. 22

SEQ ID NO: 251

DVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYIKGGGGSGGGGSKMFDAYVNTFSSTFNVRVYSTG
SNVFQTRAGGSSGGGSSGGSSVAYSNNNSIAIPTNFTISVTTEIGGGGSGGGGSGGGSTANPKTPKYKFVRIQPGQTFFVNEFYAY
LRKHFSMMGGGGSGGGGSTVYTKVDGVDVELFENKTTLPVNVAFGGGGSGGGGSYFIKGLNNLNRGMVLYLNTLTAV
PYNMRVGGGGSGGGGSLVKPSFYVYSRVKNLVQQESPFVMMMSAPPAQYELSGGGGSGGGGMLSDTLKNLSDRVVFV
LWAHGFELSGGGGSGGGGHFAIGLALYPSARIVYTACSHAAGGGGGSGGGGSSRSFIEDLLFNKVTLALMIERFVSLAID
AYPGGGGSGGGGSRAMPNMLRIMASLVLVMPASWVMRIMTWGGGGSGGGGSGVQMAPISAMVRMYIFFASFYYVW
KSYVHVGGGGSGGGGSRVWTLMNVLTLVYKVFAYANRNRFLYIIKLSGGGGSGGGGAQFAPSASAFFGMSRIEIVDTVS
ALVYDNKLSGGGGSGGGGSLMPILTALTRALTAYTVELGTEVNEFACVGGGGSGGGGSFLNRFTTTTLDNFNLVAMSSVE
LKHFFFAQDGNAAISGGGGSGGGGSSGDATTAYANSVFNICQAVTANVNALLSGGGGSGGGGHVISTSHKLVLVSNPYV
ASIKNFKSVLYYQNNVFMGGGGSGGGGSMTYRRLISMMGFKMNYQVNGYPNMFGGGGSGGGGSFGDDTVIEVQGYK
SVNITFELDERIGGGGSGGGGSNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLN
DLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDIS
TEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 23

A. SEQ ID NO: 252

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACACTACAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGAATATTACTAACCTGTGCCATTTCGGCAGGTGTT
CAACGCAACCCGGTTTGCAAGCGTGTACGCATGGAACAGAAAGCGGATTAGCAACTGCGTCGCCGACTACAGCGTG
CTCTACAACAGCGCATCATTCTCCACATTCAAGTGTTACGGAGTGTCACCCACTAAGCTGAACGACCTCTGCTTCACA
AATGTCTACGCCGATTCTTCGTGATCCGGGGAGATGAAGTCAGGCAGATTGCACCAGGACAGACTGGCAAAATCG
CTGACTACAACATAAGCTGCCAGACGATTTCACTGGCTGCGTGATTGCATGGAACAGCAATAACCTGGACTCAAAG
GTCGGCGGTAATTATAACTACCTGTATCGGCTGTTTCAGAAAGAGCAACCTGAAGCCCTTCGAGCGGGACATCTCCAC
CGAAATCTACCAGGCAGGCTCAACACCTGCAACGGAGTGGAAGGCTTCAACTGCTATTTCCCCCTGCAGTCTTACG
GTTTTAGCCAACAAACGGTGTGGGCTATCAGCCATACAGGGTGGTCGTGCTGAGCTTCGAACTGCTCCATGCCCC
CGCTACA

B. SEQ ID NO: 253

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLNITNLCPFGEVFNATRFASVYAWNRRKISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGD
EVRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVE
GFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT

Fig. 24

A. SEQ ID NO: 254

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGTTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACACTACAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCGAGTCCAGCCCACAGAATCAATCGTGCGGTTTC
CAAACATCACCAATCTCTGCCCTTCGGAGAAGTGTTTAATGCCACACGGTTTGCCTCAGTGTATGCCTGGAACCGG
AAGAGAATCTCCAACCTGCGTGGCAGACTATTCTGTGCTGTACAACAGCGCCTCCTTCTCTACTTTCAAGTGCTACGG
CGTGTCTCCTACTAAGCTGAACGATCTCTGCTTCACAAACGTGTATGCCGATTCTTTGTGATCAGAGGAGACGAAG
TGCGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGACTACAACATAAGCTGCCAGACGATTTCACTGGCTG
CGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAATTATAACTACCTCTATAGACTGTTCCGTAA
GTCTAACCTGAAGCCATTCGAGCGTGATATTAGCACCGAAATCTACCAGGCAGGTTCAACTCCTTGTAACGGAGTGG
AGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTTCCAGCCTACAAACGGAGTGGGGTACCAGCCTTATCG
GGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGCGGACCTAAGAAATCCACCAACCTGGTGA
AGAACAAGTGCCTGAATTC

B. SEQ ID NO: 255

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHLEALHNRFTQKSLSLSPGK
GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTN
VYADSFVIRGDEVRIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIYQA
GSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 25A. SEQ ID NO: 256

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAATCTTGTGACACACCTCCCCGTGCCAAGGTGCCAGGCCGGTGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGGTGAACCTGACAACCAGAACCAGCTGCCTCCTG
CTTATACCAATAGTTTTACTCGGGGCGTCTACTACCCTGACAAAGTGTTTCGGAGCAGTGCTGCTGCATAGCACCCAG
GACCTGTTCCCTCCCTTCTTCAGTAATGTCACTTGGTTCATGCAATCCACGTGTCAGGTAATAATGGTACAAAAAGG
TTCGACAACCCAGTTCTGCCCTTCAATGACGGCGTTTACTTCGCCAGTACCGAAAAGTCTAATATCATTCTGTGGTTG
GATCTTCGGAACAACCCTGGACAGTAAGACCCAGTCTCTGCTCATTGTTAATAACGCCACAAATGTCGTGATCAAAG
TTTGTGAATTTTCAGTTTTGTAAACGATCCATTCTGGGCGTCTACTACCATAAGAATAATAAGAGCTGGATGGAAAGC
GAGTTTCGAGTCTACAGCAGTGCCAATAATTGTACATTCGAGTACGTTTCTCAGCCTTCTCTGATGGACCTGGAGGG
CAAGCAGGGAAATTTCAAAAATCTCCGTGAATTTGTCTTTAAGAATATTGACGGCTACTTCAAAATCTACAGCAAGCA
CACCCCGATTAATCTGGTTCGAGACCTGCCACAGGGCTTCAGTGCACTGGAGCCCCTGGTTGATCTGCCAATCGGA
ATTAATATCACTAGGTTCCAGACCCTGCTGGCACTGCATCGTAGTTACCTCACACCTGGGGATTCTAGTTCCGGCTG
GACTGCTGGGGCAGCCGCCTACTATGTGGGATATCTCCAGCCTCGCACATTTCTGCTGAAGTATAATGAGAACGGT
ACTATTACCGACGCACTGGACTGTGCACTCGACCCACTGAGTGAGACTAAATGCACCCTCAAAAGTTTCACCGTCGA
GAAGGGTATCTACCAGACATCCAATTTCCGCGTGCAGCCTACTGAGTCCATCGTGCGCTTCCCAAATATACCAATC
TGTGCCCATTCGGTGAAGTTTTCAATGCTACTCGCTTGTCTAGTGTTTACGCATGGAACAGAAAGAGGATCTCAAAC
TGCGTGGCTGACTATAGCGTTCTGTACAATTCTGCAAGTTTTTCTACTTTTAAATGTTACGGCGTTAGTCTACCAA
CTGAACGACCTCTGTTTACCAACGTCTACGCTGACTCTTTCGTATCCGGGGCGATGAAGTTCGACAGATCGCCCC
AGGCCAGACAGGAAAGATCGCAGACTACAATTACAAGCTGCCAGATGACTTCACCGGCTGCGTTATTGCCTGGAAC
TCCAATAATCTGGACAGCAAAGTGGGTGGGAACATACTACCTCTACCGCCTCTTCAGAAAGAGTAATCTGAAGCC
GTTTGAGCGCGATATTTCCACCGAAATCTATCAGGCCGGAAGCACACCGTGCAATGGAGTCGAAGGGTTCAATTGTT
ACTTTCCGCTCCAGAGCTACGGGTTCCAGCCCACAAATGGGGTTGGATATCAGCCTTACAGGGTGGTTGTTCTGTCT
TTTGAGCTGCTGCATGCACAGCTACCGTCTGCGGGCCCAAGAAGAGCACCAATCTCGTCAAGAACAAAGTGCCTGA
ATTTCAACTTCAACGGGCTCACCGGGACCGGCTCTGACAGAGTCTAATAAGAAATTTCTGCCCTTCCAGCAGTTT
GGAAGAGACATCGCTGATACCACAGACGCCGTCCGGGATCCCCAGACACTGGAATCCTCGACATCACACCATGTA
GCTTTGGGGGAGTTAGCGTCATTACACCAGGAATAATACTAGCAATCAGGTGGCCGTCTGTACCAGGACGTGAA
TTGTACAGAAAGTTCAGTCGCTATCCACGCAGACCAGCTGACCCCGACTTGGCGCGTGTACTCCACAGGATCTAAC
GTGTTCCAGACACGTGCCGGCTGCCTGATTGGGGCTGAGCAGTCAACAATTCTACGAGTGTGACATTCCCATCG
GAGCCGGAATCTGTGCTTCTTACCAGACCCAGACAACTCTCTTCCAGGAGCCGGATCCGTTGCTTCTCAGTCAATC
ATCGCCTATACTATGAGCCTGGGTGCCGAAACTCTGTTGCTTATTCTAACAATAGCATTGCTATCCCCGACCAATTT
ACCATCTCTGTCAACCACTGAGATCCTGCCAGTCTCCATGACCAAGACCTCCGTGCACTGTACAATGTATTTGTGGA
GACTCAACCGAGTGCTCTAACCTCCTGCTGCAGTATGGATCCTTCTGCACCCAGCTCAACAGGGCACTGACCGGAAT
TGCTGTGCAACAGGACAAGAACAACACTCAGGAGGTCTTCGCACAGGTCAAGCAGATATACAAGACCCCCCTATCAA
GACTTTGGGGGATTCAACTTCTCCAGATCCTCCCCGATCCTTCTAAGCCATCAAAGCGGAGTTTTCATTGAGGATCT
GCTCTTCAACAAGGTCACCCTCGCTGACGCTGGCTTCAATTAAGCAGTACGGAGACTGTCTGGGGGACATCGCAGCA
AGAGACCTGATCTGCGCCAGAAAGTTCAACGGACTGACAGTCTGCGGCCCTGCTCACTGATGAAATGATCGCCC
AGTATACAAGTGCTCTGCTCGCCGGAACCATCACTTCCGGGTGGACCTTCGGAGCAGGCGCAGCCCTGCAGATCCC
TTTCGCCATGCAGATGGCCTACCGGTTCAATGGCATCGGCGTGACCCAGAATGTCCTGTATGAGAATCAGAAAGCTG
ATCGCAAATCAGTTCAACAGCGCCATCGGAAAAATTCAGGACTCACTCTCTAGTACCGCCTCAGCCCTGGGAAAACT
CCAGGATGTTGTGAACCAGAATGCTCAGGCTCTCAACACTCTGGTTAAACAGCTCAGCAGCAATTTCCGGTGCCATTA
GCTCCGTCTGAATGACATCCTCAGCCGTCTCGATCCACCGGAAGCTGAAGTCCAGATCGATCGTCTCATCACAGGA
CGACTGCAGAGCCTGCAGACCTACGTGACCCAGCAGCTCATCCGCGCTGCCGAAATTCGAGCCAGCGCCAATCTCG
CAGCTACAAAAATGAGCGAGTGCGTCTGGGACAGTCCAAGAGAGTTGATTTCTGCGGGAAGGGCTATCATCTCAT

Fig. 25A. continued

GTCTTTCCACAGTCTGCACCACACGGCGTGGTTTTCTGCACGTACCTACGTCCCAGCCCAGGAGAAGAACTTTA
CCACCGCTCCAGCCATTTGTCATGACGGCAAAGCCCATTTTCCGCGCGAAGGAGTTTTCGTCAGCAATGGGACTCAC
TGGTTTGTCACTCAGCGCAATTTCTATGAACCACAGATTATTACAACCGATAATACCTTCGTCACTGGTAATTGTGAC
GTAGTGATCGGCATCGTTAACAATACAGTCTATGATCCGCTGCAGCCTGAGCTCGACAGCTTCAAGGAGGAGCTGG
ACAAGTACTTCAAGAACCACACCAGCCCTGACGTGGATCTCGGCGACATTTCTGGCATTAAATGCCTCTGTCGTCAAT
ATCCAGAAGGAAATCGACCGACTGAATGAAGTCGCAAAGAATCTGAACGAGAGTCTGATTGATCTGCAGGAGCTGG
GAAAAACGAACAGTACATC

Fig. 25B. SEQ ID NO: 257

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WWQKYVSDLELSAELKTPLGDTTHTPEKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESSGQPENNYNTTPMLDSGSSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLVNLTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFDNPVLPFNDGV
YFASTEKSNIIRGWIFGTTLDSTQSLIVNNATNVVIKVECFQFCNDPFLGVYYHKNNKSWMESEFRVYSSANNCTFEYV
SQPFLLMDLEGKQGNFKNLREFVFNIDGYFKIYKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLALHRSYLTGDS
SSGWTAGAAAYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSTVEKGIYQTSNFRVQPTESIVRFPNITNLC
PFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTG
KIADYNYKLDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYG
FQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQFGRDIADTTDAV
RDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQTRAGCLIGAEHVN
NSYECDIPGAGICASYQTQTNPSGAGSVASQSIIAYTMSLGAENSVAYSNNNSIAIPTNFTISVTTEILPVSMTKTSVDCTM
YICGDSTECNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQLPDPSPKPSKRSFIEDLL
FNKVTLDAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPPLLTDEMIAQYTSALLAGTITSGWTFGAGAALQIPFAMQMAY
RFNGIGVTQNVLYENQKLIANQFNSAIGKIQDSLSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAISSVLNDILSRDLP
PEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSPFQSAHPGVVFLHVTY
VPAQEKNFHTTAPAICHGDKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDWVIGIVNNTVYDPLQPELDSF
KEELDKYFKNHTSPDVLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELGKYEQYI

Fig. 26

A. SEQ ID NO: 258

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCGTGCCAAGGTGCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACACTAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGATGACTTATCGCAGACTGATCTCCATGATGGGGT
TCAAGATGAACTACCAGGTCAATGGCTATCCCAACATGTTCCGGTGGGGGTGGTTCTGGCGGGGGTGAAGCCACGT
GATCTCTACCTCCCAAGCTGGTCTGTCCGTGAACCCCTACGTGGCCTCCATCAAAAACTTAAAGTCCGTGCTCT
ATTATCAGAATAACGTGTTTCATGGGTGGAGGGGGCTCTGGAGGTGGCGGGTCATACTTTATTAAGGGCCTGAATAA
CCTCAACAGGGGGATGGTGTCTGTATCTCAACACCCTGACTCTCGCCGTGCCTTACAATATGCGCGTGGGTGGTGGT
GGCTCTGGCGGTGGCGGTTCTATGCTGTCTGATACACTGAAGAATCTGTCCGACCGAGTGGTGTTCGTCCTGTGGG
CACACGGTTTCGAGCTGTCAGGGGGTGGAGGGTCTGGCGGAGGCGGGCATTTTCGCCATCGGTCTCGCCCTGTATT
ACCCTTCCGCACGGATCGTCTATACTGCCTGTTCCCATGCAGCAGTCGGGGGTGGAGGGTCCGGCGGAGGTGGCT
CCAGGTCTTTTATTGAGGACCTCCTGTTCAACAAGGTGACCCTGGCTCTGATGATCGAGCGGTTTGTCTCCCTGGCT
ATTGATGCATACCCAGGTGGCGGAGGGTCAAGGTGGAGGCGGGTCCCGGGCTATGCCCAACATGCTGAGAATCATG
GCATCTCTGGTGCTCATGGTGTACATGCCTGCAAGCTGGGTGATGCGAATTATGACATGGGGGGGAGGCGGTAGC
GGTGGCGGAGGCTCAAGAGTCTGGACACTCATGAACGTGCTGACTCTCGTGTACAAAGTGTTCGTTACGCCAATC
GCAACAGGTTTCTGTACATTATCAAGCTCTCCGGTGGCGGAGGTTCCGGGGGAGGGGGCGCCAGTTCGCTCCATC
CGCCTCAGCATTTCTCGGTATGAGTCGGATCGAGATTGTCGATACCGTGTCTGCACTGGTCTATGACAATAAGCTGA
GCGGAGGTGGTGGGTCCGGCGGTGGGGGGTTCCTGAACAGGTTCAACCACTCTCAACGACTTTAATCTGGTCG
CCATGTCAAGCGTCAAACTCAAGCATTTCTTCTTTGCCAGGATGGCAACGCAGCTATCTCCGGTGGAGGAGGTAG
TGGCGGCGGTGGATCTTCCGGCGATGCTACCACCGCCTACGCTAATTCCGTGTTTAAATTTGCCAGGCTGTGACT
GCTAACGTGAATGCACTGCTGTCTGGTGGCGGGGGCAGCGGGGGCGGGGGTACTGCCAACCTAAGACTCCCAAG
TACAAATTCGTCCGCATCCAGCCTGGCCAGACTTTCTTCGTGAACGAGTTTTACGCTTATCTGCGGAAGCACTTTAG
CATGATG

B. SEQ ID NO: 259

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCL
VKGFYPSDIAVEWESSGQPENNYNTTPPMLDSGSFFLYSKLTVDKSRWQQGNIFSCSVMHLEHNRFTQKSLSLSPGK
GLGGLMTYRRLISMMGFKMNYQVNGYPNMFGGGSGGGGSHVISTSHKLVLVSNPYVASIKNFKSVLYYQNNVFMGGG
GSGGGGSYFIKGLNNLNRMVLYLNTLTLAVPYNMRVGGGSGGGGSMMLSDTLKNLSDRVVFVLWAHGFELSGGGGS
GGGHFAIGLALYYPSARIVYTACSHAAVGGGSGGGGSRFIEDLLFNKVTALMIERFVSLAIDAYPGGGGSGGGGSR
AMPNMLRIMASLVLMVYMPASWVMRIMTWGGGSGGGGSRVWTLMNVLTLVYKVFAYANRNRFLYIIKLSGGGSGG
GGAQFAPSASAFFGMSRIEIVDTVSAALVYDNKLSGGGSGGGGFLNRFTTTLNDFNLVAMSSVELKHFFFAQDGNAAISG
GGGSGGGGSGDATTAYANSVFNICQAVTANVNALLSGGGSGGGGTANPKTPKYKFVRIQPGQTFVNEFYAYLRKH
FSMM

Fig. 27

A. SEQ ID NO: 260

ATGAACTTTGGTCTGCGGCTGATTTTCCTCGTCCTGACTCTCAAGGGCGTCCAGTGCCAGGTCCAGCTCACTCAGAG
CCCCGCTCTCTGGCAGTGAGCCTGGGGCAGAGAGCTACTATTAGCTGCAGGGCTAGTAAAAGCGTGTCAACCAGC
GGTTATTATACATGCATTGGTATCAGCAGAAACCCGGTCAGCCACCTAAGCTCCTCATCTACCTCACTTCCAACCTG
GAATCTGGTGTGCCAGCACGCTTTTCAGGCTCCGGAAGTGGCACAGACTTCACCCTGAATATCCACCCAGTGGAAG
AAGAGGACGCCGCTACATACTATTGTGAGCACAGCCGGGAAGTGGCATGGACTTTTGGTGGGGGCACTAAGCTGGA
GATTAAGAGAGGGGGTGGAGGTTCTGGCGGAGGGGGTTCAGGAGGAGGCGGGTCCCAGGTCCAGCTCCAGCAGT
CTGGTCCAGACCTCGTGAAACCTGGTGCTTCAGTCACCATCAGTTGCAAAGCTAGTGGCTATGCTTTCTCAAGTAGC
TGGATGAGCTGGCTCAAACAGCGTCCCGGCAAAGGACTGGAGTGGATTGGGTGGATCTTCCCAAGAGACGGTGAC
ACCAACTATAACGGTAAATTCAAGGGGAAAGCCACTCTGACCGCCGACAAGTCAAGCAGTACAGCTTATATGCAGCT
CAGTAGCCTCACTAGTGAGGACAGCGCCGTGTATTTTTCGCAAGGAGGGGCGACTATCACTATGGGATGGACTAT
TGGGGACAGGGCACCTCTGTCAACCGTGAGTTCTGAGCTGAAAACCCCTCGGTGACACTACTCACACCGAACCCA
AATCCTGTGACACCCCTCCCCCTTGCCTCGCTGTCTGGTGGTGGCAGTTCAGGGGGTGGGAGCGGGGGCCAGC
CTAGAGAGCCACAGGTCTATACACTCCCTCCCTCTAGAGAAGAGATGACCAAAAATCAGGTGTCACTGACATGCCTG
GTCAAGGGTTTCTACCCAAGCGACATTGCAGTGGAATGGGAGTCAAGTGGCCAGCCAGAGAACAAATTATAACTA
CACCTCCAATGCTCGACAGCGATGGTAGTTTCTTCTCTATTCCAAGCTGACAGTCGACAAATCTAGATGGCAGCAG
GGCAATATCTTCAGCTGTTTCAGTGATGCATGAGGCCCTGCACAACCGGTTCACTCAGAAGAGCCTGTCACTCTCCCC
CGGGAAGGGCCTCGGAGGTCTGAGGGTCCAGCCTACTGAATCCATCGTCCGGTTCCCAAATATTACCAACCTCTGC
CCTTTTCGGAGAGGTCTTCAATGCCACACGCTTTGCCAGTGTCTATGCCTGGAATCGCAAGAGGATTAGTAAGTGCCT
GGCAGACTATAGTGTGCTGTACAACCTCAGCTTCTTTCTCAACATTCAAATGCTATGGAGTGTACCAACCAAACTCAA
CGATCTGTGCTTCACTAATGTCTATGCTGACTCCTTTGTCTATTAGGGGGGATGAGGTCCGCCAGATTGCCCCCTGGTC
AGACCGGGAAGATTGCCGACTATAACTATAAGCTCCCAGATGACTTCACTGGCTGCGTGATCGCCTGGAATAGCAA
CAACCTCGATTCCAAGGTGGGCGGCAATTACAACCTACCTCTATAGACTGTTTCGAAAAGAGTAATCTCAAACCATTTGA
GCGGGACATCAGCACAGAAATCTATCAGGCTGGATCTACACCTTGCAACGGCGTGAAGGGTTCACTGTTACTTCC
CACTCCAGTCTTACGGTTTTTCAGCCCACTAACGGGGTGGGGTACCAGCCCTATCGGGTGGTGCCTGAGTTTCGA
ACTCCTGCACGCCCCCGCAACAGTCTGCGGGGCCAAAAAGTCCACTAACCTGGTGAAGAACAAGTGCCTGAACCTC

B. SEQ ID NO: 261

MNFGRLRILFLVLTGKGVQCQVQLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLTSLNLESG
VPAFSGSGSGTDFTLNHPVEEEDAATYYCQHSRELPTWFGGGTKLEIKRGGGSGGGGSGGGGSGVQLQQSGPDL
VKPGASVTISCKASGYAFSSSWMSWLKQRPKGLEWIGWIFPRDGDITNYNGKFKGKATLTADKSSSTAYMQLSSLTSED
SAVYFCARRGDYHYGMDYWGQGTSTVVSSELKTPLDGTTHTPEKSCDTPPPCPRCPGGGSSGGGSGGQPREPVYTL
PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMH
EALHNRFTQKSLSLSPGKGLGGLRVQPTESIVRFPNITNLCPPFGEVFNATRFASVYAWNRKRISNCVADYSVLVNSASFST
FKCYGVSPSTKLNDLCFTNVDYADSFVIRGDEVRIAPGQTGKIADYNYKLDDFTGCVIWNNSNLDKVVGGNYNYLYRLF
RKSNTLKPFRDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKN
KCVNF

Fig. 28A. SEQ ID NO: 262

ATGAATTTTCGGCCTGAGGCTGATTTTTCTCGTGCTGACTCTGAAAGGAGTGCAGTGTGAGGTCCAGCTGACTCAGTC
TCCAGCCTCACTGGCCGTGTCACTGGGACAGCGGCCACTATCTCATGCAGGGCCTCTAAAAGCGTGTCAACTAGC
GGATATTCCTACATGCATTGGTACCAGCAGAAACCCGGCCAGCCACCTAAACTGCTCATCTATCTCACATCCAACCT
GGAATCCGGAGTGCCAGCCAGGTTCACTGGAAGCGGATCCGGTACCGACTTCACCCTGAATATCCACCCAGTCGAA
GAGGAAGATGCAGCTACATATTACTGCCAGCATTACGCGGAACTCCCATGGACCTTTGGAGGCGGGACAAAAGTGG
AAATCAAACGGGGCGGGGGCGGATCTGGAGGCGGGGGAAGCGGGGGCGGAGGTAGTCAGGTCCAGCTCCAGCA
GTCAGGCCCTGACCTCGTCAAGCCCGCGGCCAGTGTCAACAATTAGTTGCAAGGCTTCCGGGTACGCTTTTAGCTCC
TCATGGATGTCCTGGCTCAAGCAGCGCCCTGGCAAAGGCCTCGAATGGATCGGCTGGATCTTCCCAAGGGACGGC
GATACAAACTATAATGGCAAGTTTAAAGGCAAGGCCACTCTCACCGCCGACAAATCTAGCTCTACCGCATATATGCA
GCTCTCTTCCCTGACCTCAGAAGACTCCGCTGTCTATTTCTGCGCCCCGAAGGGGAGACTACCACTACGGGATGGATT
ACTGGGGACAGGGCACCAGCGTGACAGTCTCTAGCGAACTCAAGACTCCACTGGGCGATACCACCCATACAGAGCC
TAAGAGTTGTGATACCCCAACCCCTGCCACGGTGCCCTGGGGGTGGAAGCTCCGGGGGCGGTTCCGGTGGACA
GCCTCGTGAACCCCAAGGTGTACACCCTGCCACCTTCACGAGAAGAGATGACAAAGAATCAGGTCTCACTGACCTGT
CTCGTCAAGGGGTTCTACCCTTCAGACATTGCACTGGAGTGGGAGTCAAGCGGACAGCCTGAGAATAACTACAACA
CCACCCCTCCAATGCTGGACTCTGATGGAAGCTTCTTCTGTATAGCAAGCTGACTGTCGATAAATCACGCTGGCAG
CAGGGCAATATCTTCAGTTGCTCAGTGATGCACGAAGCTCTGCACAATCGTTTTCACTCAGAAATCTCTCTCTGTCC
CCTGGCAAGGGCCTCGGTGGCCTGGTCAACCTCACTACAAGGACCCAGCTCCCTCCAGCCTACACTAACTCATTAC
TCGGGGCGTCTACTACCCAGATAAAGTCTTCAGAAGCAGCGTTCTCCATTCTACCCAGGACCTCTTCTGCCTTTCTT
TTCAAATGTCACTTGGTTTTCACGCAATCCACGTCTCCGGGACCAACGGCACAAAACGGTTCGATAATCCAGTTCTCC
CTTTCAATGATGGGGTCTATTTTCGCTTCTACCGAAAAGTCTAACATCATTCCGGGTTGGATCTTTGGGACTACACTG
GATTCCAAAACCTCAGTCTCTCCTCATTGTCAATAATGCAACTAATGTTGTTATTAAGGTCTGTGAGTTTCAGTTCTGCA
ATGACCCATTCTGGGGTCTATTACCACAAGAATAACAAGTCTGGATGGAGTCCGAATTCGAGTCTATTCCAGC
GCCAATAACTGTACATTGAAATACGTTAGTCAGCCTTTCTGATGGATCTGGAGGGTAAACAGGGCAACTTCAAGAA
CCTCGCGAGTTTGTTTTTAAGAATATTGATGGGTATTTCAAGATATACTCCAAGCATACACCTATCAACCTGGTTAG
AGACCTGCCACAGGGTTTTTTCAGCACTGGAACCTCTGGTTCGACCTCCCTATTGGAATCAACATCACACGATTCCAGA
CCCTCCTCGCTCTCCACCGTTTCATATCTGACCCCCGGCGACAGTAGCTCTGGCTGGACCGCAGGAGCAGCTGCATA
CTATGTCGGGTACCTGCAGCCTAGGACATTCTGCTGAAGTACAACGAAAATGGAACAATCACAGATGCTGTGGATT
GTGCACTCGATCCACTGTCAGAGACCAAGTGTACTCTCAAAGCTTCACCGTCGAAAAGGGGATCTACCAGACTTCA
AATTTTCGGGTGCAGCCAACTGAGTCTATCGTCCGATTTCTTAACATCACTAATCTCTGTCCATTTGGCGAGGTGTTT
AACGCTACCCGCTTTGCAAGTGTTACGCTGGAACAGGAAGCGGATCTCCAATTGCGTGGCTGATTATTCAGTCT
GTACAACAGCGCCAGTTTTTCTACTTTTAAATGCTATGGAGTGAGTCCCACCAAGCTGAATGACCTCTGCTTCACTAA
TGTTTATGCAGATTCATTTGTGATCCGAGGGGATGAAGTGAGACAGATCGCCCCTGGACAGACCGGAAAAATTGCC
GACTATAACTACAACTCCAGACGATTTACAGGTTGCGTTATCGCATGGAACCTCAAACAATCTGGACTCTAAAGTC
GGCGGAAACTATAACTACCTCTACAGGCTCTTCAGAAAGTCTAACCTGAAACCTTTTGAAGGGATATCAGCACAGA
GATATATCAGGCTGGTTCCACACCCTGTAACGGCGTTGAGGGTTTTAATTGTTACTTCCCTCTCCAGTCTTACGGTTT
CCAGCCTACAAATGGAGTGGGTTATCAGCCCTACCGCGTCGTGGTGTGCTCAGCTTTGAACTGCTCCATGCTCCTGCAA
CTGTTTGTGGTCCCAAAAAGTCCACCAATCTGGTTAAGAACAAAGTGTGTGAACTTTAACTTTAATGGGCTGACCGGA
ACAGGCGTCTCTACAGAAAGCAACAAAAAATCTCCCTTTCCAGCAGTTCCGGTAGGGATATCGCCGATACAACCGA
CGCAGTGAGGGATCCTCAGACACTGGAAATCCTGGACATCACACCATGCTCCTTCGGAGGCGTTTCCGTTATCACAC
CAGGAACATAACCTCCAACCAAGGTGGCCGTCTCTACCAGGACGTGAACTGTACAGAAGTGCCCGTCGCTATCCA
TGCTGACCAGCTGACCCCCACATGGCGGGTCTACTCAACTGGTTCTAACGTGTTCCAGACAAGGGCTGGCTGTCTC
ATTGGTGCCGAGCACGTGAACAACTCTTATGAATGCGACATCCCTATCGGGGCCGGAATTTGCGCTTCATACCAGAC
CCAGACTAATAGTCCCTCCGGAGCCGGCTCTGTGCGATCCCAGTCAATCATTGCCTATACTATGAGTCTGGGTGCCG
AGAACCTGCGTGGCATACTCTAACAATTCAATCGCTATCCCTACAAATTTCACTATTTCTGTGACAACAGAAATCCTGC
CAGTTTCCATGACAAAAACCTCAGTTGACTGCACAATGTACATTTGTGGAGACTCCACCGAGTCAGTAAATCTCCTG
CTGCAGTACGGTTCTTTTGCAGTCACTCAATCGGGCCCTCACCGGTATCGCTGTGCAACAGGATAAAAACTCA
GGAAGTTTTTGCACAGGTGAAACAGATATATAAGACACCTCCCATCAAGGACTTTGGTGGCTTCAACTTTTCCAG
TCCTGCCTGATCCAAGTAAACCATCTAACGGAGCTTTATTGAAGACCTCCTGTTCAACAAAGTGACACTGGCCGAT
GCCGGCTTCATTAAGCAGTATGGAGATTGCCTCGGGGACATCGCAGCCCGGGACCTGATCTGTGCTCAGAAGTTTA

Fig. 28A. continued

ACGGTCTGACTGTTCTCCCCCTCTGCTGACTGATGAAATGATTGCACAGTATACAAGCGCCCTCCTCGCAGGCACC
 ATCACCTCAGGGTGGACCTTTGGTGTCTGGAGCAGCCCTGCAGATCCCTTCGCCATGCAGATGGCCTACAGGTTCA
 ATGGAATCGGGGTGACCCAGAATGTGCTCTACGAAAATCAGAAAGCTCATTGCCAATCAGTTTAATTCCGCTATTGGA
 AAAATCCAGGACTCCCTGTCATCCACAGCTAGTGCTCTCGGAAAAGTGCAGGACGTGGTGAACCAGAACGCTCAGG
 CACTGAACACCCTGGTCAAGCAGCTCTCCAGTAACCTTTGGAGCCATCTCTTCAGTCCTGAACGACATTCTGTCCCGT
 CTCGATCCCCCGAGGCTGAAGTGCAGATTGATCGGCTGATTACAGGGCGGCTGCAGTCCCTGCAGACATACGTGA
 CCCAGCAGCTGATCCGCGCCGCAGAGATTCTGGGCAAGCGCCAATCTCGCCGCTACCAAGATGTCTGAGTGCGTTCT
 GGGGCAGAGTAAACGGGTGGACTTCTGTGGAAAAGGATACCATCTCATGTCTTTTCTCAGAGTGCCCCCACGGC
 GTGGTCTTCTGTCATGTCACATACGTCCCTGCTCAGGAAAAGAACTTTACCACAGCACCAGCTATCTGTCATGATGG
 CAAAGCCCATTTTCCACGAGAGGGTGTCTTCTAATGGGACCCACTGGTTTGTGACTCAGAGAACTTTTACG
 AACCACAGATTATCACCACCGACAATACTTTCTGTCAGCGGAAACTGTGATGTGGTTATCGGAATCGTCAACAATACC
 GTGTACGATCCTCTGCAGCCAGAGCTGGACAGCTTCAAGGAAGAACTGGATAAGTACTTTAAGAACCATACTTCACC
 CGATGTGGACCTCGGAGATATCTCAGGAATTAATGCATCCGTCGTCAACATCCAGAAGGAGATCGATCGGCTGAAT
 GAAGTTGCTAAAAATCTGAACGAATCACTCATTGACCTCCAGGAACTCGGCAAATACGAACAGTACATT

Fig. 28B. SEQ ID NO: 263

MNFGRLRIFLVLTCLKGVQCQVQLTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLTSLNLESG
 VPARFSGSGSGTDFTLNIIHPVEEEDAATYYCQHSRELPWTFGGGTGLEIKRGGGSGGGGSGGGGSGVQLQQSGPDL
 VKPGASVTISKASGYAFSSSWMSWLKQRPKGLEWIGWIFPRDGTNYNGKFKGKATLTADKSSSTAYMQLSSLTS
 EDSAVYFCARRGDYHYGMDYWGQGTSTVTVSSELKTPGLDTHTEPKSCDTPPPCRCPGGGSSGGGSGGQPREPQVY
 TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSV
 MHEALHNRFTQKSLSLSPGKGLGGLVNLTRTQLPPAYTNSFTRGVYYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHV
 SGTNGTKRFDNPVLPFNDGVYFASTEKSNIRGWIFGTLLDSKTQSLLIVNNATNVVIKVECFQCNDFPFLGVYHKNK
 SWMESEFRVYSSANNCTFEYVSQPFLMDLEGKQGNFKNREFVFKNIDGYFKIYKHTPINLVRDLPQGFSALEPLVDLPI
 GINITRFQTLALHRSYLTTPGDSSSGWTAGAAAYVGYLQPRTFLLKYNENGITITDAVDCALDPLSETKCTLSFTVEKGI
 YQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFT
 NVYADSFVIRGDEVRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLRLFRKSNLKPFERDISTEY
 QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVL
 TESNKKFLPFQQFGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPT
 WRVYSTGSNVFQTRAGCLIGAEHVNNSECDIPIGAGICASYQTQTNPSGAGSVASQSIIAYTMSLGAENSVAYSNNNS
 IAIPNTFTISVTTEILPVSMTKTSVDCTMYICGDSTECNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPP
 IKDFGGFNFSQILPDPSPKPSKRSFIEDLLFNKVTLDAGFIKQYGDCLGDIAARDLICAQKFNGLTVLPLLLDEMIAQYTS
 ALLAGTITSGWTFGAGAALQIPFAMQMAYRFNGIGVTQNVLYENQKLIANQFNSAIGKIQDLSLSTASALGKLQDVVNQ
 NAQALNTLVKQLSSNFGAISSVLNDILSRDPPAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLG
 QSKRVDFCGKGYHLSFPQSAPHGVVFLHVTYVPAQEKNFTTAPAICHGKAHFPREGVFSNGTHWVFTQRNFYEPQ
 IITDNTFVSGNCDVVIGIVNNTVYDPLQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLN
 ESLIDLQELGKYEQYI

Fig. 29

A. SEQ ID NO: 264

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACACAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTTGCCATCGGACTGGCCCTCTACTATCCCTC
TGCCAGAATCGTGACACTGCCTGTAGCCATGCCGCTGTGGGTGGCGGGGATCAGGTGGCGAGGGTCCCCGAGT
CCAGCCCACAGAATCAATCGTGCGGTTTCCAAACATACCAATCTCTGCCCTTCGGAGAAGTGTTAATGCCACAC
GGTTTGCCTCAGTGTATGCCTGGAACCGGAAGAGAATCTCCAACCTGCGTGGCAGACTATTCTGTGCTGTACAACAG
CGCCTCCTTCTCTACTTTCAAGTGCTACGGCGTGTCTCTACTAAGCTGAACGATCTCTGCTTCACAAACGTGTATGC
CGATTCTTTGTGATCAGAGGAGACGAAGTGCGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGACTACAAC
TATAAGCTGCCAGACGATTTCACTGGCTGCGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAA
TTATACTACCTCTATAGACTGTTCCGTAAGTCTAACCTGAAGCCATTGAGCGTGATATTAGCACCGAAATCTACCA
GGCAGGTTCAACTCCTTGTAACGGAGTGGAGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTTCCAGCCTA
CAAACGGAGTGGGGTACCAGCCTTATCGGGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGC
GGACCTAAGAAATCCACCAACCTGGTGAAGAACAAGTGCGTGAATTC

B. SEQ ID NO: 265

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRI
SNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAWN
SNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFEL
LHAPATVCGPKKSTNLVKNKCVNF

Fig. 30

A. SEQ ID NO: 266

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGCGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGTTTCGTGAACGAGTCTACGCCTATCTGAGAAAAGC
ACTTCTCCATGATGGGGGGCGGAGGTAGTGCCGAGGTGGCTCCCGAGTCCAGCCCACAGAATCAATCGTGCGGT
TTCAAACATCACCAATCTCTGCCCCTTCGGAGAAGTGTTAATGCCACACGGTTTGCCTCAGTGATGCCTGGAAC
CGGAAGAGAATCTCCAACCTGCGTGCGAGACTATTCTGTGCTGTACAACAGCGCCTCCTTCTCTACTTTCAAGTGCTA
CGGCGTGTCTCTACTAAGCTGAACGATCTCTGCTTCACAAACGTGTATGCCGATTCCTTTGTGATCAGAGGAGACG
AAGTGCAGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGACTACAACATAAGCTGCCAGACGATTTCACTGG
CTGCGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAATTATAACTACCTCTATAGACTGTTCC
GTAAGTCTAACCTGAAGCCATTCGAGCGTGATATTAGCACCGAAATCTACCAGGCAGGTTCAACTCCTTGTAACGGA
GTGGAGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTTCCAGCCTACAAACGGAGTGGGGTACCAGCCTT
ATCGGGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGCGGACCTAAGAAATCCACCAACCTG
GTGAAGAACAAGTGCCTGAATTTT

B. SEQ ID NO: 267

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLFVNEFYAYLRKHFSMMGGGGSGGGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADY
SVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSK
VGGNYNYLYRLFRKSNLKPFRDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATV
CGPKKSTNLVKNKCVNF

Fig. 31

A. SEQ ID NO: 268

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCAGGCCGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCAATCGGGCTCGCACTGTACTATCCTA
GTGCCAGGATCGTGATACCGCTTGTAGTCACGCAGCTGTGGCGCGGCGGAGGTTCTGGCGGTGGGGGATCTTTCG
TGAACGATTTCTATGCTTACCTGCGCAAACACTTCTCCATGATGGCGGTGGAGGGTCTGGCGGGGGAGGCTCAC
GGGTCCAGCCTACAGAGTCTATTGTGCGGTTTCCCAATATCACCATCTGTGCCATTTGGCGAGGTGTTTAACGCA
ACCAGGTTTCGCTCTGTCTATGCATGGAATCGGAAGCGGATCAGTAACCTGCGTCGCTGATTACTCTGTCTGTATAA
CAGCGCCTCTTTCAGCACCTTTAAGTGCTACGGCGTCTCTCCACCAAGCTGAACGACCTGTGCTTCACTAACGTGT
ACGCCGATAGCTTTGTGATCCGGGGCGACGAGGTCCGCCAGATTGCTCCCGGCCAGACCGGAAAGATCGCTGACT
ACAACATAAACTGCCTGACGATTTACCGGTTGCGTGATCGCTTGGAATAGTAACAATCTCGACAGCAAAGTCGGC
GGGAACTATAACTACCTCTACCGGCTCTTTAGAAAGAGCAACCTGAAGCCTTTTGAACGGGATATTAGCACCGAAAT
CTACCAGGCAGGCAGCACCCCTTGCAATGGCGTCGAGGGCTTCAACTGCTATTTCCCACTCCAGTCTTATGGCTTCC
AGCCTACCAATGGCGTGGGATATCAGCCATATCGCGTGGTGGTCCTCTCCTTTGAGCTCCTGCATGCTCCAGCCACC
GTGTGCGGTCCAAAAAAGAGCACTAACCTCGTCAAGAACAAGTGCGTCAACTTT

B. SEQ ID NO: 269

MQVSTAALAVLLCTMALCNQVLSAPLAADTPACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSRVQPTESIVRFP
NITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLDLCFTNVYADSFVIRGDEVRI
APGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGNNYLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCY
FPLQSYGFQPTNGVGYPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 32

A. SEQ ID NO: 270

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACCGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCCATTGGCCTCGCCCTGTATTACCTTC
TGCCCGGATCGTGTATACAGCATGCTCTCACGTCGAGTGGGGGGCGGTGGCTCCGGCGGTGGCGGAAGCTTTGT
GAACGAGTTCTATGCCTACCTGAGAAAGCACTTCTCTATGATGGGTGGCGGAGGCTCCGGAGGGGGTGGCTCTCTG
GTGAAGCCTTCTTTCTACGTCTACTCCAGAGTGAAGAATCTCGGAGGTGGCGGTTCTGGTGGCGGAGGTTCTAGGG
TCCAGCCAACCGAATCCATCGTGCGATTCCCCAATATCACAAACCTGTGCCCTTTGGGGAGGTGTTCAATGCTACC
AGATTTGCCTCAGTGTACGCATGGAACAGAAAGAGGATTAGTAACTGCGTGGCCGACTATAGCGTGCTGTATAACA
GCGCCAGCTTCTCTACCTTCAAGTGCTACGGCGTGTCTCCTACCAAGCTCAACGATCTCTGCTTCACCAACGTGTAT
GCCGATTCTTCGTGATTAGGGGCGATGAGGTGCGACAGATCGCCCCTGGACAGACCGGAAAGATCGCCGATTATA
ACTACAAACTGCCTGATGACTTCACCGGTTGCGTGATCGCCTGGAACCTCAACAACCTGGACTCCAAGGTCGGTGG
CAACTATAATTACCTGTACAGGCTGTTCAAGGAAGTCCAATCTGAAGCCTTTTGAACGAGATATCAGCACCGAAATCTA
CCAGGCCGATCTACCCCATGCAACGGTGTGCAAGGCTTTAACTGTTACTTTCTCTCCAGAGTTATGGCTTCCAGC
CAACCAATGGGGTGGGCTATCAGCCTTATCGAGTGGTCGTGCTGCTCCTTTGAACTCCTGCATGCCCCAGCTACTGTC
TGTGGCCCCAAGAAATCCACCAATCTCGTGAAAAACAAGTGCGTCAATTTT

B. SEQ ID NO: 271

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSLVKPSFYVYSRV
KNLGGGGSGGGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLVNSASFSTFKCYGVSP
TKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGNNYNYLYRLFRKSNLKP
FERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 33

A. SEQ ID NO: 272

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACCGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTTGCCATCGGACTGGCCCTGTACTATCCTTC
TGCCAGAATCGTGTACACCGCCTGTTCTCATGCCGCTGTGGGTCTGGGCGGACTGCGAGTCCAGCCCACAGAATCA
ATCGTGCGGTTTTCCAAACATCAACATCTCTGCCCCTTCGGAGAAGTGTTAATGCCACACGGTTTGCCTCAGTGTA
TGCCTGGAACCGGAAGAGAACTCTCCAACGCGTGCCAGACTATTCTGTGCTGTACAACAGCGCCTCCTTCTCTACTT
TCAAGTGCTACGGCGTGTCTCTACTAAGCTGAACGATCTCTGCTTCACAAACGTGTATGCCGATTCTTTGTGATCA
GAGGAGACGAAGTGCAGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGACTACAACTATAAGCTGCCAGACG
ATTTCACTGGCTGCGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAATTATAACTACCTCTATA
GACTGTTCCGTAAGTCTAACCTGAAGCCATTGAGCGTGATATTAGCACCGAAATCTACCAGGCAGGTTCAACTCCT
TGTAACGGAGTGGAGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTTCCAGCCTACAAACGGAGTGGGGT
ACCAGCCTTATCGGGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGCGGACCTAAGAAATCC
ACCAACCTGGTGAAGAACAAGTGCGTGAATTC

B. SEQ ID NO: 273

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNKRISNCVAD
YSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDS
KVGGNYNLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPAT
VCGPKKSTNLVKNKCVNF

Fig. 34

A. SEQ ID NO: 274

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACCGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCCATTGGCCTGGCCCTGTACTATCCCTC
CGCCAGAAATCGTGTACACCGCTTGTAGTCACGCCCGAGTGGGGCTCGGAGGCCTGGGTCTCGGCGGAGTCCGAGT
CCAGCCCAACAGAAATCAATCGTGCAGTTTCCAAACATACCAATCTCTGCCCTTCGGAGAAAGTGTAAATGCCACAC
GGTTTGCCTCAGTGTATGCCTGGAACCGGAAGAGAATCTCCAATGCGTGGCAGACTATTCTGTGCTGTACAACAG
CGCCTCCTTCTCTACTTTCAAGTGCTACGGCGTGTCTCTACTAAGCTGAACGATCTCTGCTTCACAAACGTGTATGC
CGATTCTTTGTGATCAGAGGAGACGAAGTGCGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGACTACAAC
TATAAGCTGCCAGACGATTTCACTGGCTGCGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAA
TTATAACTACCTCTATAGACTGTTCCGTAAGTCTAACCTGAAGCCATTGAGCGTGATATTAGCACCGAAATCTACCA
GGCAGGTTCAACTCCTTGTAAACGGAGTGGAGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTTCCAGCCTA
CAAACGGAGTGGGGTACCAGCCTTATCGGGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGC
GGACCTAAGAAATCCACCAACCTGGTGAAGAACAAGTGCGTGAATTC

B. SEQ ID NO: 275

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGLGGLGLGLRLVQPTESIVRFPNITNLCPFGEVFNATRFAVYAWNRKRIS
NCVADYSVLVNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNS
NNLDSKVGGNYNYLRLFRKSNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELL
HAPATVCGPKKSTNLVKNKCVNF

Fig. 35

A. SEQ ID NO: 276

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGTTTCGTGAACGAGTTCTACGCCTATCTGAGAAAGC
ACTTCAGCATGATGGGACTGGGCGGTCTGCGAGTCCAGCCACAGAATCAATCGTGCGGTTTCCAAACATCACCAA
TCTCTGCCCCCTTCGGAGAAGTGTTAATGCCACACGGTTTGCCTCAGTGTATGCCTGGAACCGGAAGAGAATCTCCA
ACTGCGTGGCAGACTATTCTGTGCTGTACAACAGCGCCTCCTTCTCTACTTTCAAGTGCTACGGCGTGTCTCCTACTA
AGCTGAACGATCTCTGCTTCACAAACGTGTATGCCGATTCTTTGTGATCAGAGGAGACGAAGTGCGACAGATTGCT
CCTGGACAGACCGGGAAGATTGCCGACTACAACATAAGCTGCCAGACGATTTCACTGGCTGCGTTATTGCCTGGA
ATTCAAACAACCTCGATTCCAAAGTGGGCGGGAATTATAACTACCTCTATAGACTGTTCCGTAAGTCTAACCTGAAGC
CATTTCGAGCGTGATATTAGCACCGAAATCTACCAGGCAGGTTCAACTCCTTGTAACGGAGTGGAGGGATTCAACTGC
TACTTCCCACTGCAGTCCTATGGGTTCCAGCCTACAAACGGAGTGGGGTACCAGCCTTATCGGGTCGTTGTGCTGTC
CTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGCGGACCTAAGAAATCCACCAACCTGGTGAAGAACAAGTGCGTGA
ATTC

B. SEQ ID NO: 277

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLFVNEFYAYLRKHFSMMGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRRKISNCVADYSVLNSA
SFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGNNYNY
LYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSEFELLHAPATVCGPKKSTN
LVKNKCVNF

Fig. 36

A. SEQ ID NO: 278

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTGAGTACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACCGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCATTTTGCCATTGGACTGGCACTCTATTACCCAAG
TGCCAGGATCGTCTACACTGCCTGCAGTCACGCAGCCGTGCGGGGAGGCGGTTCTGGAGGGGGTGGCTCTTTTCGT
GAACGAGTTTTACGCCTACCTGAGGAAGCACTTTAGCATGATGGGCCTCGGGGGTCTCCGCGTGCAGCCAACAGAA
TCCATTGTCCGCTTCCCCAATATTACAAACCTGTGCCATTGCGAGAAAGTGTAAATGCCACCAGATTGCGCTCCGTG
TATGCTTGGAACAGAAAGCGCATCTCTAACTGCGTCGCCGACTACAGTGTGCTGTACAACAGCGCAAGTTTTTCCAC
ATTCAAGTGTTATGGGGTGTACCAACCAAACTGAACGATCTCTGCTTACAAACGTGTACGCCGACTCCTTCGTCA
TCCGCGGCGACGAAGTGAGACAGATCGCACCCGGGCGAGCTGGAAAGATCGCAGACTATAACTACAAGCTGCCAG
ACGATTTACCCGGGTGCGTCATTGCCTGGAACAGCAATAACCTCGACAGCAAAGTGGGGGGCAATTACAATATCT
GTATAGACTGTTCCGCAAGTCCAACCTGAAACCTTTGAGAGAGACATCAGTACAGAAATCTATCAGGCCGGTCTA
CACCATGTAATGGTGTGGAAGGGTTCAACTGCTACTTCCCTCTGCAGTCATATGGCTTCCAGCCAATAATGGGGTG
GGATACCAGCCTTATAGGGTGGTCGTGCTGAGCTTTGAGCTGCTGCACGCACCCGCCACCGTGTGCGGGCCAAAAA
AGTCCACTAACCTGGTGAAGAACAAGTGCCTCAATTC

B. SEQ ID NO: 279

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGLGGLRVQPTESIVRFPNITNLCP
FGEVFNATRFASVYAWNKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVRIAPGQTG
KIADYNYKLDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCFPLQSYG
FQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 37

A. SEQ ID NO: 280

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCACTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCAATCGGACTCGCACTGTATTACCCCTC
AGCCAGGATCGTGTATACTGCAGTCACGCTGCCGTGCGCGGGGGGTAGTGGGGGAGGCGGATCCTTTGT
GAATGAGTTCTATGCTTACCTGAGAAAGCACTTCAGCATGATGGGCGGTGGGGGAAGCGGCGGTGGAGGATCCCT
CGTGAAACCCTCCTTCTATGTCTACTCACGGGTGAAGAACCTGGGCCTCGGAGGTCTCAGAGTCCAGCCTACCGAG
TCTATCGTGAGGTTTCCAAACATCACTAATCTGTGCCCTTTCGGAGAAAGTGTAAACGCCACCCGGTTTGCCTCAGT
GTACGCTTGGAATAGGAAGCGGATCTCAAATTGCGTGGCAGATTACAGCGTGCTGTACAACCTCCGCCTCATTACAGTA
CATTCAAGTGCTATGGCGTGAGCCCAACCAAGCTGAACGATCTGTGCTTCACAAACGTGTACGCAGATTCTTCGTC
ATCAGAGGGGATGAAGTCAGACAGATCGCTCCAGGCCAGACAGGAAAGATCGCAGATTATAATTATAAACTCCCTG
ACGATTTACCCGATGCGTGATCGCTGGAACAGTAATAACCTGGATTCAAAAAGTGGGCGGTAACATAATTACCTG
TACAGACTGTTACGGAAGAGCAACCTGAAGCCATTTGAACGCGACATTTCCACCGAAATCTACCAGGCAGGAAGCA
CACCTGTAAATGGCGTGGAGGGCTTTAACTGCTATTTCCCCTGCAGTCCTATGGTTTTTCAGCCCACAAATGGGGTG
GGGTACCAGCCCTACCGGGTCGTGGTGCTGAGCTTCGAACTCCTGCACGCACCAGCCACTGTCTGTGGACCCAAGA
AATCCACTAACCTCGTGAAGAACAAGTGCCTGAACTTC

B. SEQ ID NO: 281

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPPGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGSLVKPSFYVYSRV
KNLGLGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDL
CFTNVYADSFVIRGDEVIRQIAPGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFRDIST
EIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 38

A. SEQ ID NO: 282

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCACTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCAGGCCGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACCGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCTATCGGACTGGCCCTCTACTATCCTTC
CGCTCGGATTGTCTACACTGCCTGCAGCCATGCTGCAGTGACCCAGAAATCACTGAGCCTCAGCCCTGGCAAAGGT
CTGGGAGGCCTCAGAGTCCAGCCTACTGAGAGCATCGTGCGCTTCCCAAACATCACAAACCTGTGCCCTTTTGGAG
AAGTCTTCAATGCCACTCGGTTTGCTTCAGTCTATGCTTGAATAGGAAGCGGATTAGCAATTGCGTGCGCGACTAC
TCAGTGCTGTACAATAGCGCAAGTTTCAGCACCTTCAAGTGCTATGGAGTCTCCCCAACCAAACTCAATGACCTGTG
CTTCACCAACGTGTACGCTGATAGCTTTGTGATCAGAGGTGACGAAGTGCGCCAGATTGCCCTGGTCAGACCGGA
AAGATTGCCGACTACAATTACAACTGCCAGACGATTTACAGGATGCGTGATCGCTTGAATAGCAACAACCTGGA
CTCTAAAGTGGGGGGCAACTACAATTACCTGTACCGGCTCTTTCGCAAGTCTAACCTGAAGCCTTTTGAGAGAGACA
TTAGCACCGAAATCTACCAGGCTGGAAGCACACCATGCAACGGAGTGGAGGGCTTCAATTGCTACTTCCCTCTCCA
GAGCTATGGTTTTTCAGCCCACTAACGGTGTGCGTTACCAGCCATACAGAGTGGTCGTGCTGTCAATTTGAGCTGCTCC
ATGCCCCCGCTACAGTCTGTGGACCTAAAAAGAGCACCAATCTGGTGAAGAACAATGCGTCAACTTC

B. SEQ ID NO: 283

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTKRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGSSGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVTQKSLSLSPGKGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAW
NRKRISNCVADYSVLNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCV
IAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVV
LSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 39

A. SEQ ID NO: 284

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGCCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACTACAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCATTTGCCATTGGTCTGGCACTCTACTACCCATC
AGCAGAATCGTGTACACCCGCTGCTCCCATGCTGCAGTGGGTGGAGGGGGAAGCGGAGGGGGATCTTTCTG
CAACGAATTCTACGCCTACCTGCGGAAGCACTTCAGCATGATGGCGGGCGGGGGCAGCGGAGGGGGTGGTCACT
CGTGAAGCCAAGCTTCTACGTCTACTCTAGAGTGAAGAACCTGACCCAGAAAGTCACTGTCCCTGTACCTGGCAAG
GGTCTCGGAGGCCTCAGGGTGCAGCCAACCGAAAGCATTGTGCGATTTCCCAACATCACTAATCTCTGTCCCTTTGG
CGAAGTGTTCACGCAACCCGGTTTGCATCAGTGTATGCCTGGAATCGGAAGAGGATCTCCAATGCGTGGCCGAT
TACAGCGTGCTGTATAATTCAGCCAGCTTCTCCACTTTCAAGTGCTACGGGGTCTCTCTACCAAACTCAACGACCTC
TGCTTTACCAATGTCTACGCTGACAGCTTTGTGATCCGGGGCGATGAAGTCCGGCAGATTGCACCAGGACAGACCG
GGAAAATCGCCGATTACAATAAGCTGCCCCGACGATTTACAGGCTGCGTGATCGCCTGGAATTCTAACAATCTG
GATAGCAAGGTGGGCGGAAATTACAATACTGTACCGACTGTTCCGGAAGTCAAATCTGAAGCCCTTTGAACGGG
ATATCTCCACCGAAATCTATCAGGCCGGAAGTACTCCCTGCAACGGGGTGAAGGGTTCAACTGTTACTTTCCCTC
CAGTCTTACGGATTCCAGCCTACCAACGGAGTGGGCTACCAGCCCTATAGAGTGGTCGTGCTGCTCTTTGAGCTGCT
GCACGCCCCAGCTACAGTGTGCGGCCCTAAGAAGTCAACCAACCTCGTGAAAAATAAGTGCCTCAATTTT

B. SEQ ID NO: 285

MQVSTAALAVLLCTMALCNQVLSAPLAADTPACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSLVKPSFYVYSRV
KNLTQKSLSLSPGKGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRRKISNCVADYSVLNYSASFSTFKC
YGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRK
SNLKPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKC
VNF

Fig. 40

A. SEQ ID NO: 286

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGGCCAGTGTCATCTTCCTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACTACAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTCCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTTGCCATCGGCCTGGCCCTGTACTATCCCTC
TGCCAGTAATCGTGACACTGCCTGCTCTCATGCTGCCGTGAGCCTGTCTCTGAGCCCTGGCAAAGGACTGGGTGGC
CTCCGAGTCCAGCCACAGAATCAATCGTGCGGTTTCCAAACATCACCATCTCTGCCCTTCGGAGAAGTGTTTAA
TGCCACACGGTTTTGCCTCAGTGATGCCTGGAACCGGAAGAGAATCTCCAAGTGCCTGGCAGACTATTCTGTGCTGT
ACAACAGCGCCTCCTTCTCTACTTTCAAGTGCTACGGCGTGTCTCCTACTAAGCTGAACGATCTCTGCTTCACAAACG
TGTATGCCGATTCTTTGTGATCAGAGGAGACGAAGTGCGACAGATTGCTCCTGGACAGACCGGGAAGATTGCCGA
CTACAATAAGCTGCCAGACGATTTCACTGGCTGCGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGG
GCGGGAATTATAACTACCTCTATAGACTGTTCCGTAAGTCTAACCTGAAGCCATTCGAGCGTGATATTAGCACCGAA
ATCTACCAGGCAGGTTCAACTCCTTGTAACGGAGTGGAGGGATTCAACTGCTACTTCCCACTGCAGTCCTATGGGTT
CCAGCCTACAAACGGAGTGGGGTACCAGCCTTATCGGGTCGTTGTGCTGTCCTTTGAGCTGCTCCACGCTCCTGCA
ACTGTTTGCGGACCTAAGAAATCCACCAACCTGGTGAAGAACAAGTGCCTGAATTC

B. SEQ ID NO: 287

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYPSARIVYTACSHAAVSLSLSPGKGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRRK
RISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAW
NSNNLDSKVGGNYNYLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSE
LLHAPATVCGPKKSTNLVKNKCVNF

Fig. 41

A. SEQ ID NO: 288

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTACGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACTTCGCCATTGGGCTGGCTCTGTATTACCCCTC
AGCCAGAATCGTCTATACCGCATGCTCCCATGCAGCTGTCGGGGGTGGCGGTAGTGGGGGGGGGTAGCTTCGT
CAATGAGTTCTACGCTACCTGAGGAAACATTTCTCCATGATGGGTGGCGGGGAAGTGGCGGGGTGGCAGTCT
GGTGAAGCCCTCCTTCTACGTGTATTCTCGAGTGAAGAATCTCTCCCTCAGTCTGTCCCCTGGCAAAGGTCTGGGG
GCCTCAGGGTGCAGCCACCGAGTCCATCGTCAGGTTCCCCAACATCACAACCTGTGCCCTTTGGGGAGGTCTT
CAACGCCACTCGCTTTGCTTCTGTCTACGCTTGGAACAGGAAGCGAATCAGTAACTGCGTCGCCGATTACTCCGTGC
TGTATAATTCCGCCTCATTGACACCTTCAAGTGCTACGGCGTGTCTCCTACCAAGCTCAACGATCTCTGCTTCACCA
ATGTCTACGCAGACAGTTTCGTGATCAGAGGCGATGAGGTCCGCCAGATTGCCCCAGGGCAGACCGGAAAAATCGC
CGACTATAATTACAAGCTGCCTGATGACTTCACCGGGTGCCTGATCGCATGGAATCCAACAACCTCGACTCCAAAG
TGGGAGGGAACATAACTATCTGTACCGCCTGTTGAGAAAGAGCAACCTGAAACCTTTTGAGAGGGATATCTCAACT
GAAATCTATCAGGCCGGGTCCACCCCATGTAATGGGGTGGAAGGGTTCAACTGCTATTTCCCTCTGCAGTCTTACG
GGTTCAGCCTACCAATGGAGTCGGCTACCAGCCCTACAGAGTCGTGGTGCTGTCTTTGAACTCCTGCACGCCCC
TGCCACCGTCTGCGGCCCAAAGAAATCCACCAATCTGGTGAAAAATAAGTGCGTCACTTT

B. SEQ ID NO: 289

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSLVKPSFYVYSRV
KNLSLSLSPGKGLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGV
SPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGNNYNYLYRLFRKSNL
KPFERDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 42

A. SEQ ID NO: 290

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCACTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAACATAACACCACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCACCTTGCAATCGGACTCGCCCTGTACTACCCTA
GCGCCAGGATTGCTATACCGCATGTCGGAAGCACTTCAGCATGATGGGAGGGGGTGGCAGCGGAGGGGGAGGTTCT
GTCAACGAGTTCTACGCATATCTGCGGAAGCACTTCAGCATGATGGGAGGGGGTGGCAGCGGAGGGGGAGGTTCT
CTGGTCAAGCCTAGCTTTTACGTGTACAGTCGAGTCAAGAACCTCGGTGGATCAGCCGGTGGGTGAGGATCTGGCT
CTAGCGGTGGAAGCAGTGGTGCATCTGGAACCGGTACAGCTGGCGGTACTGGATCTGGAAGCGGGACCGGAAGCG
GGAGAGTGCAGCCACAGAGTCAATCGTGCGGTTTCTAACATCACAAACCTCTGCCATTTGGGGAGGTGTTCAA
CGCCACCAGGTTTGTCTCCGTCTATGCCTGGAATAGGAAGCGCATTAGCAATTGCGTGGCCGACTATTCACTGCTGT
ACAACCTCTGCTTCTTCAGCACATTCAAGTGTTACGGCGTGAGCCCCACCAAGCTCAATGACCTGTGCTTTACCAAC
GTGTATGCCGACTCTTTCGTGATCAGGGGGGACGAGGTCCGACAGATTGCCCTGGCCAGACAGGGAAGATTGCT
GACTATAACTACAACTGCCCCGACGATTTCACTGGCTGCGTCATCGCATGGAACAGCAACAATCTGGACAGCAAAGT
GGGCGGGAATTACAATTACCTGTATAGGCTCTCCGCAAAAGTAATCTGAAGCCCTTCGAGAGGGGATATCAGCACTG
AAATCTATCAGGCCGGCTCAACTCCTTGCAATGGAGTCGAAGGGTTCAACTGCTATTTCCCTCTGCAGAGCTATGGT
TTTCAGCCCACTAACGGGGTGGGATATCAGCCATATCGGGTCGTGGTGCTGTCATTCGAGCTGCTGCATGCACCTG
CCACAGTGTGCGGACCTAAGAAGAGCACTAACCTGGTCAAGAACAAGTGCGTGAATTTT

B. SEQ ID NO: 291

MQVSTAALAVLLCTMALCNQVLSAPLAADTPACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSLVKPSFYVYSRV
KNLGGSAGGSGSGSSGSSGASGTGTAGGTGSGSGTGSGRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRR
RISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAW
NSNNLDSKVGGNYNYLYRLFRKSNLKPFRDISTEIYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFE
LLHAPATVCGPKKSTNLVKNKCVNF

Fig. 43

A. SEQ ID NO: 292

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTTCATAGCTGACTACT
TTGAGACGAGCAGCCAGTGCTCCAAGGCCAGTGTCATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
CAGTGAGGAGTGGGTCCAGAAATACGTCAGTGACCTGGAGCTGAGTGCCGAGCTCAAAACCCCACTTGGTGACACA
ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAG
GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
GAGAACAATAACAACACACGCCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
AAGACCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCATTTGCTATTGGCCTGGCTCTCTACTACCCAAG
CGCAAGGATTGTCTACACCGCCTGTAGCCATGACCCGTGCGGTGGGGCGGGAGTGGGGCGGGGAGCGGGGATCCC
TGAACGAATTCTACGCCTATCTGAGGAAGCACTTTAGCATGATGGGCGGGGGAAGCGGGCGGGGGGATCCC
TGGTCAAACCTAGCTTTTACGTGTACTACGGGTCAAGAATCTGGGCGGGTCTGGAGGGGGCTCCGAAGGTGGAG
GGAGCGAGGGAGGCGGGAGCGAAGGGGGCGGGTCCGAGGGTGGGGGCAGCGAGGGAGGGGGCAGCGGCGGC
GGAAGTAGGGTCCAGCCCACAGAGTCCATTGTGAGGTTCCCAAACATACCAATCTCTGCCCTTTCGGCGAAGTCTT
CAACGCCACTAGGTTTGCCAGTGTCTACGCTTGGAATAGAAAGCGCATTAGCAACTGCGTGGCCGATTACTCCGTCC
TGTACAATAGCGCCAGCTTTTCCACCTTCAAGTGCTACGGAGTGAGCCCTACCAAGCTGAACGACCTCTGTTTACA
AACGTGTACGCCGATAGCTTCGTGATTAGAGGAGACGAGGTGCGGCAGATTGCCCTGGGCAGACCGGCAAGATC
GCCGACTACAATTACAAGCTGCCCCGACGACTTTACCGGCTGCGTCATCGCCTGGAATAGCAACAACCTCGACAGTAA
AGTGGGGGGCAATTATAACTACCTCTATAGACTGTTCCGAAAGAGCAATCTGAAGCCATTTGAGCGGGATATCAGCA
CCGAAATCTACCAGGCTGGAAGCACCCCATGCAACGGGGTGAAGGGTCAACTGCTACTTTCCACTGCAGAGCTA
CGGCTTCCAGCCCACTAATGGAGTGGGCTATCAGCCCTATAGAGTGGTGGTCTCAGCTTCGAACTGCTGCATGCT
CCCCCACCCTGTGCGGGCCTAAGAAATCCACCAATCTGGTGAAGAACAAGTGCCTGAATTTT

B. SEQ ID NO: 293

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGPENNYNTTPMLSDSGSFLLYSLKTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLHFAIGLALYYPSARIVYTACSHAAVGGGGSGGGGSFVNEFYAYLRKHFSMMGGGGSGGGGSLVKPSFYVYSRV
KNLGGSGGGSEGGGSEGGGSEGGGSEGGGSEGGGSGGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNR
KRISNCVADYSVLNYSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIA
WNSNNLDSKVGGNYNYLYRLFRKSNLKPFRDISTEIQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVL
FELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 44

A. SEQ ID NO: 294

ATGCAGGTCTCCACTGCTGCCCTTGCCGTCCTCCTCTGCACCATGGCTCTCTGCAACCAGGTCTCTCTGCACCACT
 TGCTGCTGACACGCCGACCGCTGCTGCTTCAGCTACACCTCCCGACAGATTCCACAGAATTTATAGCTGACTACT
 TTGAGACGAGCAGCCAGTGTCTCAAGGCCAGTGTATCTTCTTAACCAAGAGAGGCCGGCAGGTCTGTGCTGACCC
 CAGTGAGGAGTGGGTCCAGAAATACGTGACCTGGAGCTGAGTGCCGAGCTCAAACCCCACTTGGTGACACA
 ACTCACACAGAGCCCAAATCTTGTGACACACCTCCCCCGTGCCCAAGGTGCCCAGGCGGTGGAAGCAGCGGAGGT
 GGAAGTGGAGGACAGCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAG
 GTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCAGCGACATCGCCGTGGAGTGGGAGAGCAGCGGGCAGCCG
 GAGAACAATAACAACACCGCTCCCATGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACCGTGGA
 CAAGAGCAGGTGGCAGCAGGGGAACATCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCGCTTCACGCAG
 AAGAGCCTCTCCCTGTCTCCGGGTAAAGGCCTCGGTGGCCTGCGAGTCCAGCCACAGAATCAATCGTGCGGTTTC
 CAAACATCACCAATCTCTGCCCTTCGGGAGAAGTGTTAATGCCACACGGTTTGCCTCAGTGTATGCCTGGAACCGG
 AAGAGAATCTCCAATGCGTGGCAGACTATTCTGTGCTGTACAACAGCGCTCCTTCTACTTTCAAGTGCTACGG
 CGTGTCTCTACTAAGCTGAACGATCTCTGCTTCAAAACGTGTATGCCGATTCTTTGTGATCAGAGGAGACGAAG
 TGCGACAGATTGCTCCTGGACAGACCGGGAACATTGCCGACTACAATAAGCTGCCAGACGATTTCACTGGCTG
 CGTTATTGCCTGGAATTCAAACAACCTCGATTCCAAAGTGGGCGGGAATTATAACTACCTCTATAGACTGTTCCGTAA
 GTCTAACCTGAAGCCATTCGAGCGTGATATTAGCACCGAAATCTACCAGGCAGGTTCAACTCCTTGTAACGGAGTGA
 AGGGATTCAACTGCTACTTCCCACTGCAGTCTATGGGTTCCAGCCTACATATGGAGTGGGGTACCAGCCTTATCGG
 GTCGTTGTGCTGTCTTTGAGCTGCTCCACGCTCCTGCAACTGTTTGCGGACCTAAGAAATCCACCAACCTGGTGAA
 GAACAAGTGCCTGAATTC

B. SEQ ID NO: 295

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
 WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLNYSASFSTFKCYGVSPTKLNDLCFT
 NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVKGFNCFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 45

SEQ ID NO: 296

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSTSRQIPQNFADYFETSSQCSKPSVIFLTRGRQVCADPSEE
 WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESSGQPENNYNTTPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLNYSASFSTFKCYGVSPTKLNDLCFT
 NVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVEGFNCFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFGGSGGGSEGG
 GSEGGGSEGGGSEGGGSEGGGSGGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLN
 SASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNY
 NYLYRLFRKSNLKPFERDISTEYQAGSTPCNGVKGFNCFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKS
 TNLVKNKCVNF

Fig. 46

SEQ ID NO: 297

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
 WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
 NVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFGGSAGGSGSG
 SSGGSSGASGTGTAGGTGSGSGTSGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYN
 SASFSTFKCYGVSPTKLNLCFTNVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNY
 NYLYRLFRKSNLKPFERDISTEYQAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKS
 TNLVKNKCVNF

Fig. 47

SEQ ID NO: 298

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
 WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
 NVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
 NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 48

SEQ ID NO: 299

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
 WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
 GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
 NVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDISTEY
 QAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFSLSLSPGKGLG
 GLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFTNVYA
 DSFVIRGDEVQRQIAPGQTGNIADYNYKLPDDFTGCVIAWNSNNLDSKVGGNYYLYRLFRKSNLKPFERDISTEYQAGS
 TPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNF

Fig. 49

SEQ ID NO: 300

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
QAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFGGSGGGSEGG
GSEGGGSEGGGSEGGGSEGGGSGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYN
SASFSTFKCYGVSPTKLNLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNY
NYLYRLFRKSNLKPFERDISTEYQAGSTPCNGVEGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKK
STNLVKNKCVNF

Fig. 50

SEQ ID NO: 301

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
QAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFGGSAGGSGSG
SSGGSSGASGTGTAGGTGSGSGTGSGRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYN
SASFSTFKCYGVSPTKLNLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNY
NYLYRLFRKSNLKPFERDISTEYQAGSTPCNGVEGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKK
STNLVKNKCVNF

Fig. 51

SEQ ID NO: 302

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTEPKSCDTPPPCPRCPGGGSSGGGSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNLCFT
NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
QAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFGGSGGGSEGG
GSEGGGSEGGGSEGGGSEGGGSGGSRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYN
SASFSTFKCYGVSPTKLNLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLPPDFTGCVIAWNSNNLDSKVGGNY
NYRYRLFRKSNLKPFERDISTEYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVLSFELLHAPATVCGPKK
STNLVKNKCVNF

Fig. 52

SEQ ID NO: 303

MQVSTAALAVLLCTMALCNQVLSAPLAADTPTACCFSYTSRQIPQNFIADYFETSSQCSKPSVIFLTRGRQVCADPSEE
WVQKYVSDLELSAELKTPLGDTTHTPEPKSCDTPPPCPRCPGGSSGGSSGGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQGNIFSCSVMHEALHNRFTQKSLSLSPGK
GLGGLRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFT
NVYADSFVIRGDEVQRQIAPGQTGNIADYNYKLDDFTGCVIAWNSNNLDSKVGGNYNYLYRLFRKSNLKPFERDISTEY
QAGSTPCNGVKGFNCYFPLQSYGFQPTYGVGYQPYRVVVLSEFLLHAPATVCGPKKSTNLVKNKCVNFGGSAGGSGSG
SSGSSSGASGTGTAGGTGSGSGTGSGRVQPTESIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYN
SASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGDEVQRQIAPGQTGKIADYNYKLDDFTGCVIAWNSNNLDSKVGGNY
NYRYRLFRKSNLKPFERDISTEYQAGSTPCNGVEGFNCYFPLQSYGFQPTNGVGYQPYRVVVLSEFLLHAPATVCGPKK
STNLVKNKCVNF

Fig. 53A.

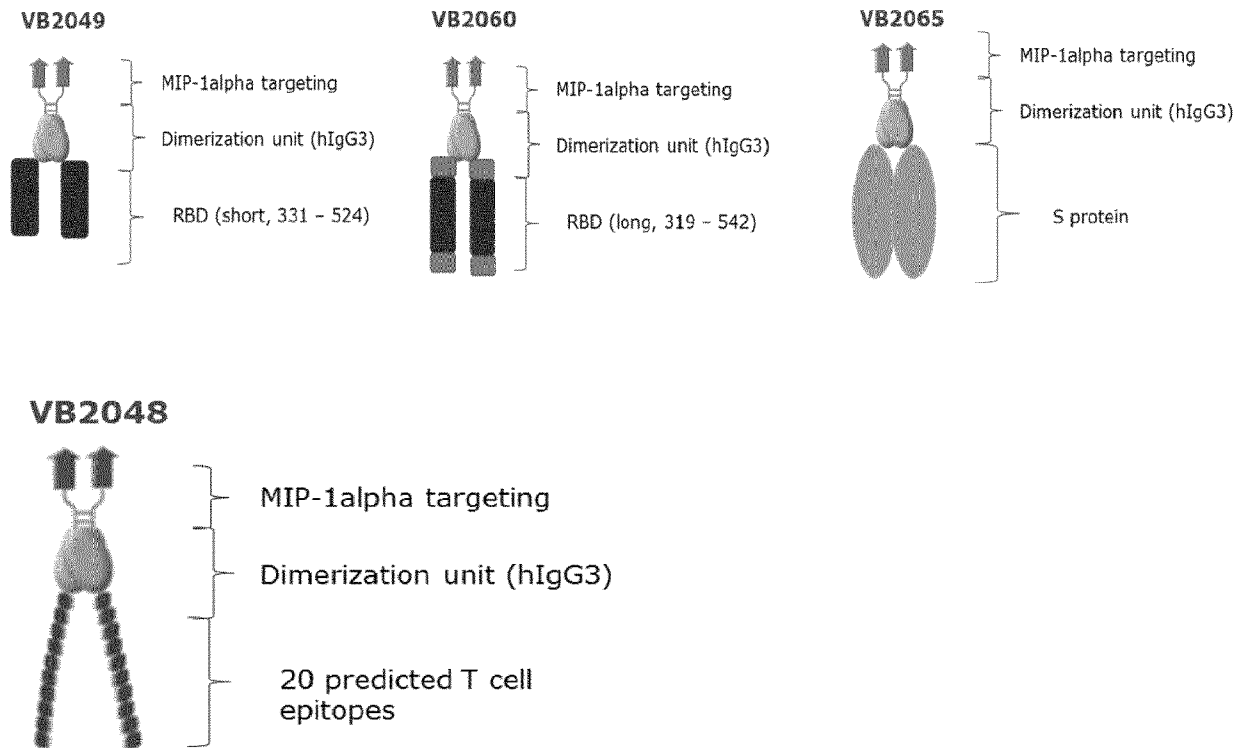


Fig. 53B.

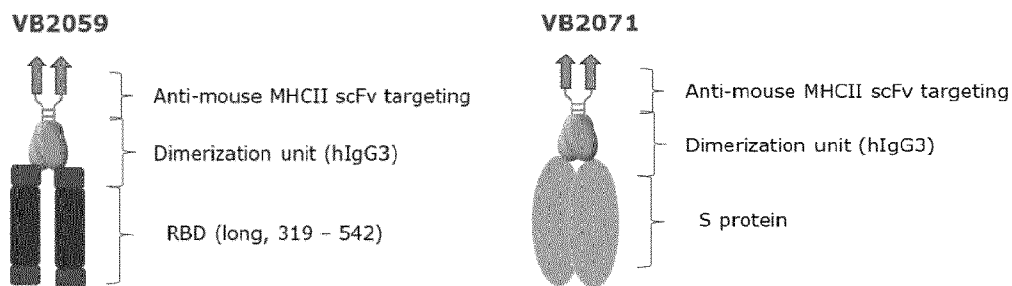


Fig. 53C.

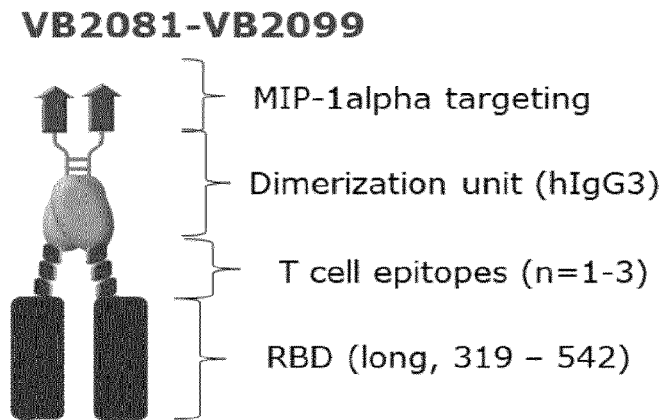


Fig. 53D.

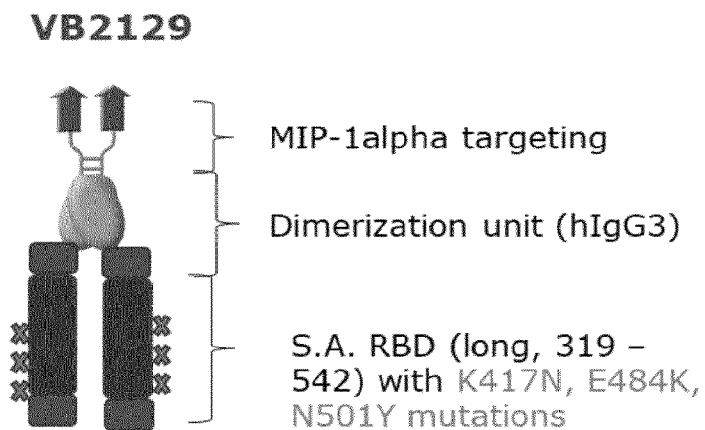


Fig. 53E.

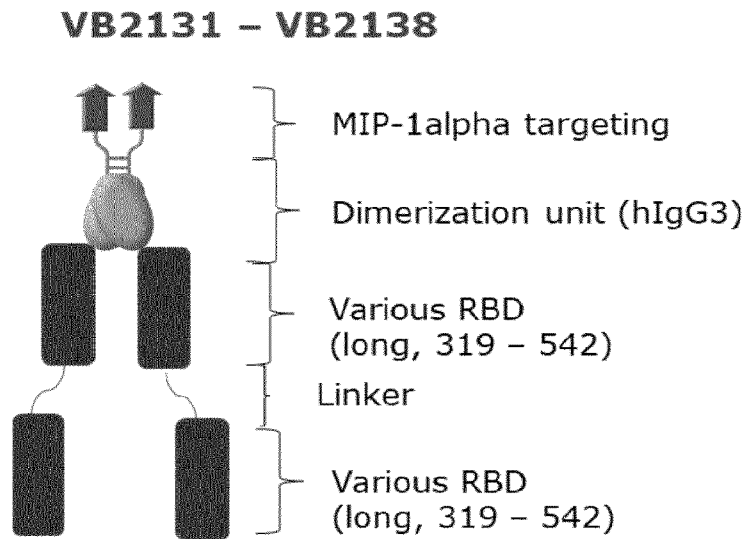


Fig. 54

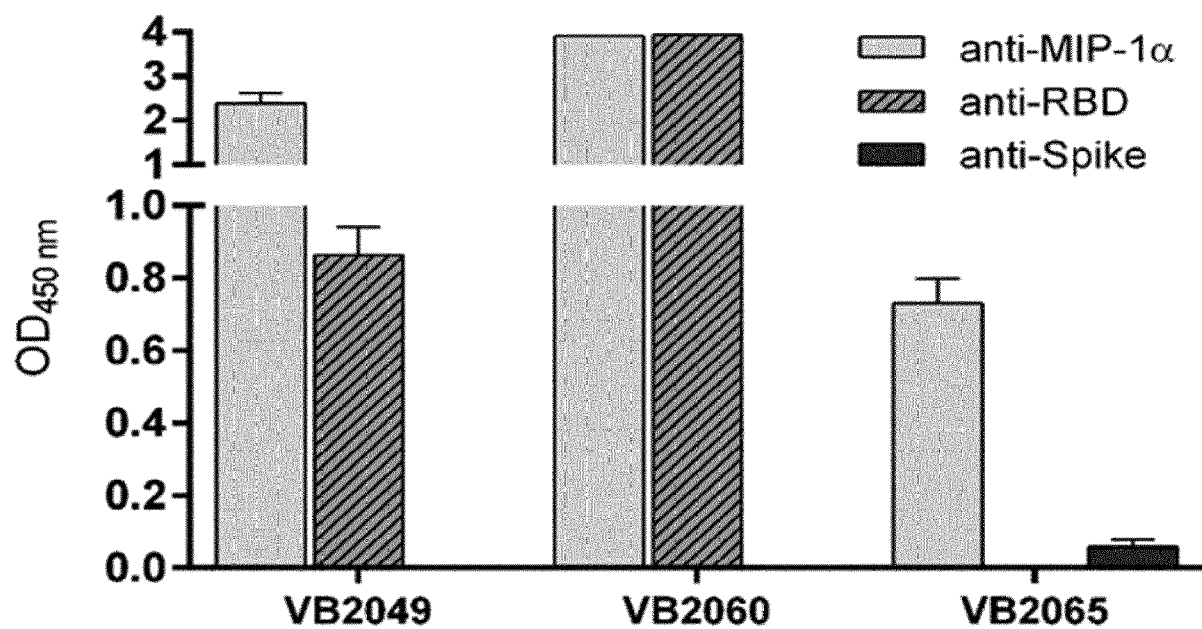


Fig. 55A.

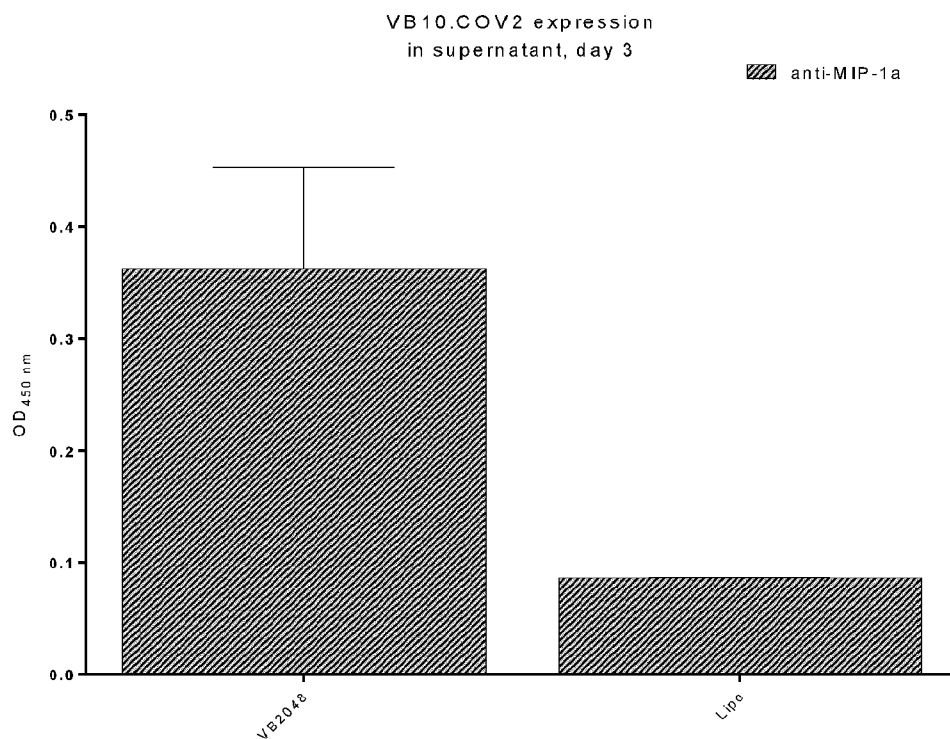


Fig. 55B.

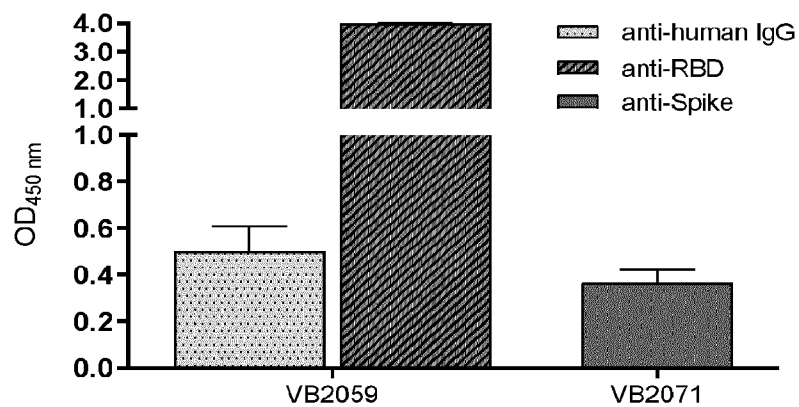


Fig. 55C.

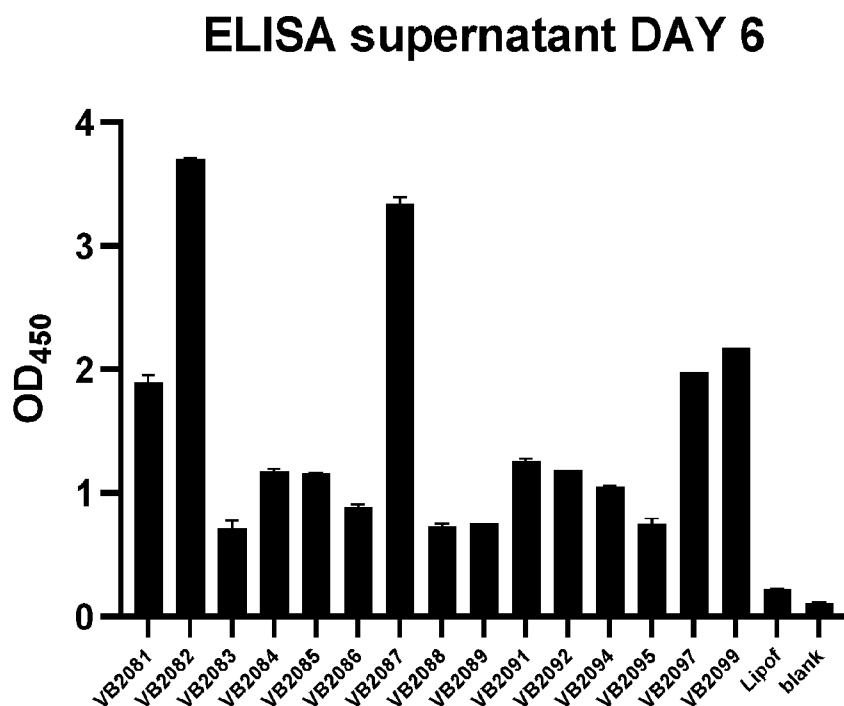


Fig. 55D.

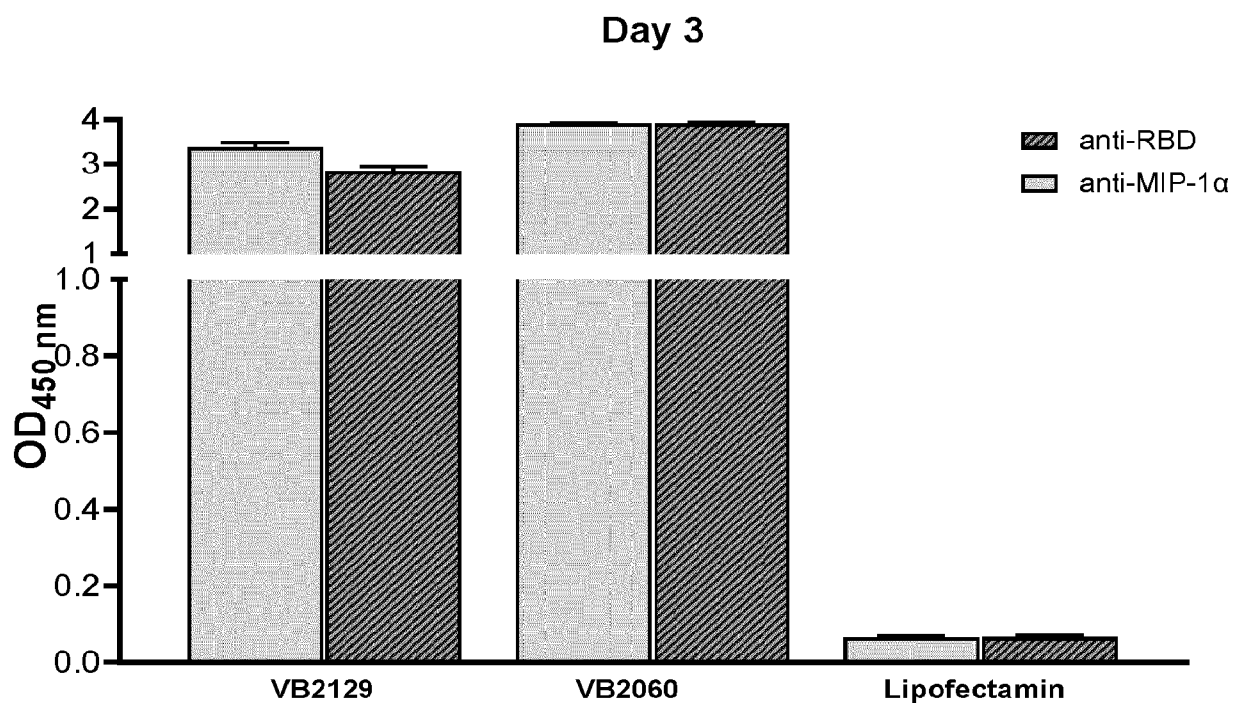


Fig. 55E.

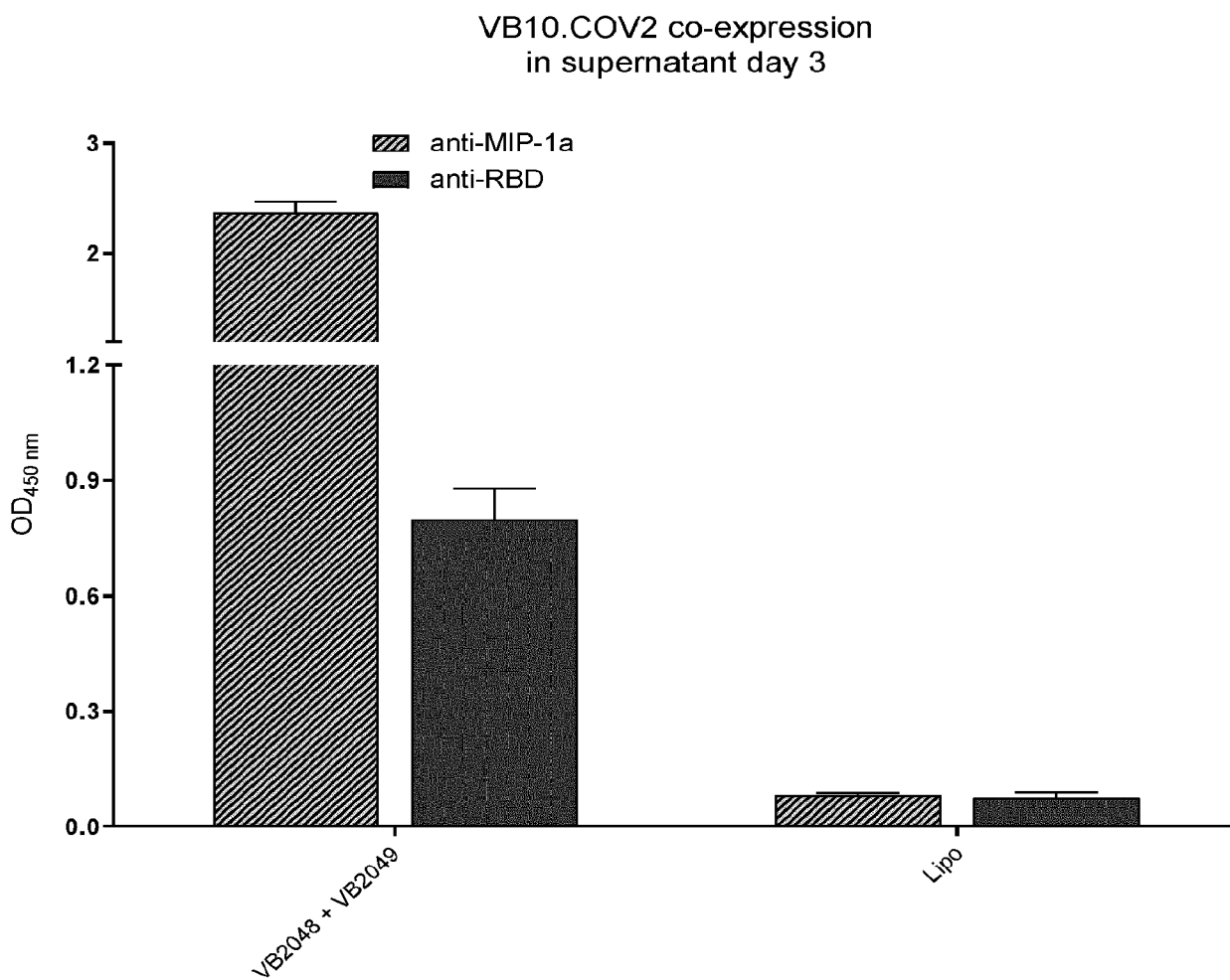


Fig. 56

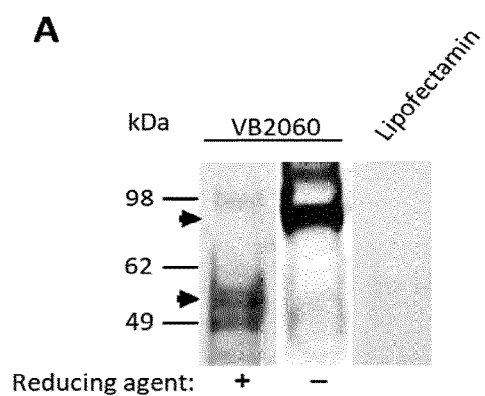


Fig. 57A.

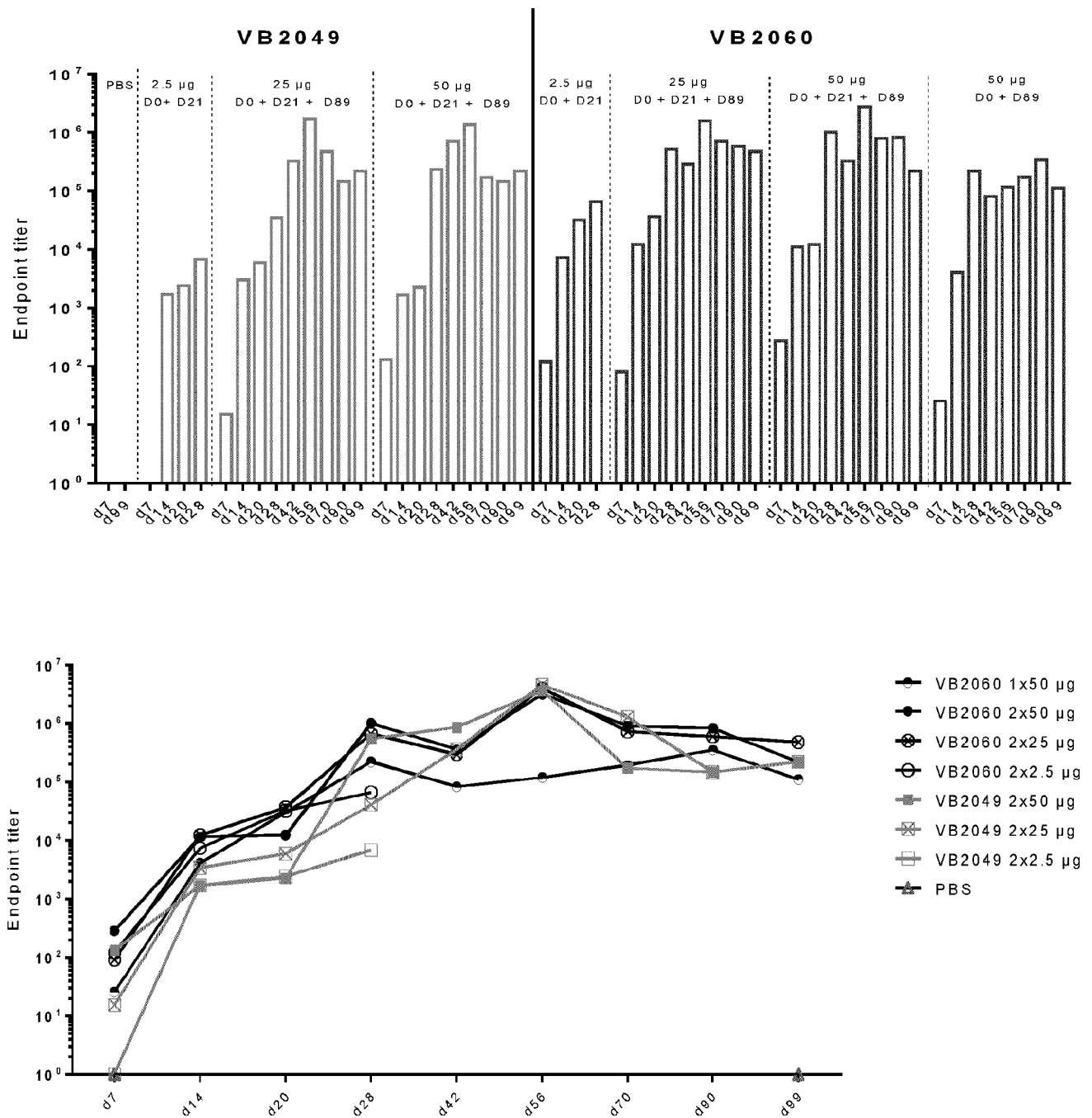


Fig. 57B.

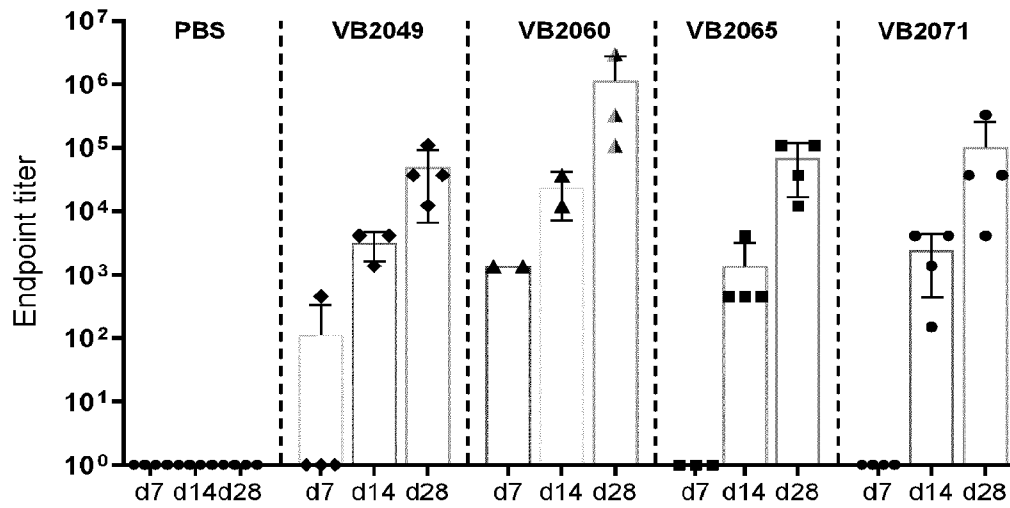


Fig. 57C.

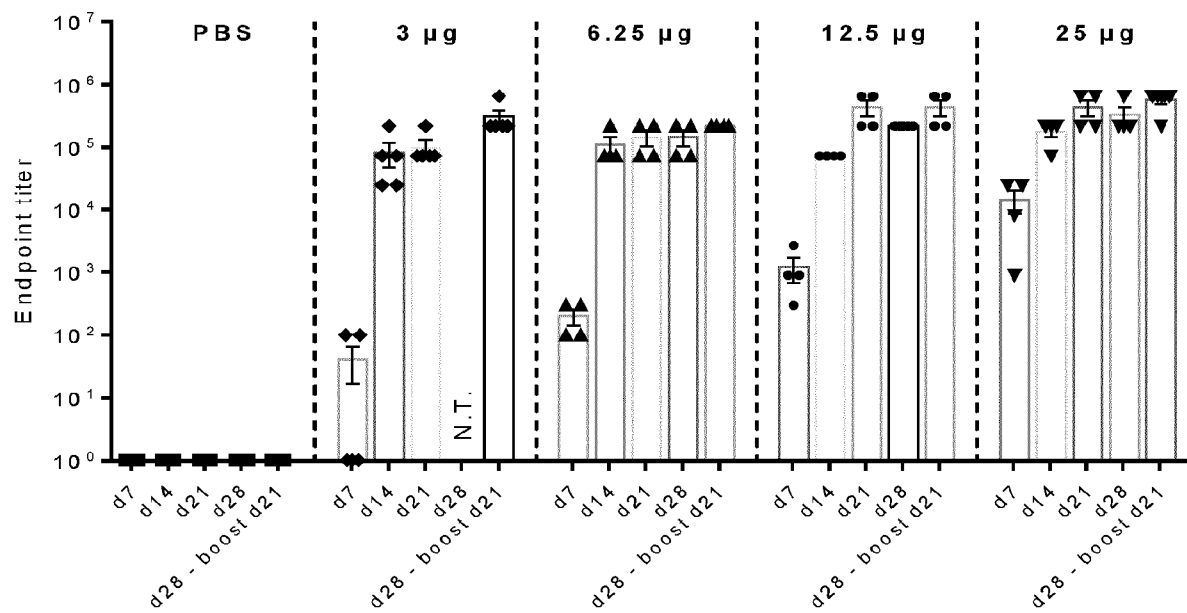


Fig. 57D.

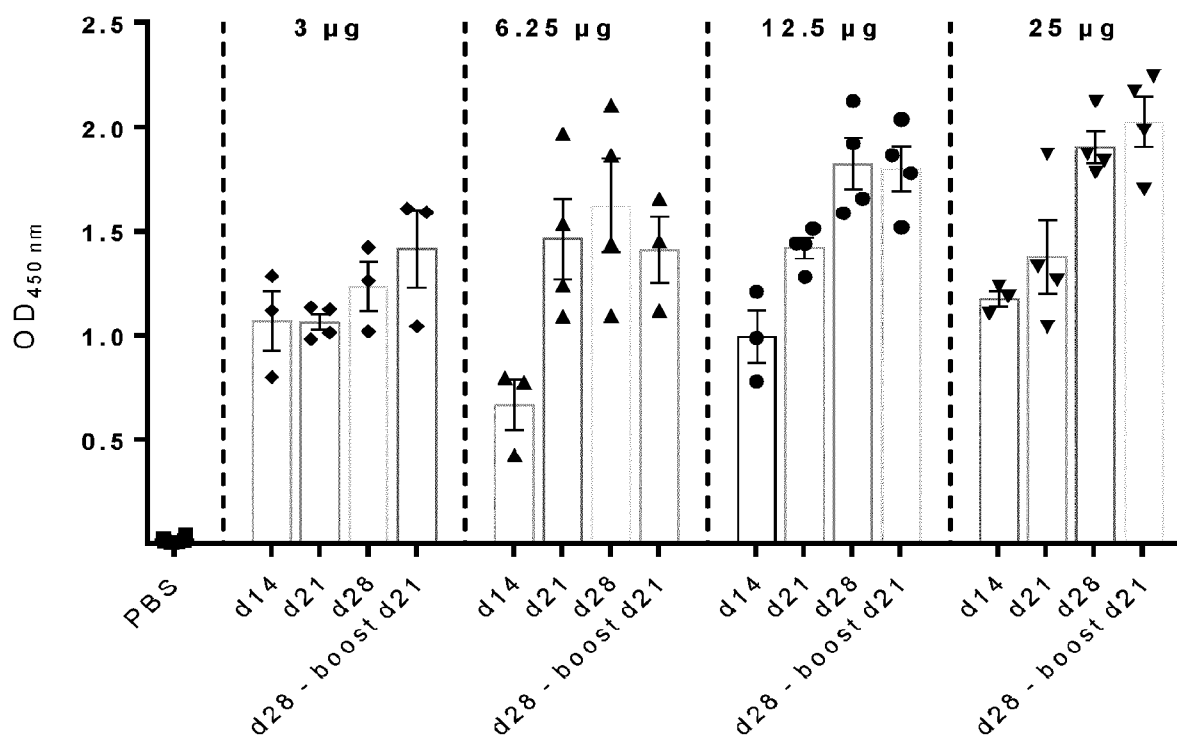


Fig. 57E.

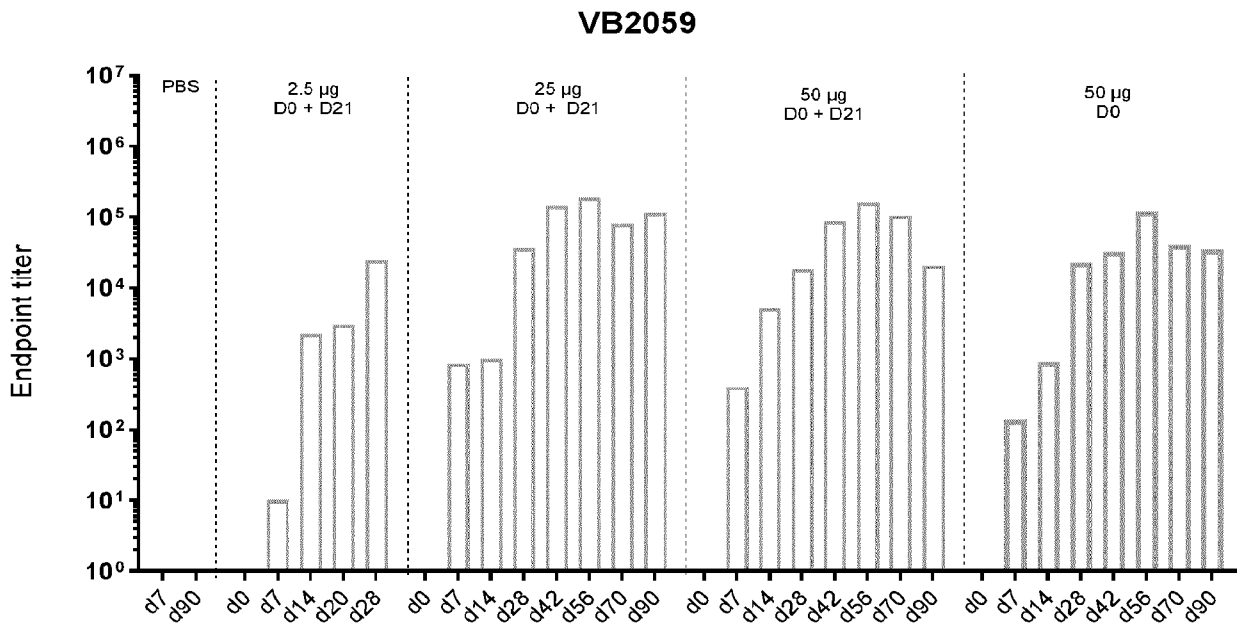


Fig. 57F.

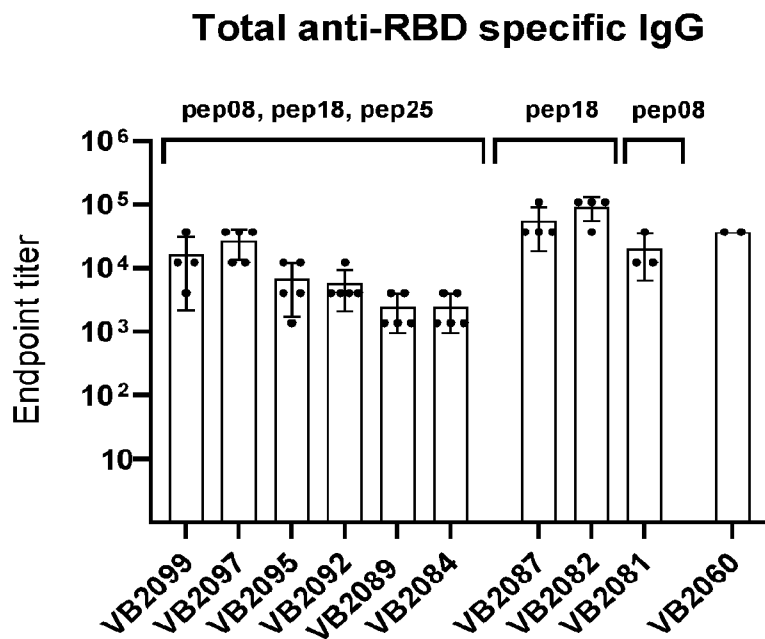


Fig. 57G.

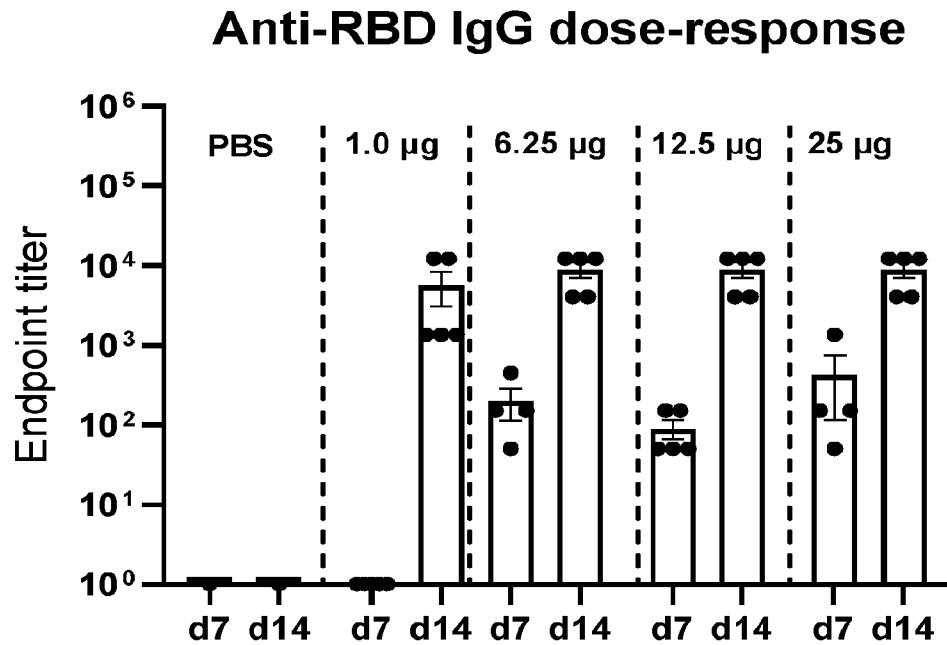


Fig. 57H.

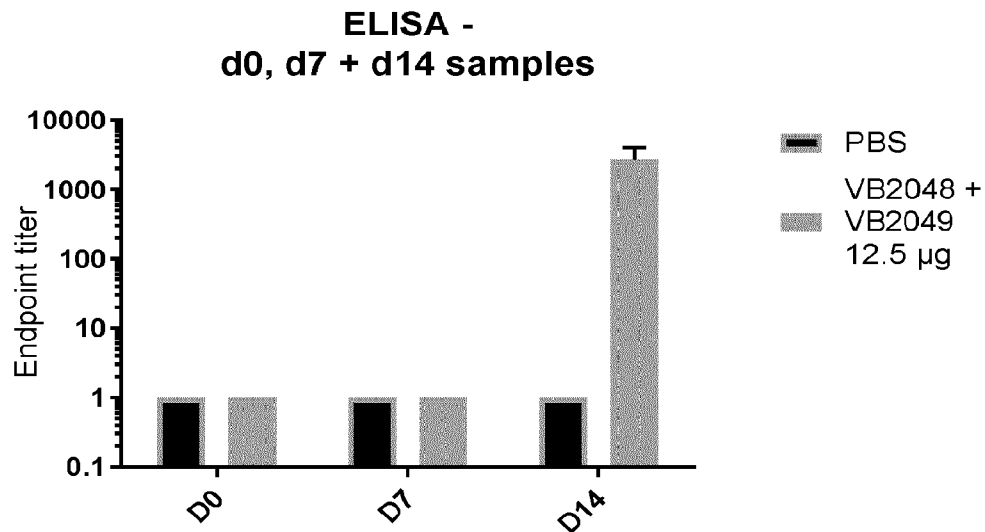
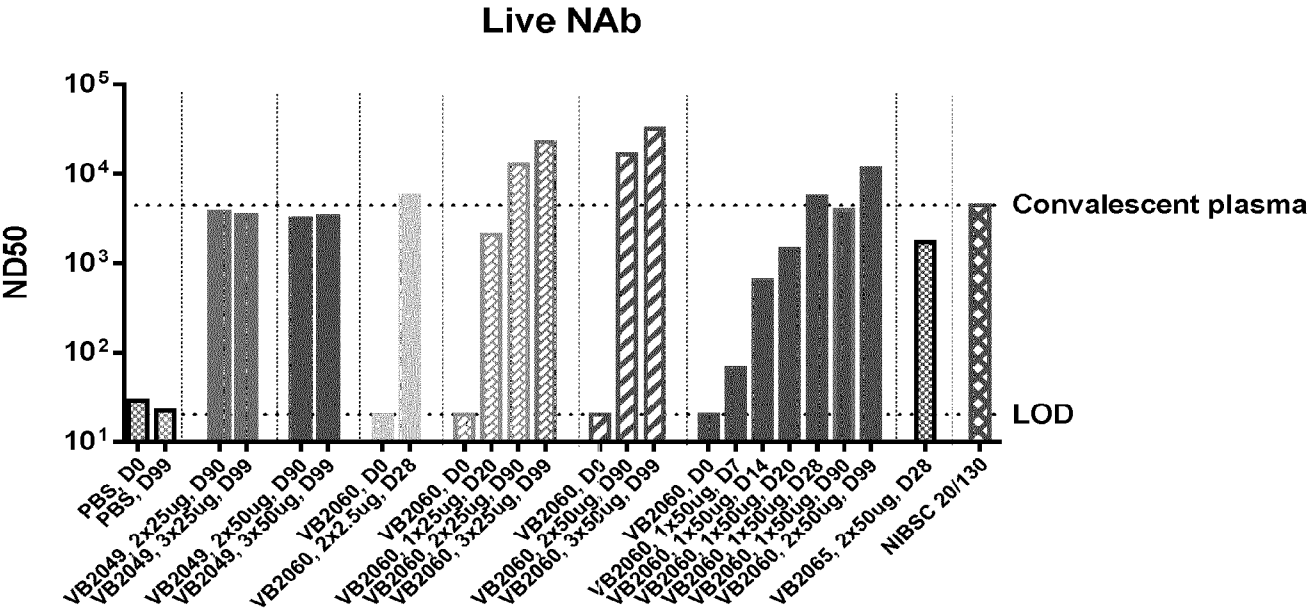


Fig. 58

A:



B:

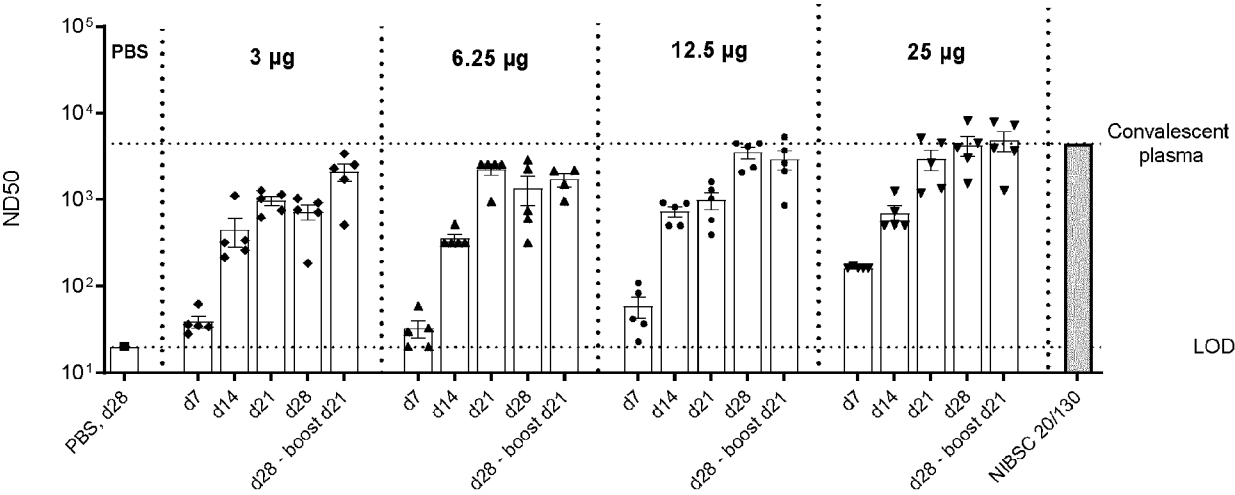


Fig. 59

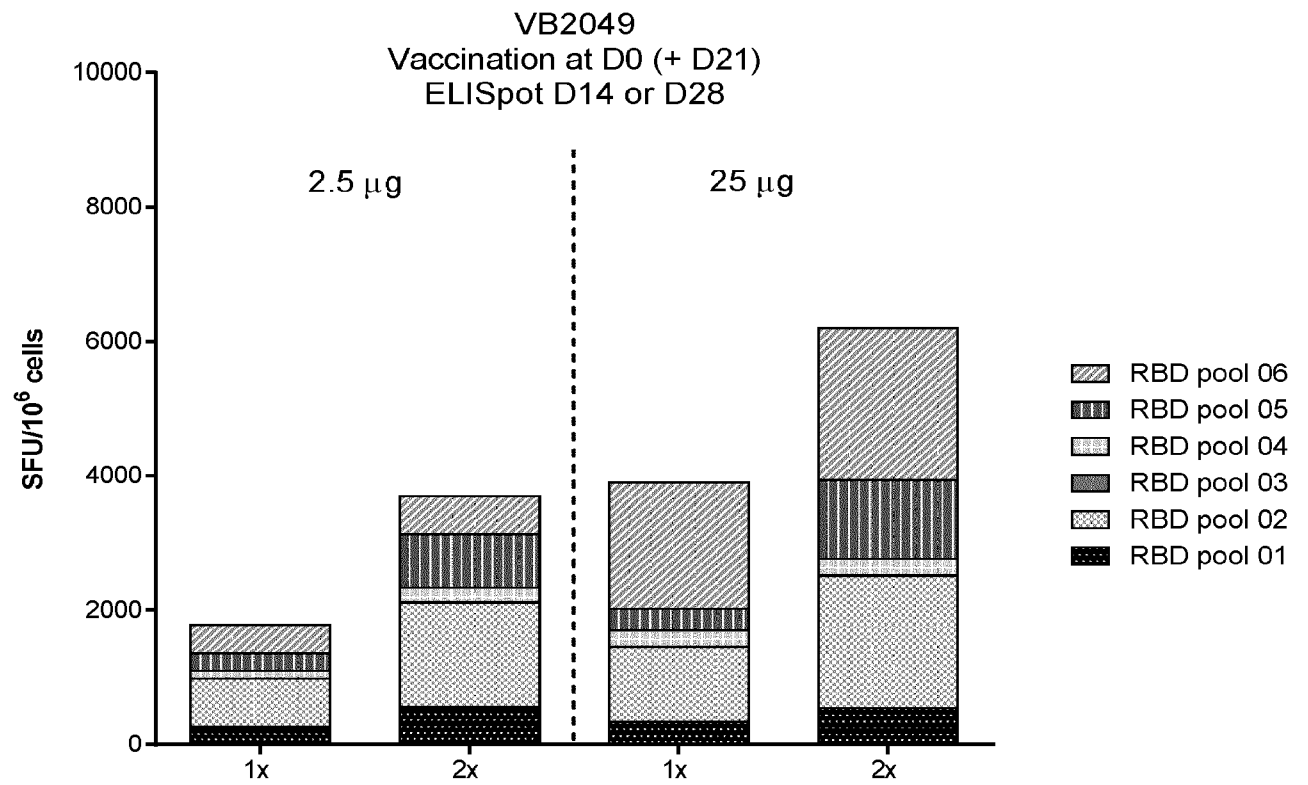


Fig. 60A.

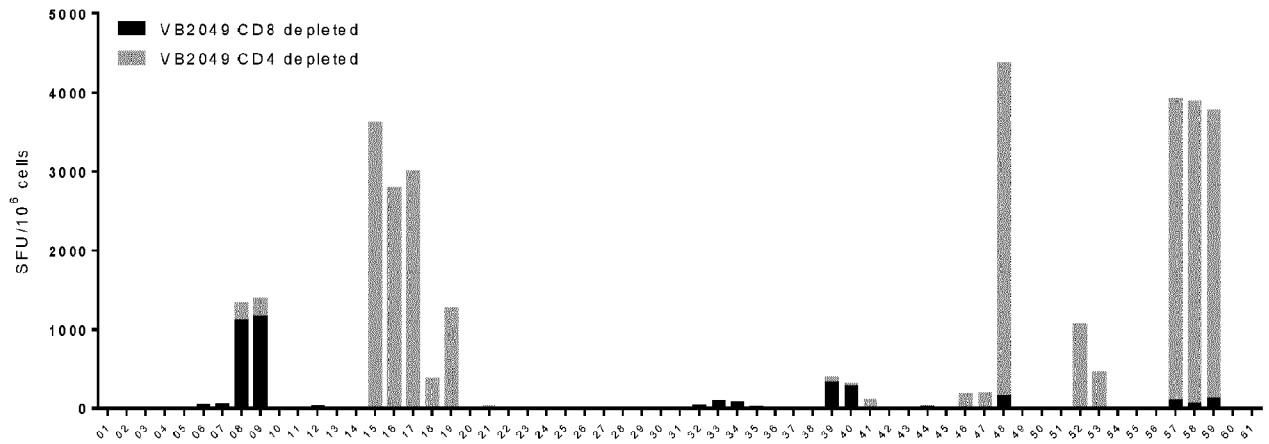


Fig. 60B.

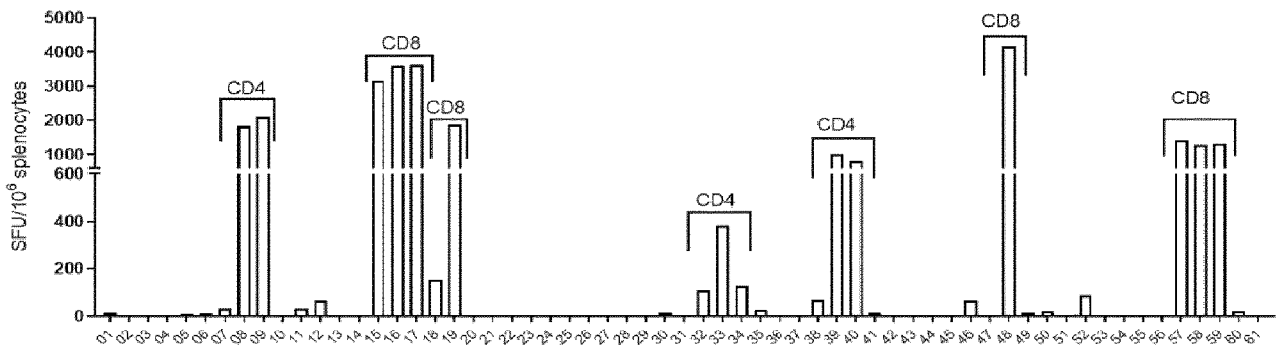
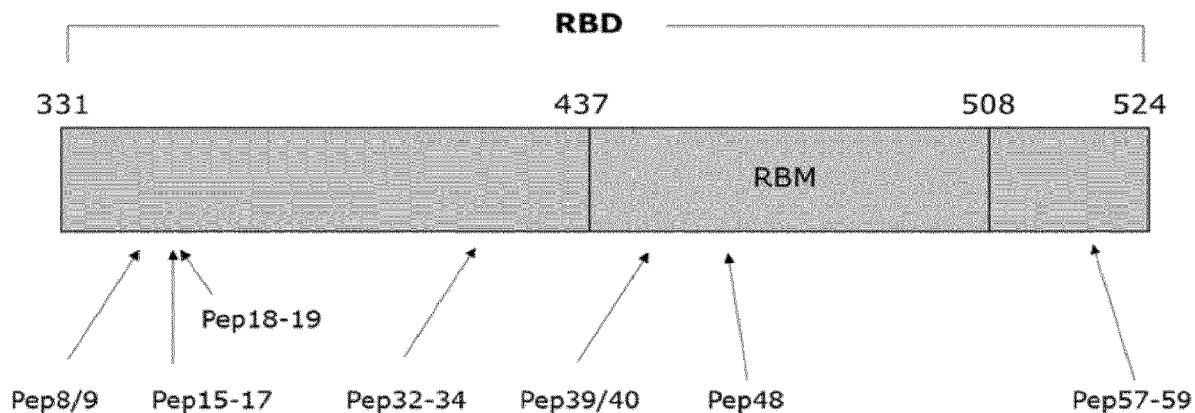


Fig. 60C.



Dominant peptides no./ SEQ ID NO:	sequence	Amino acid	CD4 or CD8 dominated response
08/304	AWNRRKRISNCVADYS	355-369	CD4 (medium)
09/305	RKRISNCVADYSVLY	358-370	CD4 (medium)
15/306	SFSTFKCYGVSP TKL	374-388	CD8 (strong)
16/307	TFKCYGVSP TKLNDL	377-391	CD8 (strong)
17/308	CYGVSP TKLNDLCFT	380-394	CD8 (strong)
18/309	VSPTKLNDLCFTNVY	383-397	CD8 (weak)
19/310	TKLNDLCFTNVYADS	386-400	CD8 (medium)
39/311	VGGNYNYLYRLFRKS	445-459	CD4 (weak)
40/312	NYNYLYRLFRKSNLK	448-462	CD4 (weak)
46/313	RDISTEIYQAGSTPC	465-479	CD8 (weak)
47/314	STEIYQAGSTPCNGV	468-482	CD8 (weak)
48/315	IYQAGSTPCNGVEGF	471-485	CD8 (strong)
52/316	EGFNCYFPLQSYGFQ	484-498	CD8 (medium)
53/317	NCYFPLQSYGFQPTN	487-501	CD8 (weak)
57/318	PTNGVGYQP YRVVVL	499-511	CD8 (strong)
58/319	GVGYQP YRVVVL SFE	502-516	CD8 (strong)
59/320	YQP YRVVVL SFELLH	505-519	CD8 (strong)

Fig. 61A.

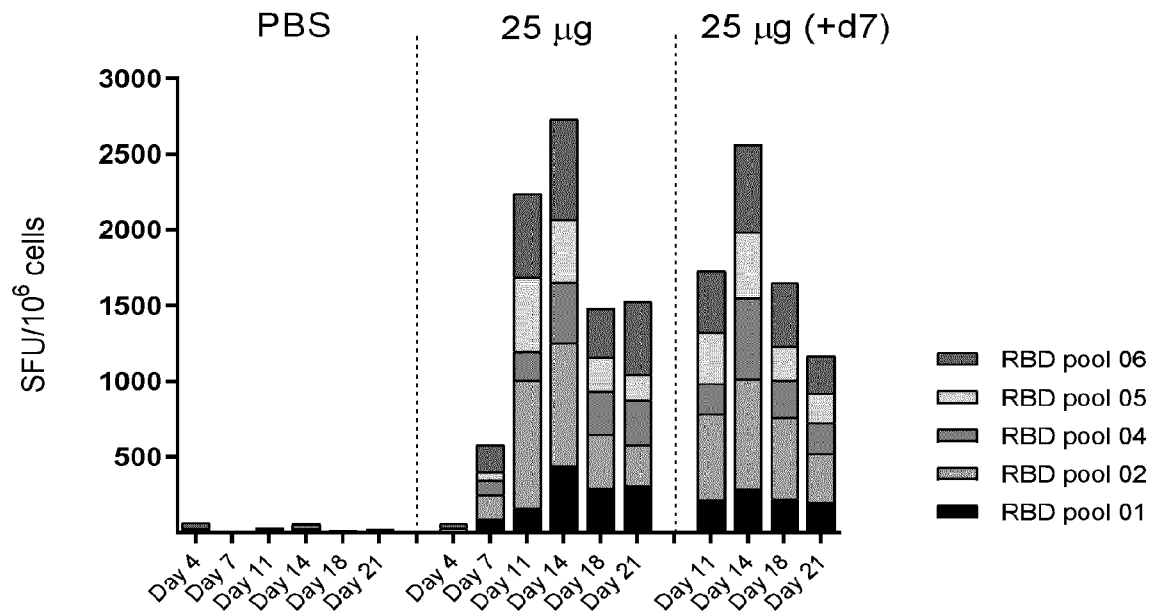


Fig. 61B.

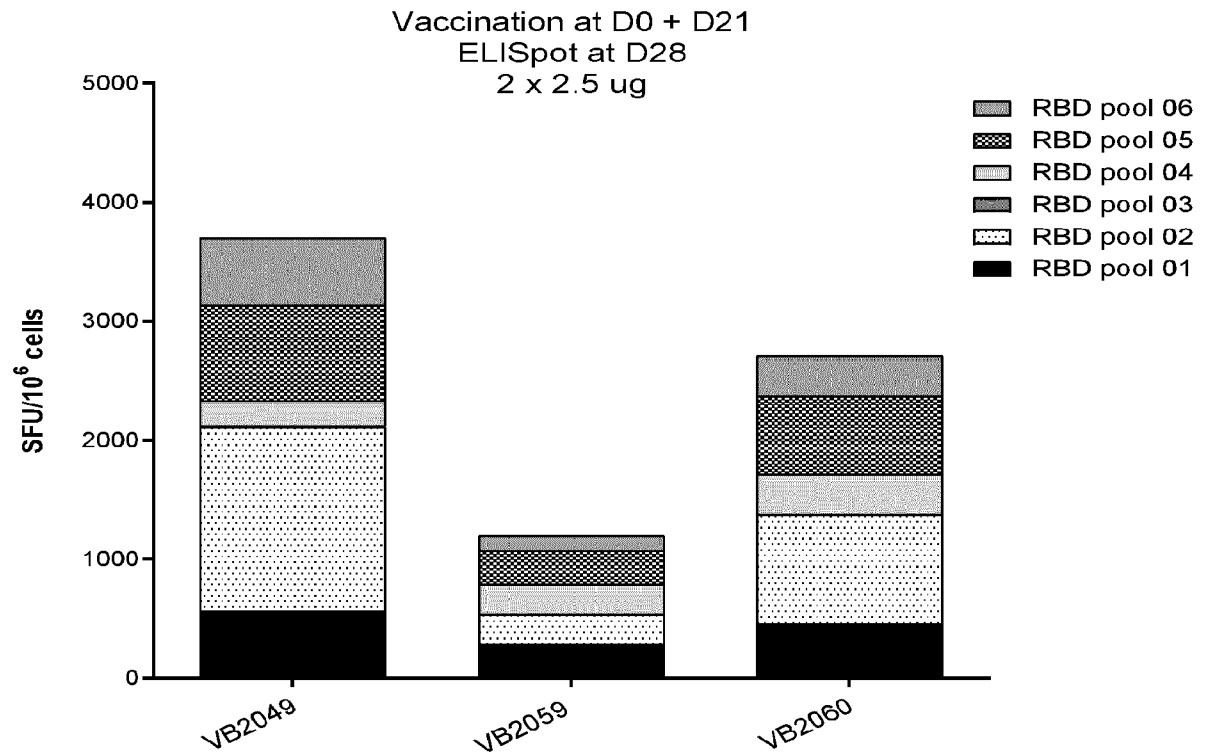


Fig. 62

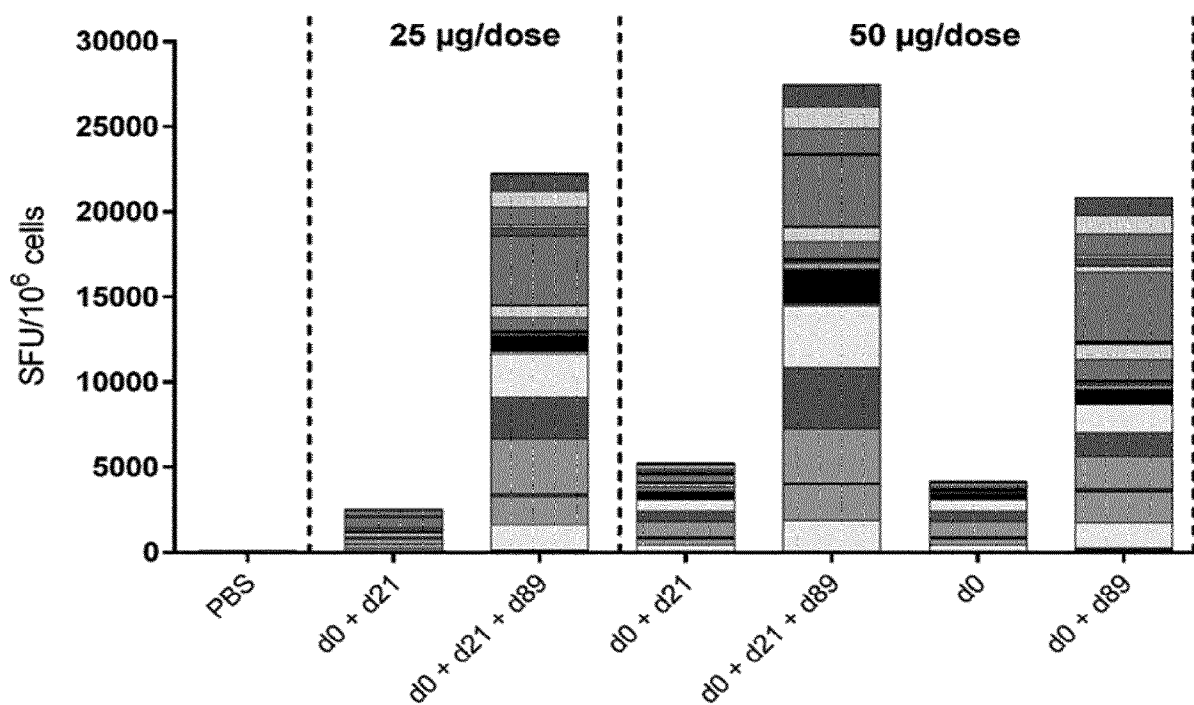
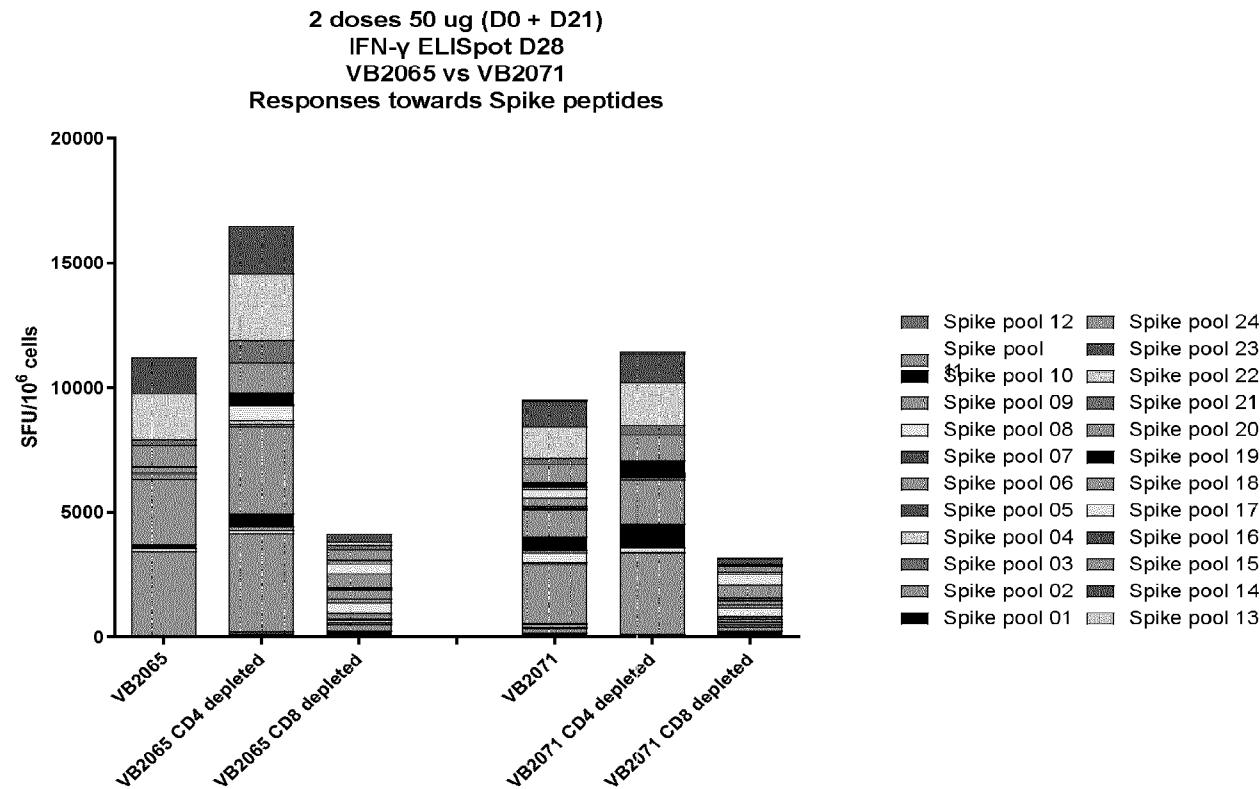


Fig. 63

A:



B:

RBD with S.A. mutations

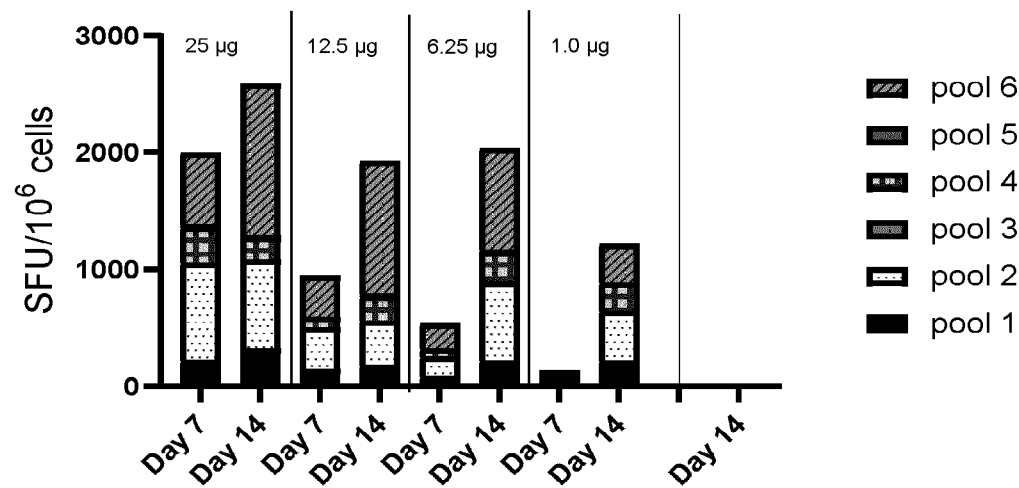


Fig. 64A.

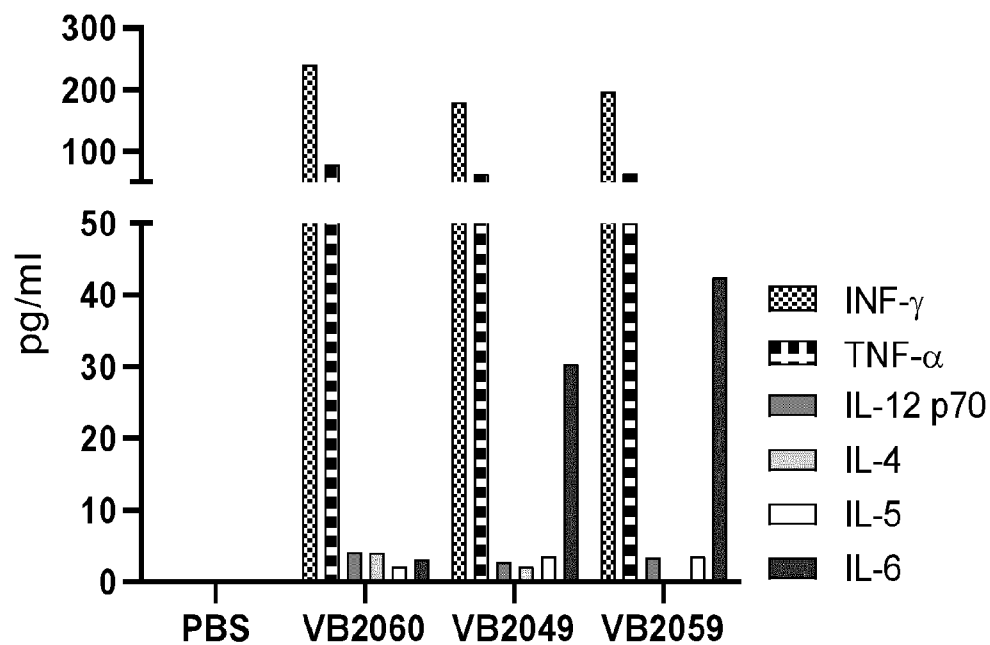


Fig. 64B.

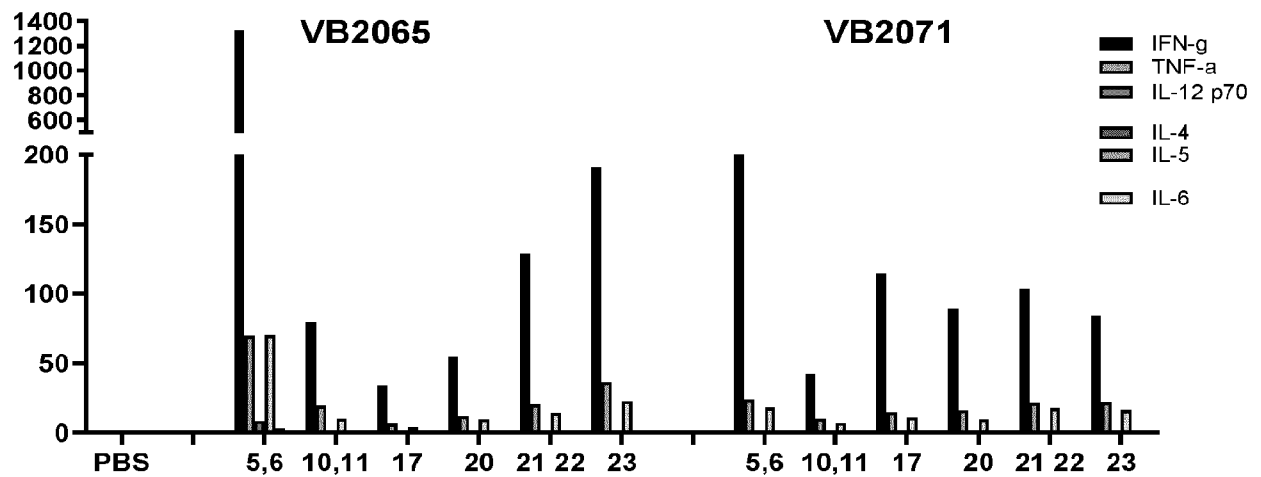


Fig. 65

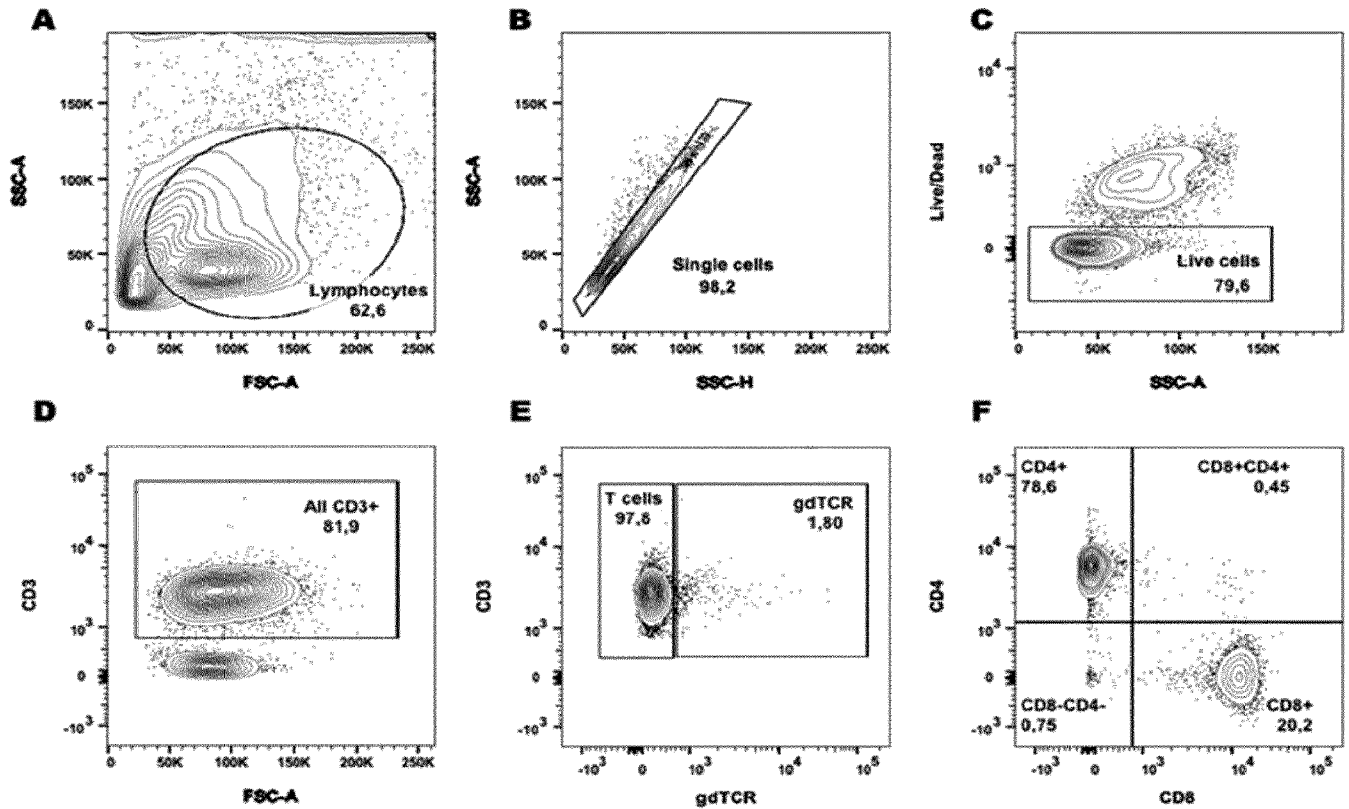


Fig. 66

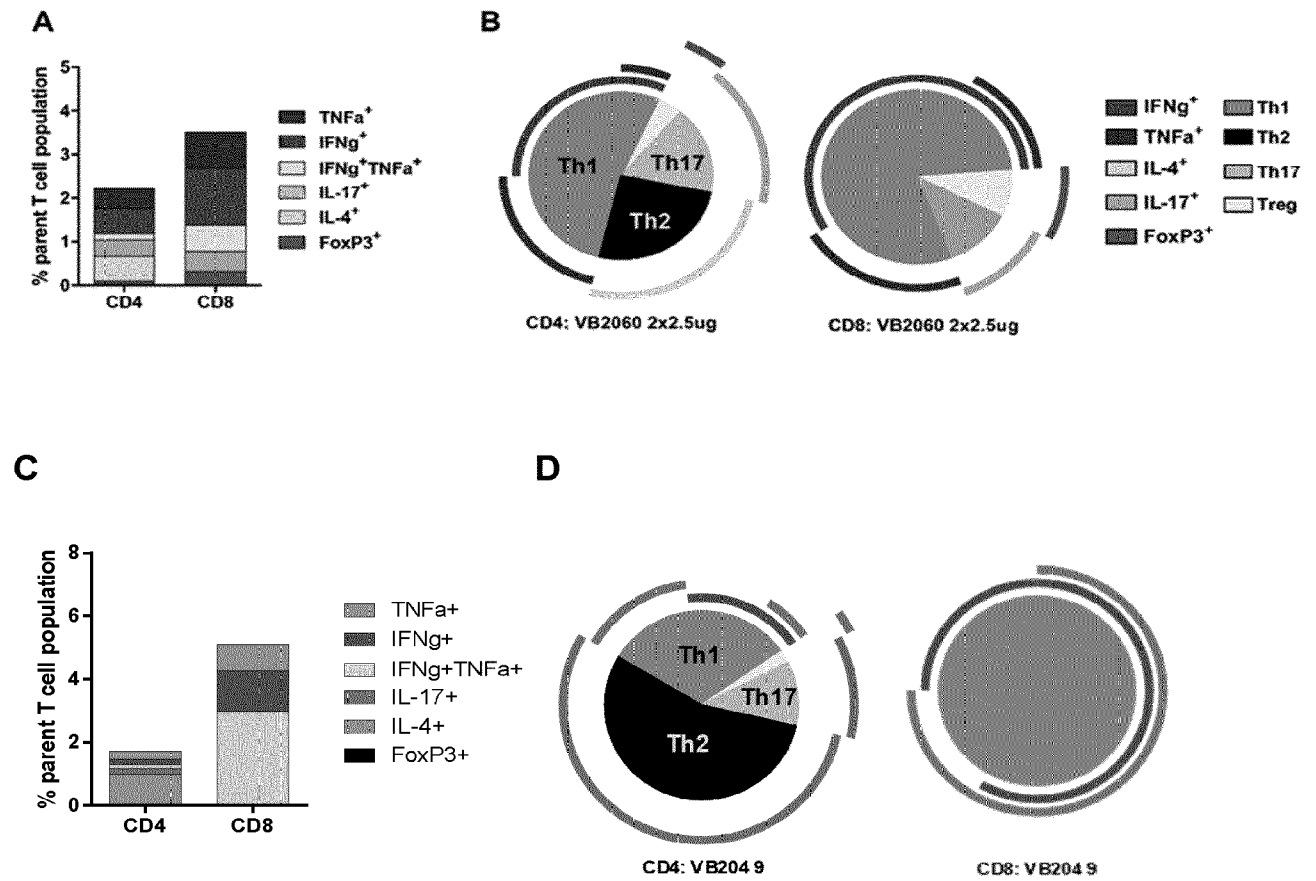


Fig. 67

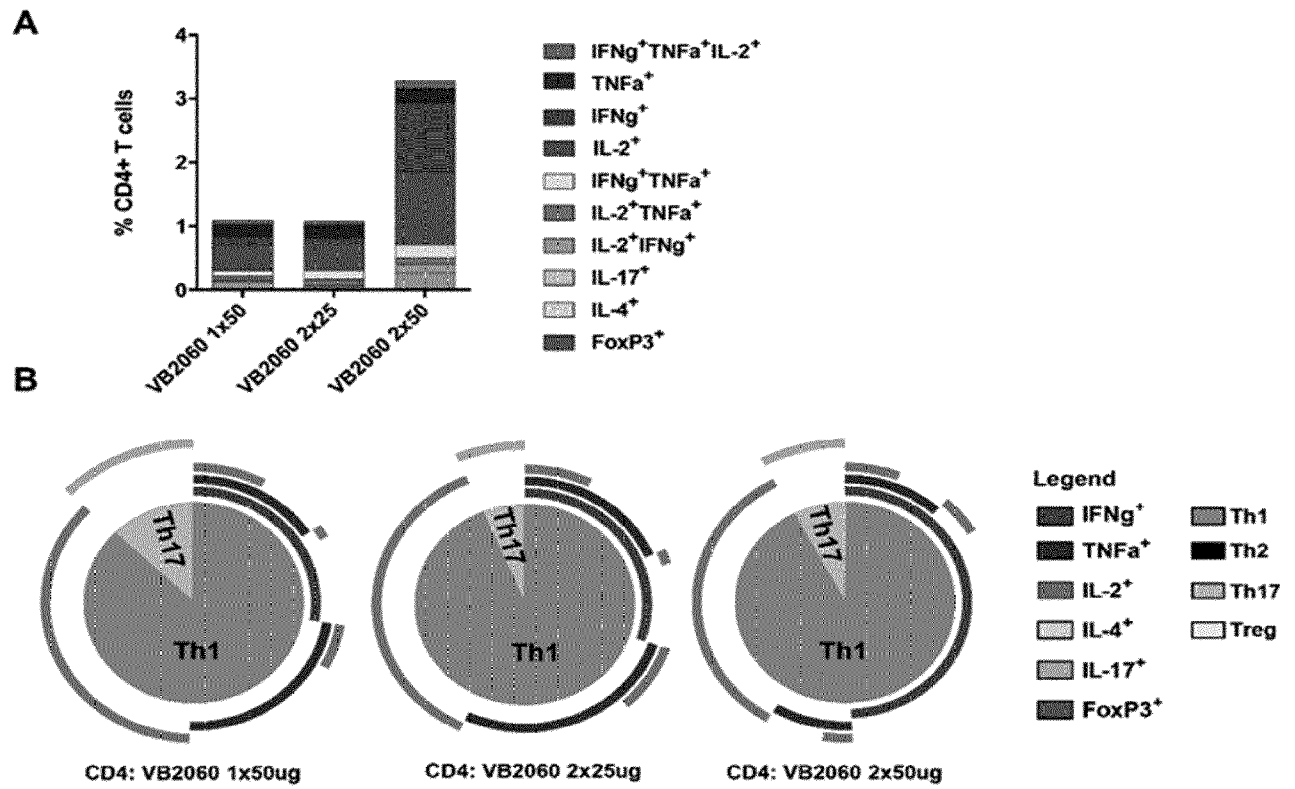


Fig. 68

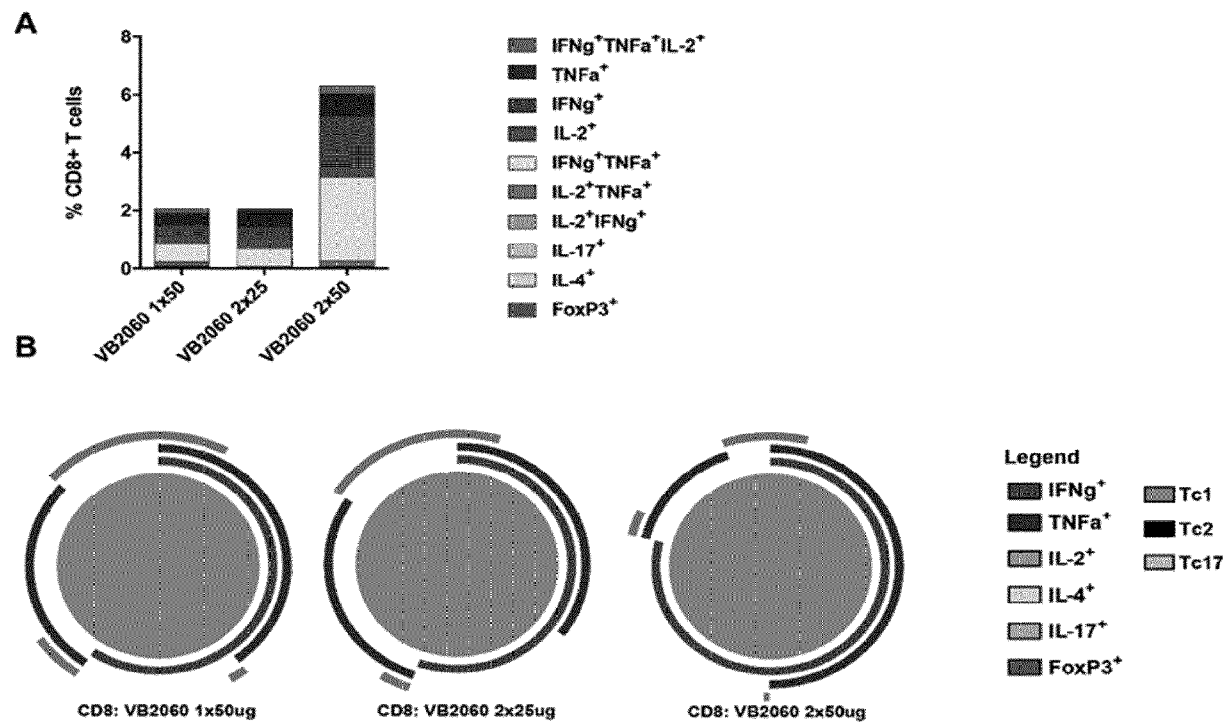


Fig. 69

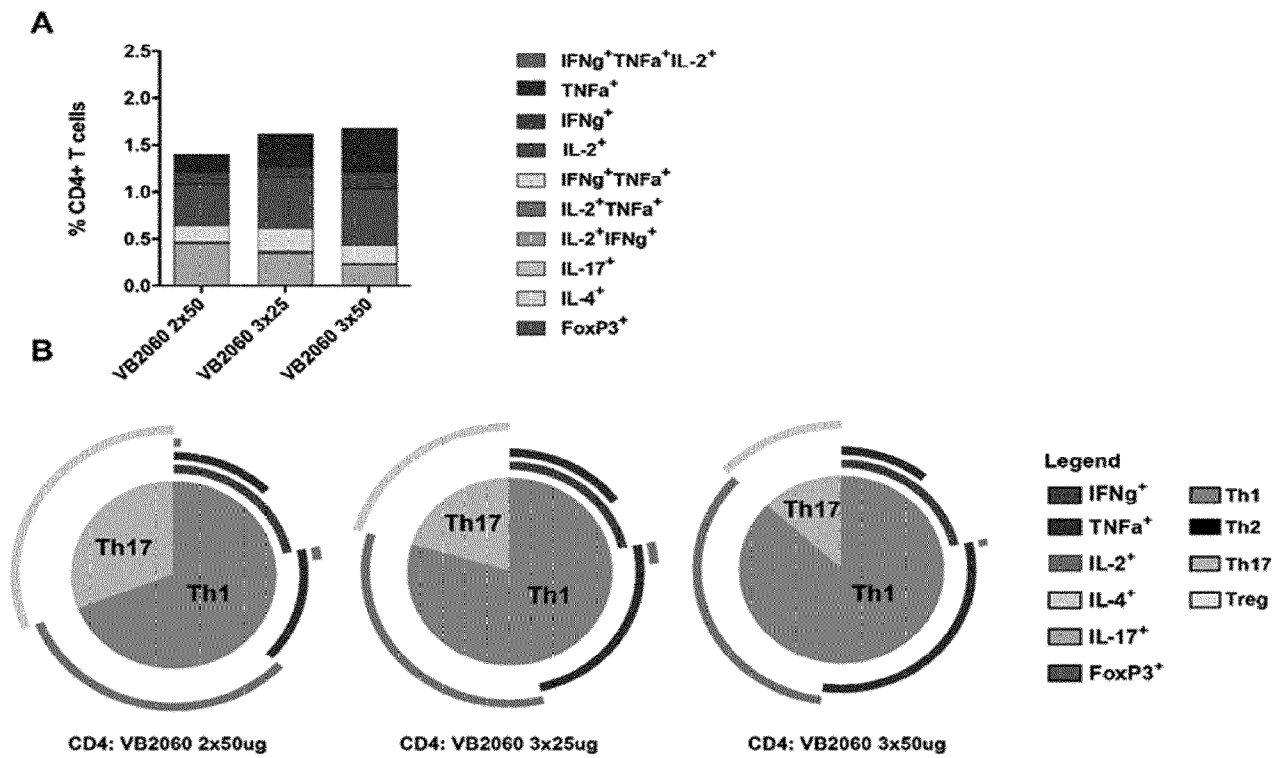


Fig. 70

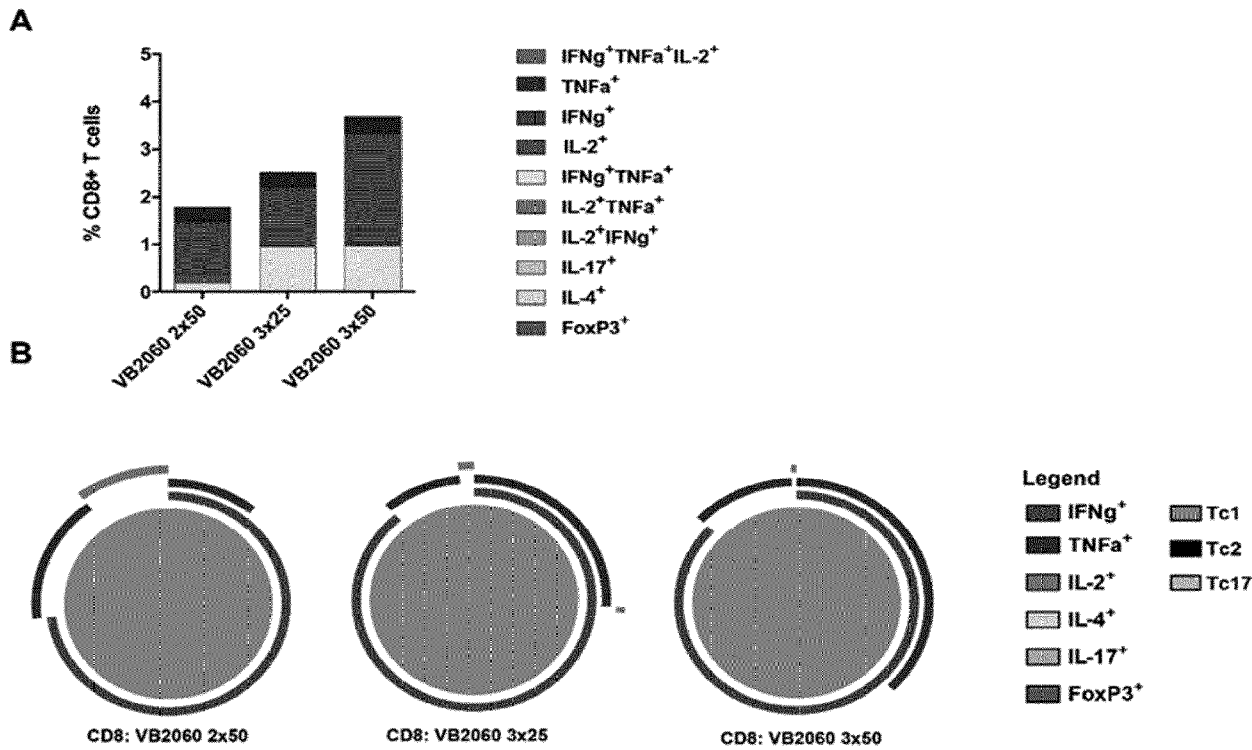


Fig. 71

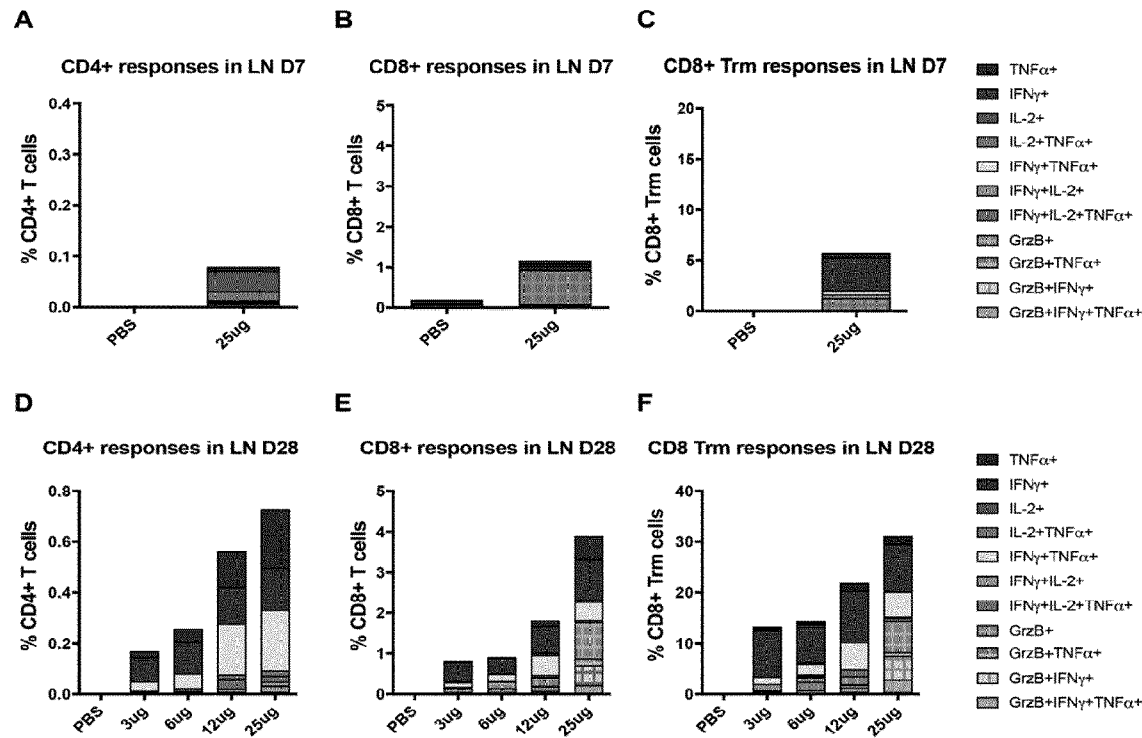


Fig. 72

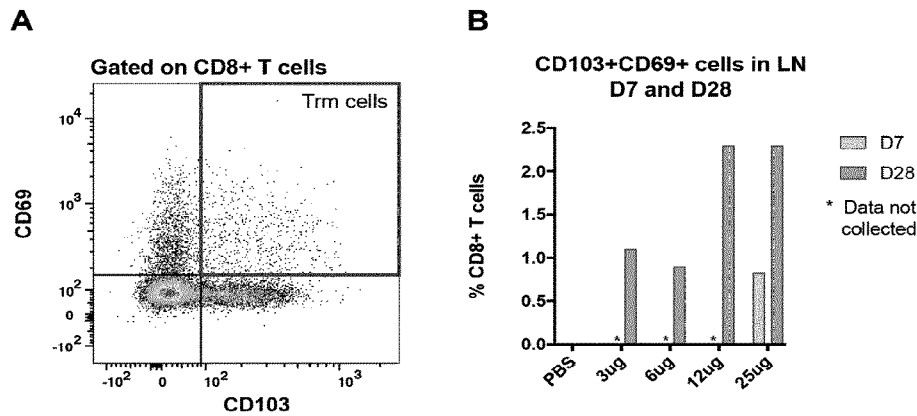


Fig. 73

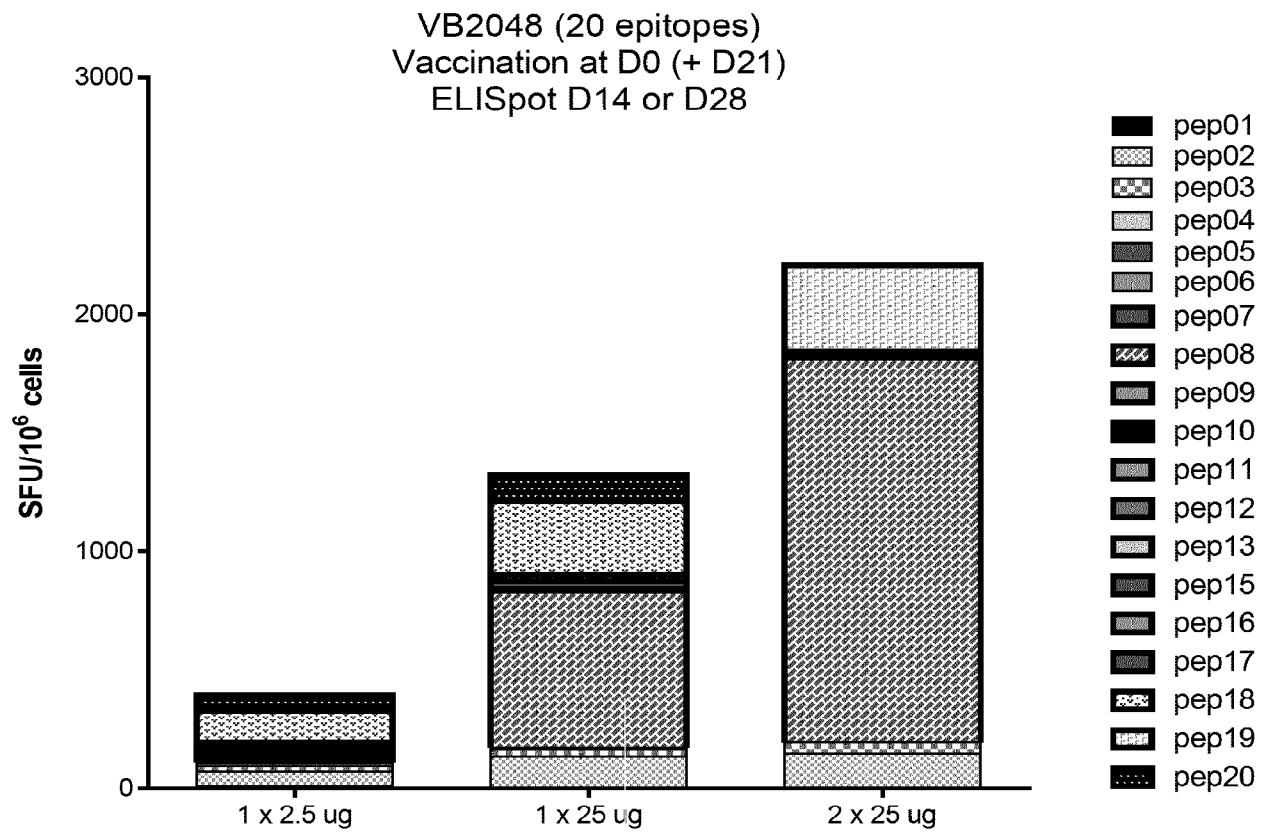


Fig. 74

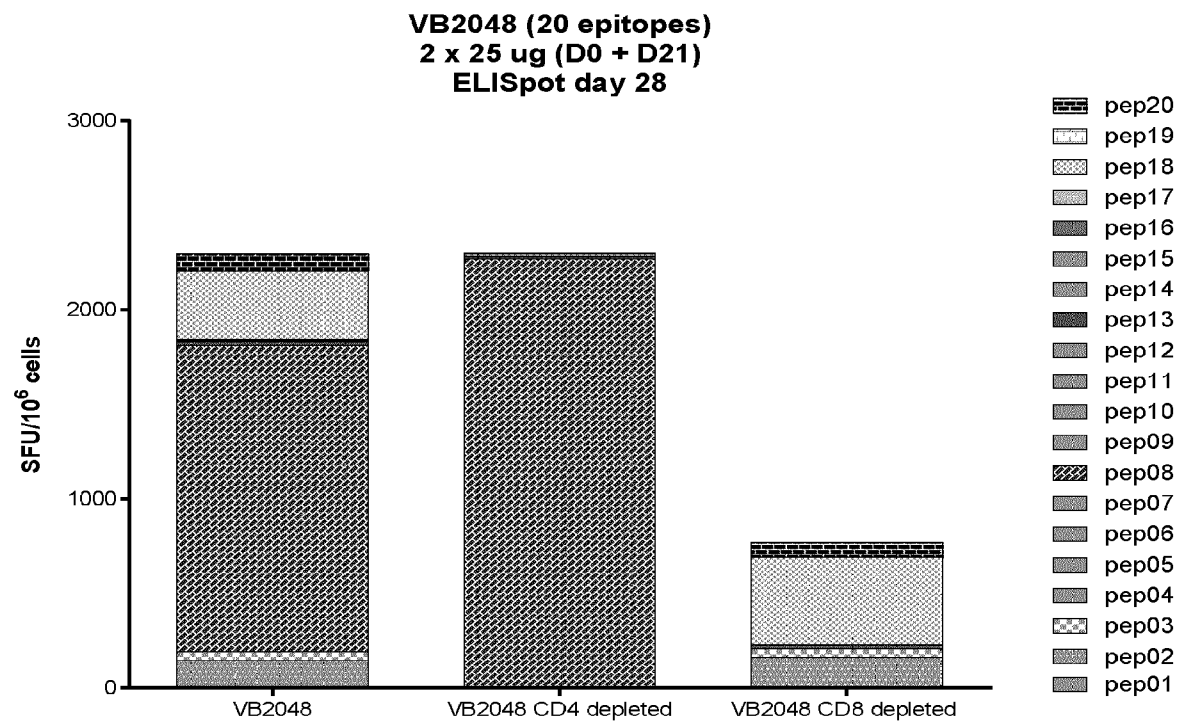


Fig. 75

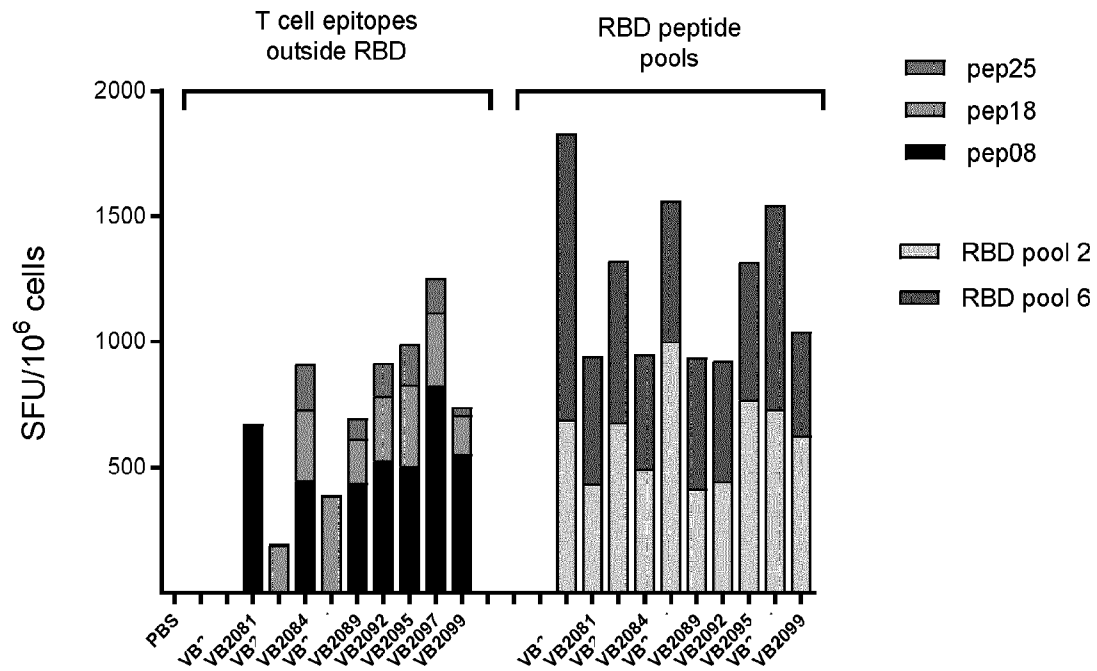


Fig. 76

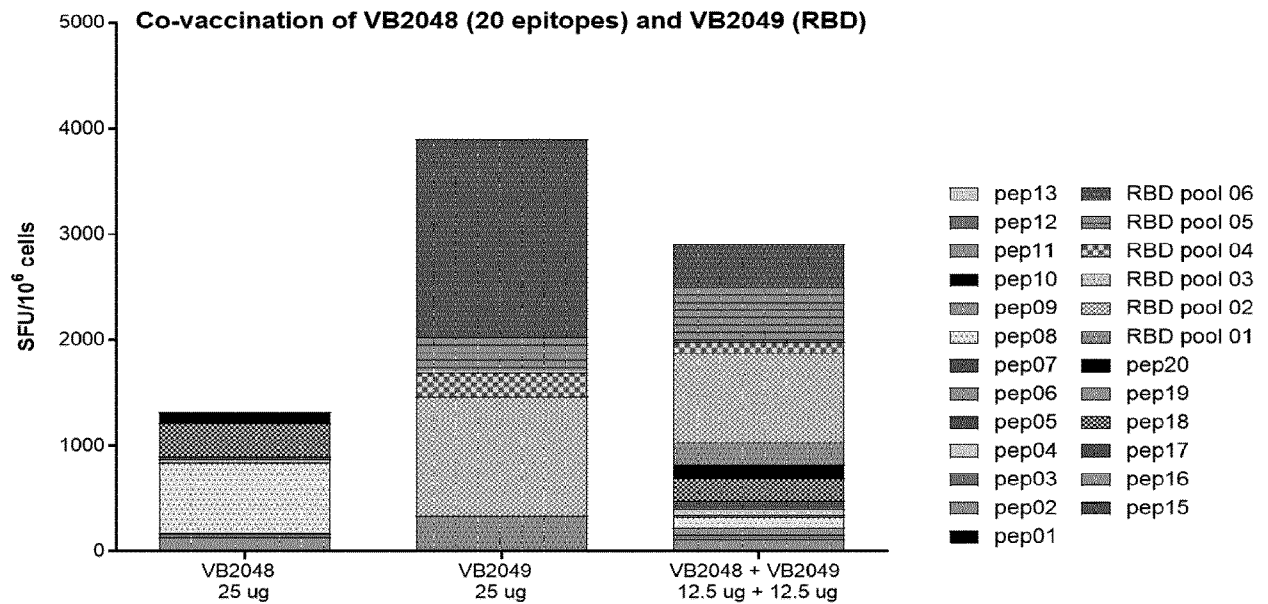


Fig. 77

SEQ ID NO: 321

MNFGRLRLIFLVLTCLKGVQC |
 DIQMTQTSSLSASLGDRVTISCSASQDINNYLNWYQQKPDGTVKLLIYYTSSLHSGVPSRFSGSGSGTDYS
 LTISNLEPEDIATYYCQQYSKFPRTFGGGKLEIKR | GGGGSGGGGSGGGGS |
 QIQLVQSGPELKKPGETVKISCKASGYTFINYGMMWVKQTPGKGLKWMGWINTYSGEPTYPPDFKGRFAFS
 LETSASTAYLQLNNLKNEDMATYFCARGDYYGPFNDWQGTTTLTVSS

Fig. 78

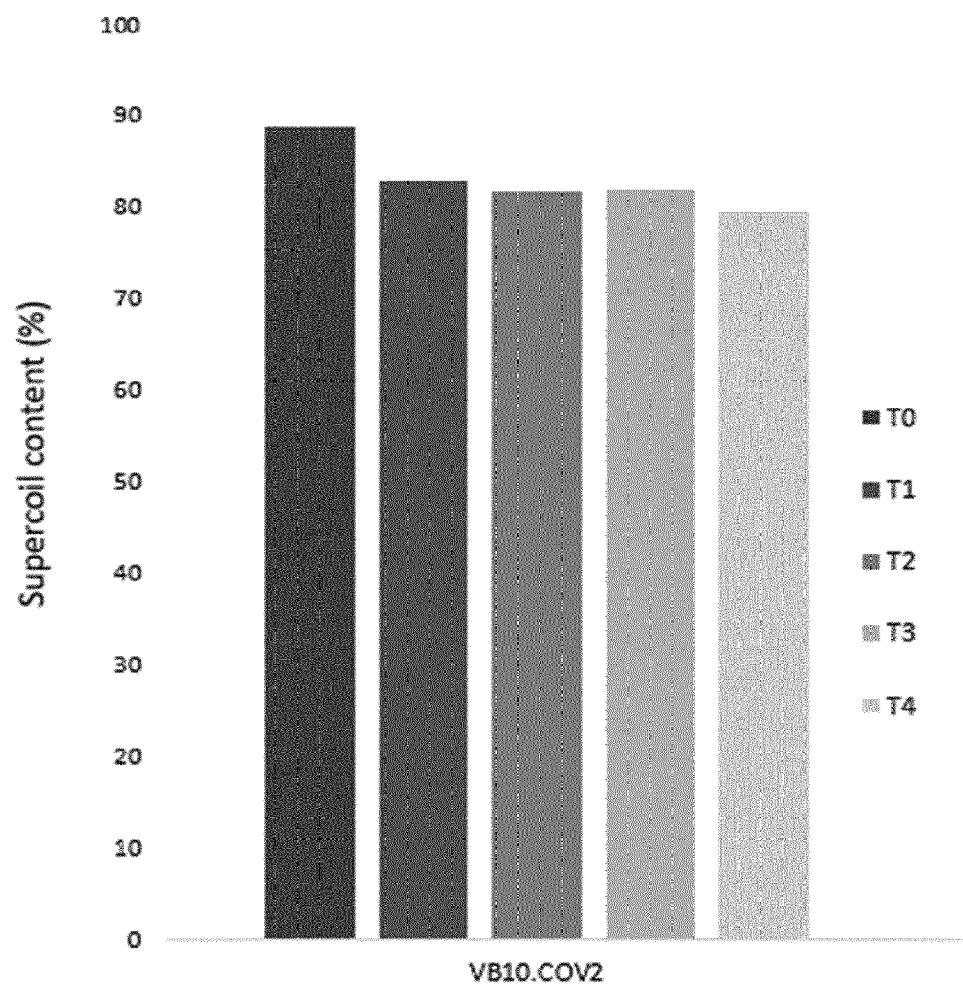


Fig. 1

SEQ ID NO: 230

MFVFLVLLPLVSSQCVNLTTTRTQLPPAYTNSFTRGVVYPDKVFRSSVLHSTQDLFLPFFSNVTWFHAIHVSGTNGTKRFD
NPVLPFNDGVYFASTEKSNIIRGWIFGTTLDSTKQSLIVNNATNVVIKVEFQFCNDPFLGVYYHKNNKSWMESEFRVYS
SANNCTFEYVSQPFLMDLEGKQGNFKNLREFVFKNIDGYFKIYSKHTPINLVRDLPQGFSALEPLVDLPIGINITRFQTLAL
HRSYLTPGDSSSGWTAGAAAYVGYLQPRTFLLKYNENGTITDAVDCALDPLSETKCTLKSFTVEKGIYQTSNFRVQPT
SIVRFPNITNLCPFGEVFNATRFASVYAWNRKRISNCVADYSVLYNSASFSTFKCYGVSPTKLNDLCFTNVYADSFVIRGD
EVRQIAPGQTGKIADYNYKL PDDFTGCVIAWNSNNLDSKVGGNYNLYRLFRKSNLKPFERDISTEIQAGSTPCNGVEG
FNCYFPLQSYGFQPTNGVGYQPYPYRVVLSFELLHAPATVCGPKKSTNLVKNKCVNFNFNGLTGTGVLTESNKKFLPFQQ
FGRDIADTTDAVRDPQTLEILDITPCSFGGVSVITPGTNTSNQVAVLYQDVNCTEVPVAIHADQLTPTWRVYSTGSNVFQT
RAGCLIGAEHVNNSEYCDIPGAGICASYQTQTNSPRRARSVASQSIIAYTMSLGAENSVAYSNNNSIAIPTNFTISVTTEILPV
SMTKTSVDCTMYICGDSTECNLLLQYGSFCTQLNRALTGIAVEQDKNTQEVFAQVKQIYKTPPIKDFGGFNFSQILPDPS
KPSKRSFIEDLLFNKVTADAGFIKQYGDCLGDIAARDLCAQKFNGLTVL PPLLTDEMQYTSALLAGTITSGWTFGAGAA
LQIPFAMQMAYRFNGIGVTVQNVLYENQKLIANQFN SAIGKIQDSLSTASALGKLQDVVNQNAQALNTLVKQLSSNFGAIS
SVLNDILSRLDKVEAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLSFPQS
APHGVVFLHVTYVPAQEKNFTTAPAICHGKAHFPREGVFVSNGTHWFVTQRNFYEPQIITTDNTFVSGNCDVVIGIVNNT
VYDPLQPELDSFKEELDKYFKNHTSPDVLGDISGINASVUNIQKEIDRLNEVAKNLNESLIDLQELGKYEYQIKWPWYIWL
GFIAGLIAIVMTIMLCCMTSCCCLKGCCSCGSCCKFDEDDSEPV LKGVLHYT