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(54) POLYPEPTIDES TARGETING SARS-COV-2 AND RELATED COMPOSITIONS AND METHODS

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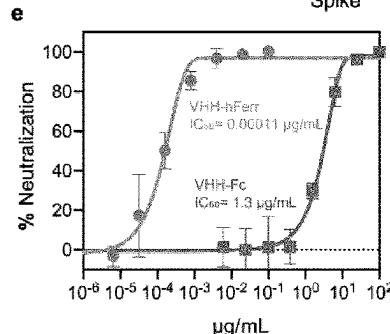
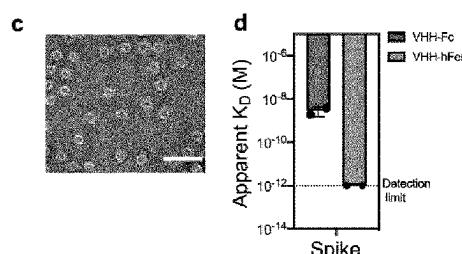
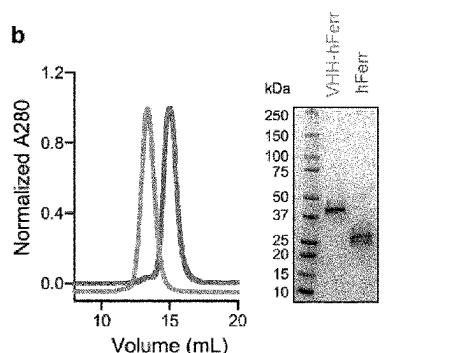
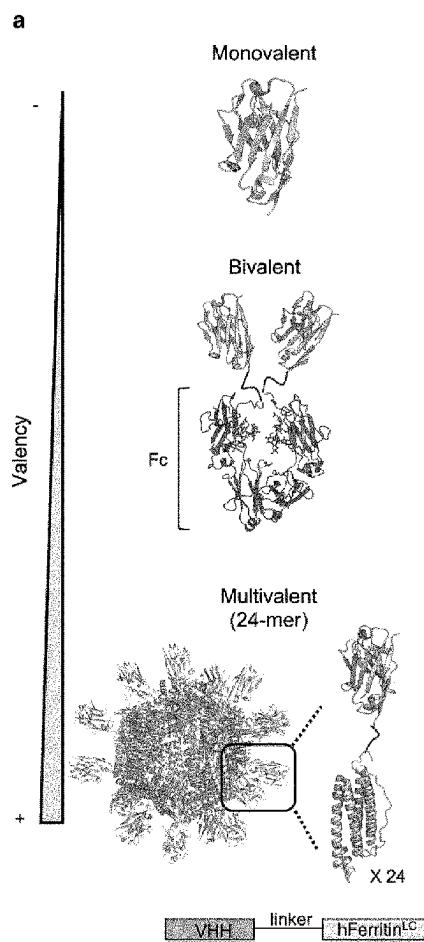
(52) U.S. Cl.

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(57)

ABSTRACT

Provided herein is a fusion protein comprises a nanocage monomer linked to a SARS-CoV-2 binding moiety, wherein a plurality of the fusion proteins self-assemble to form a nanocage. Also provided is a tri-specific antibody construct targeting SARS-CoV-2. Also provided is a fusion polypeptide comprising (1) a fragment crystallizable (Fc) region linked to (2) a nanocage monomer or subunit thereof, wherein the Fc region comprises the I253A mutation, wherein numbering is according to the EU index.

Specification includes a Sequence Listing.

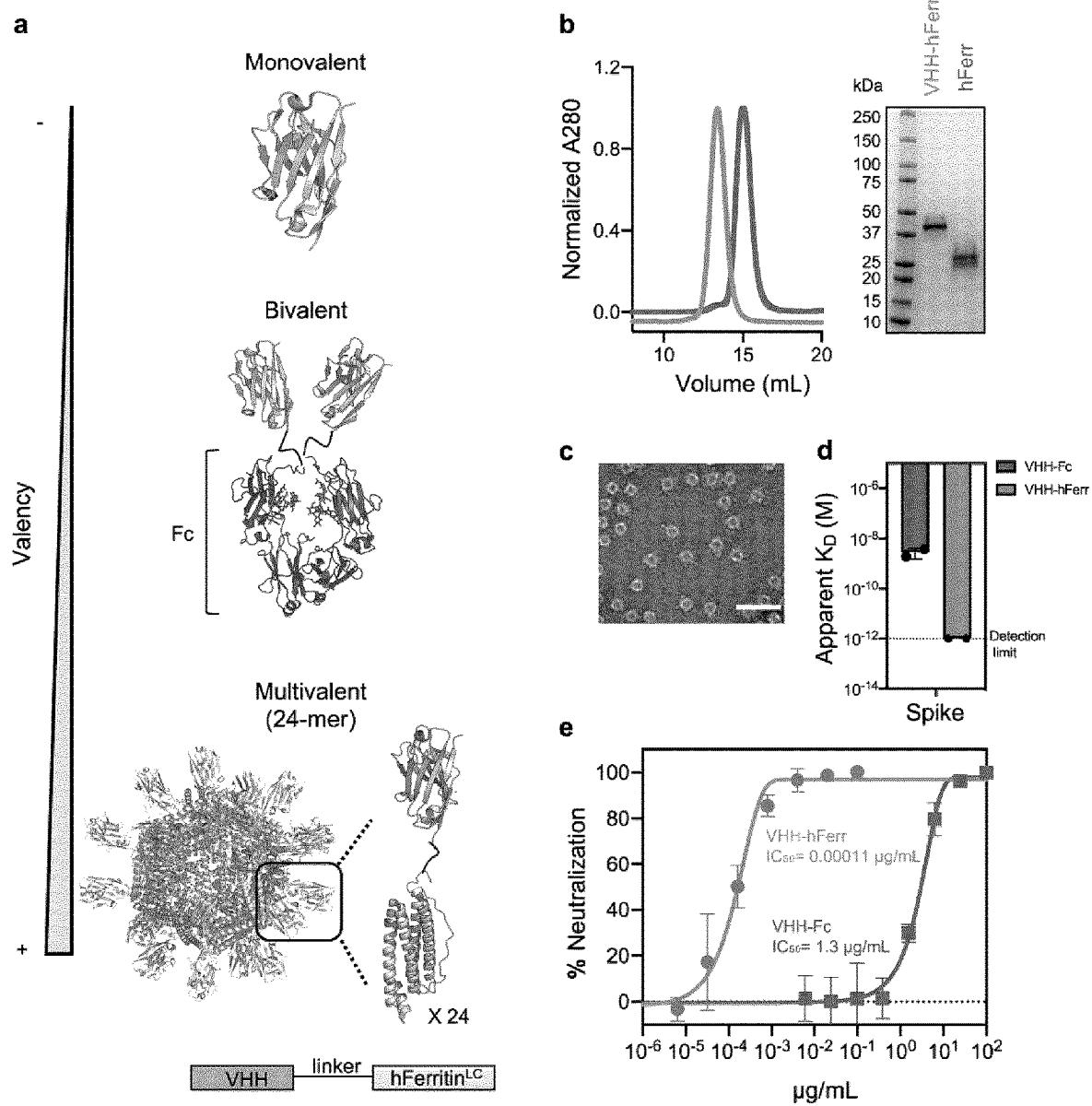


Figure 1

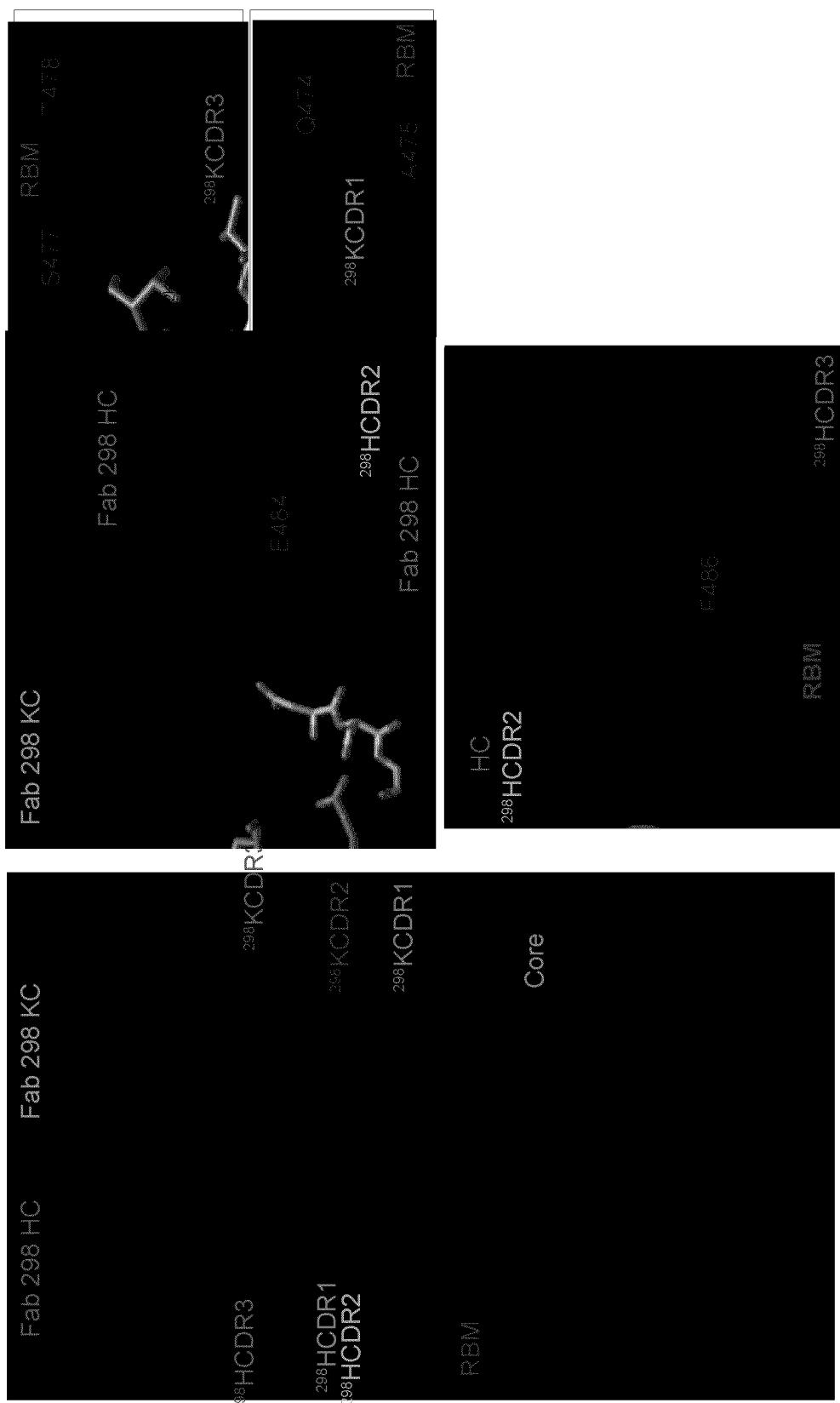


Figure 2a

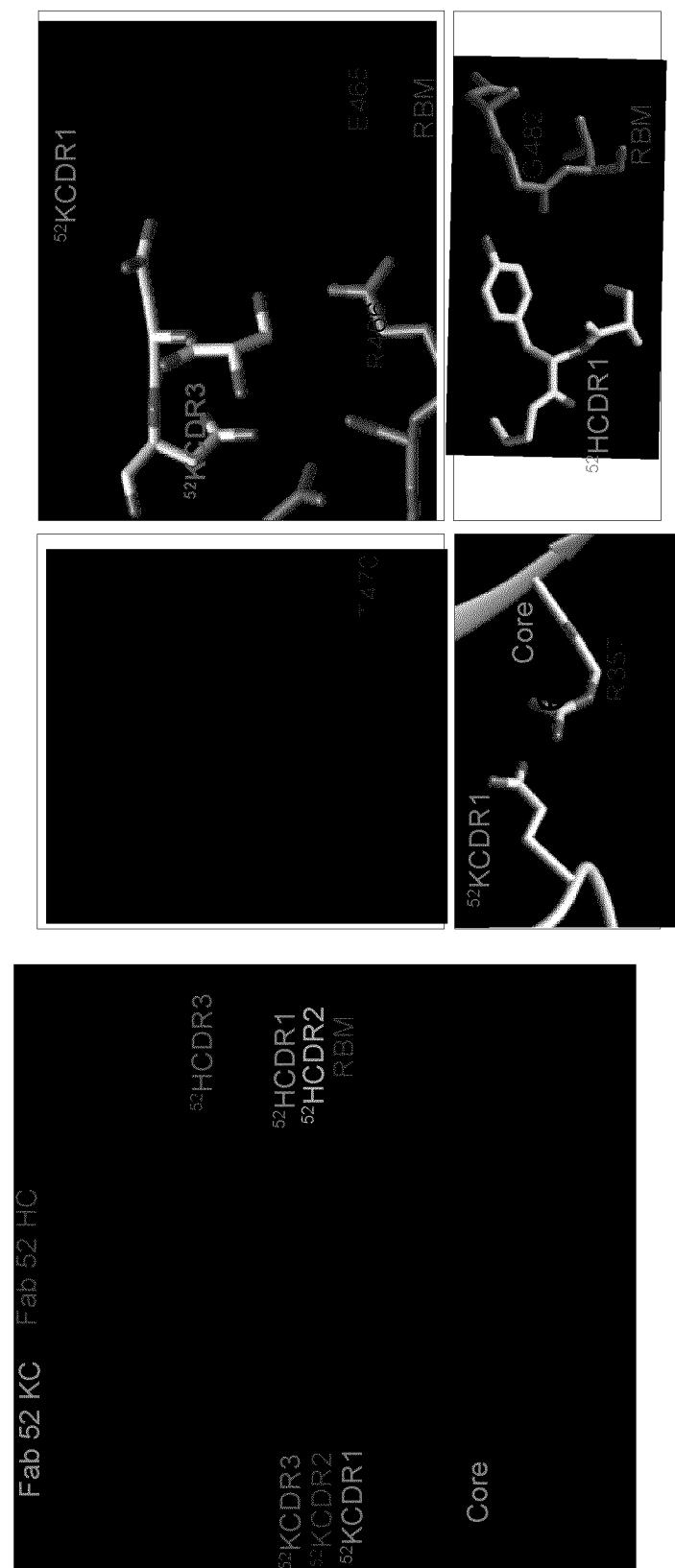


Figure 2b

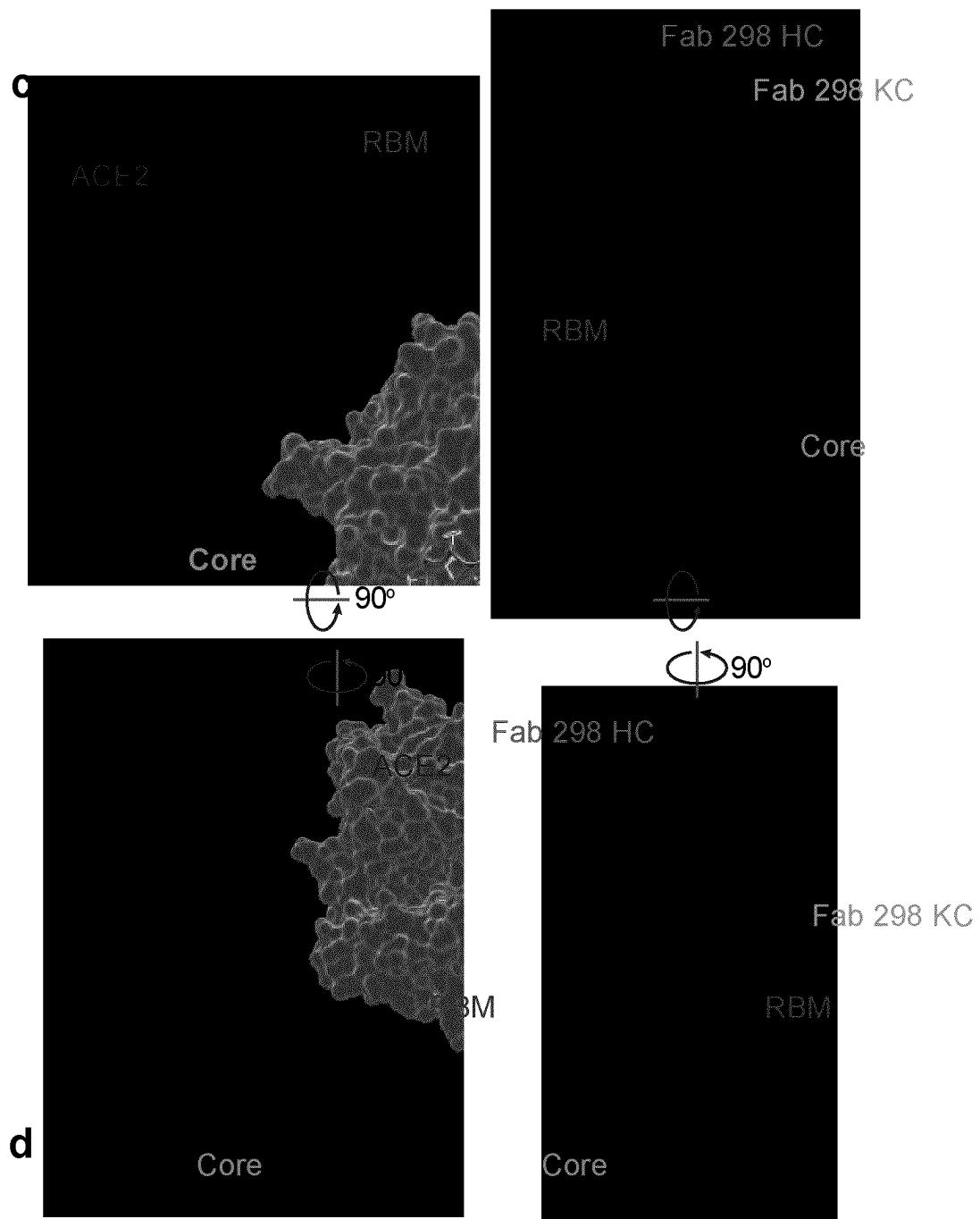


Figure 2c and 2d

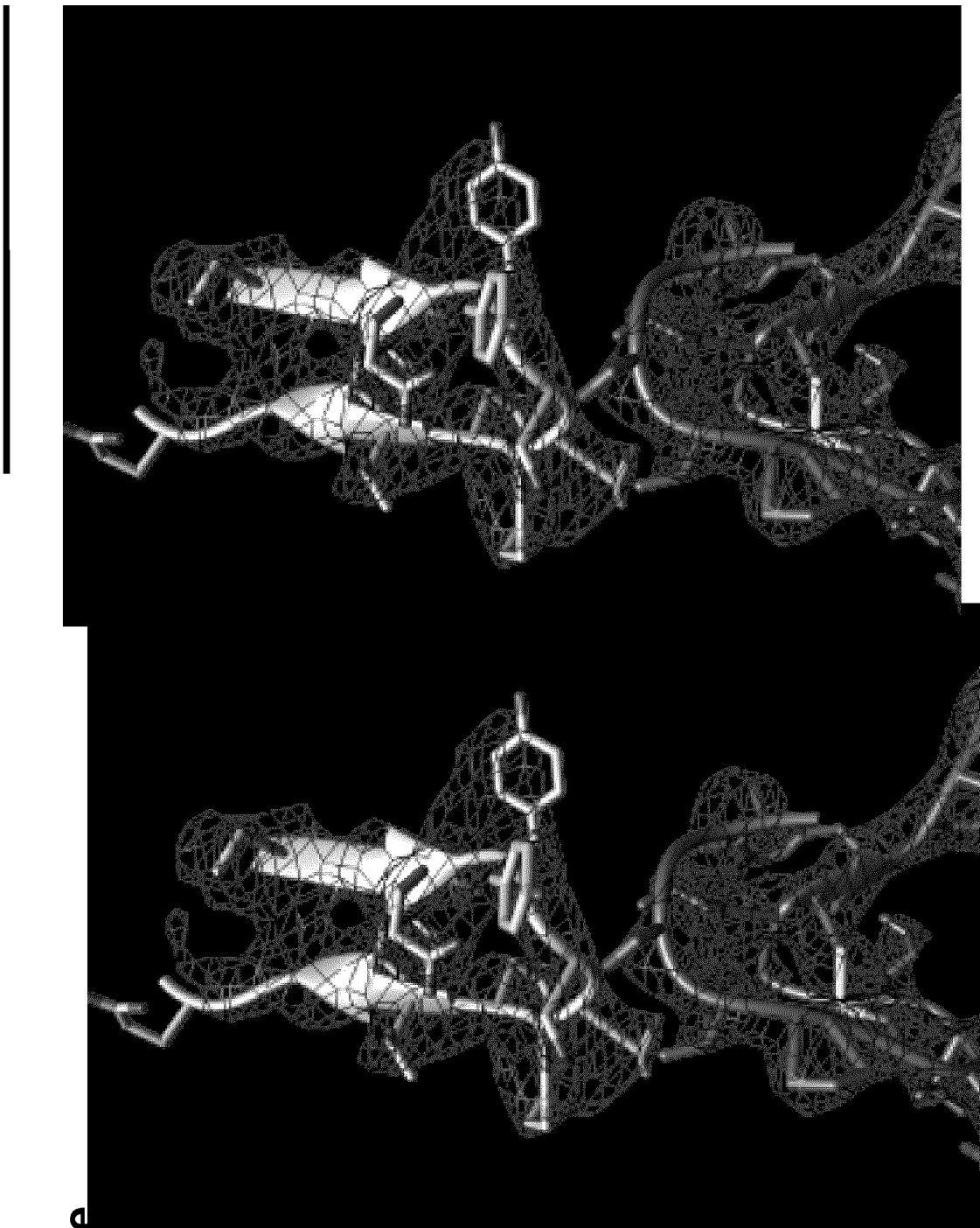


Figure 2e

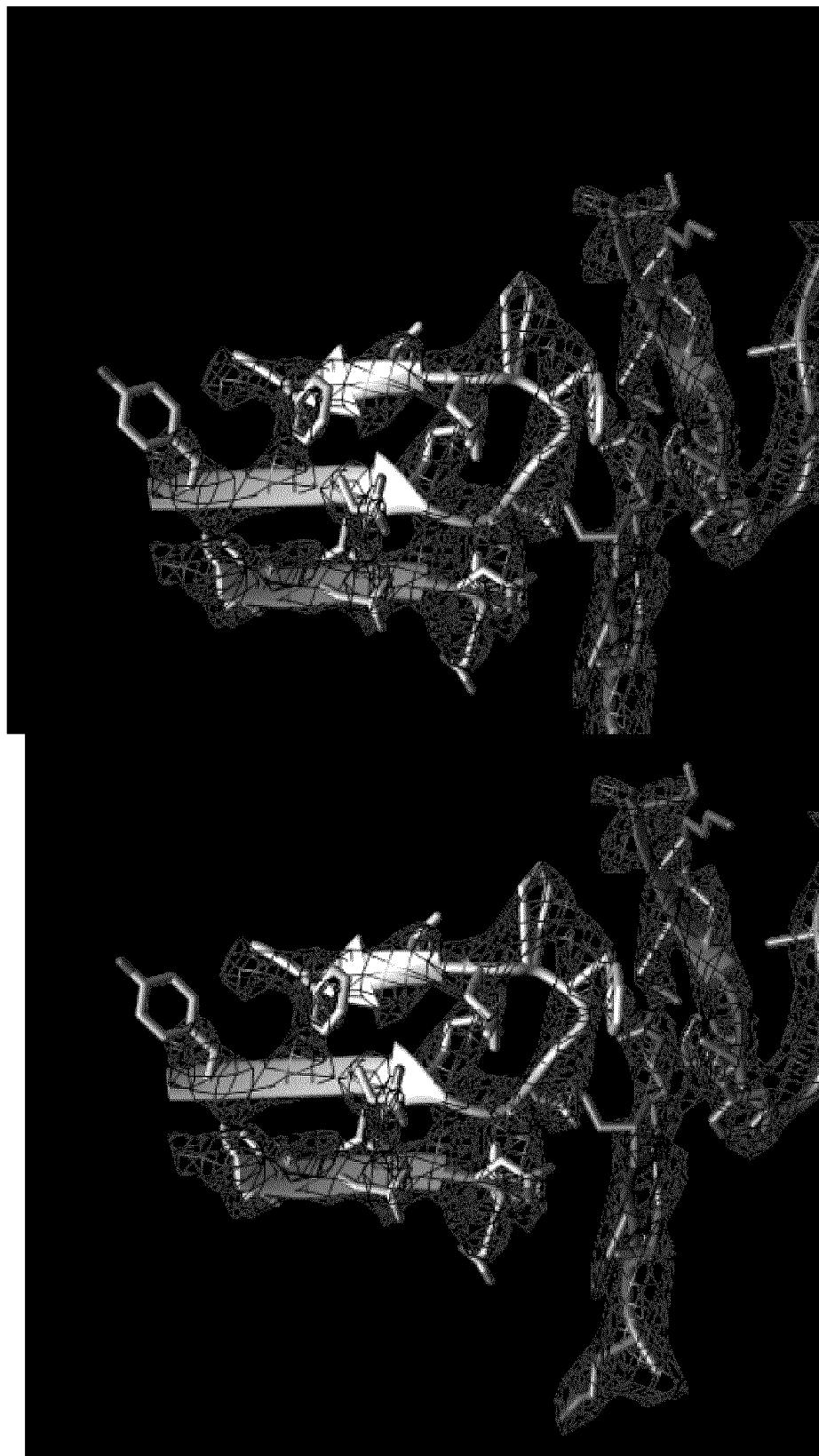


Figure 2f

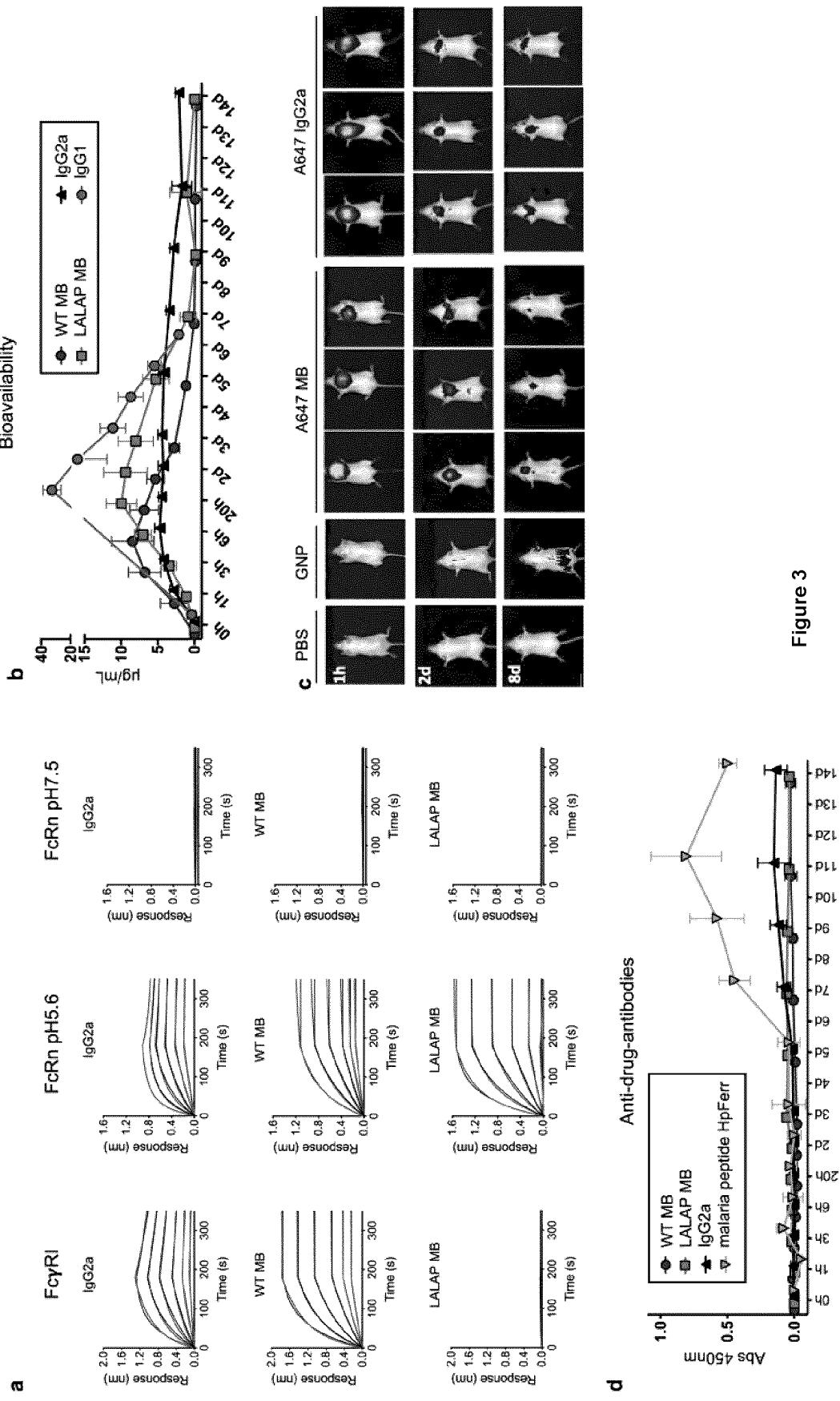


Figure 3

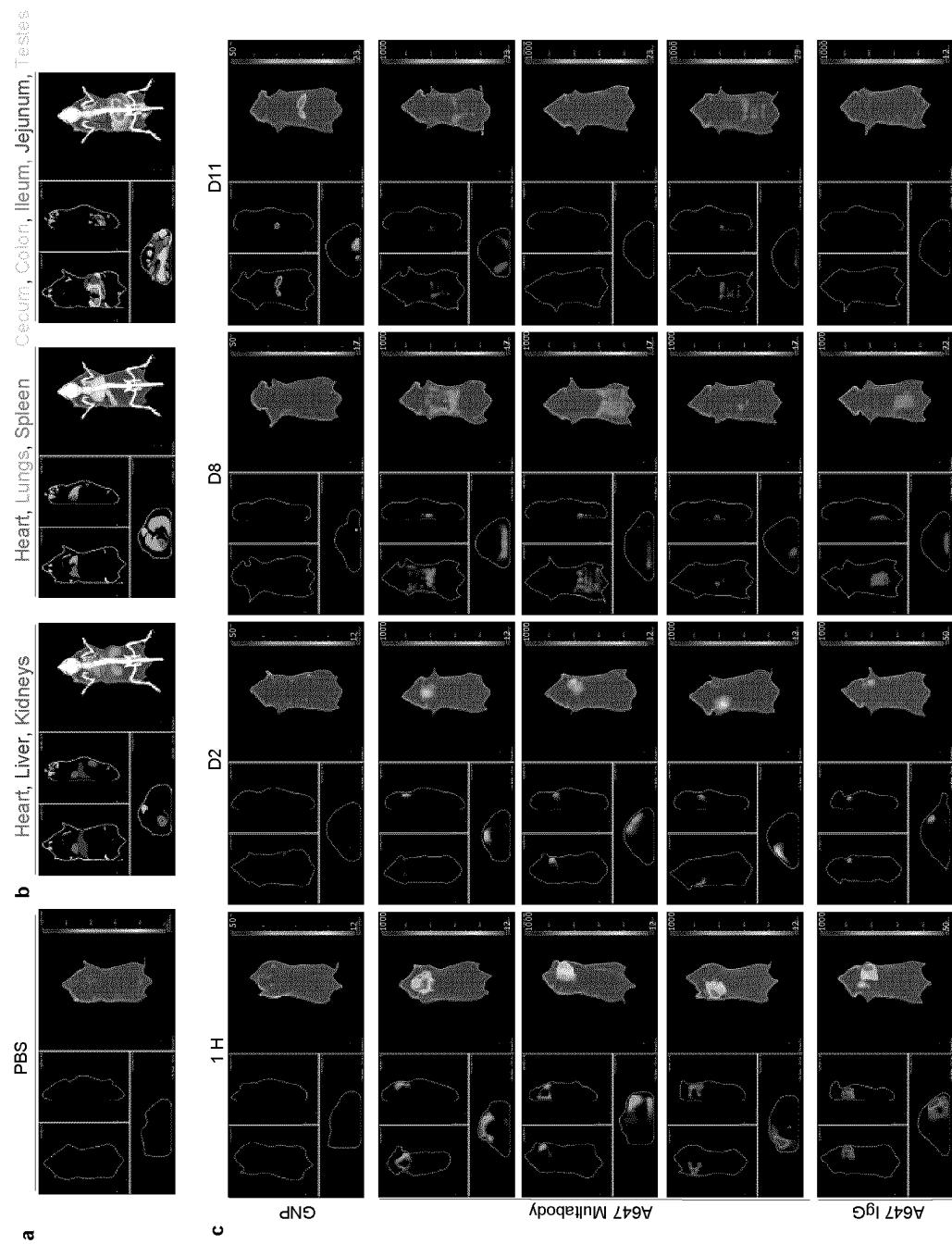
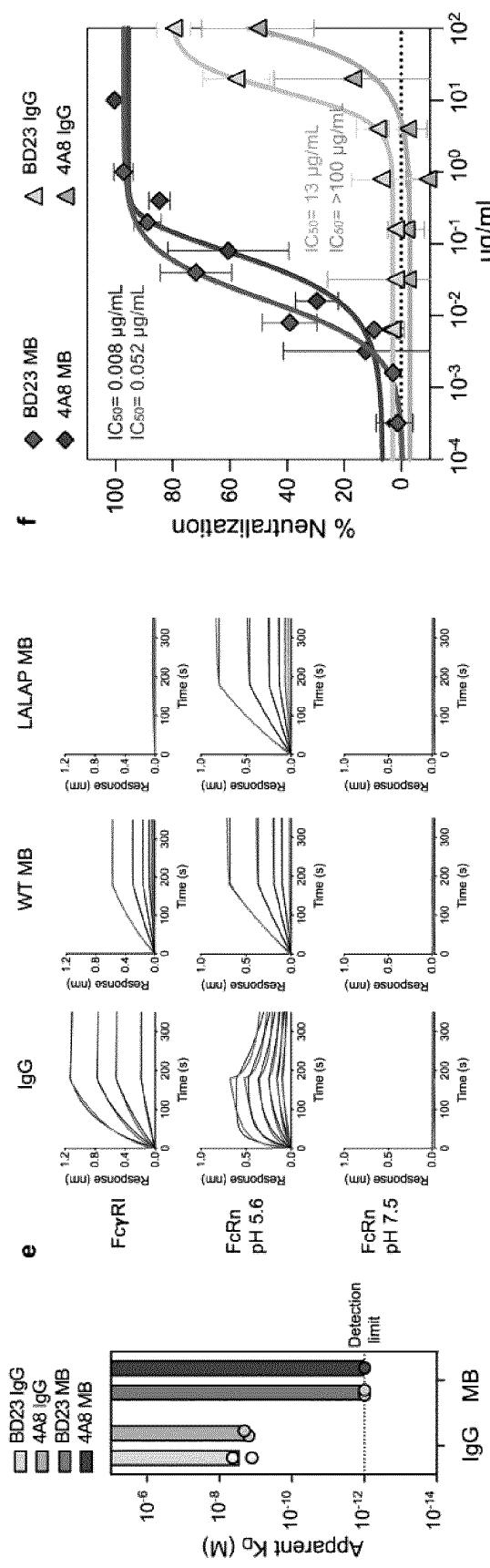
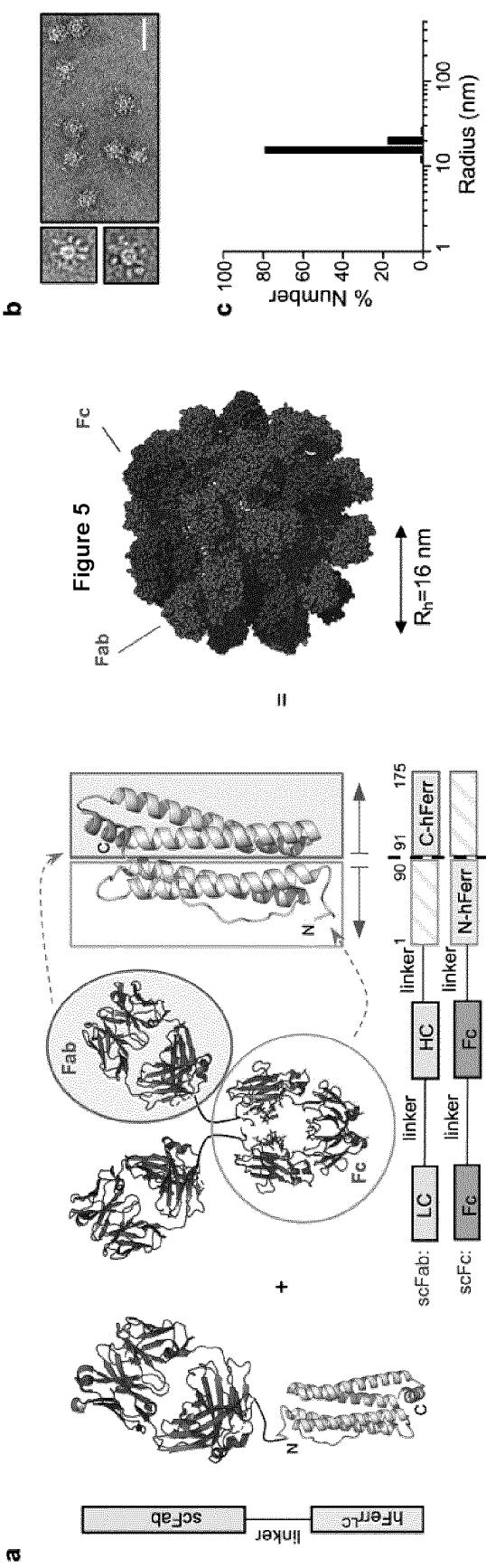


Figure 4



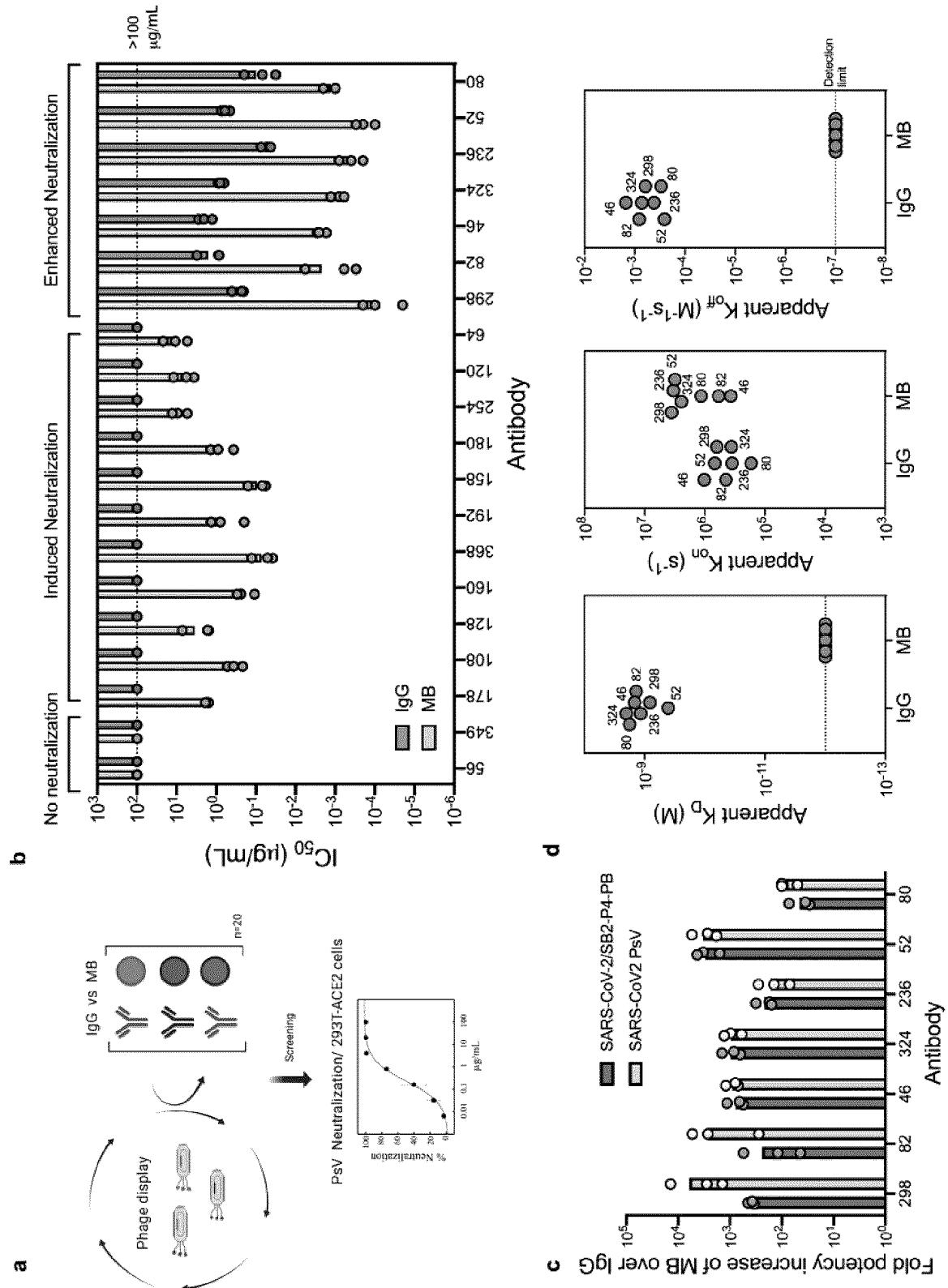


Figure 6

a

No-neutralization

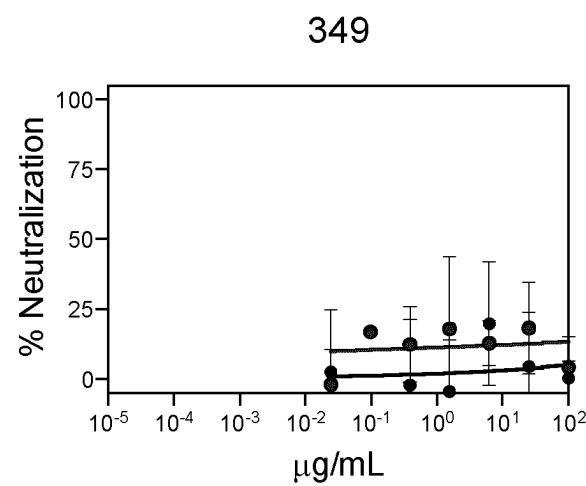
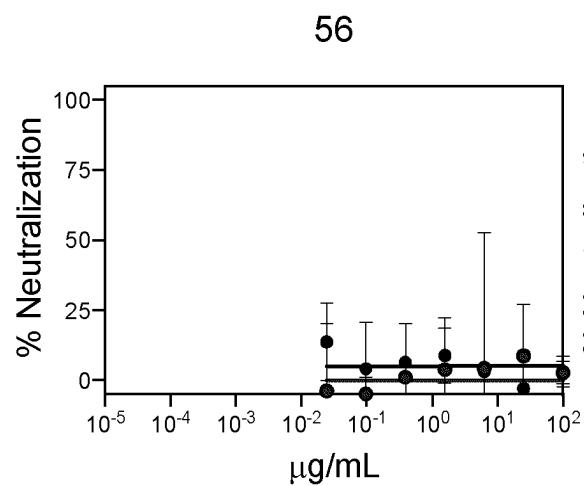


Figure 7a (part 1)

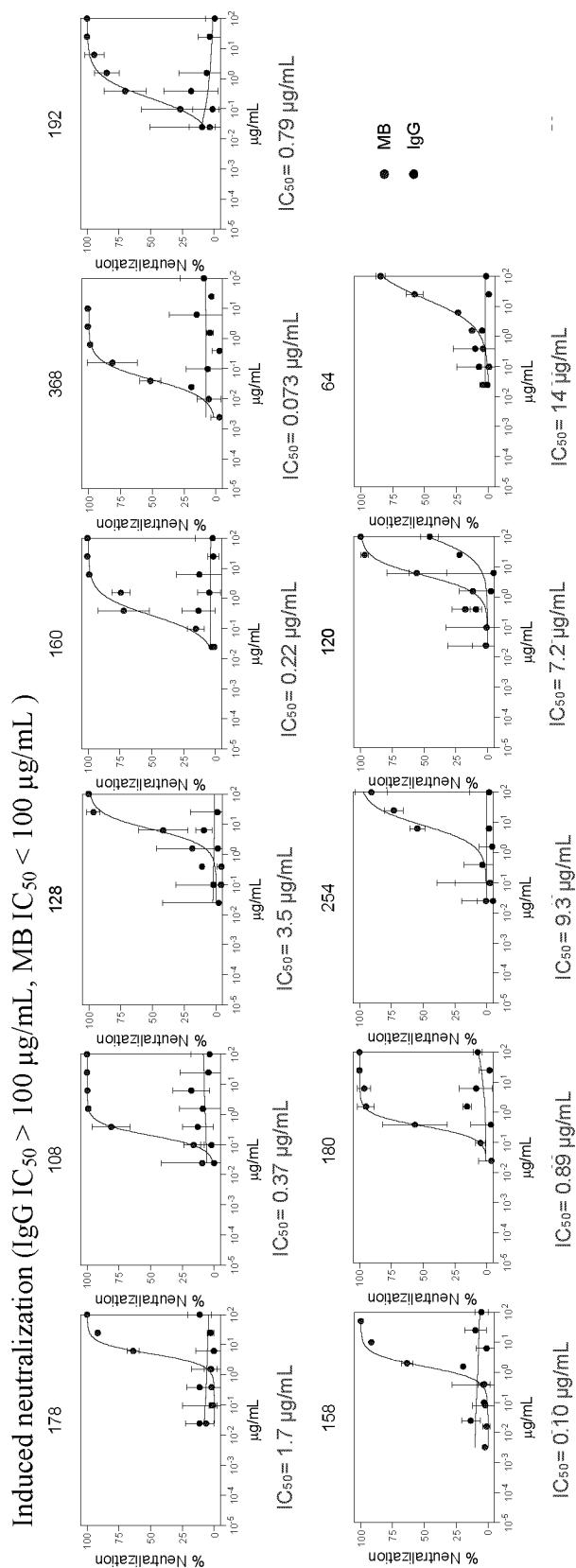


Figure 7a (part 2)

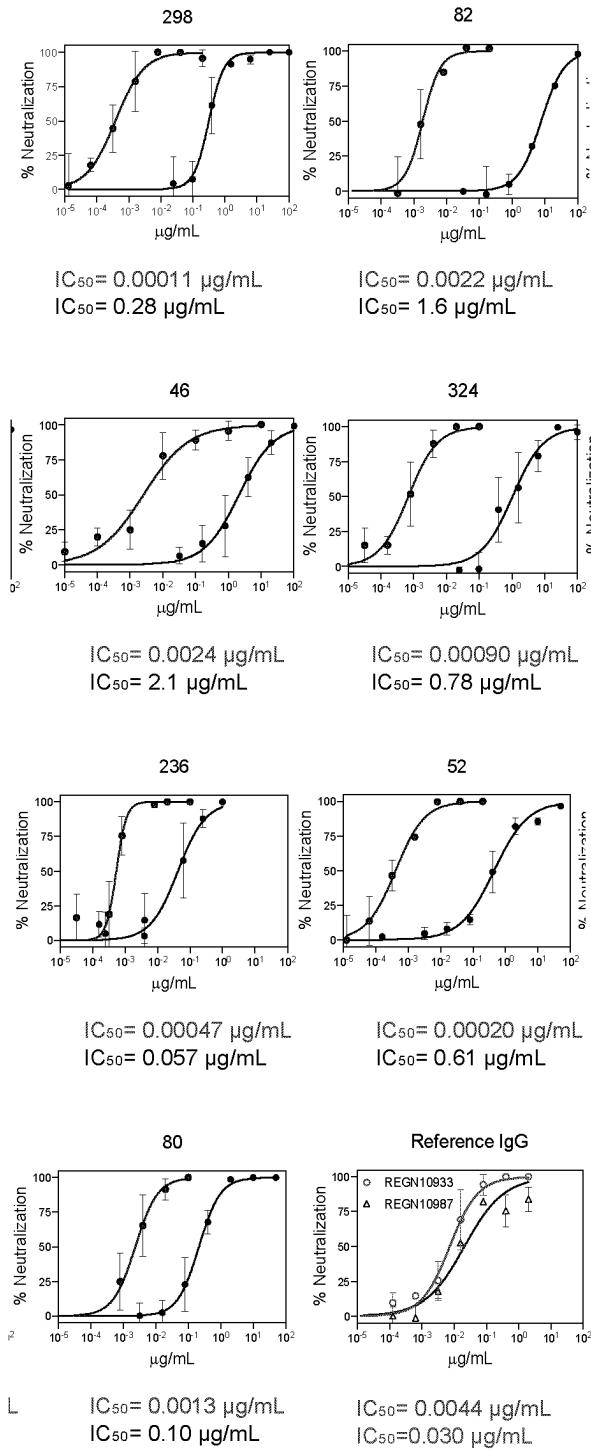


Figure 7a (part 3)

b

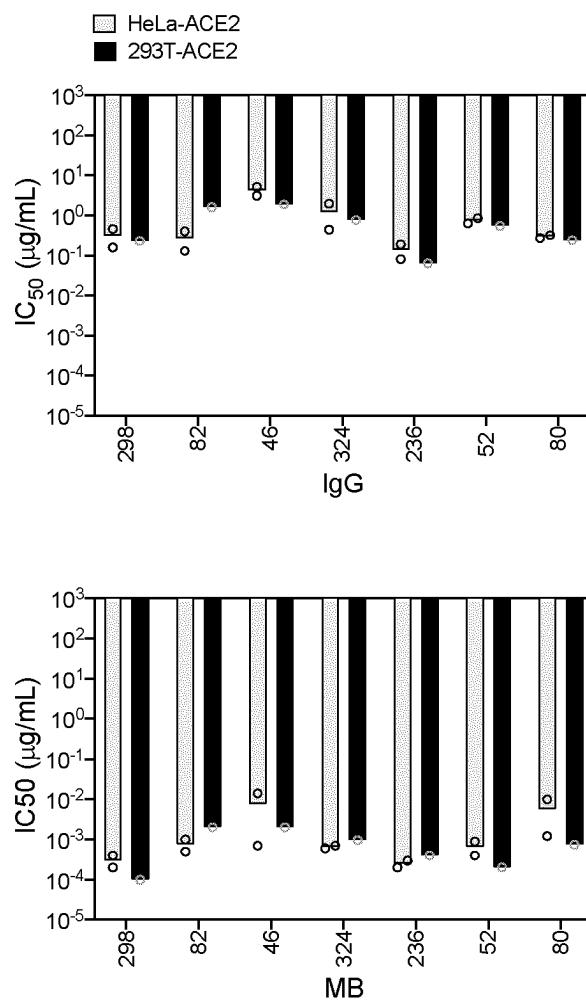


Figure 7b

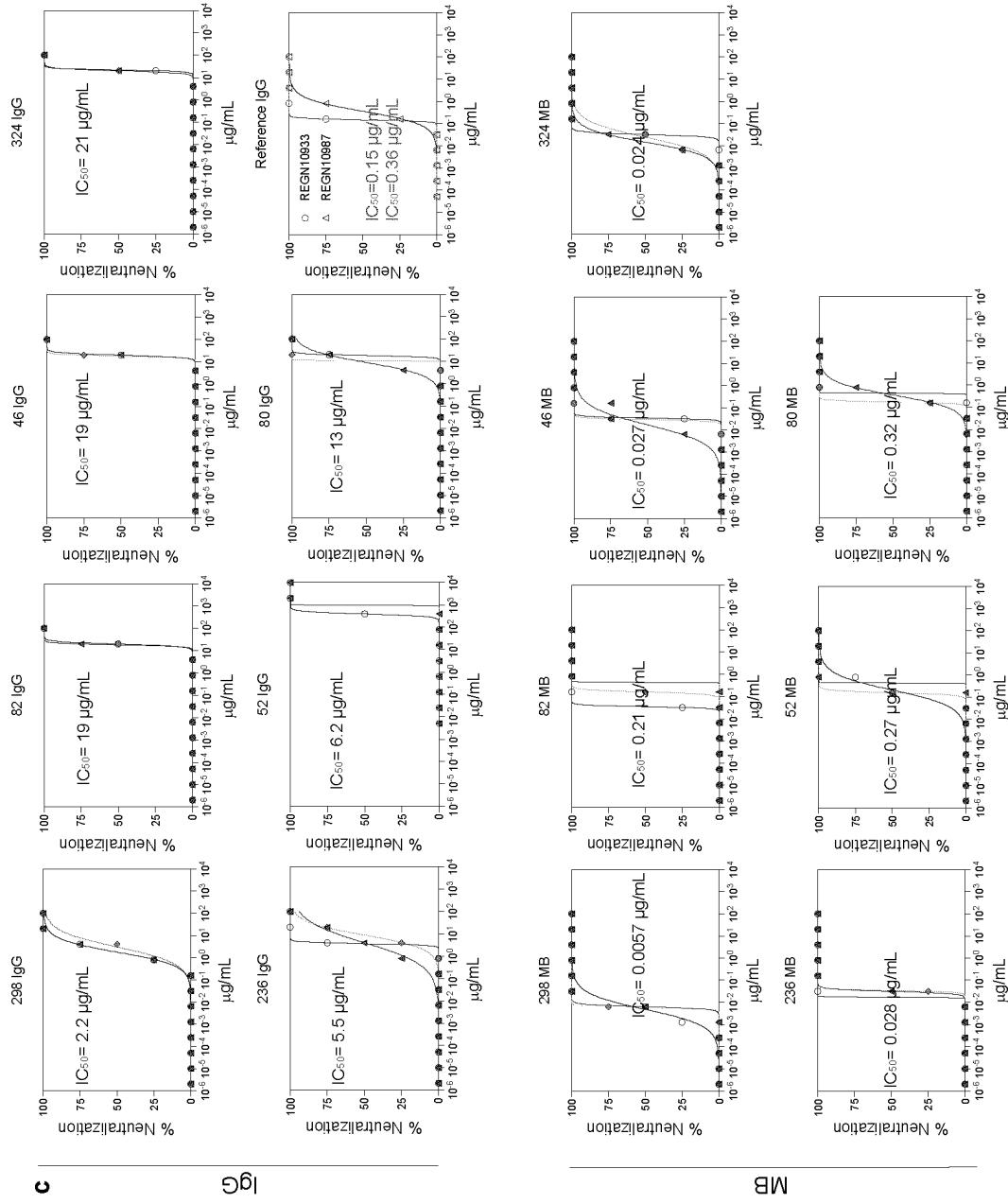


Figure 7c

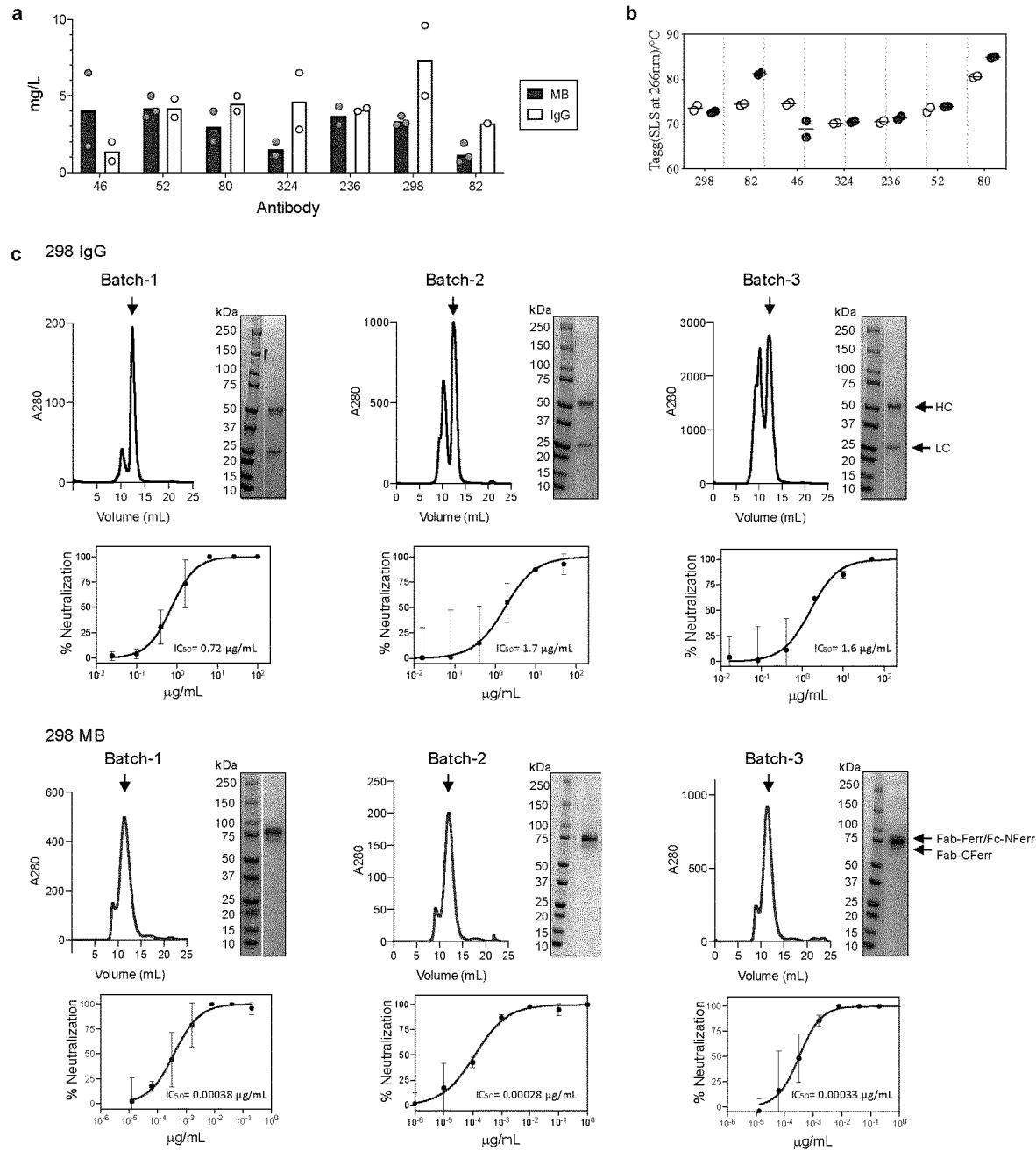


Figure 8

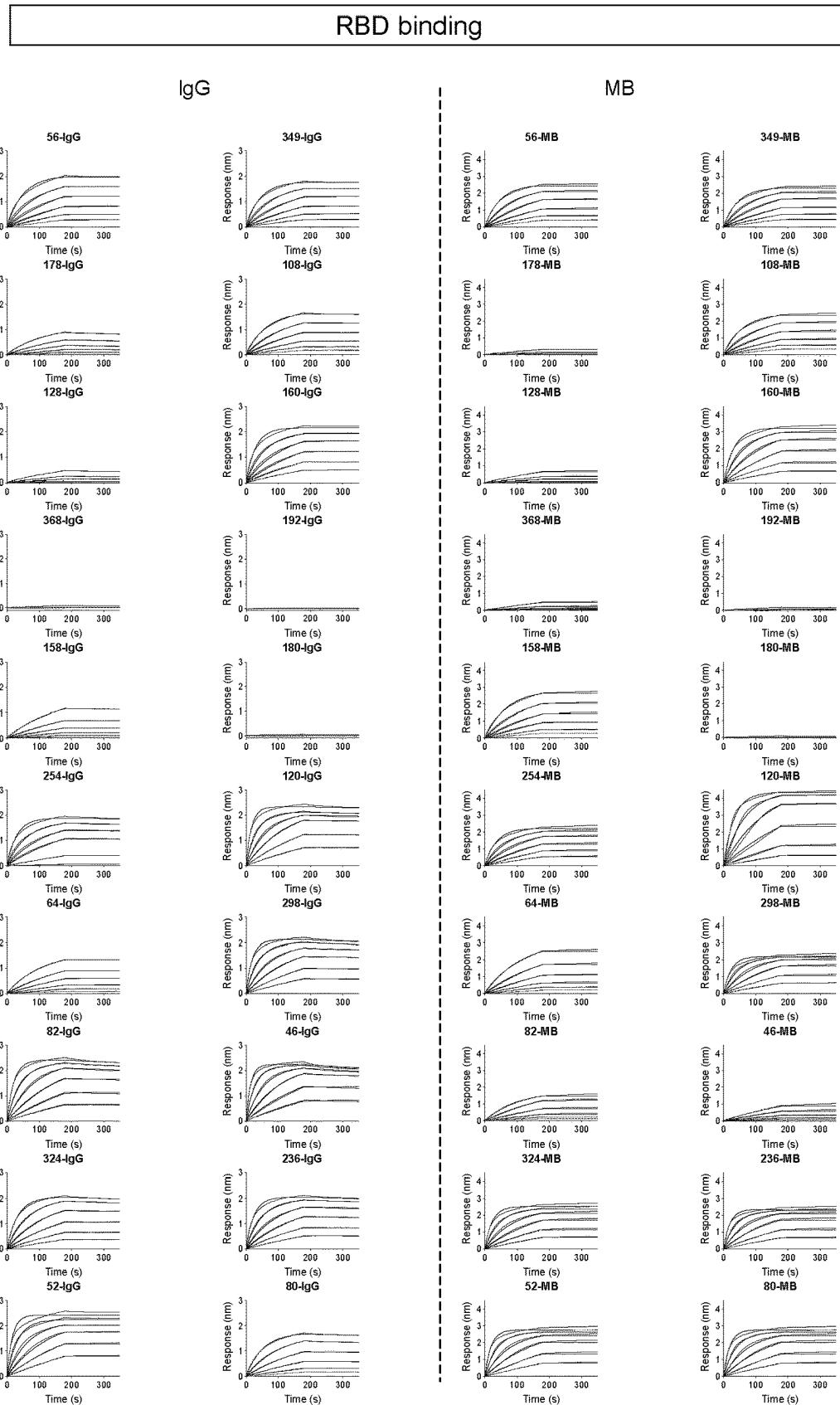


Figure 9 (part 1)

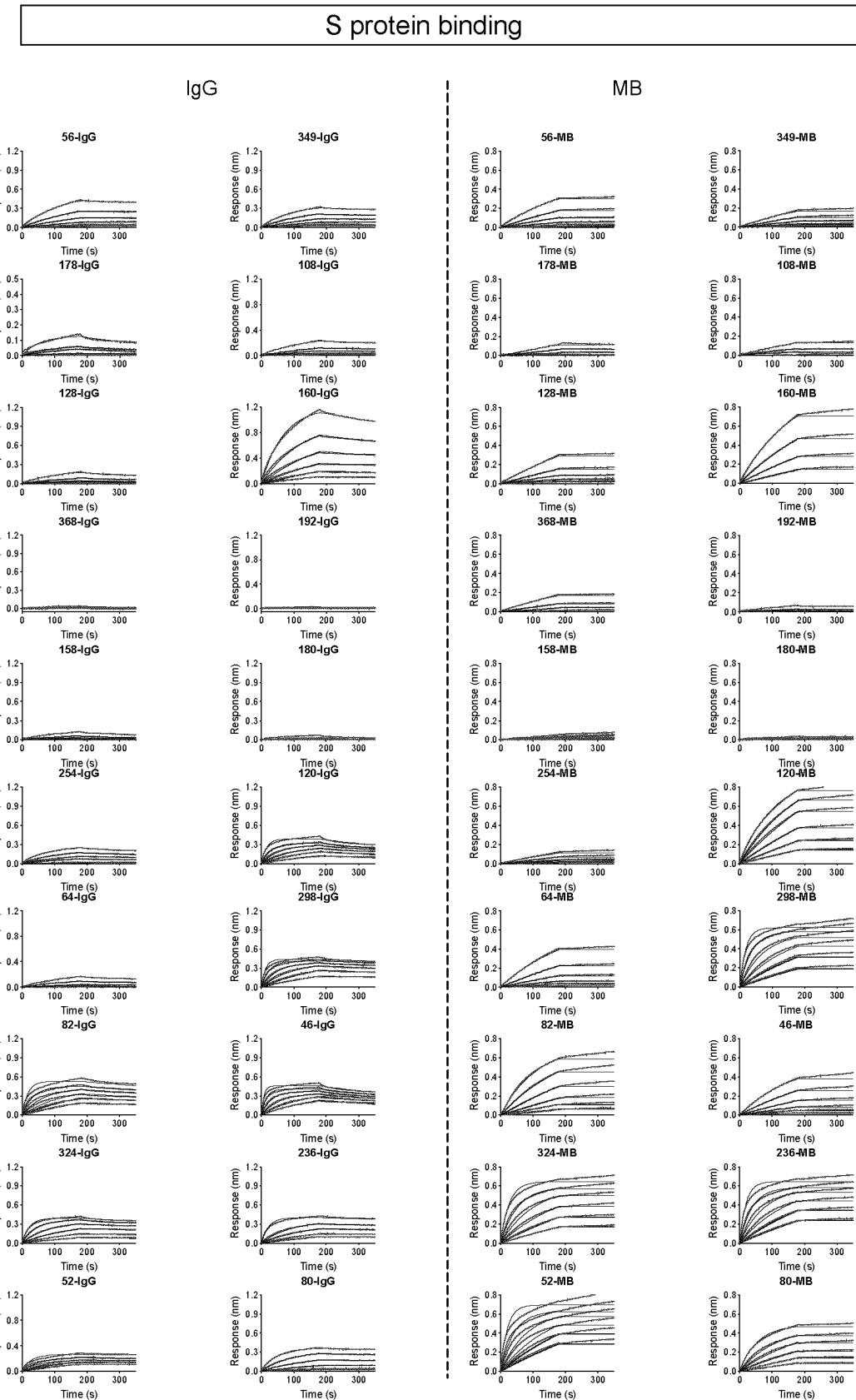


Figure 9 (part 2)

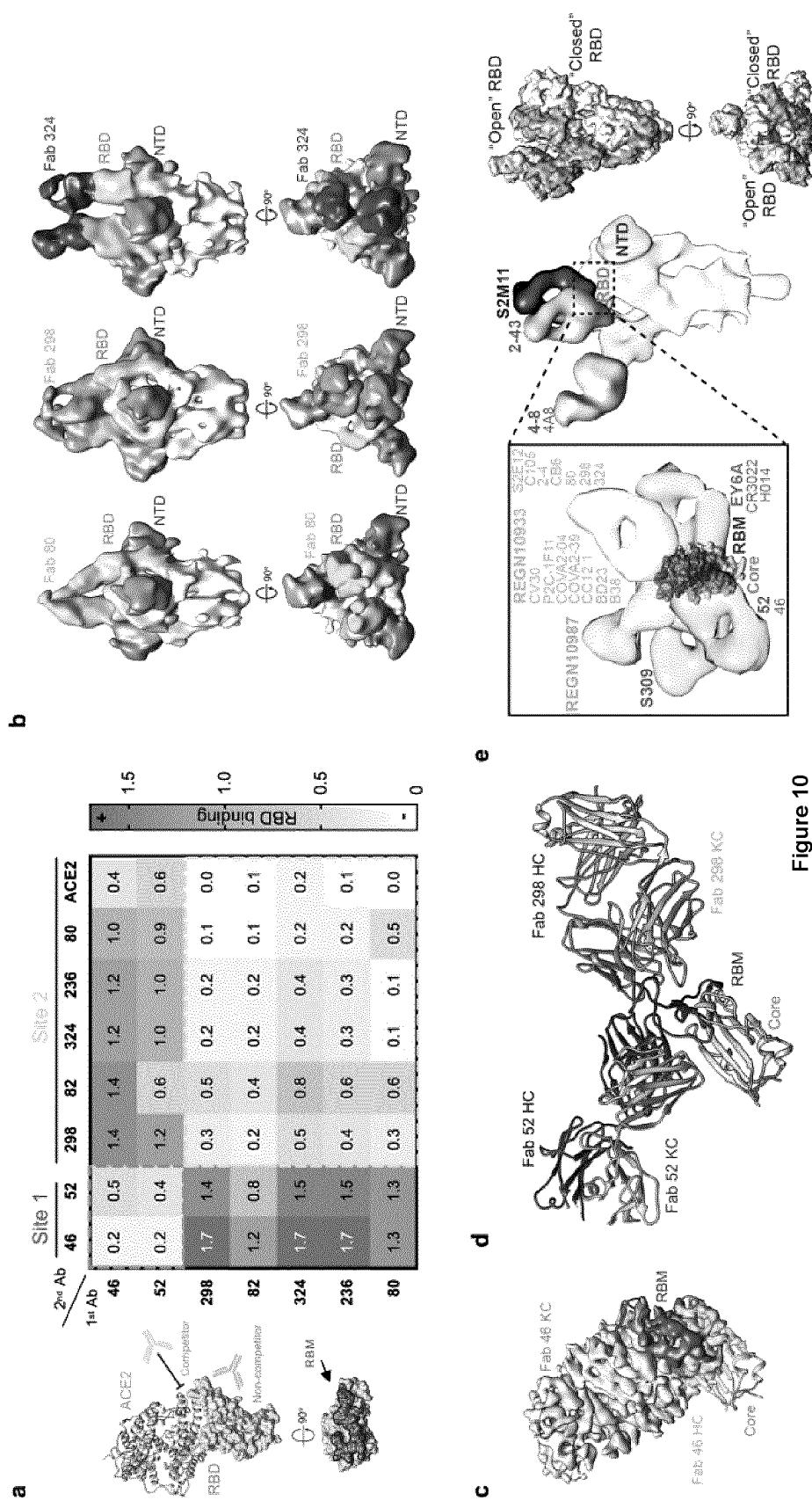


Figure 10



Figure 11

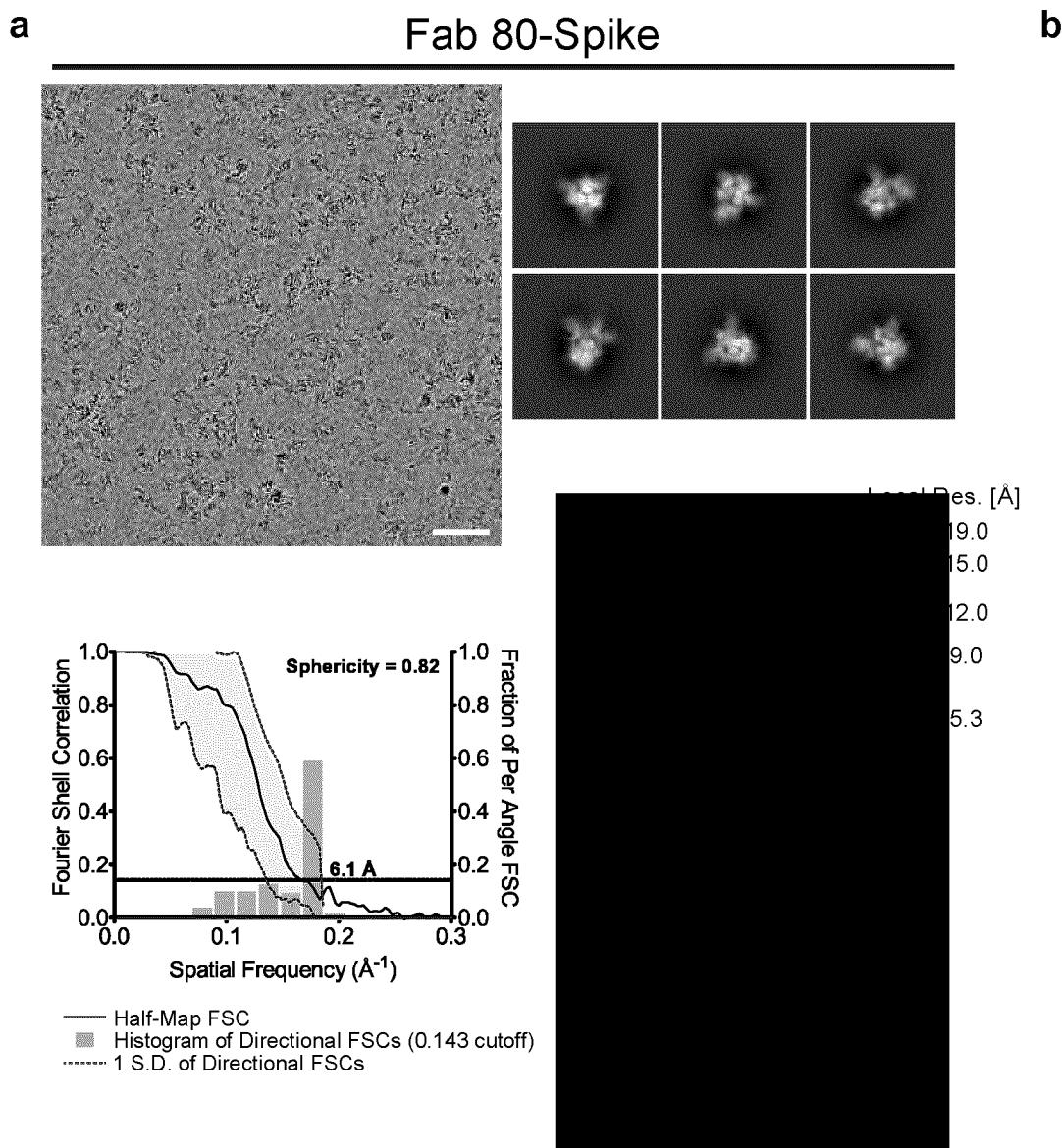


Figure 12a

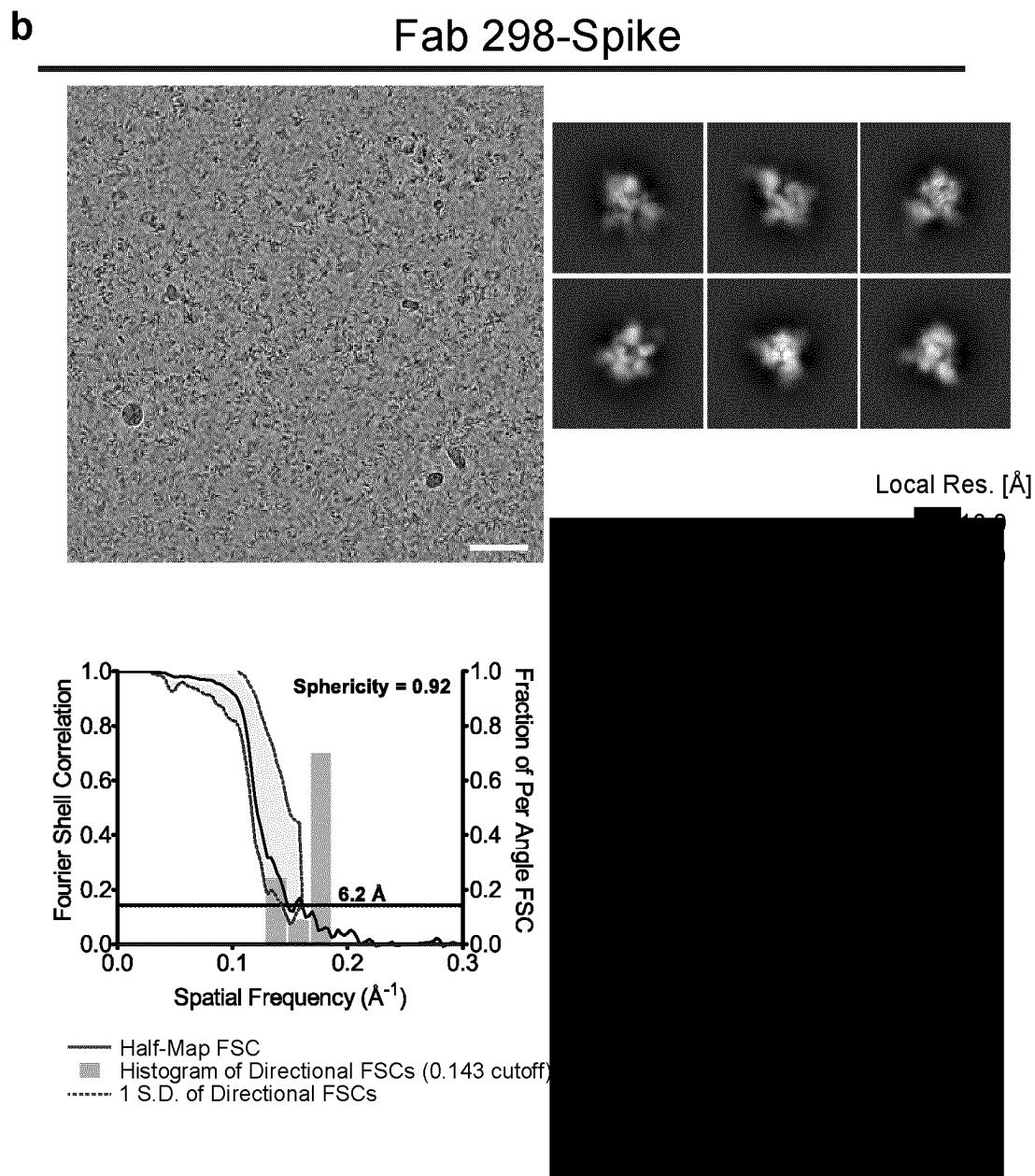


Figure 12b

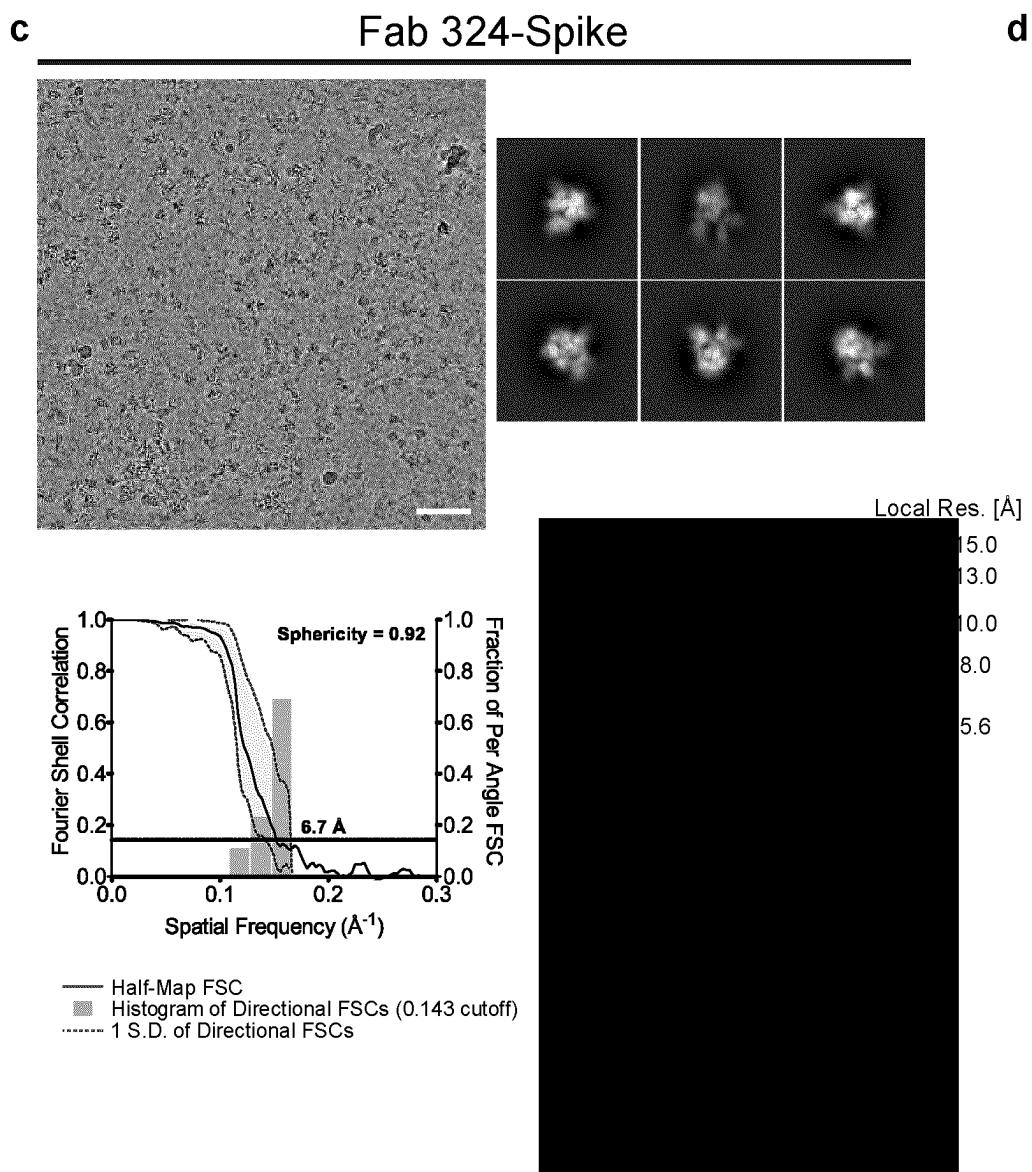


Figure 12c

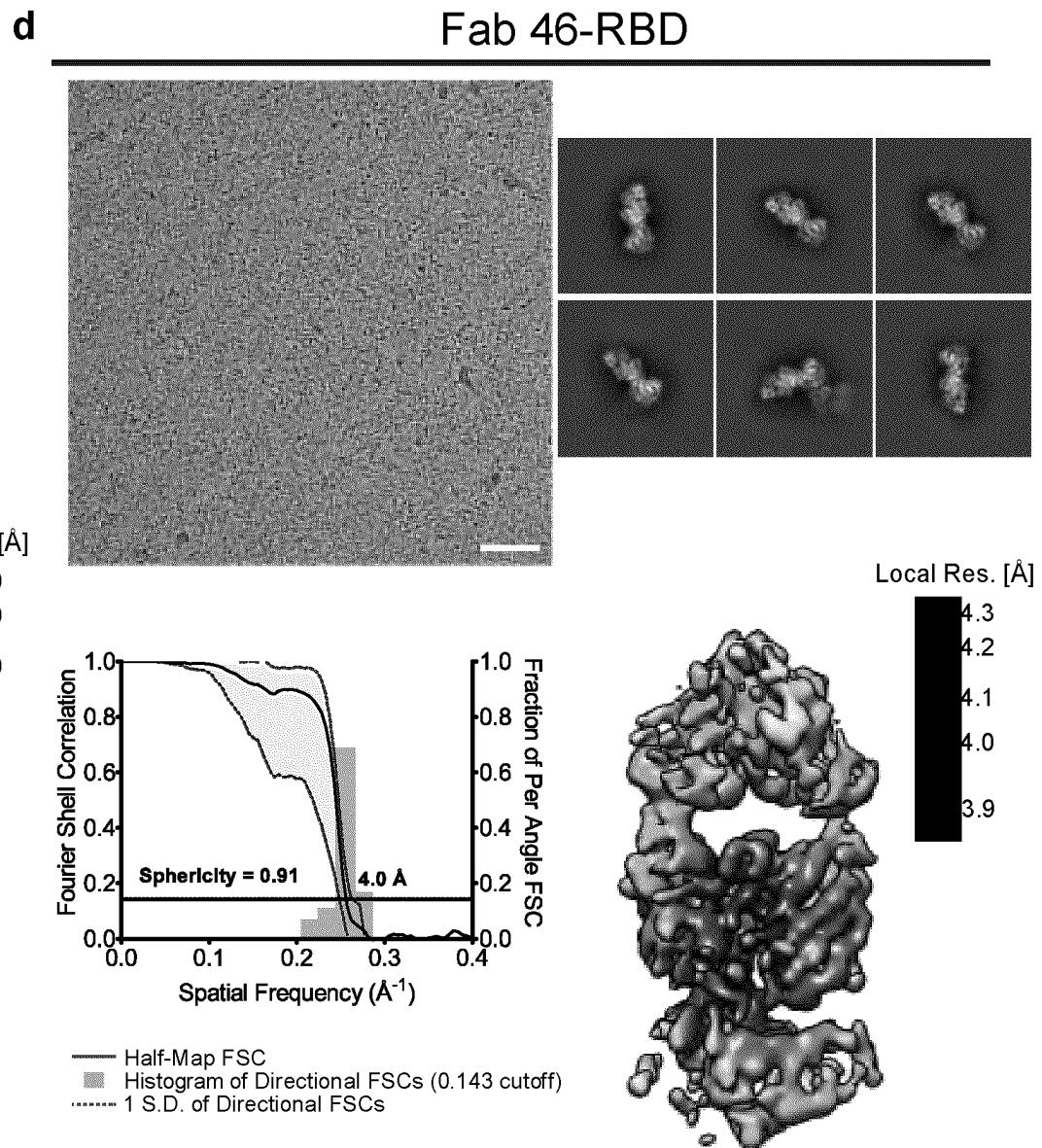
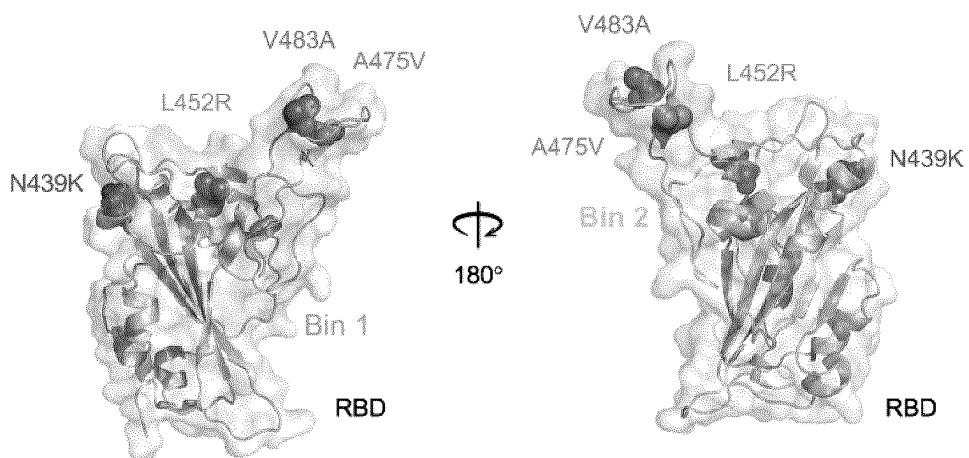
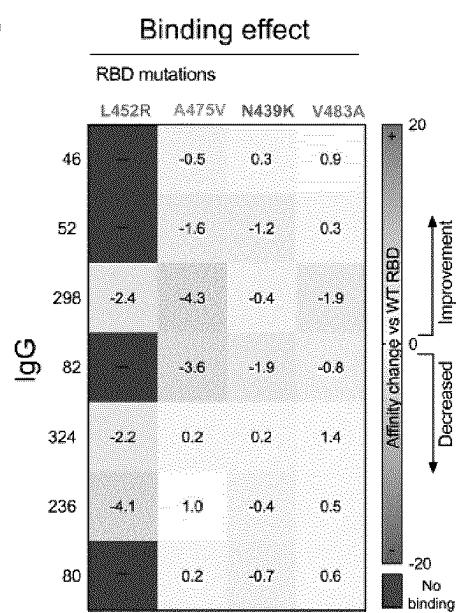


Figure 12d

a



b



c

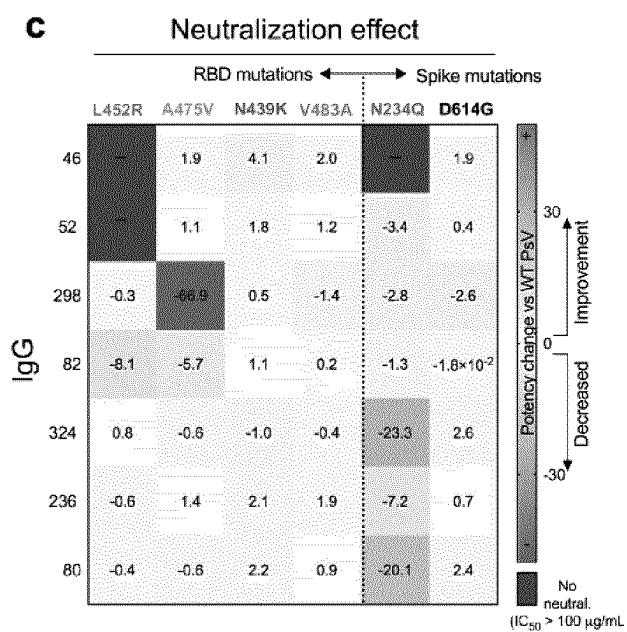


Figure 13a, 13b, 13c

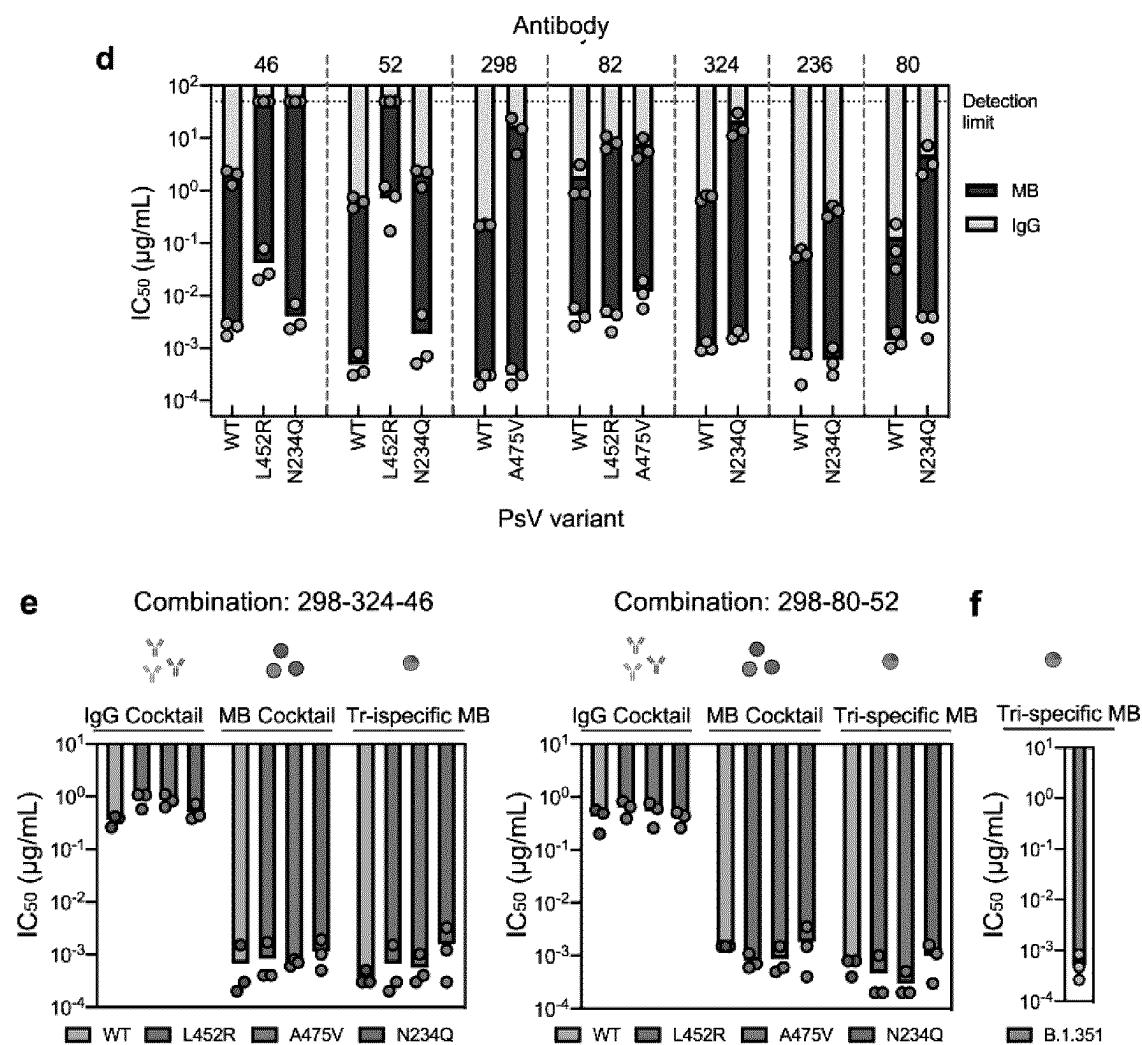


Figure 13d, 13e, 13f

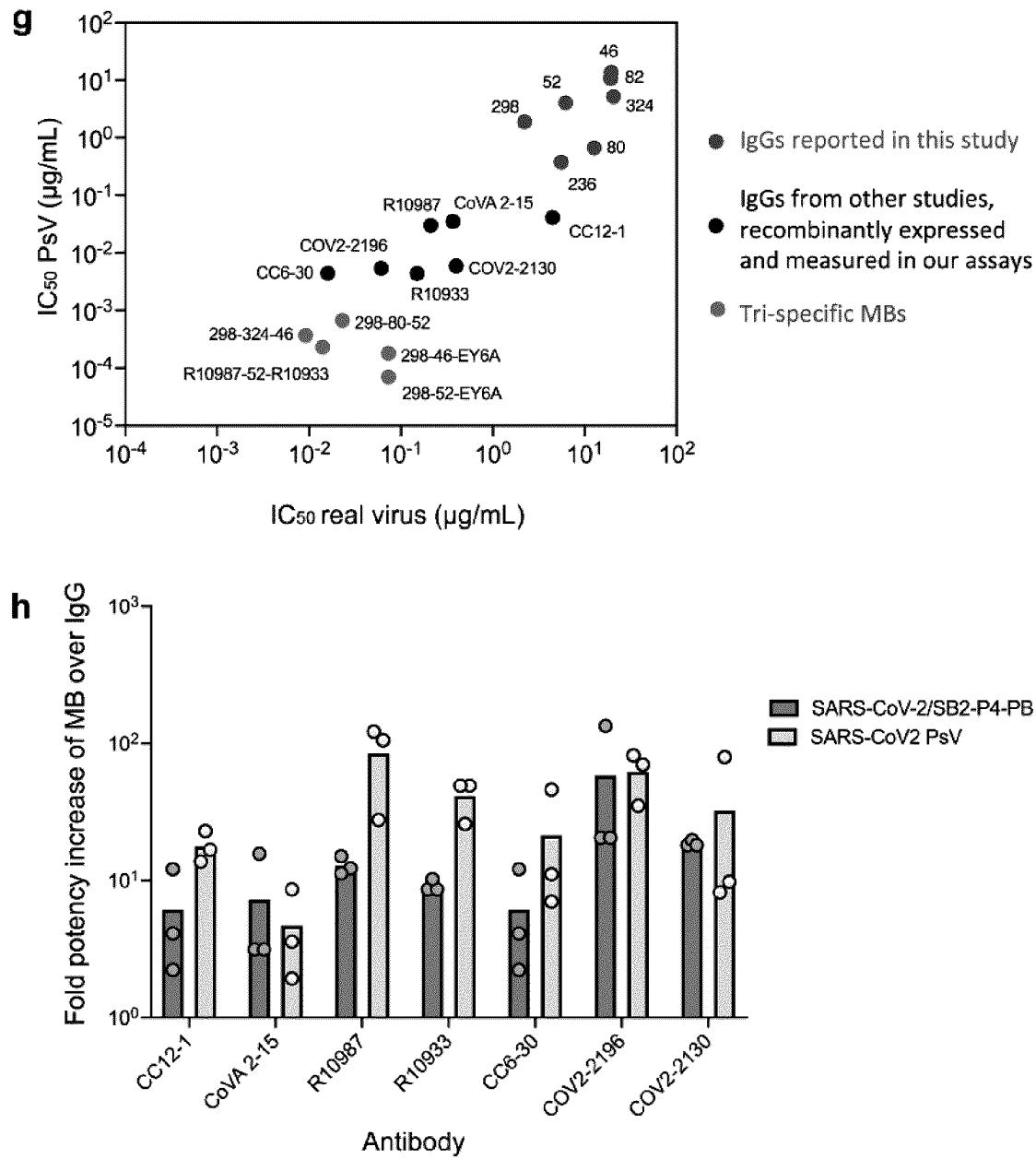


Figure 13g, 13h

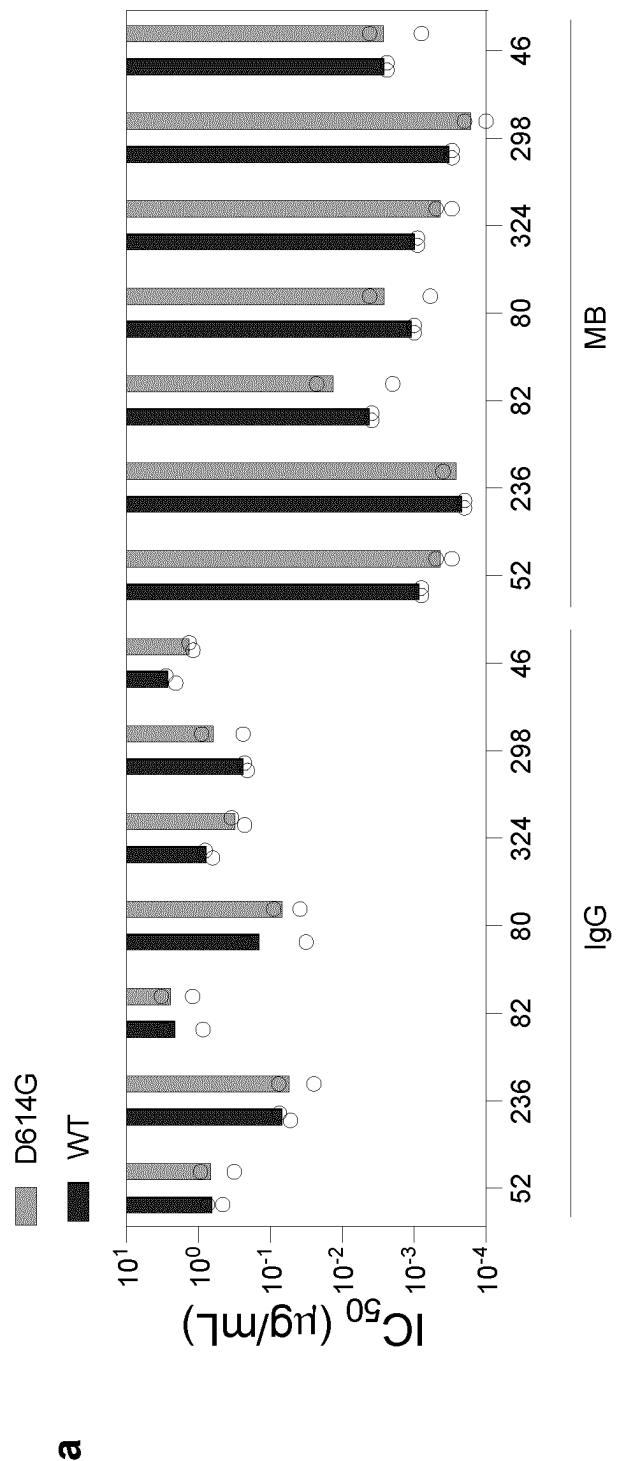


Figure 14a

b

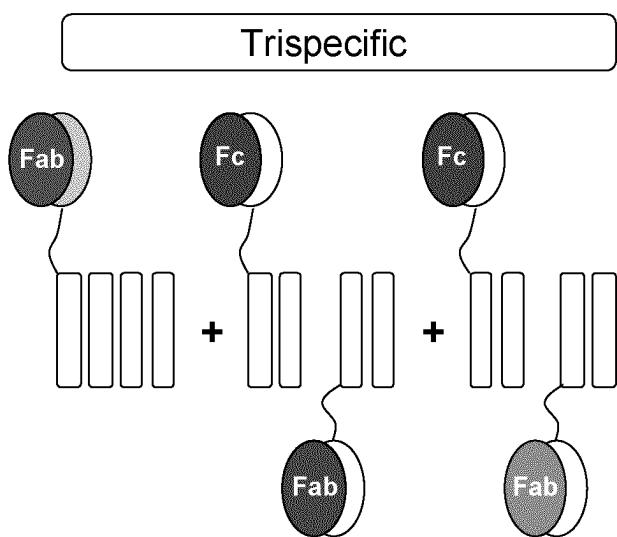


Figure 14b

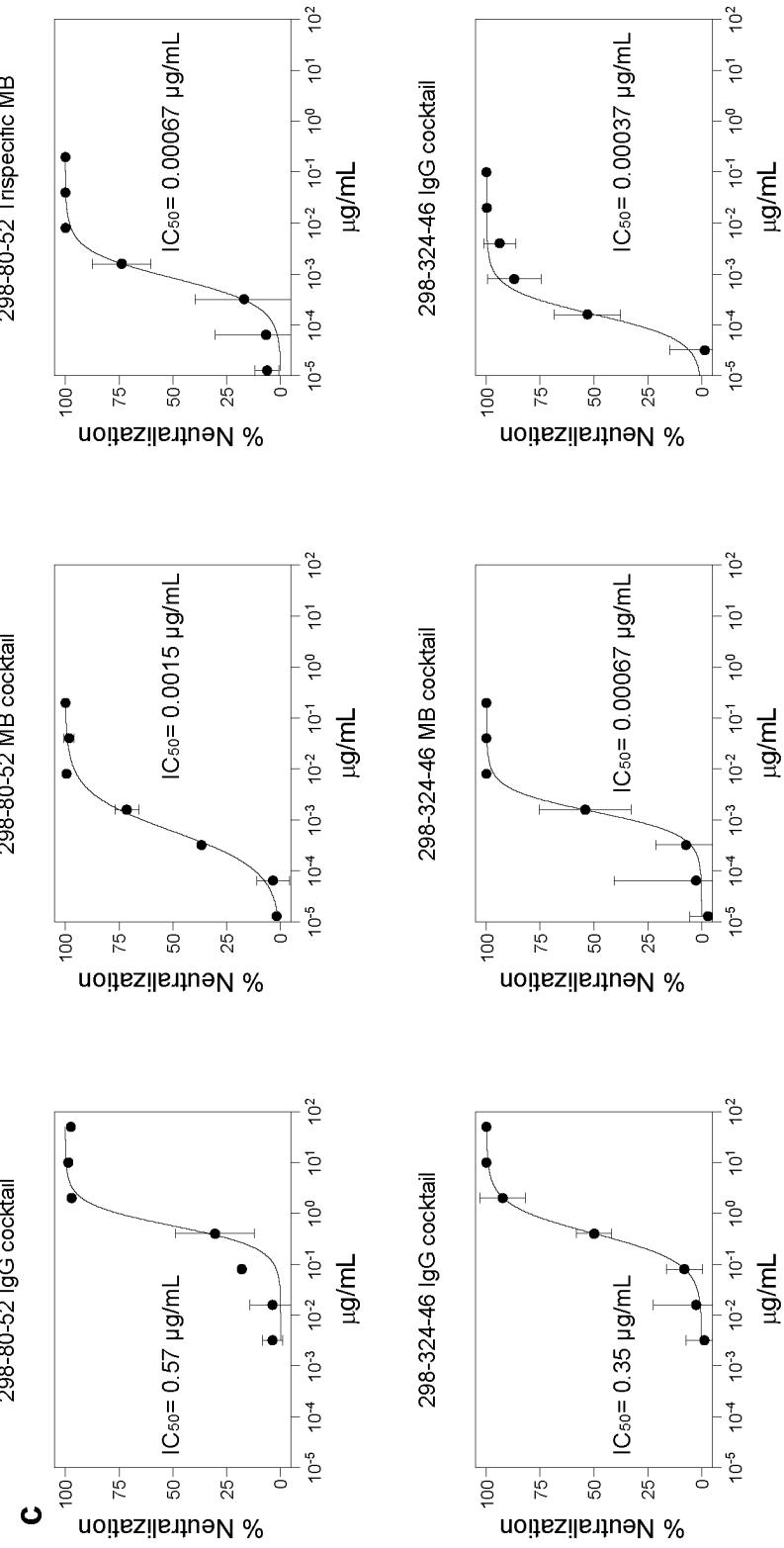


Figure 14c

d

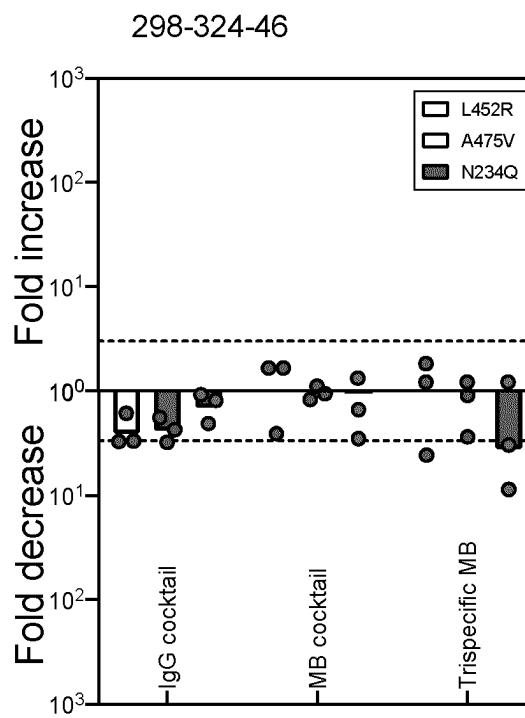
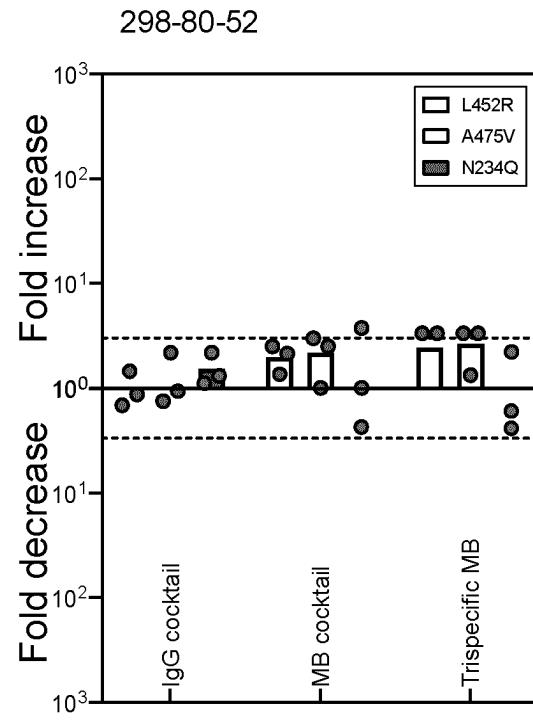


Figure 14d

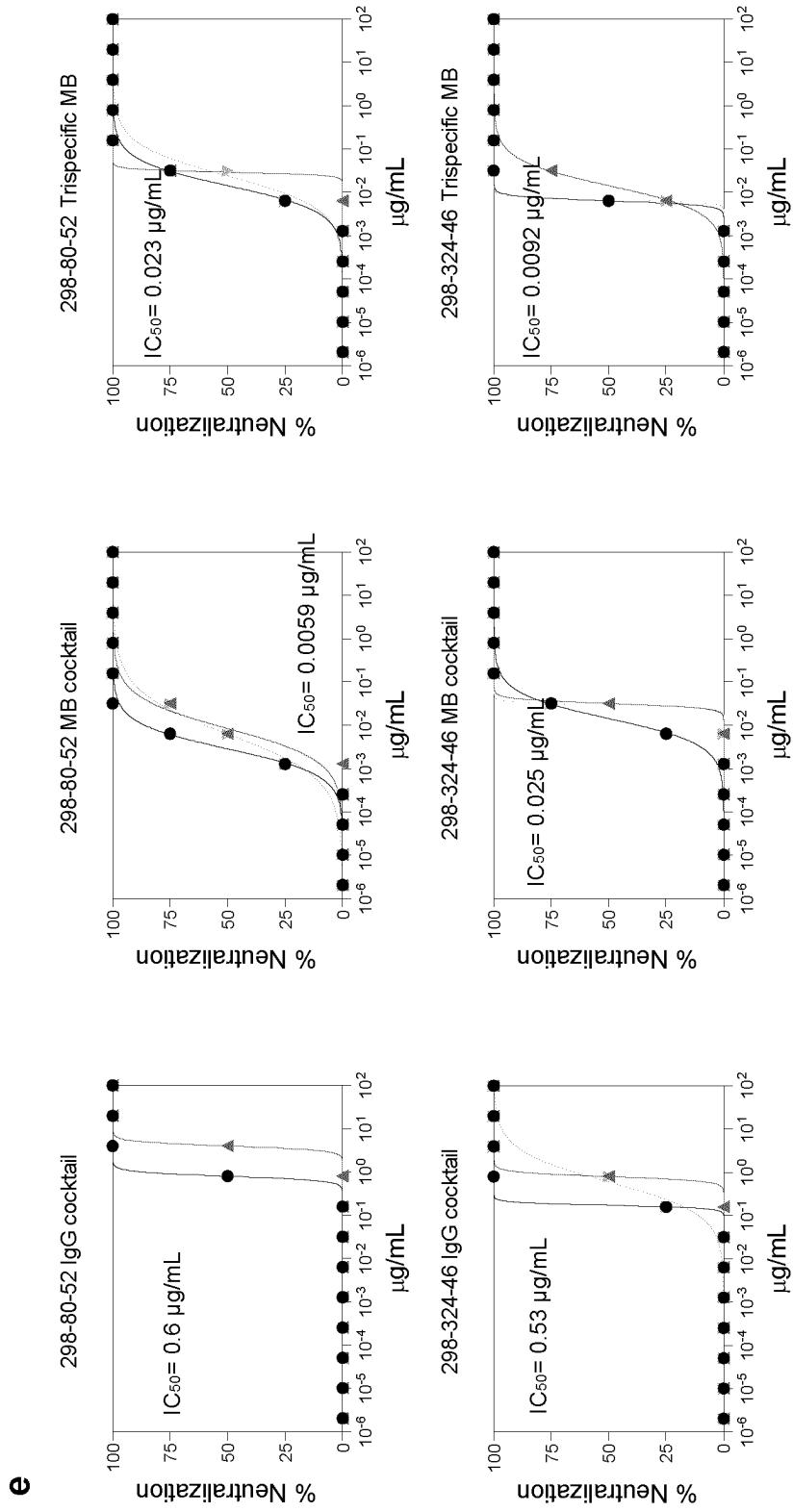


Figure 14e

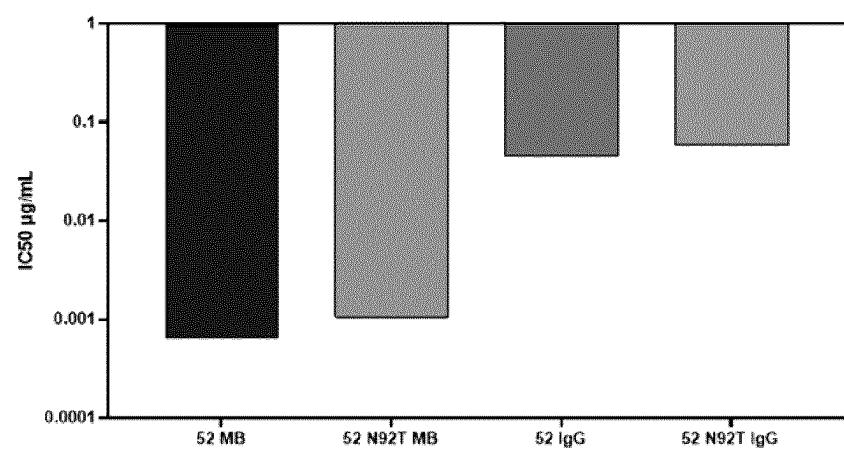


Figure 15

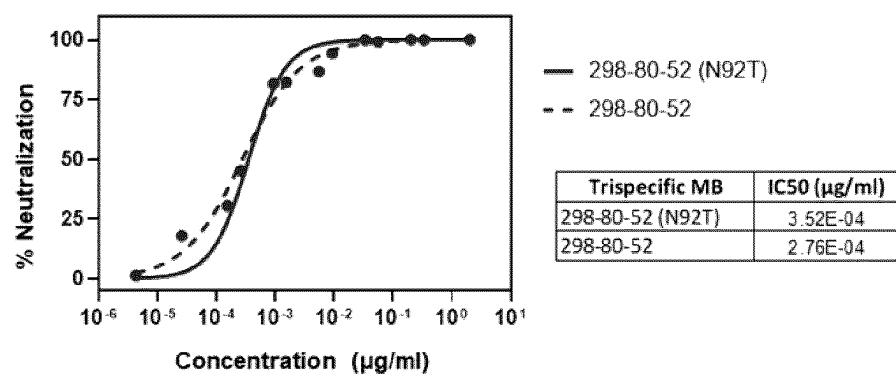


Figure 16

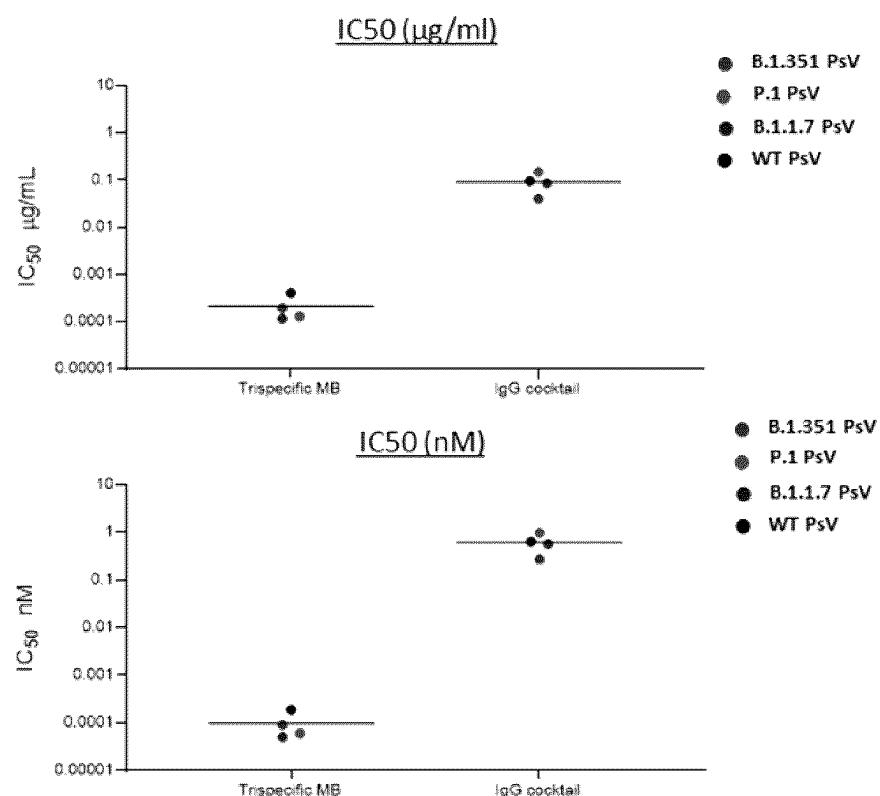


Figure 17

POLYPEPTIDES TARGETING SARS-COV-2 AND RELATED COMPOSITIONS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This patent application is a U.S. National Stage Application of International Patent Application No. PCT/CA2021/051426, filed Oct. 8, 2021, which claims priority to and the benefit of U.S. Provisional Patent Application No. 63/089,782, filed Oct. 9, 2020, U.S. Provisional Patent Application No. 63/197,236, filed Jun. 4, 2021, and U.S. Provisional Patent Application No. 63/220,929, filed Jul. 12, 2021, all of which are incorporated herein by reference in their entireties.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. The ASCII copy, created on Sep. 19, 2023, is named RBT-001WOUS_SL.txt and is 199,342 bytes in size.

FIELD

[0003] The present invention relates to polypeptides. In particular, the present invention relates to SARS-CoV-2-specific polypeptides and related constructs, compositions, and methods.

BACKGROUND

[0004] Nanoparticles have contributed to advancements in various disciplines. Their use has the potential to confer targeted delivery and allows the engineering of ordered micro-arrays, slow release and caged micro-environments for catalytic processes.

[0005] For the fabrication of nanoparticles that contain sensitive and metastable proteins, protein self-assembly is an attractive method. Indeed, self-assembled nanoparticles form under physiological conditions through non-covalent interactions and reliably yield uniform and often symmetric nanocapsules or nanocages.

[0006] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes coronavirus disease 2019 (COVID-19), the respiratory illness responsible for the COVID-19 pandemic.

[0007] A need exists for improved compositions and methods for treating and/or preventing SARS-CoV-2.

SUMMARY OF THE INVENTION

[0008] In accordance with an aspect, there is provided a fusion protein comprising a nanocage monomer linked to a SARS-CoV-2 binding moiety, wherein a plurality of the fusion proteins self-assemble to form a nanocage.

[0009] In an aspect, the SARS-CoV-2 binding moiety targets the SARS-CoV-2 S glycoprotein.

[0010] In an aspect, the SARS-CoV-2 binding moiety decorates the interior and/or exterior surface, preferably the exterior surface, of the assembled nanocage.

[0011] In an aspect, the SARS-CoV-2 binding moiety comprises an antibody or fragment thereof.

[0012] In an aspect, the antibody or fragment thereof comprises a Fab fragment.

[0013] In an aspect, the antibody or fragment thereof comprises a scFab fragment, a scFv fragment, a sdAb fragment, a VHH domains or a combination thereof.

[0014] In an aspect, the antibody or fragment thereof comprises a heavy and/or light chain of a Fab fragment.

[0015] In an aspect, the SARS-CoV-2 binding moiety comprises single chain variable domain VHH-72, BD23 and/or 4A8.

[0016] In an aspect, the SARS-CoV-2 binding moiety comprises an mAb listed in Table 4.

[0017] In an aspect, the SARS-CoV-2 binding moiety comprises mAb 298, 324, 46, 80, 52, 82, or 236 from Table 4.

[0018] In an aspect, the SARS-CoV-2 binding moiety is linked at the N- or C-terminus of the nanocage monomer, or wherein there is a first SARS-CoV-2 binding moiety linked at the N-terminus and a second SARS-CoV-2 binding moiety linked at the C-terminus of the nanocage monomer, wherein the first and second SARS-CoV-2 binding moieties are the same or different.

[0019] In an aspect, the nanocage monomer comprises a first nanocage monomer subunit linked to the SARS-CoV-2 binding moiety; wherein the first nanocage monomer sub-unit self-assembles with a second nanocage monomer sub-unit to form the nanocage monomer.

[0020] In an aspect, the SARS-CoV-2 binding moiety is linked at the N- or C-terminus of the first nanocage monomer, or wherein there is a first SARS-CoV-2 binding moiety linked at the N-terminus and a second SARS-CoV-2 binding moiety linked at the C-terminus of the first nanocage monomer subunit, wherein the first and second SARS-CoV-2 binding moieties are the same or different.

[0021] In an aspect, the fusion protein is provided in combination with the second nanocage monomer subunit.

[0022] In an aspect, the second nanocage monomer sub-unit is linked to a bioactive moiety.

[0023] In an aspect, the bioactive moiety comprises an Fc fragment.

[0024] In an aspect, the Fc fragment is an IgG1 Fc fragment.

[0025] In an aspect, the Fc fragment comprises one or more mutations, such as LS,YTE,LALA,I253A, and/or LALAP, that modulate the half-life of the fusion protein from, for example, minutes or hours to several days, weeks, or months.

[0026] In an aspect, the Fc fragment is an scFc fragment.

[0027] In an aspect, from about 3 to about 100 nanocage monomers, such as 24, 32, or 60 monomers, or from about 4 to about 200 nanocage monomer subunits, such as 4, 6, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, or more, optionally in combination with one or more whole nanocage monomers, self-assemble to form a nanocage.

[0028] In an aspect, the nanocage monomer is selected from ferritin, apoferritin, encapsulin, SOR, lumazine synthase, pyruvate dehydrogenase, carboxysome, vault proteins, GroEL, heat shock protein, E2P, MS2 coat protein, fragments thereof, and variants thereof.

[0029] In an aspect, the nanocage monomer is apoferritin, optionally human apoferritin.

[0030] In an aspect, the first and second nanocage monomer subunits interchangeably comprise the “N” and “C” regions of apoferritin.

[0031] In an aspect, the “N” region of apoferritin comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0032] MSSQIRQNYSTDVEAVNSLVNLQLQASY-TYLSLGFYFDRDDVALEGVSHFFRELA-EEKR-EGYERLLKMQNQRGGRALFQDIKKPAEDEW.

[0033] In an aspect, the “C” region of apoferritin comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0034] GKTPDAMKAAMALEKKLNQALLDLHAL-GSARTDPHLCDFLETHFLDEEVKLICKMG-DHLTNLHRLGGPEAGLGEYLFERLTLRHD

[0035] or

[0036] GKTPDAMKAAMALEKKLNQALLDLHAL-GSARTDPHLCDFLETHFLDEEVKLICKMG-DHLTNLHRLGGPEAGLGEYLFERLTLKHD.

[0037] In an aspect, the fusion protein further comprises a linker between the nanocage monomer subunit and the bioactive moiety.

[0038] In an aspect, the linker is flexible or rigid and comprises from about 1 to about 30 amino acid residues, such as from about 8 to about 16 amino acid residues.

[0039] In an aspect, the linker comprises a GGS repeat, such as 1, 2, 3, 4, or more GGS repeats.

[0040] In an aspect, the linker comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0041] GGGGSGGGGSGGGGSGGGGGSGGGGGSGGG.

[0042] In an aspect, the fusion protein further comprises a C-terminal linker.

[0043] In an aspect, a C-terminal linker comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0044] GGSGGGSGGGSGGGSGGGSGGGSG. In accordance with an aspect, there is provided a nanocage comprising at least one fusion protein described herein and at least one second nanocage monomer subunit that self-assembles with the fusion protein to form a nanocage monomer.

[0045] In an aspect, each nanocage monomer comprises the fusion protein described herein.

[0046] In an aspect, from about 20% to about 80% of the nanocage monomers comprise the fusion protein described herein.

[0047] In an aspect, the nanocage comprises at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 different SARS-CoV-2 binding moieties, such as 3 different SARS-CoV-2 binding moieties.

[0048] In an aspect, the nanocage is multivalent and/or multispecific.

[0049] In an aspect, the nanocage comprises one of more mAbs from Table 4.

[0050] In an aspect, the nanocage comprises 3 mAbs from Table 4.

[0051] In an aspect, the nanocage comprises mAbs 298, 324, 46, 52, 80, 82 and/or 236 from Table 4.

[0052] In an aspect, the nanocage comprises a 4:2:1:1: ratio of scFab1-human apoferritin:scFc-human N-Ferritin:scFab2-C-Ferritin:scFab3-C-Ferritin.

[0053] In an aspect, the nanocage carries a cargo molecule, such as a pharmaceutical agent, a diagnostic agent, and/or an imaging agent.

[0054] In an aspect, the cargo molecule is not fused to the fusion protein and is contained in the nanocage internally.

[0055] In an aspect, the cargo molecule is a protein and is fused to the fusion protein such that the cargo molecule is contained in the nanocage internally.

[0056] In an aspect, the cargo molecule is a fluorescent protein, such as GFP, EGFP, Ametrine, and/or a flavin-based fluorescent protein, such as a LOV-protein, such as iLOV.

[0057] In accordance with an aspect, there is provided a tri-specific antibody construct targeting SARS-CoV-2.

[0058] In accordance with an aspect, there is provided a SARS-CoV-2 therapeutic or prophylactic composition comprising the nanocage or the antibody described herein.

[0059] In accordance with an aspect, there is provided a nucleic acid molecule encoding the fusion protein described herein.

[0060] In accordance with an aspect, there is provided a vector comprising the nucleic acid molecule described herein.

[0061] In accordance with an aspect, there is provided a host cell comprising the vector described herein and producing the fusion protein described herein.

[0062] In accordance with an aspect, there is provided a method for treating and/or preventing SARS-CoV-2, the method comprising administering the nanocage or the antibody or the composition described herein.

[0063] In accordance with an aspect, there is provided a use of the nanocage or the antibody or the composition described herein for treating and/or preventing SARS-CoV-2.

[0064] In accordance with an aspect, there is provided the nanocage or the antibody or the composition described herein for use in treating and/or preventing SARS-CoV-2.

[0065] In accordance with an aspect, there is provided a polypeptide comprising an amino acid sequence having at least 70% identity to any sequence listed in the following Table:

QVQLVQSGAEVKPGASVKVSCKASGYT PTSYGISWVRQAPGQGLEWMGWISAYN GNTNYAQKLQGRVTMTRDTSTTVYME SSLRSEDTAVYYCARDIGPIDYWGQGT TVSS	DIQMTQSPSSLSASVGDRVTITCRASQGI SSYLAWSQQKPGKAPKLLIYDASNLLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYY CQQANSFPSTFGQGTKVEIKR
EVQLLESGGGLVQPGGSLRLSCAASGFT FSNYGMHWVRQAPGKGLEWVSGIISAG SITNYADSVKGRFTIISRDNSKNTLYLQM SLRAEDTAVYYCAGNHAGTTVSEYFQH WGQGTLLTVSS	DIQMTQSPSSLSASVGDRVTITCRASQSIS SWLAWYQQKPGKAPKLLIYDTSNLETGVP SRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYTTPWTFQGQGTRLEIKR

- continued

QVQLVQSGAEVKKPGASVKVSCKASGYT FTDYHMHWVRQAPGQGLEWMGNPNS GGTNYAQKFQGRVTMTRDTSTSTVYME SSLRSEDTAVYYCARDISSWYEITKFDPW GQGTLTVSS	EIVMTQSPATLSVSPGERATLSCAKASQSV SGTYLAWYQQKPGQAPRLLIYGASTRAT GIPARFSGSGSGTEFTLTISLQSEDFAVY YCLQTHSYPPTFQGQTKVEIKR
QVQLVQSGAEVKKPGASVKVSCKASGYIF SRYAIHWVRQAPGQGLEWMGNNPISG NTDYAPNFQGRVTMTRDTSTSTVYME SLRSEDTAVYYCARDGSQLAYLVEYFQH WGQGTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQVIT NNLAWYQQKPGKAPKLLIYDASLETGVP SRFSGSGSGTDFTLTISLQPEDFATYYC QQSYTFPYTFQGQTKVEIKR
QVQLVQSGAEVKKPGASVKVSCKASGYT FTHYYMHHWVRQAPGQGLEWMGIINPSS SASYSQKQFQGRVTMTRDTSTSTVYME SLRSEDTAVYYCARDGRYGSQSYFPDYW GQGTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQNIS RYLNWYQQKPGKAPKLLIYDASLETGVP SRFSGSGSGTDFTLTISLQPEDFATYYC QQANGFPPTFGQGQTKLEIKR
QVQLVQSGAEVKKPGASVKVSCKASGYT FTGHDMHWVRQAPGQGLEWMGIINPSG GSTSYAQKFQGRVTMTRDTSTSTVYME SSLRSEDTAVYYCARANSRLRYYYGMDVW GQGTMVTVSS	DIQMTQSPSSLSASVGDRVITTCRASQSV SSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLKISRVEAED YCQQGYTTPYTFQGQGQTKLEIKR
QVQLVQSGAEVKKPGSSVKVSCKASGYT FTSYIDINWVRQAPGQGLEWMGAIMPMPG TANYAQKFQGRVTITADESTSTAYMEL LRLSEDTAVYYCARSGSSGYYYGWGQGTLV TVSS	DIVMTQSPSLPVTGEPASIICRSSQSL HSNGYNYLDWYLQKPGQSPOLLITYLGSN RASGVPDFRSFGSGSGTDFTLKISRVEAED VGVYYCMQALQTPYTFQGQGQTKLEIKR
QVQLVQSGAEVKKPGSSVKVSCKASGGT FSSYAIISWVRQAPGQGLEWMGNPNS GGANYAQKFQGRVTITADESTSTAYMEL SLRSEDTAVYYCSTYYDSSGYSTDYWG QGTLTVSS	DIVMTQSPSLPVTGEPASIICRSSQSL HSNGYNYLDWYLQKPGQSPOLLITYAASSL QSGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCMQALQTPYTFQGQGQTKLEIKR
QVQLVQSGAEVKKPGASVKVSCKASGYT FTGYYMHHWVRQAPGQGLEWMWINPLN GGTINFAPKFQGRVTMTRDTSTSTVYME SSLRSEDTAVYYCARDPGGSYSNDAFDI WGQGTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQSI RYLNWYQQKPGKAPKLLIYDASLETGVP SRFSGSGSGTDFTLTISLQPEDFATYYC QQANSFPLTFGGGTKVDIKR
QVQLVQSGAEVKKPGSSVKVSCKASGYT FTSYAMHHWVRQAPGQGLEWMGRISPRS GGTKYQAQRFQGRVTITADESTSTAYMEL SLRSEDTAVYYCAREAVAGTHPQAGDFD LWGRGTLTVSS	DIVMTQSPSLPVTGEPASIICRSSQSL HSNGYNYLDWYLQKPGQSPOLLITYAASSL QSGVPDRFSGSGSGTDFTLKISRVEAEDV GVYYCQQYYSPYTFQGQGQTKLEIKR
EVLQLESGGGLVQPGGSLRLSCAASGFT FSSSAMHHWVRQAPGKGLEWVSAIGTGG DTYYADSVKGRFTISRDNSKNLYLQMNS LRAEDTAVYYCAREGDGYNFYPDYWG GTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQGI SSYLAWYQQKPGKAPKLLIYDASSLQIGV PSRFSGSGSGTDFTLTISLQPEDFATYY CLQSYSTPPWTFQGQGQTKVEIKR
QVQLVQSGAEVKKPGASVKVSCKASGYT FTSYIDINWVRQAPGQGLEWMGMDPSG GSTSYAQKFQGRVTMTRDTSTSTVYME SSLRSEDTAVYYCAKDFGGTRYDYWYF DLWGRGTLTVSS	EIVMTQSPATLSVSPGERATLSCAKASQSV SSRYLAWYQQKPGQAPRLLIYGASTRAT GIPARFSGSGSGTEFTLTISLQSEDFAVY YCQQYYTTPTFQGQGQTKLEIKR
EVLQLESGGGLVQPGGSLRLSCAASGFP FSQHGMHWVRQAPGKGLEWVSAIDRSG SYIYYADSVKGRFTISRDNSKNLYLQMNN SLRAEDTAVYYCARDTYGGKVTYFDYWG GQTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQGI SSHLLAWYQQKPGKAPKLLIYDASLETGVP PSRFSGSGSGTDFTLTISLQPEDFATYY CQQTYSTPPWTFQGQGQTKVEIKR
QVQLVQSGAEVKKPGASVKVSCKASGGT FSTYGIISWVRQAPGQGLEWMGWISPNS GGTDLAQKFQGRVTMTRDTSTSTVYME SSLRSEDTAVYYCASDPRDDIAGGYWGQ GTLTVSS	DIVMTQSPDSLAVSLGERATINCKSSQSV LYSSMNKNYLAWYQQKPGQOPPKLLIYWA STRESGVPDFRSFGSGSGTDFTLTISLQ EDVAVYYCQQYYSTPPPTFGQGQTKLEIKR

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QVQLVQSGAEVKKPGASVKVSCKASGG FSTS AFY WVR QAPG QGLEWMGWINPYT GGT NYA QKF QGRVTMTRDTSTSTVYME SSL RSE D TAVYYCARSRALYGSYFDY WGQGTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQVIS NYLAWYQQPKGKAPKLLIYDASNLETGV SRFSGSGSGTDFLTISLQPEDFATYYC QQSFSPPPFGQGTRLEIKR
EVQLLESGGGLVQPGRSLRSLSCAASGFT FSSYAMS WVR QAPG KGLEWVSTIYSGGS TYYADSVKGRFTISRDNSKNTLYLQMNSL RAEDTAVYYCARGDSRDAFDIWGQGTMV TVSS	DIQMTQSPSSLSASVGDRVITTCRASQSI SWLAWYQQPKGKAPKLLIYDASNLETGV PSRFSGSGSGTDFLTISLQPEDFATYY CQQSYSTPPTFGPGTKVDI KR
QVQLVQSGAEVKKPGASVKVSCKASGGT FNNYGI SWVR QAPG QGLEWMGWMNPN SGNTGYA QKF QGRVTMTRDTSTSTVYME LSSL RSE D TAVYYCARVGDYGYD YIVSPFD LGCRGTLTVSS	DIQMTQSPSSLSASVGDRVITTCRASQSI TYLNWYQQPKGKAPKLLIYDASNLETGV SRFSGSGSGTDFLTISLQPEDFATYYC QQSYSTPPTFGQGTRKVEIKR
QVQLVQSGAEVKKPGASVKVSCKASGGT FTSYG I SWVR QAPG QGLEWMGWMNPN GNIGY A QKF QGRVTMTRDTSTSTVYME SSL RSE D TAVYYCARS RGI QLL P RGM DV GQGTTTVSS	DIVMTQSPLSLPVTPGE P ASI SCRSSQSL HSNGY NYLDWYLQKPGQSPQ LLIY LGSN RASGPDR FSGSGSGTDFLT KIS RVEAED VG VY YCM QAL QTPPTFGQGTRLEIKR
QVQLVQSGAEVKKPGSSVKVSCKASGGT FTSYG I SWVR QAPG QGLEWMGGI I PIFGT TTNYA QKF QGRV ITIAD KST STAY MEL SS LRSE D TAVYYCAR S TREL PEV VDWY FDLW TVSS	DIQMTQSPSSLSASVGDRVITTCRASQGI SNNL NWYQQPKGKAPKLLIYAA S SLE SGV PSRFSGSGSGTDFLTISLQPEDFATYY CQQGNGFP LT F GPG TKV D I KR
QVQLVQSGAEVKKPGSSVKVSCKASGGT FNR YAFS WVR QAPG QGLEWMGGI I PIFGT ANYA QKF QGRV ITIAD E ST STAY MEL SS RSE D TAVYYCAR S TREL PEV VDWY FDLW GRGTLTVSS	DIVMTQSPLSLAVSLGERATINCKSSQSV LYSSNNKNL AWYQQPKGQPPKLLIYWA STRESGV PDR FSGSGSGTDFLTISLQA EDVA VYYCQ QYY SAPL TFGGGT KVEIKR

[0066] or a functional fragment thereof.

[0067] In an aspect, the polypeptide comprises at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the listed sequence.

[0068] In an aspect, the polypeptide consists of at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the listed sequence.

[0069] In accordance with an aspect, there is provided an antibody or fragment thereof comprising the polypeptide described herein.

[0070] In accordance with an aspect, there is provided a fusion polypeptide comprising (1) a fragment crystallizable (Fc) region linked to (2) a nanocage monomer or subunit thereof, wherein the Fc region comprises the I253A mutation, wherein numbering is according to the EU index.

[0071] In an aspect, the Fc region further comprises the LALAP (L234A/L235A/P329G) mutations, wherein numbering is according to the EU index.

[0072] In an aspect, the Fc region is an IgG1 Fc region.

[0073] In an aspect, the nanocage monomer is a ferritin monomer.

[0074] In an aspect, the ferritin monomer is a ferritin light chain.

[0075] In an aspect, the ferritin light chain is a human ferritin light chain.

[0076] In an aspect, the Fc region is linked via an amino acid linker to the nanocage monomer or subunit thereof.

[0077] In an aspect, the Fc region is linked to the N-terminus of the nanocage monomer or subunit thereof.

[0078] In an aspect, the Fc region is a single chain Fc (scFc).

[0079] In an aspect, the Fc region is an Fc monomer.

[0080] In accordance with an aspect, there is provided a self-assembled polypeptide complex comprising:

[0081] (a) a plurality of first fusion polypeptides, each first fusion polypeptide comprising (1) an Fc region linked to (2) a nanocage monomer or subunit thereof, and

[0082] (b) a plurality of second fusion polypeptides, each second fusion polypeptide comprising (1) a SARS-CoV-2-binding antibody fragment linked to (2) a nanocage monomer or subunit thereof.

[0083] In an aspect, the nanocage monomer is a ferritin monomer.

[0084] In an aspect, the nanocage monomer is a ferritin light chain.

[0085] In an aspect, the self-assembled polypeptide complex does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.

[0086] In an aspect, the nanocage monomer is a human ferritin light chain.

[0087] In an aspect, the SARS-CoV-2-binding antibody fragment binds to the receptor binding domain or the Spike protein of SARS-CoV-2.

[0088] In an aspect, the SARS-CoV-2-binding antibody fragment comprises a light chain variable domain and a heavy chain variable domain.

[0089] In an aspect, the SARS-CoV-2-binding antibody fragment comprises an Fab of an antibody that is capable of binding to SARS-CoV-2.

[0090] In an aspect, the SARS-CoV-2-binding antibody fragment comprises a VK domain and a VH domain.

- [0091] In an aspect, the self-assembled polypeptide complex is characterized by a 1:1 ratio of first fusion polypeptides to second fusion polypeptides.
- [0092] In an aspect, the Fc region is an IgG1 Fc region.
- [0093] In an aspect, the Fc region is linked to the nanocage monomer or subunit thereof via an amino acid linker.
- [0094] In an aspect, the Fc region is linked to the N-terminus of the nanocage monomer or subunit thereof.
- [0095] In an aspect, the self-assembled polypeptide complex comprises at total of least 24 fusion polypeptides.
- [0096] In an aspect, the self-assembled polypeptide complex comprises a total of at least 32 fusion polypeptides.
- [0097] In an aspect, the self-assembled polypeptide complex has a total of about 32 fusion polypeptides.
- [0098] In accordance with an aspect, there is provided a self-assembled polypeptide complex comprising:
- [0099] (a) a plurality of first fusion polypeptides, each first fusion polypeptide comprising (1) an IgG1 Fc region linked to (2) a human ferritin monomer or subunit thereof, wherein the IgG1 Fc region comprises the LALAP (L234A/L235A/P329G) and I253A mutations, wherein numbering is according to the EU index, and
- [0100] (b) a plurality of second fusion polypeptides, each second fusion polypeptide comprising (1) a Fab fragment of an antibody that is capable of binding to a SARS-CoV-2 protein, the Fab fragment being linked to (2) a human ferritin monomer or subunit thereof.
- [0101] In an aspect:
- [0102] (1) each first fusion polypeptide comprises a ferritin monomer subunit which is C-half-ferritin and each second fusion polypeptide comprises a ferritin monomer subunit which is N-half-ferritin; or
- [0103] (2) each first fusion polypeptide comprises a ferritin monomer subunit which is N-half ferritin and each second fusion polypeptide comprises a ferritin monomer subunit which is C-half-ferritin.
- [0104] In an aspect, the self-assembled polypeptide complex is characterized by a 1:1 ratio of first fusion polypeptides to second fusion polypeptides.
- [0105] In an aspect, each first fusion polypeptide comprises a ferritin monomer subunit which is C-half-ferritin.
- [0106] In an aspect, the IgG1 Fc region is linked to the C-half-ferritin via an amino acid linker.
- [0107] In an aspect, the IgG1 Fc region is linked to the C-half-ferritin via the N-terminus of the C-half-ferritin.
- [0108] In an aspect, each second fusion polypeptide comprises a ferritin monomer subunit which is N-half-ferritin.
- [0109] In an aspect, the Fab fragment is linked to the N-half-ferritin via an amino acid linker.
- [0110] In an aspect, the Fab fragment is linked to the N-half-ferritin via the N-terminus of the N-half-ferritin.
- [0111] In an aspect, the self-assembled polypeptide complex further comprises a plurality of third fusion polypeptides, each third fusion polypeptide comprising (1) a human ferritin monomer linked to (2) a Fab fragment of an antibody that is capable of binding to a SARS-CoV-2 protein.
- [0112] In an aspect, the self-assembled polypeptide complex is characterized by a 1:1:2 ratio of first fusion polypeptides to second fusion polypeptides to third fusion polypeptides.
- [0113] In an aspect, the self-assembled polypeptide complex comprises at total of least 24 fusion polypeptides.
- [0114] In an aspect, the self-assembled polypeptide complex comprises a total of at least 32 fusion polypeptides.
- [0115] In an aspect, the self-assembled polypeptide complex has a total of 32 fusion polypeptides.
- [0116] In an aspect, wherein the Fab fragment comprises a VK domain and a VH domain, wherein
- [0117] (1) the VK domain has an amino acid sequence of SEQ ID NO: 11 and the VH domain has an amino acid sequence of SEQ ID NO:12;
- [0118] (2) the VK domain has an amino acid sequence of SEQ ID NO:17 and the VH domain has an amino acid sequence of SEQ ID NO:18;
- [0119] (3) the VK domain has an amino acid sequence of the VK within SEQ ID NO:25 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:26;
- [0120] (4) the VK domain has an amino acid sequence of the VK within SEQ ID NO:27 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:28;
- [0121] (5) the VK domain has an amino acid sequence of the VK within SEQ ID NO:29 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:30;
- [0122] (6) the VK domain has an amino acid sequence of the VK within SEQ ID NO:31 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:32;
- [0123] (7) the VK domain has an amino acid sequence of the VK within SEQ ID NO:33 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:34;
- [0124] (8) the VK domain has an amino acid sequence of the VK within SEQ ID NO:35 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:36;
- [0125] (9) the VK domain has an amino acid sequence of the VK within SEQ ID NO:37 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:38;
- [0126] (10) the VK domain has an amino acid sequence of the VK within SEQ ID NO:39 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:40;
- [0127] (11) the VK domain has an amino acid sequence of the VK within SEQ ID NO:41 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:42;
- [0128] (12) the VK domain has an amino acid sequence of the VK within SEQ ID NO:43 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:44;
- [0129] (13) the VK domain has an amino acid sequence of the VK within SEQ ID NO:45 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:46;
- [0130] (14) the VK domain has an amino acid sequence of the VK within SEQ ID NO:47 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:48;
- [0131] (15) the VK domain has an amino acid sequence of the VK within SEQ ID NO:49 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:50;

- [0132] (16) the VK domain has an amino acid sequence of the VK within SEQ ID NO:51 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:52;
- [0133] (17) the VK domain has an amino acid sequence of the VK within SEQ ID NO:53 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:54;
- [0134] (18) the VK domain has an amino acid sequence of the VK within SEQ ID NO:55 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:56;
- [0135] (19) the VK domain has an amino acid sequence of the VK within SEQ ID NO:57 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:58;
- [0136] (20) the VK domain has an amino acid sequence of the VK within SEQ ID NO:59 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:60;
- [0137] (21) the VK domain has an amino acid sequence of the VK within SEQ ID NO:61 or SEQ ID NO:62 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:63; or
- [0138] (22) the VK domain has an amino acid sequence of the VK within SEQ ID NO:64 and the VH domain has an amino acid sequence of the VH within SEQ ID NO:65.
- [0139] In an aspect, the human ferritin monomer is human ferritin light chain.
- [0140] In an aspect, the self-assembled polypeptide complex does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.
- [0141] In accordance with an aspect, there is provided a method of treating, ameliorating, or preventing a SARS-CoV-2-related condition, the method comprising administering to a subject a composition comprising the self-assembled polypeptide complex described herein.
- [0142] In an aspect, the subject is a mammal.
- [0143] In an aspect, the subject is human.
- [0144] The novel features of the present invention will become apparent to those of skill in the art upon examination of the following detailed description of the invention. It should be understood, however, that the detailed description of the invention and the specific examples presented, while indicating certain aspects of the present invention, are provided for illustration purposes only because various changes and modifications within the spirit and scope of the invention will become apparent to those of skill in the art from the detailed description of the invention and claims that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0145] The present invention will be further understood from the following description with reference to the Figures, in which:
- [0146] FIG. 1. Avidity enhances binding and neutralization of VHH against SARS-CoV-2. a Schematic representation of a monomeric VHH domain and its multimerization using a conventional Fc (dark red) scaffold or human apo-ferritin (gray). b Size exclusion chromatography and SDS-PAGE of apoferritin alone (gray) and VHH-72 apoferritin particles (gold). c Negative stain electron microscopy of VHH-72 apoferritin particles. (Scale bar 50 nm, representative of two independent experiments). d Comparison of the

binding avidity (apparent K_D) of VHH-72 to SARS-CoV-2 S protein when displayed in a bivalent (dark red) or 24-mer (gold) format. Bars indicate the mean values of n=2 biologically independent experiments. Apparent K_D lower than 10^{-1} =M (dash line) is beyond the instrument detection limit. e Neutralization potency against SARS-CoV-2 PsV (color coding is as in (d)). One representative out of two biologically independent replicates with similar results is shown. Mean values ±SD of two technical replicates is represented in the plot. Median IC₅₀ values of the two biologically independent replicates are shown.

[0147] FIG. 2. Binding interfaces of Fab 52 and 298 and the RBD. Interaction of Fab 298 (a) and 52 (b) with RBD (light and dark green for the core and RBM regions, respectively) is mediated by complementarity determining regions (CDR) heavy (H) 1 (yellow), H2 (orange), H3 (red), kappa light (K) 1 (light blue) and K3 (purple). Critical binding residues are shown as sticks (insets). H-bonds and salt bridges are depicted as black dashed lines. L and H chains of Fabs are shown in tan and white, respectively. c) Bottom and side views of ACE2 (left) and Fab 298 (right) bound to RBD. RBD side-chains that are part of the binding interface of the ACE2-RBD and Fab 298-RBD complexes are depicted in pink, while RBD side-chains unique to a given interface are shown in yellow. Surfaces of ACE2, variable regions of Fab 298 HC and Fab 298 KC are shown in white, grey and tan, respectively. The RBD is colored as in (a). d) Superposition of Fabs 46 (light pink) and 52 (dark pink) when bound to the RBD (green) reveals a distinct angle of approach for the two mAbs. Stereo-image of the composite omit map electron density contoured at 1.3 sigma at the interfaces of e) 298-RBD and f) 52-RBD.

[0148] FIG. 3. Bioavailability, biodistribution, and immunogenicity of a mouse surrogate Multabody. a Binding kinetics of WT and Fc-modified (LALAP mutation) MB to mouse FcγRI (left) and mouse FcRn at endosomal (middle) and physiological (right) pH in comparison to the parental IgG. Two-fold dilution series from 100 to 3 nM (IgG) and 10 to 0.3 nM (MB) were used. Red lines represent raw data; black lines represent global fits. b Five male C57BL/6 mice per group were used to assess the serum concentration of a surrogate mouse MB, a Fc-modified MB (LALAP mutation), and parental mouse IgGs (IgG1 and IgG2a subtypes) after subcutaneous administration of 5 mg/kg. c MB and IgG2a samples were labeled with Alexa-647 for visualization of their biodistribution post subcutaneous injection into three male BALB/c mice/group via live noninvasive 2D whole body imaging. 15 nm fluorescently-labeled gold nanoparticles (GNP), which have a similar Rh value as the Multabody are shown as a comparator. d Five male C57BL/6 mice per group were used to assess any anti-drug antibody response induced by the mouse surrogate Multabody in comparison to parental IgG and a species-mismatched malaria PfCSP peptide fused to *Helicobacter pylori* ferritin (HpFerr). Mean values ±SD of n=5 mice is shown in (b) and (d).

[0149] FIG. 4. 3D biodistribution of a surrogate mouse Multabody is comparable to its parental IgG. The biodistribution of 15 nm gold nanoparticles (GNP), MB and IgG samples labeled with Alexa-647 were visualized post subcutaneous injection into BALB/c mice via live non-invasive 3D whole body imaging. a) Representative 3D rendered fluorescent image overlaid with CT scan from PBS injected control. b) Depiction of the localization of major mouse

organs overlaid with CT scan. c) 3D rendered fluorescent images overlaid with CT scan at 1 h (1H), two days (D2), eight days (D8) and 11 days (D11) post subcutaneous injection of gold nanoparticles (top), MB (three middle panels) or IgG (bottom panel). Each 3D image set is displayed showing dorsal view overlaid with CT scan (right), as well as a selected frontal (top left), medial (middle), and transverse (bottom left) planes based on signal localization. 3D fluorescent images were mapped to a rainbow look-up Table (LUT), with color scale minimum set to background and maximum set to $50 \text{ pmol M}^{-1} \text{ cm}^{-1}$ (GNP) or $1000 \text{ pmol M}^{-1} \text{ cm}^{-1}$ (MB and IgG).

[0150] FIG. 5. Protein engineering to multimerize IgG-like particles against SARS-CoV-2. A Schematic representation of the human apo ferritin split design. b Negative stain electron micrograph of the MB. (Scale bar 50 nm, representative of two independent experiments). c Hydrodynamic radius (R_h) of the MB. d Avidity effect on the binding (apparent K_c) of 4A8 (purple) and BD23 (gray) to the SARS-CoV-2 Spike. e Sensograms of BD23 IgG and MB with different Fc sequence variants binding to FcγRI (top row), FcRn at endosomal pH (middle row) and FcRn at physiological pH (bottom row). Red lines represent raw data whereas black lines represent global fits. f Neutralization of SARS-CoV-2 PsV by 4A8 and BD23 IgGs and MBs. Representative data of three biologically independent samples. The mean values $\pm SD$ for two technical replicates is shown in each neutralization plot. Median IC_{50} values of the three biologically independent replicates are indicated.

[0151] FIG. 6. The Multobody enhances the potency of human mAbs from phage display. a Work flow for the identification of potent anti-SARS-CoV-2 neutralizers using the MB technology. Created with Biorender. b Comparison of neutralization potency between IgGs (cyan) and MBs (pink) that display the same human Fab sequences derived from phage display. c IC_{50} values fold increase upon multimerization. d Apparent affinity (K_D), association (k_{on}), and dissociation (k_{off}) rates of the most potent neutralizing MBs (pink) compared to their IgG counterparts (cyan) for binding the SARS-CoV-2 S protein. Three biological replicates and their mean are shown for IC_{50} values in (b) and (c).

[0152] FIG. 7. Neutralization of SARS-CoV-2 RBD-targeting Multabodies and their parental IgGs. a) Representative neutralization titration curves of 20 antibodies against SARS-CoV-2 PsV when displayed as IgGs (black) and MBs (dark red). The mean IC_{50} values of three biological replicates are displayed for comparison. The mean values $\pm SD$ for two technical replicates are shown in each neutralization plot. b) Neutralization profiles of selected IgGs and MBs against SARS-CoV-2 PsV targeting 293T-ACE2 (black) and HeLa-ACE2 (gray) target cells. The mean IC_{50} value and individual IC_{50} values of three and two biological replicates are shown for 293T-ACE2 and HeLa-ACE2 cells, respectively. c) Neutralization titration curves of three biological replicates (different shades of gray) against the authentic SARS-CoV-2/SB2-P4-PB strain. The mean IC_{50} is indicated. Neutralization potencies of recombinant mAbs REGN10933 (red) and REGN10987 (blue) are included in (a) and (c) as benchmarks for comparison.

[0153] FIG. 8. Expression yields and homogeneity of SARS-CoV-2 RBD-targeting Multabodies. a) Yield (mg/L) of the seven most potent IgGs (white) and their respective MBs (dark red). Mean values $\pm SD$ for two biologically independent samples. b) Aggregation temperature (Tagg, °

C.) comparison as in (a). The solid line denotes the mean Tagg value of two biologically independent samples. c) SEC chromatograms of 298 IgG (top row, black) and 298 MB (bottom row, dark red) from three independent expressions and purifications. Prior to SEC, in both cases, the samples were purified using Protein A affinity chromatography. The arrows indicate the peak used to perform a PsV neutralization assay from each batch. IC_{50} values ($\mu\text{g/mL}$) are noted. Mean values $\pm SD$ for two technical replicates are shown in each neutralization plot.

[0154] FIG. 9. Binding profiles of IgGs and MBs. Sensograms of IgGs and MBs binding to RBD (left) and S protein (right) of SARS-CoV-2 immobilized onto Ni-NTA biosensors. 2-fold dilution series from 125 to 4 nM (IgG), and 16 to 0.5 nM (MB) were used. Red lines represent raw data, whereas black lines represent global fits.

[0155] FIG. 10. Epitope delineation of the most potent mAb specificities. a Surface and cartoon representation of RBD (light green for the core and dark green for RBM) and ACE2⁶⁶ (light brown) binding. Heat map showing binding competition experiments. High signal responses (red) represent low competition while low signal responses (white) correspond to high competition. Epitope bins are highlighted by dashed-line boxes. b 15.0 Å filtered cryo-EM reconstruction of the Spike (gray) in complex with Fab 80 (yellow), 298 (orange), and 324 (red). The RBD and NTD are shown in green and blue, respectively. c Cryo-EM reconstruction of the Fab 46 (pink) and RBD (green) complex. A RBD⁶⁶ secondary structure cartoon is fitted into the partial density observed for the RBD. d Crystal structure of the ternary complex formed by Fab 52 (purple), Fab 298 (orange), and RBD (green). e Composite image depicting the side and top view of the unliganded (PDB 6XM4) and the antibody-bound SARS-CoV-2 spike with available PDB or EMD entries^{3,4,9,10,13,15,17,67,68,69,70,72}. Inset: close up view of antibodies targeting different antigenic sites on the RBD. The mAb with the lowest reported IC_{50} value against SARS-CoV-2 PsV was selected as a representative antibody of the bin (highlighted in bold) and those antibodies with similar binding epitopes are listed in the same color below (color coding of Spike, NTD and RBD as in (b)). Individual protomers in the unliganded spike are shown in white, pink, and purple.

[0156] FIG. 11. Epitope binning. mAb binding competition experiments to His-tagged RBD as measured by biolayer interferometry (BLI). 50 $\mu\text{g/ml}$ of mAb 1 was incubated for 3 min followed by incubation with 50 $\mu\text{g/ml}$ of mAb 2 for 5 min.

[0157] FIG. 12. Cryo-EM analysis of the Fab-Spike and Fab-RBD complexes. Representative cryo-EM micrograph (scale bar 50 nm, top left), selected 2D class averages (top right), Fourier shell correlation curve from the final 3D non-uniform refinement (bottom left) and local resolution (A) plotted on the surface of the cryo-EM map (bottom right) are shown for the Fab 80-Spike complex (a), the Fab 298-Spike complex (b), the Fab 324-Spike complex (c), and the Fab 46-RBD complex (d).

[0158] FIG. 13. Multabodies overcome SARS-CoV-2 sequence diversity. a Cartoon representation of the RBD showing four naturally occurring mutations as spheres. The epitopes of mAbs 52 (light pink) and 298 (yellow) are shown as representative epitopes of each bin. b Affinity and c IC_{50} fold-change comparison between WT and mutated RBD and PsV, respectively. d Neutralization potency of IgG (gray

bars) vs MB (dark red bars) against SARS-CoV-2 PsV variants in comparison to WVT PsV. e Neutralization potency comparison of two IgG cocktails (three IgGs), monospecific MB cocktails (three MBs) and tri-specific MBs against WT SARS-CoV-2 PsV and variants. mAbs sensitive to one or more PsV variants (d) were selected to generate the cocktails and the tri-specific MBs. f Neutralization potency of the tri-specific 298-80-52 MB against SARS-CoV-2 B.1.351 PsV variant. g IC₅₀ values in PsV (y-axis) and replication competent SARS-CoV-2 virus (SB2-P4-PB; x-axis) demonstrating the ability of tri-specific MBs (red) to enhance potency across a wide range of mAb characteristics (blue and black). h IC₅₀ values fold increase upon multimerization. The mean of three biological replicates is shown in (b-h).

[0159] FIG. 14. MBs potently overcome SARS-CoV-2 sequence variability. a) Comparison of the neutralization potency of selected IgGs and MBs against WT PsV (dark red) and the more infectious D614G PsV (grey). b) Schematic representation of a tri-specific MB generated by combination of three Fab specificities and the Fc fragment using the MB split design. c) Cocktails and tri-specific MBs that combine the specificities of mAbs 298, 80 and 52, or 298, 324 and 46 were generated and tested against WT PsV. The mean values ±SD for two technical replicates is represented in each representative neutralization plot. Source data are provided as a Source Data file. d) Neutralization potency change of cocktails and tri-specific MBs against pseudotyped SARS-CoV-2 variants in comparison to WT PsV. PsV variants that were sensitive to individual antibodies within the cocktails were selected. The area within the dotted lines represents a 3-fold change in IC50 value. This threshold was established as the cut-off for increased sensitivity (up bars) or increased resistance (down bars). e) Neutralization titration curves showing three biological replicates of cocktails and tri-specific MBs against the authentic SARS-CoV-2/SB2-P4-PB strain. Mean IC50 values of three biologically independent replicates are shown.

[0160] FIG. 15. The N92T mutation did not have any effects in potency as both an IgG or as a monospecific MB in a WT pseudovirus neutralization assay.

[0161] FIG. 16. The 298-80-52 trispecific MB containing the N92T mutation in the VL of mAb 52 was screened in a P1 PsV neutralization assay and the results confirmed that there was no loss in potency observed compared to the parental trispecific MB.

[0162] FIG. 17. An example trispecific MB, 298-80-52, was assessed for potency across the variants of concern (VOCS) in pseudovirus neutralization assays.

DETAILED DESCRIPTION OF CERTAIN ASPECTS

Definitions

[0163] Unless otherwise explained, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Definitions of common terms in molecular biology may be found in Benjamin Lewin, *Genes V*, published by Oxford University Press, 1994 (ISBN 0-19-854287-9); Kendrew et al. (eds.), *The Encyclopedia of Molecular Biology*, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9); and Robert A. Meyers (ed.), *Molecular Biology and Biotechnology: a Comprehensive*

Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8). Although any methods and materials similar or equivalent to those described herein can be used in the practice for testing of the present invention, the typical materials and methods are described herein. In describing and claiming the present invention, the following terminology will be used.

[0164] It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting. Many patent applications, patents, and publications are referred to herein to assist in understanding the aspects described. Each of these references are incorporated herein by reference in their entirety.

[0165] In understanding the scope of the present application, the articles "a", "an", "the", and "said" are intended to mean that there are one or more of the elements. Additionally, the term "comprising" and its derivatives, as used herein, are intended to be open ended terms that specify the presence of the stated features, elements, components, groups, integers, and/or steps, but do not exclude the presence of other unstated features, elements, components, groups, integers and/or steps. The foregoing also applies to words having similar meanings such as the terms, "including", "having" and their derivatives.

[0166] It will be understood that any aspects described as "comprising" certain components may also "consist of" or "consist essentially of," wherein "consisting of" has a closed-ended or restrictive meaning and "consisting essentially of" means including the components specified but excluding other components except for materials present as impurities, unavoidable materials present as a result of processes used to provide the components, and components added for a purpose other than achieving the technical effect of the invention. For example, a composition defined using the phrase "consisting essentially of" encompasses any known acceptable additive, excipient, diluent, carrier, and the like. Typically, a composition consisting essentially of a set of components will comprise less than 5% by weight, typically less than 3% by weight, more typically less than 1%, and even more typically less than 0.1% by weight of non-specified component(s).

[0167] It will be understood that any component defined herein as being included may be explicitly excluded from the claimed invention by way of proviso or negative limitation. For example, in some aspects the nanocages and/or fusion proteins described herein may exclude a ferritin heavy chain and/or may exclude an iron-binding component.

[0168] In addition, all ranges given herein include the end of the ranges and also any intermediate range points, whether explicitly stated or not.

[0169] Terms of degree such as "substantially", "about" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of up to and including at least ±5% of the modified term if this deviation would not negate the meaning of the word it modifies. For example, the term "about" may encompass a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value."

[0170] The abbreviation, "e.g." is derived from the Latin *exempli gratia*, and is used herein to indicate a non-limiting

example. Thus, the abbreviation “e.g.” is synonymous with the terms “for example,” or “such as.” The word “or” is intended to include “and” unless the context clearly indicates otherwise.

[0171] The term “subject” as used herein refers to any member of the animal kingdom, typically a mammal. The term “mammal” refers to any animal classified as a mammal, including humans, other higher primates, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Typically, the mammal is human.

[0172] The terms “protein nanoparticle,” “nanocage,” and “multabody” are used interchangeably herein and refer to a multi-subunit, protein-based polyhedron shaped structure. The subunits or nanocage monomers are each composed of proteins or polypeptides (for example a glycosylated polypeptide), and, optionally of single or multiple features of the following: nucleic acids, prosthetic groups, organic and inorganic compounds. Non-limiting examples of protein nanoparticles include ferritin nanoparticles (see, e.g., Zhang, Y. Int. J. Mol. Sci., 12:5406-5421, 2011, incorporated by reference herein), encapsulin nanoparticles (see, e.g., Sutter et al., Nature Struct. and Mol. Biol., 15:939-947, 2008, incorporated by reference herein), Sulfur Oxygenase Reductase (SOR) nanoparticles (see, e.g., Urich et al., Science, 311:996-1000, 2006, incorporated by reference herein), lumazine synthase nanoparticles (see, e.g., Zhang et al., J. Mol. Biol., 306: 1099-1114, 2001) or pyruvate dehydrogenase nanoparticles (see, e.g., Izard et al., PNAS 96: 1240-1245, 1999, incorporated by reference herein). Ferritin, apoferitin, encapsulin, SOR, lumazine synthase, and pyruvate dehydrogenase are monomeric proteins that self-assemble into a globular protein complexes that in some cases consists of 24, 60, 24, 60, and 60 protein subunits, respectively. Ferritin and apoferitin are generally referred to interchangeably herein and are understood to both be suitable for use in the fusion proteins, nanocages, and methods described herein. Carboxysome, vault proteins, GroEL, heat shock protein, E2P and MS2 coat protein also produce nanocages are contemplated for use herein. In addition, fully or partially synthetic self-assembling monomers are also contemplated for use herein.

[0173] It will be understood that each nanocage monomer may be divided into two or more subunits that will self-assemble into a functional nanocage monomer. For example, ferritin or apoferitin may be divided into an N- and C-subunit, e.g., an N- and C-subunit obtained by dividing full-length ferritin substantially in half, so that each subunit may be separately bound to a different SARS-CoV-2 binding moiety or bioactive moiety for subsequent self-assembly into a nanocage monomer and then a nanocage. Each subunit may, in aspects, bind a SARS-CoV-2 binding moiety and/or bioactive moiety at both termini, either the same or different. By “functional nanocage monomer” it is intended that the nanocage monomer is capable of self-assembly with other such monomers into a nanocage as described herein.

[0174] The terms “ferritin” and “apoferitin” are used interchangeably herein and generally refer to a polypeptide (e.g., a ferritin chain) that is capable of assembling into a ferritin complex which typically comprises 24 protein subunits. It will be understood that the ferritin can be from any species. Typically, the ferritin is a human ferritin. In some embodiments, the ferritin is a wild-type ferritin. For example, the ferritin may be a wild-type human ferritin. In

some embodiments, a ferritin light chain is used as a nanocage monomer, and/or a subunit of a ferritin light chain is used as a nanocage monomer subunit. In some embodiments, assembled nanocages do not include any ferritin heavy chains or other ferritin components capable of binding to iron.

[0175] The term “multispecific,” as used herein, refers to the characteristic of having at least two binding sites at which at least two different binding partners, e.g., an antigen or receptor (e.g., Fc receptor), can bind. For example, a nanocage that comprises at least two Fab fragments, wherein each of the two Fab fragments binds to a different antigen, is “multispecific.” As an additional example, a nanocage that comprises an Fc fragment (which is capable of binding to an Fc receptor) and an Fab fragment (which is capable of binding to an antigen) is “multispecific.”

[0176] The term “multivalent,” as used herein, refers to the characteristic of having at least two binding sites at which a binding partner, e.g., an antigen or receptor (e.g., Fc receptor), can bind. The binding partners that can bind to the at least two binding sites may be the same or different.

[0177] The term “antibody”, also referred to in the art as “immunoglobulin” (Ig), used herein refers to a protein constructed from paired heavy and light polypeptide chains; various Ig isotypes exist, including IgA, IgD, IgE, IgG, such as IgG₁, IgG₂, IgG₃, and IgG₄, and IgM. It will be understood that the antibody may be from any species, including human, mouse, rat, monkey, llama, or shark. When an antibody is correctly folded, each chain folds into a number of distinct globular domains joined by more linear polypeptide sequences. For example, in the case of IgGs, the immunoglobulin light chain folds into a variable (V_L) and a constant (CL) domain, while the heavy chain folds into a variable (V_H) and three constant (C_{H1}, C_{H2}, C_{H3}) domains. Interaction of the heavy and light chain variable domains (V_H and V_L) results in the formation of an antigen binding region (Fv). Each domain has a well-established structure familiar to those of skill in the art.

[0178] The light and heavy chain variable regions are responsible for binding the target antigen and can therefore show significant sequence diversity between antibodies. The constant regions show less sequence diversity, and are responsible for binding a number of natural proteins to elicit important immunological events. The variable region of an antibody contains the antigen binding determinants of the molecule, and thus determines the specificity of an antibody for its target antigen. The majority of sequence variability occurs in six hypervariable regions, three each per variable heavy and light chain; the hypervariable regions combine to form the antigen-binding site, and contribute to binding and recognition of an antigenic determinant. The specificity and affinity of an antibody for its antigen is determined by the structure of the hypervariable regions, as well as their size, shape and chemistry of the surface they present to the antigen.

[0179] An “antibody fragment” as referred to herein may include any suitable antigen-binding antibody fragment known in the art. The antibody fragment may be a naturally-occurring antibody fragment, or may be obtained by manipulation of a naturally-occurring antibody or by using recombinant methods. For example, an antibody fragment may include, but is not limited to a Fv, single-chain Fv (scFv; a molecule consisting of V_L and V_H connected with a peptide linker), Fc, single-chain Fc, Fab, single-chain Fab,

$F(ab')_2$, single domain antibody (sdAb; a fragment composed of a single V_L or V_H), and multivalent presentations of any of these.

[0180] By the term “synthetic antibody” as used herein, is meant an antibody which is generated using recombinant DNA technology. The term should also be construed to mean an antibody which has been generated by the synthesis of a DNA molecule encoding the antibody and which DNA molecule expresses an antibody protein, or an amino acid sequence specifying the antibody, wherein the DNA or amino acid sequence has been obtained using synthetic DNA or amino acid sequence technology which is available and well known in the art.

[0181] The term “epitope” refers to an antigenic determinant. An epitope is the particular chemical groups or peptide sequences on a molecule that are antigenic, that is, that elicit a specific immune response. An antibody specifically binds a particular antigenic epitope, e.g., on a polypeptide. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5, about 9, about 11, or about 8 to about 12 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., “Epitope Mapping Protocols” in *Methods in Molecular Biology*, Vol. 66, Glenn E. Morris, Ed (1996).

[0182] The term “antigen” as used herein is defined as a molecule that provokes an immune response. This immune response may involve either antibody production, or the activation of specific immunologically-competent cells, or both. The skilled artisan will understand that any macromolecule, including virtually all proteins or peptides, can serve as an antigen. Furthermore, antigens can be derived from recombinant or genomic DNA. A skilled artisan will understand that any DNA, which comprises a nucleotide sequence or a partial nucleotide sequence encoding a protein that elicits an immune response therefore encodes an “antigen” as that term is used herein. Furthermore, one skilled in the art will understand that an antigen need not be encoded solely by a full length nucleotide sequence of a gene. It is readily apparent that the aspects described herein include, but are not limited to, the use of partial nucleotide sequences of more than one gene and that these nucleotide sequences could be arranged in various combinations to elicit the desired immune response. Moreover, a skilled artisan will understand that an antigen need not be encoded by a “gene” at all. It is readily apparent that an antigen can be synthesized or can be derived from a biological sample. Such a biological sample can include, but is not limited to a tissue sample, a cell, or a biological fluid.

[0183] “Encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (e.g., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting therefrom. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces

the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0184] The term “expression” as used herein is defined as the transcription and/or translation of a particular nucleotide sequence driven by its promoter.

[0185] “Isolated” means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in a living animal is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural state is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

[0186] Unless otherwise specified, a “nucleotide sequence encoding an amino acid sequence” includes all nucleotide sequences that are degenerate versions of each other and that encode the same amino acid sequence. The phrase nucleotide sequence that encodes a protein or an RNA may also include introns to the extent that the nucleotide sequence encoding the protein may in some version contain an intron (s).

[0187] By the term “modulating,” as used herein, is meant mediating a detectable increase or decrease in the level of a response in a subject compared with the level of a response in the subject in the absence of a treatment or compound, and/or compared with the level of a response in an otherwise identical but untreated subject. The term encompasses perturbing and/or affecting a native signal or response thereby mediating a beneficial therapeutic response in a subject, typically, a human.

[0188] The term “operably linked” refers to functional linkage between a regulatory sequence and a heterologous nucleic acid sequence resulting in expression of the latter. For example, a first nucleic acid sequence is operably linked with a second nucleic acid sequence when the first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences are contiguous and, where necessary to join two protein coding regions, in the same reading frame.

[0189] “Parenteral” administration of composition includes, e.g., subcutaneous (s.c.), intravenous (i.v.), intramuscular (i.m.), or intrasternal injection, or infusion techniques. Also included are inhalation and intranasal administration.

[0190] The term “polynucleotide” as used herein is defined as a chain of nucleotides. Furthermore, nucleic acids are polymers of nucleotides. Thus, nucleic acids and polynucleotides as used herein are interchangeable. One skilled in the art has the general knowledge that nucleic acids are polynucleotides, which can be hydrolyzed into the monomeric “nucleotides.” The monomeric nucleotides can be hydrolyzed into nucleosides. As used herein polynucleotides include, but are not limited to, all nucleic acid sequences which are obtained by any means available in the art, including, without limitation, recombinant means, i.e., the cloning of nucleic acid sequences from a recombinant

library or a cell genome, using ordinary cloning technology and PCR, and the like, and by synthetic means.

[0191] As used herein, the terms "peptide," "polypeptide," and "protein" are used interchangeably, and refer to a compound comprised of amino acid residues covalently linked by peptide bonds. A protein or peptide must contain at least two amino acids, and no limitation is placed on the maximum number of amino acids that can comprise a protein's or peptide's sequence. Polypeptides include any peptide or protein comprising two or more amino acids joined to each other by peptide bonds. As used herein, the term refers to both short chains, which also commonly are referred to in the art as peptides, oligopeptides and oligomers, for example, and to longer chains, which generally are referred to in the art as proteins, of which there are many types. "Polypeptides" include, for example, biologically active fragments, substantially homologous polypeptides, oligopeptides, homodimers, heterodimers, variants of polypeptides, modified polypeptides, derivatives, analogs, fusion proteins, among others. The polypeptides include natural peptides, recombinant peptides, synthetic peptides, or a combination thereof.

[0192] By the term "specifically binds," as used herein with respect to an antibody, is meant an antibody which recognizes a specific antigen, but does not substantially recognize or bind other molecules in a sample. For example, an antibody that specifically binds to an antigen from one species may also bind to that antigen from one or more species. But, such cross-species reactivity does not itself alter the classification of an antibody as specific. In another example, an antibody that specifically binds to an antigen may also bind to different allelic forms of the antigen. However, such cross reactivity does not itself alter the classification of an antibody as specific. In some instances, the terms "specific binding" or "specifically binding," can be used in reference to the interaction of an antibody, a protein, or a peptide with a second chemical species, to mean that the interaction is dependent upon the presence of a particular structure (e.g., an antigenic determinant or epitope) on the chemical species; for example, an antibody recognizes and binds to a specific protein structure rather than to proteins generally. If an antibody is specific for epitope "A", the presence of a molecule containing epitope A (or free, unlabeled A), in a reaction containing labeled "A" and the antibody, will reduce the amount of labeled A bound to the antibody.

[0193] The terms "therapeutically effective amount", "effective amount" or "sufficient amount" mean a quantity sufficient, when administered to a subject, including a mammal, for example a human, to achieve a desired result, for example an amount effective to cause a protective immune response. Effective amounts of the compounds described herein may vary according to factors such as the molecule, age, sex, species, and weight of the subject. Dosage or treatment regimes may be adjusted to provide the optimum therapeutic response, as is understood by a skilled person. For example, administration of a therapeutically effective amount of the fusion proteins described herein is, in aspects, sufficient to treat and/or prevent COVID-19.

[0194] Moreover, a treatment regime of a subject with a therapeutically effective amount may consist of a single administration, or alternatively comprise a series of applications. The frequency and length of the treatment period depends on a variety of factors, such as the molecule, the age

of the subject, the concentration of the agent, the responsiveness of the patient to the agent, or a combination thereof. It will also be appreciated that the effective dosage of the agent used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. The fusion proteins described herein may, in aspects, be administered before, during or after treatment with conventional therapies for the disease or disorder in question. For example, the fusion proteins described herein may find particular use in combination with conventional treatments for viral infections.

[0195] The term "transfected" or "transformed" or "transduced" as used herein refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A "transfected" or "transformed" or "transduced" cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

[0196] The phrase "under transcriptional control" or "operatively linked" as used herein means that the promoter is in the correct location and orientation in relation to a polynucleotide to control the initiation of transcription by RNA polymerase and expression of the polynucleotide.

[0197] A "vector" is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Numerous vectors are known in the art including, but not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. Thus, the term "vector" includes an autonomously replicating plasmid or a virus. The term should also be construed to include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds, liposomes, and the like. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus vectors, retroviral vectors, and the like.

[0198] Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

[0199] The term "pharmaceutically acceptable" means that the compound or combination of compounds is compatible with the remaining ingredients of a formulation for pharmaceutical use, and that it is generally safe for administering to humans according to established governmental standards, including those promulgated by the United States Food and Drug Administration.

[0200] The term "pharmaceutically acceptable carrier" includes, but is not limited to solvents, dispersion media, coatings, antibacterial agents, antifungal agents, isotonic and/or absorption delaying agents and the like. The use of pharmaceutically acceptable carriers is well known.

[0201] "Variants" are biologically active fusion proteins, antibodies, or fragments thereof having an amino acid sequence that differs from a comparator sequence by virtue of an insertion, deletion, modification and/or substitution of one or more amino acid residues within the comparative sequence. Variants generally have less than 100% sequence identity with the comparative sequence. Ordinarily, however, a biologically active variant will have an amino acid sequence with at least about 70% amino acid sequence identity with the comparative sequence, such as at least about 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%,

80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity. The variants include peptide fragments of at least 10 amino acids that retain some level of the biological activity of the comparator sequence. Variants also include polypeptides wherein one or more amino acid residues are added at the N- or C-terminus of, or within, the comparative sequence. Variants also include polypeptides where a number of amino acid residues are deleted and/or optionally substituted by one or more amino acid residues. Variants also may be covalently modified, for example by substitution with a moiety other than a naturally occurring amino acid or by modifying an amino acid residue to produce a non-naturally occurring amino acid.

[0202] “Percent amino acid sequence identity” is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the sequence of interest, such as the polypeptides of the invention, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. None of N-terminal, C-terminal, or internal extensions, deletions or insertions into the candidate sequence shall be construed as affecting sequence identity or homology. Methods and computer programs for the alignment are well known in the art, such as “BLAST”.

[0203] “Active” or “activity” for the purposes herein refers to a biological and/or an immunological activity of the fusion proteins described herein, wherein “biological” activity refers to a biological function (either inhibitory or stimulatory) caused by the fusion proteins.

[0204] The fusion proteins described herein may include modifications. Such modifications include, but are not limited to, conjugation to an effector molecule. Modifications further include, but are not limited to conjugation to detectable reporter moieties. Modifications that extend half-life (e.g., pegylation) are also included. Modifications for de-immunization are also included. Proteins and non-protein agents may be conjugated to the fusion proteins by methods that are known in the art. Conjugation methods include direct linkage, linkage via covalently attached linkers, and specific binding pair members (e.g., avidin-biotin). Such methods include, for example, that described by Greenfield et al., Cancer Research 50, 6600-6607 (1990), which is incorporated by reference herein and those described by Amon et al., Adv. Exp. Med. Biol. 303, 79-90 (1991) and by Kiseleva et al., Mol. Biol. (USSR)25, 508-514 (1991), both of which are incorporated by reference herein.

Fusion Proteins

[0205] Described herein are fusion proteins. The fusion proteins comprise a nanocage monomer linked to a SARS-CoV-2 binding moiety. A plurality of the fusion proteins self-assemble to form a nanocage. In this way, the SARS-CoV-2 binding moiety may decorate the interior surface of the assembled nanocage, the exterior surface of the assembled nanocage, or both.

[0206] The SARS-CoV-2 binding moiety is typically an antibody or a fragment thereof and, while it can target any part of the SARS-CoV-2 virus, it typically targets the SARS-CoV-2 S glycoprotein. It will be understood that the SARS-CoV-2 binding moiety need not be an antibody or

fragment thereof and may be a molecule such as a protein that binds and blocks the virus or an RBD domain in the virus, for example.

[0207] It will be understood that the antibody or fragment thereof may comprise, for example, a heavy and/or light chain of a Fab fragment. The antibody or fragment thereof may comprise a scFab fragment, a scFv fragment, a sdAb fragment, and/or a VHH region for example. It will be understood that any antibody or fragment thereof may be used in the fusion proteins described herein.

[0208] Generally, the fusion protein described herein is associated with a Fab light chain and/or heavy chain, which may be produced separately or contiguously with the fusion protein.

[0209] For example, the SARS-CoV-2 binding moiety may comprise single chain variable domain VHH-72, BD23 and/or 4A8. Alternatively or additionally, the SARS-CoV-2 binding moiety may be selected from any one or a combination of the mAbs listed in Table 4 herein. For example, the SARS-CoV-2 binding moiety may be selected from any one or a combination of mAbs 298, 324, 46, 80, 52, 82, and 236 from Table 4.

[0210] In certain aspects, the nanocage monomer described herein may be split into subunits, allowing for more SARS-CoV-2 binding moieties or other moieties to be attached thereto in various ratios. For example, in aspects, the nanocage monomer comprises a first nanocage monomer subunit linked to the SARS-CoV-2 binding moiety. In use, the first nanocage monomer subunit self-assembles with a second nanocage monomer subunit to form the nanocage monomer. As described above, a plurality of the nanocage monomers self-assemble to form a nanocage. The nanocage monomer subunits may be provided alone or in combination and may have the same or a different SARS-CoV-2 binding moiety fused thereto.

[0211] A nanocage made from the nanocage monomers and/or nanocage monomer subunits described herein may have bioactive moieties included in addition to one or more SARS-CoV-2 binding moieties.

[0212] For example, the bioactive moiety may comprise, for example, one or both chains of an Fc fragment. The Fc fragment may be derived from any type of antibody as will be understood but is, typically, an IgG1 Fc fragment. The Fc fragment may further comprise one or more mutations, such as LS,YTE,LALA,I253A, and/or LALAP, that modulate the half-life and/or effector functions of the fusion protein and/or the resulting assembled nanocage comprising the fusion protein. For example, the half-life may be in the scale of minutes, days, weeks, or even months.

[0213] Moreover, other substitutions in the fusion proteins and nanocages described herein are contemplated, including Fc sequence modifications and addition of other agents (e.g. human serum albumin peptide sequences), that allow changes in bioavailability and will be understood by a skilled person. Furthermore, the fusion proteins and nanocages described herein can be modulated in sequence or by addition of other agents to mute immunogenicity and anti-drug responses (therapeutic, e.g. matching sequence to host, or addition of immunosuppressive therapies [such as, for example, methotrexate when administering infliximab for treating rheumatoid arthritis or induction of neonatal tolerance, which is a primary strategy in reducing the incidence of inhibitors against FVIII (reviewed in: DiMichele D M, Hoots W K, Pipe S W, Rivard G E, Santagostino

E. International workshop on immune tolerance induction: consensus recommendations. Haemophilia. 2007; 13:1-22, incorporated herein by reference in its entirety]).

[0214] In certain embodiments, fragment crystallizable (Fc) regions comprise an I253A mutation. In some embodiments, Fc regions further comprise the LALAP (L234A/L235A/P329G) mutations. Unless otherwise noted, numbering of mutations throughout this disclosure is according to the EU index.

[0215] In some embodiments, the Fc region is an IgG1 Fc region, (e.g., a human IgG1 Fc region), that is, except for mutations noted herein, the Fc region comprises a Fc chains that each have an amino acid sequence that is substantially similar to that of the chains within a wild type IgG1 Fc. In some embodiments, the wild type reference IgG1 Fc is a human IgG1 Fc, in which each Fc chain has an amino acid sequence of SEQ ID NO: 24.

[0216] For example, an IgG1 Fc region may comprise an Fc chain with an amino acid sequence that is at least 85%, at least 87.5%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical to that of an Fc chain within a wild-type IgG1 Fc. In some embodiments, an IgG1 Fc region comprises an Fc chain that comprises the Fc mutations specifically described for that IgG1 Fc region, but has an amino acid sequence that is otherwise 100% identical to an Fc chain within a wild type IgG1 Fc.

[0217] In some embodiments, the Fc region is a single chain Fc (scFc), which comprises two Fc chains linked together by a covalent linker, e.g., via an amino acid linker. In some embodiments, the Fc region is an Fc monomer, which comprises a single Fc chain.

[0218] In cases where the antibody or fragment thereof comprises two chains, such as a first and second chain in the case of a Fc fragment, or a heavy and light chain, the two chains are optionally separated by a linker. The linker may be flexible or rigid, but it typically flexible to allow the chains to fold appropriately. The linker is generally long enough to impart some flexibility to the fusion protein, although it will be understood that linker length will vary depending upon the nanocage monomer and bioactive moiety sequences and the three-dimensional conformation of the fusion protein. Thus, the linker is typically from about 1 to about 130 amino acid residues, such as from about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, or 125 to about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, or 130 amino acid residues, such as from about 50 to about 90 amino acid residues, such as 70 amino acid residues.

[0219] The linker may be of any amino acid sequence and, in one typical example, the linker comprises a GGS repeat and, more typically, the linker comprises about 2, 3, 4, 5, or 6 GGS repeats, such as about 4 GGS repeats. In specific aspects, the linker comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0220] GGGSGGGGSGGGGSGGGGSGGGSG
GGGSGGGSGGGGSGGGGSGGGG
SGGGGSGGGGSGGGGSGGGGS.

[0221] In certain embodiments, linkers are used within fusion polypeptides and/or within single-chain molecules such as scFc's. In some embodiments, the linker is an amino acid linker. For example, a linker as employed herein may

comprise from about 1 to about 100 amino acid residues, e.g., about 1 to about 70, about 2 to about 70, about 1 to about 30, or about 2 to about 30 amino acid residues. In some embodiments, the linker comprises at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 amino acid residues.

[0222] In certain embodiments, the linker comprises a glycine-serine sequence, e.g., a (G_nS)_m sequence (e.g., GGS, GGGS, or GGGGS sequence) that is present in at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, or at least 14 copies within the linker.

[0223] In typical aspects, the antibody or fragment thereof binds specifically to an antigen associated with SARS-CoV-2. Typically, the antigen is associated with SARS-CoV-2 and the antibody or fragment thereof comprises, for example, a binding domain from Table 4, such as binding domain 298, 52, 46, 80, 82, 236, 324 or combinations thereof.

[0224] In certain embodiments, the SARS-CoV-2-binding antibody fragment is capable of binding to the receptor binding domain (RBD) of SARS-CoV-2. In certain embodiments, the SARS-CoV-2-binding antibody fragment is capable of binding to the Spike protein (S protein) of SARS-CoV-2. In some embodiments, the SARS-CoV-2-binding antibody fragment is capable of binding to the N-terminal Domain (NTD) of the S protein of SARS-CoV-2.

[0225] In some embodiments, the SARS-CoV-2-binding antibody fragment comprises a heavy chain variable region (e.g., a V_H or V_HH). In certain embodiments, the SARS-CoV-2-binding antibody fragment comprises a heavy chain variable domain (e.g., V_H) and a light chain variable domain (e.g., a V_L or V_K). In certain embodiments, the SARS-CoV-2-binding antibody fragment comprises an Fab which comprises a heavy chain variable domain (e.g., V_H) and a light chain variable domain (e.g., a V_L or V_K).

[0226] In some embodiments, the SARS-CoV-2-binding antibody fragment comprises a V_H heavy chain variable domain and a V_K light chain variable domain. In some embodiments, the SARS-CoV-2-binding antibody fragment comprises an Fab which comprises a V_H heavy chain variable domain and V_K a light chain variable domain.

[0227] In a specific example, the antibody or fragment thereof comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to one or more of the following sequences:

Fc chain 1:
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVGVEVHNAAKTKPREEQYNSTYRWSQLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPVPLSD
GSFFLYSKLTVDKSRWQQGNVFSCSVLHEALTHSHYTQKSLSLSPGK;

Fc chain 2:
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVGVEVHNAAKTKPREEQYNSTYRWSQLTVLHQ
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRE
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPVPLDS

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DGSFFFLYSKLTVDKSRWQQGNVFCSCVLHEALHSHYTOQKSLSLSP
GK;

298 light chain
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQK
PGQPPKLLIYWASTRESGPDRFSGSGSGTDFTLTISSLQAEDVA
VYYCQQYYSPTPTFGQGTTKLEIKRTVAAPSVIFPPSDEQLKSGT
ASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

298 Fab heavy chain
QVQLVQSGAEVKKPGASVKVSCKASGGTFSTYGIISWVRQAPGQGL
EWMGWISPNSGGTDLAQKFQGRVTMTRDTSTTVYMELSSLRSED
TAVYYCASPDDIAGGYWGQGTLTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAVLQSSG
LYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

52 light chain
DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPK
LIIYAAASSLEGVPSRPSRGSGSGTDFTLTISSLQPEDFATYYCQQ
GNGFPLTFGPGTVDIKRTVAAPSVIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

52 Fab heavy chain
QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYGIISWVRQAPGQGL
EWMGGIIPMFGTNTYAQKFQGRVTITADKSTSTAYMELSSLRSED
TAVYYCARDRGDTIDYWQGTLTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAVLQSSGLY
SLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

46 light chain
DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPK
LIIYDASNLETGVPSRPSRGSGSGTDFTLTISSLQPEDFATYYCQQ
SYSTPFTFGPGTVVDIKRTVAAPSVIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

46 Fab heavy chain
EVQLLESGGGVLPQGRSLRLSCAASGFTFSSYAMSWVRQAPGKGL
EWVSTIYSGGSTYYADSVKGRFTISRDNSKNTLYLQMNLRAEDT
AVYYCARGDSRDAFDIWGQGTMVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAVLQSSGLY
SLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

80 light chain
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQK
PGQPPKLLIYWASTRESGPDRFSGSGSGTDFTLTISSLQAEDVA
VYYCQQYYSAPLTFGGGTKVEIKRTVAAPSVIFPPSDEQLKSGT

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ASWVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS

LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

80 Fab heavy chain
QVQLVQSGAEVKKPGSSVKVSCKASGGTFNRYAFSIVRQAPGQGL
EWMGGIPIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSED
TAVYYCARSTRELPEVVDWYFDLWGRGLTVSSASTKGPSVFPL
APSSKSTSGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAV
LQSSGLYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

82 light chain
DIQMTQSPSSLSASVGDRVTITCRASQVISNYLAWYQQKPGKAPK
LIIYDASNLETGVPSRPSRGSGSGTDFTLTISSLQPEDFATYYCQQ
SFSPPPTFGQGTRLEIKRTVAAPSVIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

82 Fab heavy chain
QVQLVQSGAEVKKPGASVKVSCKASGGSFSTSAYWVRQAPGQGL
EWMGWINPYTGGTNYAQKFQGRVTMTRDTSTTVYMELSSLRSED
TAVYYCARSRALYGSGYFDYWGQGTLTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAVLQ
SGLYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

236 light chain
DIVMTQSPSLPVPGEPAISCRSSQSLLHSNGNYLDWYLOKP
GQSPOLLIYLGSNRASCVPDRPSGSGSGTDFTLKISRVEADVG
YYCMQALQTPTFGQGTRLEIKRTVAAPSVIFPPSDEQLKSGTA
SVVCLLNFFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL
SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

236 Fab heavy chain
QVQLVQSGAEVKKPGASVKVSCKASGGFTSYGINWVRQAPGQGL
EWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTTVYMELSSLRSED
TAVYYCARSRIQLLPRGMWDVGQGTTTVSSASTKGPSVFPLAPS
SKSTSGGTAALGCLVKDYPFPEPVTWSNNSGALTSGVHTFPAVLQ
SGLYSLSSVTPSSSLGTQTYICNVNHPNSNTKVDKKVEPKSC

324 light chain
DIQMTQSPSSLSASVGDRVTITCRASQISITTYLNWYQQKPGKAPK
LIIYDASNLETGVPSRPSRGSGSGTDFTLTISSLQPEDFATYYCQQ
SYSTPFTFGQGTTKVEIKRTVAAPSVIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

324 Fab heavy chain
QVQLVQSGAEVKKPGASVKVSCKASGGTFNNYGIISWVRQAPGQGL
EWMGWMNPNSGNTGYAQKFQGRVTMTRDTSTTVYMELSSLRSED
TAVYYCARVGDYGDYIVSPFDLWGRGLTVSSASTKGPSVFPLA

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PSSKSTSGGTAALGCLVKDYFPEPVTVWSWNSGALTSGVHTFPAPL  
QSSGLYSLSSVVTVPSLGTQTYICNVNHPNSNTKVDKKVEPKS  
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[0228] or combinations thereof.

[0229] In further aspects, the antibody or fragment thereof is conjugated to or associated with a further moiety, such as a detectable moiety (e.g., a small molecule, fluorescent molecule, radioisotope, or magnetic particle), a pharmaceutical agent, a diagnostic agent, or combinations thereof and may comprise, for example, an antibody-drug conjugate.

[0230] In aspects wherein the bioactive moiety is a detectable moiety, the detectable moiety may comprise a fluorescent protein, such as GFP, EGFP, Ametrine, and/or a flavin-based fluorescent protein, such as a LOV-protein, such as iLOV.

[0231] In aspects wherein the bioactive moiety is a pharmaceutical agent, the pharmaceutical agent may comprise for example, a small molecule, peptide, lipid, carbohydrate, or toxin.

[0232] In typical aspects, the nanocage assembled from the fusion proteins described herein comprises from about 3 to about 100 nanocage monomers, such as from about 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 55, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, or 98 to about 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 55, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, or 100 nanocage monomers, such as 24, 32, or 60 monomers. The nanocage monomer may be any known nanocage monomer, natural, synthetic, or partly synthetic and is, in aspects, selected from ferritin, apoferritin, encapsulin, SOR, lumazine synthase, pyruvate dehydrogenase, carboxysome, vault proteins, GroEL, heat shock protein, E2P, MS2 coat protein, fragments thereof, and variants thereof. Typically, the nanocage monomer is ferritin or apoferritin.

[0233] When apoferritin is chosen as the nanocage monomer, typically the first and second nanocage monomer subunits interchangeably comprise the "N" and "C" regions of apoferritin. It will be understood that other nanocage monomers can be divided into bipartite subunits much like apoferritin as described herein so that the subunits self-assemble and are each amenable to fusion with a bioactive moiety.

[0234] In some embodiments, the nanocage monomer is a ferritin monomer. The term "ferritin monomer," is used herein to refer to a single chain of a ferritin that, in the presence of other ferritin chains, is capable of self-assembling into a polypeptide complex comprising a plurality of ferritin chains. In some embodiments, ferritin chains self-assembled into a polypeptide complex comprising 24 or more ferritin chains. In some embodiments, the ferritin monomer is a ferritin light chain. In some embodiments, the ferritin monomer does not include a ferritin heavy chain or other ferritin components capable of binding to iron.

[0235] In some embodiments, each fusion polypeptide within the self-assembled polypeptide complex comprises a ferritin light chain or a subunit of a ferritin light chain. In

these embodiments, the self-assembled polypeptide complex does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.

[0236] In some embodiments, the ferritin monomer is a human ferritin chain, e.g., a human ferritin light chain, e.g., a human ferritin light chain having the sequence of at least residues 2-175 of SEQ ID NO:1. In some embodiments, the ferritin monomer is a mouse ferritin chain.

[0237] A "subunit" of a ferritin monomer refers to a portion of a ferritin monomer that is capable of spontaneously associating with another, distinct subunit of a ferritin monomer, so that the subunits together form a ferritin monomer, which ferritin monomer, in turn, is capable of self-assembling with other ferritin monomers to form a polypeptide complex.

[0238] In some embodiments, the ferritin monomer subunit comprises approximately half of a ferritin monomer. As used herein, the term "N-half ferritin" refers to approximately half of a ferritin chain, which half comprises the N-terminus of the ferritin chain. As used herein, the term "C-half ferritin" refers to approximately half a ferritin chain, which half comprises the C-terminus of the ferritin chain. The exact point at which a ferritin chain may be divided to form the N-half ferritin and the C-half ferritin may vary depending on the embodiment. In the context of ferritin monomer subunits based on human ferritin light chain, for example, the halves may divided at a point that corresponds to a position between about position 75 to about position 100 of SEQ ID NO:1. For example, in some embodiments, an N-half ferritin based on a human ferritin light chain has an amino acid sequence corresponding to residues 1-95 of SEQ ID NO:1 (or a substantial portion thereof), and a C-half ferritin based on a human ferritin light chain has an amino acid sequence corresponding to residues 96-175 of SEQ ID NO:1 (or a substantial portion thereof).

[0239] In some embodiments, the halves are divided at a point that corresponds to a position between about position 85 to about position 92 of SEQ ID NO:1. For example, in some embodiments, an N-half ferritin based on a human ferritin light chain has an amino acid sequence corresponding to residues 1-90 of SEQ ID NO:1 (or a substantial portion thereof), and a C-half ferritin based on a human ferritin light chain has an amino acid sequence corresponding to residues 91-175 of SEQ ID NO:1 (or a substantial portion thereof).

[0240] Typically, the "N" region of apoferritin comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0241] MSSQIRQNYSSTDVEAVNSLVNLQLQASY-TYLSLGFYFDRDDVALEGVSHFFRELA EEKREGYERLLKMQNQRGGRALFQDIKKPAEDEW.

[0242] Typically, the "C" region of apoferritin comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0243] GKTPDAMKAAMALEKKLNQALLDLHAL-GSARTDPHLCDLFLETHFLDEEVKLICKMG DHLTNLHRLGGPEAGLGEYLFERLTLRHD

[0244] or

[0245] GKTPDAMKAAMALEKKLNQALLDLHAL-GSARTDPHLCDLFLETHFLDEEVKLICKMG DHLTNLHRLGGPEAGLGEYLFERLTLKHD.

[0246] In aspects, the fusion protein described herein, further comprises a linker between the nanocage monomer subunit and the bioactive moiety, much like the linker described above. Again, the linker may be flexible or rigid, but it typically flexible to allow the bioactive moiety to retain activity and to allow the pairs of nanocage monomer subunits to retain self-assembly properties. The linker is generally long enough to impart some flexibility to the fusion protein, although it will be understood that linker length will vary depending upon the nanocage monomer and bioactive moiety sequences and the three-dimensional conformation of the fusion protein. Thus, the linker is typically from about 1 to about 30 amino acid residues, such as from about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 to about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 amino acid residues, such as from about 8 to about 16 amino acid residues, such as 8, 10, or 12 amino acid residues.

[0247] The linker may be of any amino acid sequence and, in one typical example, the linker comprises a GGS repeat and, more typically, the linker comprises about 2, 3, 4, 5, or 6 GGS repeats, such as about 4 GGS repeats. In specific aspects, the linker comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0248] GGGGSGGGGSGGGGGSGGGGGSGGGGGSG

[0249] Similarly, the fusion protein may further comprising a C-terminal linker for improving one or more attributes of the fusion protein. In aspects, the comprises a GGS repeat and, more typically, the linker comprises about 2, 3, 4, 5, or 6 GGS repeats, such as about 4 GGS repeats. In specific aspects, the C-terminal linker comprises or consists of a sequence at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to:

[0250] GGSGGSGGSGGSGGGSGGGSGGGSG

[0251] Also described herein is a pair of the fusion proteins described above, wherein the pair self-assembles to form a nanocage monomer, wherein the first and second nanocage monomer subunits are fused to different SARS-CoV-2 binding moieties. This provides multivalency and/or multispecificity to a single nanocage monomer assembled from the pair of subunits.

[0252] A substantially identical sequence may comprise one or more conservative amino acid mutations. It is known in the art that one or more conservative amino acid mutations to a reference sequence may yield a mutant peptide with no substantial change in physiological, chemical, or functional properties compared to the reference sequence; in such a case, the reference and mutant sequences would be considered "substantially identical" polypeptides. Conservative amino acid mutation may include addition, deletion, or substitution of an amino acid; a conservative amino acid substitution is defined herein as the substitution of an amino acid residue for another amino acid residue with similar chemical properties (e.g. size, charge, or polarity).

[0253] In a non-limiting example, a conservative mutation may be an amino acid substitution. Such a conservative amino acid substitution may substitute a basic, neutral, hydrophobic, or acidic amino acid for another of the same group. By the term "basic amino acid" it is meant hydrophilic amino acids having a side chain pK value of greater than 7, which are typically positively charged at physiological pH. Basic amino acids include histidine (His or H),

arginine (Arg or R), and lysine (Lys or K). By the term "neutral amino acid" (also "polar amino acid"), it is meant hydrophilic amino acids having a side chain that is uncharged at physiological pH, but which has at least one bond in which the pair of electrons shared in common by two atoms is held more closely by one of the atoms. Polar amino acids include serine (Ser or S), threonine (Thr or T), cysteine (Cys or C), tyrosine (Tyr or Y), asparagine (Asn or N), and glutamine (Gln or Q). The term "hydrophobic amino acid" (also "non-polar amino acid") is meant to include amino acids exhibiting a hydrophobicity of greater than zero according to the normalized consensus hydrophobicity scale of Eisenberg (1984). Hydrophobic amino acids include proline (Pro or P), isoleucine (Ile or I), phenylalanine (Phe or F), valine (Val or V), leucine (Leu or L), tryptophan (Trp or W), methionine (Met or M), alanine (Ala or A), and glycine (Gly or G).

[0254] "Acidic amino acid" refers to hydrophilic amino acids having a side chain pK value of less than 7, which are typically negatively charged at physiological pH. Acidic amino acids include glutamate (Glu or E), and aspartate (Asp or D).

[0255] Sequence identity is used to evaluate the similarity of two sequences; it is determined by calculating the percent of residues that are the same when the two sequences are aligned for maximum correspondence between residue positions. Any known method may be used to calculate sequence identity; for example, computer software is available to calculate sequence identity. Without wishing to be limiting, sequence identity can be calculated by software such as NCBI BLAST2 service maintained by the Swiss Institute of Bioinformatics (and as found at ca.expasy.org/tools/blast/), BLAST-P, Blast-N, or FASTA-N, or any other appropriate software that is known in the art.

[0256] The substantially identical sequences of the present invention may be at least 85% identical; in another example, the substantially identical sequences may be at least 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100% (or any percentage there between) identical at the amino acid level to sequences described herein. In specific aspects, the substantially identical sequences retain the activity and specificity of the reference sequence. In a non-limiting embodiment, the difference in sequence identity may be due to conservative amino acid mutation(s).

[0257] The polypeptides or fusion proteins of the present invention may also comprise additional sequences to aid in their expression, detection or purification. Any such sequences or tags known to those of skill in the art may be used. For example, and without wishing to be limiting, the fusion proteins may comprise a targeting or signal sequence (for example, but not limited to ompA), a detection tag, exemplary tag cassettes include Strep tag, or any variant thereof; see, e.g., U.S. Pat. No. 7,981,632, His tag, Flag tag having the sequence motif DYKDDDDK, Xpress tag, Avi tag, Calmodulin tag, Polyglutamate tag, HA tag, Myc tag, Nus tag, S tag, SBP tag, Softag 1, Softag 3, V5 tag, CREB-binding protein (CBP), glutathione S-transferase (GST), maltose binding protein (MBP), green fluorescent protein (GFP), Thioredoxin tag, or any combination thereof; a purification tag (for example, but not limited to a His₅ or His₆), or a combination thereof.

[0258] In another example, the additional sequence may be a biotin recognition site such as that described by Cronan et al in WO 95/04069 or Voges et al in WO/2004/076670. As

is also known to those of skill in the art, linker sequences may be used in conjunction with the additional sequences or tags.

[0259] More specifically, a tag cassette may comprise an extracellular component that can specifically bind to an antibody with high affinity or avidity. Within a single chain fusion protein structure, a tag cassette may be located (a) immediately amino-terminal to a connector region, (b) interposed between and connecting linker modules, (c) immediately carboxy-terminal to a binding domain, (d) interposed between and connecting a binding domain (e.g., scFv or scFab) to an effector domain, (e) interposed between and connecting subunits of a binding domain, or (f) at the amino-terminus of a single chain fusion protein. In certain embodiments, one or more junction amino acids may be disposed between and connecting a tag cassette with a hydrophobic portion, or disposed between and connecting a tag cassette with a connector region, or disposed between and connecting a tag cassette with a linker module, or disposed between and connecting a tag cassette with a binding domain.

[0260] Also encompassed herein are isolated or purified fusion proteins, polypeptides, or fragments thereof immobilized onto a surface using various methodologies; for example, and without wishing to be limiting, the polypeptides may be linked or coupled to the surface via His-tag coupling, biotin binding, covalent binding, adsorption, and the like. The solid surface may be any suitable surface, for example, but not limited to the well surface of a microtiter plate, channels of surface plasmon resonance (SPR) sensor-chips, membranes, beads (such as magnetic-based or sepharose-based beads or other chromatography resin), glass, a film, or any other useful surface.

[0261] In other aspects, the fusion proteins may be linked to a cargo molecule; the fusion proteins may deliver the cargo molecule to a desired site and may be linked to the cargo molecule using any method known in the art (recombinant technology, chemical conjugation, chelation, etc.). The cargo molecule may be any type of molecule, such as a therapeutic or diagnostic agent.

[0262] In some aspects, the cargo molecule is a protein and is fused to the fusion protein such that the cargo molecule is contained in the nanocage internally. In other aspects, the cargo molecule is not fused to the fusion protein and is contained in the nanocage internally. The cargo molecule is typically a protein, a small molecule, a radioisotope, or a magnetic particle.

[0263] The fusion proteins described herein specifically bind to their targets. Antibody specificity, which refers to selective recognition of an antibody for a particular epitope of an antigen, of the antibodies or fragments described herein can be determined based on affinity and/or avidity. Affinity, represented by the equilibrium constant for the dissociation of an antigen with an antibody (K_D), measures the binding strength between an antigenic determinant (epitope) and an antibody binding site. Avidity is the measure of the strength of binding between an antibody with its antigen. Antibodies typically bind with a K_D of 10^{-5} to 10^{-11} M. Any K_D greater than 10^{-4} M is generally considered to indicate non-specific binding. The lesser the value of the K_D , the stronger the binding strength between an antigenic determinant and the antibody binding site. In aspects, the antibodies described herein have a K_D of less than 10^{-4} M,

10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, 10^{-12} M, 10^{-13} M, 10^{-14} M, or 10^{-15} M.

[0264] Also described herein are nanocages comprising at least one fusion protein described herein and at least one second nanocage monomer subunit that self-assembles with the fusion protein to form a nanocage monomer. Further, pairs of the fusion proteins are described herein, wherein the pair self-assembles to form a nanocage monomer and wherein the first and second nanocage monomer subunits are fused to different bioactive moieties.

[0265] It will be understood that the nanocages may self-assemble from multiple identical fusion proteins, from multiple different fusion proteins (and therefore be multivalent and/or multispecific), from a combination of fusion proteins and wild-type proteins, and any combination thereof. For example, the nanocages may be decorated internally and/or externally with at least one of the fusion proteins described herein in combination with at least one anti-SARS-CoV-2 antibody. In typical aspects, from about 20% to about 80% of the nanocage monomers comprise the fusion protein described herein. In view of the modular solution described herein, the nanocages could in theory comprise up to twice as many bioactive moieties as there are monomers in the nanocage, as each nanocage monomer may be divided into two subunits, each of which can independently bind to a different bioactive moiety. It will be understood that this modularity can be harnessed to achieve any desired ratio of bioactive moieties as described herein in specific example to a 4:2:1:1 ratio of four different bioactive moieties. For example, the nanocages described herein may comprise at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 different bioactive moieties. In this way, the nanocages can be multivalent and/or multispecific and the extent of this can be controlled with relative ease.

[0266] In aspects, the nanocages described herein may further comprise at least one whole nanocage monomer, optionally fused to a bioactive moiety that may be the same or different from the bioactive moiety described herein as being linked to a nanocage monomer subunit.

[0267] In typical aspects, the nanocages described herein comprise a first, second, and third fusion protein to a subunit or the monomer, and optionally at least one whole nanocage monomer, optionally fused to a bioactive moiety, wherein the bioactive moieties of the first, second, and third fusion proteins and of the whole nanocage monomer are all different from one another.

[0268] More typically, the first, second, and third fusion proteins each comprise an antibody or Fc fragment thereof fused to N- or C-half ferritin, wherein at least one of the first, second, and third fusion proteins is fused to N-half ferritin and at least one of the first, second, and third fusion proteins is fused to C-half ferritin. For example, the antibody or fragment thereof of the first fusion protein is typically an Fc fragment; the second and third fusion proteins typically each comprise an antibody or fragment thereof specific for a different antigen of a virus such as SARS-CoV-2 and the whole nanocage monomer is fused to a bioactive moiety that is specific for another different antigen, optionally of the same virus such as SARS-CoV-2.

[0269] In aspects, the antibody or fragment thereof of the second fusion protein is 46 or 52; and the antibody or fragment thereof of the third fusion protein is 324 or 80. In

a typical aspect, the nanocage described herein comprises the following four fusion proteins, optionally in a 4:2:1:1 ratio:

- [0270] a. 298 (optionally sc298) fused to full length ferritin;
- [0271] b. Fc (optionally scFc) fused to N-ferritin;
- [0272] c. 46 or 52 (optionally sc46 or sc52) fused to C-ferritin; and
- [0273] d. 324 or 80 (optionally sc324 or sc80) fused to C-ferritin.

[0274] In aspects, the nanocage described herein comprises or consists of sequences at least 70% (such as at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to one or more of the following sequences, where ferritin subunits are in bold, linkers are underlined, light chains are italicized, and heavy chains are in lowercase:

a. 298-hFerr:
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQK
PGQPPKLLIYWASTRESGVPDFRSGSGSGTDFTLTISLQAEDVA
VYYCQQYYSTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGS
GGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGTFSTYGISWVRQAPGQGLEWMGWISPNSGGTDLAQKFQGRVTM
TRDTSTSTVYMELSSLRSEDTAVYYCASDPRDDIAGGYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDGGGGGGGGGGGGGGGGGGGGGGGGG
MSSQIRQNYSTDVEAAVNSLVNLYLQASYTYLSLGFYFDRDDVAL
EGVSHFFRELAEEKREGYERLLKMQNQRGGRALFQDIKPAEDEW
GKTPDAMKAAMALEKKLNQALLDLHALGSARTDPHLCDFLETHFL
DEEVKLIKMGDHLTNLHRLGGPEAGLGEYLFERLTLRHD
 or
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQK
PGQPPKLLIYWASTRESGVPDFRSGSGSGTDFTLTISLQAEDVA
VYYCQQYYSTPPTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGS
GGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGTFSTYGISWVRQAPGQGLEWMGWISPNSGGTDLAQKFQGRVTM
TRDTSTSTVYMELSSLRSEDTAVYYCASDPRDDIAGGYWGQGTLV
TVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDGGGGGGGGGGGGGGGGGGGGGGGGG

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SSQIRQNYSTDVEAAVNSLVNLYLQASYTYLSLGFYFDRDDVALE
GVSHFFRELAEEKREGYERLLKMQNQRGGRALFQDIKPAEDEWG
KTPDAMKAAMALEKKLNQALLDLHALGSARTDPHLCDFLETHFLD
EEVKLIKMGDHLTNLHRLGGPEAGLGEYLFERLTLRHD
 b. Fc-N-hFerr 1253A
DKTHTCPPCPAPEAAGGPSVFLFPPPKDTLMASRTPEVTCVVVD
VSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSR
EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDL
DGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSP
GKGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
SGGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
VFLFPPPKDTLMASRTPEVTCVVVDVSHEDEPEVKFNWYVGVEV
HNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALG
APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFPY
SDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVVMHEALHNHYTQKSLSLSPKGKGKGKGKGKGKGKG
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
FYFDRDDVALEGVSHFFRELAEEKREGYERLLKMQNQRGGRALFQ
DIKPAEDEW
 c1. 52-C-hFerr
DIQMTQSPSSLSASVGDRVTITCRASQGISSNLNWYQQKPGKAPK
LLIYASSLESQVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQ
GNGFPLTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGGGG
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
YGISSWVRQAPGQGLEWMGGIIPMFGETTNYAQKFQGRVTITADKST
STAYMELSSLRSEDTAVYYCARDRGDTIDYWQGQGLTVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPNTKV
DKKVEPKSCDGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
AAMALEKKLNQALLDLHALGSARTDPHLCDFLETHFLDEEVKLIK
KMGDHLTNLHRLGGPEAGLGEYLFERLTLRHD
 c2. 46-C-hFerr
DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPK
LLIYDASNLETGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQ
SYSTPPTFGPGTKVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCL
LNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT

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LSKADYEKKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGGG  

GGGGGGSGGGGSGGGGGGGGGGGGGGGGGGGGGGGGGGGGG  

GGGGGGGGGGSEVQLLESGGGLVQPGRSLRSLCAASGFTFSSYAMS  

WVRQAPGKGLEWVSTIYSGGTYYADSVKGRFTISRDNSKNLYL  

QMNSLRAEDTAVYYCARGDSRDAFDIWGGTMTVSSASTKGPSV  

FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVWSNGALTSGVHTF  

PAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHPNSNTKVDKKV  

EPKSCDGGGGSGGGGGGGGGGGGGGGGGGGGGGGGGKTPDAMKAAMA  

LEKKLNQALLDLHALGSARTDPHLCDFLETHFLDEEVKLIKKGMD  

HLTNLHRLGGPEAGLGEYLFERLTLRHD  
  

d1. 324-C-hFerr  

DIQMTQSPSSLASVGDRVTITCRASQSITTLNWYQQPKGKAPK  

LLIYDASNLEATGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQ  

SYSTPPTFGQGTKEIKRTVAAPSFVIFPPSDEQLKSGTASVVCL  

LNNFYPREAKVQWKVDNALQSGNSQESVTEEQDSKDSTYLSSTLT  

LSKADYEKKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGGG  

GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG  

GGGGGGGGGGGGGGGGQVQLVQSGAEVKKPGASVKVSKCASGGTFNN  

YGISWVRQAPQGLEWMGNMNPNSGNTGYAQKFQGRVTMRTDTST  

STVYMELSSLRSEDTAVYYCARVGDYIVSPFDLWGRGTLVT  

SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVWSNS  

GALTSGVHTFPPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNH  

PSNTKVDKKVEPKSCDGGGGGGGGGGGGGGGGGGGGGGGGGGGG  

TPDAMKAAMALEKKLNQALLDLHALGSARTDPHLCDFLETHFLDE  

EVKLIKKGMDHLTNLHRLGGPEAGLGEYLFERLTLRHD  
  

d2. 80-C-hFerr  

DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQOK  

PGOPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLAEDVA  

VYYCQQQYYASPLTFGGTKVEIKRTVAAPSFVIFPPSDEQLKSGT  

ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY  

LSSTLTSSKADYEKKVYACEVTHQGLSSPVTKSFNRGECGGGGG  

GGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG  

GGGGGGGGGGGGGGGGGGGGGGQVQLVQSGAEVKKPGSSVKVSKCAS  

GGTFNRYAFSWVRQAPQGLEWMGGIIPFGTANYAQKFQGRVTI  

TADESTSTAYMELSSRSEDTAVYYCARSTRELPEVVDWYFDLWG  

RGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE  

TVWSNGALTSGVHTFPPAVLQSSGLYSLSSVTVPSSSLGTQTY  

ICNVNHPNSNTKVDKKVEPKSCDGGGGGGGGGGGGGGGGGGGG  

GSGGGKTPDAMKAAMALEKKLNQALLDLHALGSARTDPHLCDFL  

ETHFLDEEVKLIKKGMDHLTNLHRLGGPEAGLGEYLFERLTLRHD

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[0275] In one aspect, provided are self-assembled polypeptide complexes comprising a plurality of fusion polypeptides as disclosed herein. In many embodiments, self-assembled polypeptide complexes comprise (1) a plurality of first fusion polypeptides, each first fusion polypeptide comprising an Fc region linked to a nanocage monomer (e.g., ferritin monomer, e.g., human ferritin monomer, or subunit thereof), as disclosed herein; and (2) a plurality of second fusion polypeptides, each second fusion polypeptide comprising a SARS-CoV-2-binding antibody fragment (e.g., an Fab fragment of an antibody that is capable of binding to SARS-CoV-2 protein (e.g., the Spike protein or a receptor-binding domain (RBD))), the SARS-CoV-2-binding antibody fragment being linked to a nanocage monomer (e.g., ferritin monomer, e.g., human ferritin monomer) or subunit thereof. In some embodiments, self-assembled polypeptide complex further comprises a plurality of third fusion polypeptides, each third fusion polypeptide being distinct from the second fusion polypeptide and each comprising (1) a nanocage monomer (e.g., ferritin monomer, e.g., human ferritin monomer) linked to (2) a SARS-CoV-2-binding antibody fragment (e.g., Fab fragment of an antibody that is capable of binding to a SARS-CoV-2 protein).

[0276] In some embodiments, one of the fusion polypeptides (e.g., the first fusion polypeptide or the second fusion polypeptide) comprises an N-half nanocage monomer (e.g., an N-half ferritin) (but not a full-length nanocage (e.g., ferritin) monomer), and one of the other fusion polypeptides comprises a C-half nanocage monomer (e.g., a C-half ferritin) (but not a full-length nanocage (e.g., ferritin) monomer). In many of these embodiments, the ratio of fusion polypeptides comprising the N-half nanocage monomer (e.g., N-half ferritin) to the fusion polypeptides comprising the C-half nanocage monomer (e.g., C-half ferritin) within the self-assembled polypeptide complex is about 1:1.

[0277] In some embodiments, the self-assembled polypeptide complex comprises 24 fusion polypeptides. In some embodiments, the self-assembled polypeptide complex comprises more than 24 fusion polypeptides, e.g., at least 26, at least 28, at least 30, at least 32 fusion polypeptides, at least 34 fusion polypeptides, at least 36 fusion polypeptides, at least 38 fusion polypeptides, at least 40 fusion polypeptides, at least 42 fusion polypeptides, at least 44 fusion polypeptides, at least 46 fusion polypeptides, or at least 48 fusion polypeptides. In some embodiments, the self-assembled polypeptide complex comprises 32 fusion polypeptides.

[0278] In some embodiments, the self-assembled polypeptide complex comprises at least 4, at least 5, least 6, at least 7, or at least 8 first fusion polypeptides.

[0279] In some embodiments, the self-assembled polypeptide complex comprises at least 4, at least 5, least 6, at least 7, or at least 8 second fusion polypeptides.

[0280] In some embodiments, the self-assembled polypeptide complex further comprises at least 4, at least 5, least 6, at least 7, at least 8, at least 9, at least 10, least 11, at least 12, at least 13, at least 14, at least 15, or at least 16 third fusion polypeptides.

[0281] In some embodiments, the self-assembled polypeptide complex comprises a ratio of approximately 1:1, 1:2, 1:3, or 1:4 of first fusion polypeptides to all other fusion polypeptides.

[0282] In some embodiments, each fusion polypeptide within the self-assembled polypeptide complex comprises a ferritin light chain or a subunit of a ferritin light chain. In

these embodiments, the self-assembled polypeptide complex does not comprise any ferritin heavy chains, subunits of ferritin heavy chains, or other ferritin components capable of binding to iron.

[0283] Also described herein are compositions comprising the nanocage, such as therapeutic or prophylactic compositions. Related methods and uses for treating and/or preventing COVID-19 are also described, wherein the method or use comprises administering the nanocage or composition described herein to a subject in need thereof.

[0284] Also described herein are nucleic acid molecules encoding the fusion proteins and polypeptides described herein, as well as vectors comprising the nucleic acid molecules and host cells comprising the vectors.

[0285] Polynucleotides encoding the fusion proteins described herein include polynucleotides with nucleic acid sequences that are substantially the same as the nucleic acid sequences of the polynucleotides of the present invention. "Substantially the same" nucleic acid sequence is defined herein as a sequence with at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95% identity to another nucleic acid sequence when the two sequences are optimally aligned (with appropriate nucleotide insertions or deletions) and compared to determine exact matches of nucleotides between the two sequences.

[0286] Suitable sources of polynucleotides that encode fragments of antibodies include any cell, such as hybridomas and spleen cells, that express the full-length antibody. The fragments may be used by themselves as antibody equivalents, or may be recombined into equivalents, as described above. The DNA deletions and recombinations described in this section may be carried out by known methods, such as those described in the published patent applications listed above in the section entitled "Functional Equivalents of Antibodies" and/or other standard recombinant DNA techniques, such as those described below.

[0287] Another source of DNAs are single chain antibodies produced from a phage display library, as is known in the art.

[0288] Additionally, expression vectors are provided containing the polynucleotide sequences previously described operably linked to an expression sequence, a promoter and an enhancer sequence. A variety of expression vectors for the efficient synthesis of antibody polypeptide in prokaryotic, such as bacteria and eukaryotic systems, including but not limited to yeast and mammalian cell culture systems have been developed. The vectors of the present invention can comprise segments of chromosomal, non-chromosomal and synthetic DNA sequences.

[0289] Any suitable expression vector can be used. For example, prokaryotic cloning vectors include plasmids from *E. coli*, such as colE1, pCRI, pBR322, pMB9, pUC, pKSM, and RP4. Prokaryotic vectors also include derivatives of phage DNA such as M13 and other filamentous single-stranded DNA phages. An example of a vector useful in yeast is the 2p plasmid. Suitable vectors for expression in mammalian cells include well-known derivatives of SV-40, adenovirus, retrovirus-derived DNA sequences and shuttle vectors derived from combination of functional mammalian vectors, such as those described above, and functional plasmids and phage DNA.

[0290] Additional eukaryotic expression vectors are known in the art (e.g., P.J. Southern & P. Berg, *J. Mol. Appl.*

Genet, 1:327-341 (1982); Subramani et al, *Mol. Cell. Biol.*, 1: 854-864 (1981); Kaufmann & Sharp, "Amplification And Expression of Sequences Cotransfected with a Modular Dihydrofolate Reductase Complementary DNA Gene," *J. Mol. Biol.*, 159:601-621 (1982); Kaufmann & Sharp, *Mol. Cell. Biol.*, 159:601-664 (1982); Seahill et al., "Expression And Characterization Of The Product Of A Human Immune Interferon DNA Gene In Chinese Hamster Ovary Cells," *Proc. Nat'l Acad. Sci USA*, 80:4654-4659 (1983); Urlaub & Chasin, *Proc. Nat'l Acad. Sci USA*, 77:4216-4220, (1980), all of which are incorporated by reference herein).

[0291] The expression vectors typically contain at least one expression control sequence that is operatively linked to the DNA sequence or fragment to be expressed. The control sequence is inserted in the vector in order to control and to regulate the expression of the cloned DNA sequence. Examples of useful expression control sequences are the lac system, the trp system, the tac system, the trc system, major operator and promoter regions of phage lambda, the control region of fd coat protein, the glycolytic promoters of yeast, e.g., the promoter for 3-phosphoglycerate kinase, the promoters of yeast acid phosphatase, e.g., Pho5, the promoters of the yeast alpha-mating factors, and promoters derived from polyoma, adenovirus, retrovirus, and simian virus, e.g., the early and late promoters or SV40, and other sequences known to control the expression of genes of prokaryotic or eukaryotic cells and their viruses or combinations thereof.

[0292] Also described herein are recombinant host cells containing the expression vectors previously described. The fusion proteins described herein can be expressed in cell lines other than in hybridomas. Nucleic acids, which comprise a sequence encoding a polypeptide according to the invention, can be used for transformation of a suitable mammalian host cell.

[0293] Cell lines of particular preference are selected based on high level of expression, constitutive expression of protein of interest and minimal contamination from host proteins. Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines, such as but not limited to, HEK 293 cells, Chinese Hamster Ovary (CHO) cells, Baby Hamster Kidney (BHK) cells and many others. Suitable additional eukaryotic cells include yeast and other fungi. Useful prokaryotic hosts include, for example, *E. coli*, such as *E. coli* SG-936, *E. coli* HB 101, *E. coli* W3110, *E. coli* X1776, *E. coli* X2282, *E. coli* DH1, and *E. coli* MRC1, *Pseudomonas*, *Bacillus*, such as *Bacillus subtilis*, and *Streptomyces*.

[0294] These present recombinant host cells can be used to produce fusion proteins by culturing the cells under conditions permitting expression of the polypeptide and purifying the polypeptide from the host cell or medium surrounding the host cell. Targeting of the expressed polypeptide for secretion in the recombinant host cells can be facilitated by inserting a signal or secretory leader peptide-encoding sequence (See, Shokri et al, (2003) *Appl Microbiol Biotechnol.* 60(6): 654-664, Nielsen et al, *Prot. Eng.*, 10:1-6 (1997); von Heinje et al., *Nucl. Acids Res.*, 14:4683-4690 (1986), all of which are incorporated by reference herein) at the 5' end of the antibody-encoding gene of interest. These secretory leader peptide elements can be derived from either prokaryotic or eukaryotic sequences. Accordingly suitably, secretory leader peptides are used, being amino acids joined to the

N-terminal end of a polypeptide to direct movement of the polypeptide out of the host cell cytosol and secretion into the medium.

[0295] The fusion proteins described herein can be fused to additional amino acid residues. Such amino acid residues can be a peptide tag to facilitate isolation, for example. Other amino acid residues for homing of the antibodies to specific organs or tissues are also contemplated.

[0296] It will be understood that a Fab-nanocage can be generated by co-transfection of HC-ferritin and LC. Alternatively, single-chain Fab-ferritin nanocages can be used that only require transfection of one plasmid, as shown in FIG. 1C. This can be done with linkers of different lengths between the LC and HC for example 60 or 70 amino acids. When single-chain Fabs are used, it can be ensured that the heavy chain and light chain are paired. Tags (e.g. Flag, HA, myc, His6x, Strep, etc.) can also be added at the N terminus of the construct or within the linker for ease of purification as described above. Further, a tag system can be used to make sure many different Fabs are present on the same nanoparticle using serial/additive affinity chromatography steps when different Fab-nanoparticle plasmids are co-transfected. This provides multi-specificity to the nanoparticles. Protease sites (e.g. TEV, 3C, etc.) can be inserted to cleave linkers and tags after expression and/or purification, if desired.

[0297] Any suitable method or route can be used to administer the fusion proteins described herein. Routes of administration include, for example, oral, intravenous, intraperitoneal, subcutaneous, or intramuscular administration.

[0298] It is understood that the fusion proteins described herein, where used in a mammal for the purpose of prophylaxis or treatment, will be administered in the form of a composition additionally comprising a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include, for example, one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the binding proteins. The compositions of the injection may, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the mammal.

[0299] Although human antibodies are particularly useful for administration to humans, they may be administered to other mammals as well. The term "mammal" as used herein is intended to include, but is not limited to, humans, laboratory animals, domestic pets and farm animals.

[0300] In one aspect, provided are methods that may be useful for treating, ameliorating, or preventing a SARS-CoV-2-related condition, generally comprising a step of administering a composition comprising a self-assembled polypeptide complex of the present disclosure to a subject.

[0301] A "SARS-CoV-2-related condition" refers to a condition (e.g., symptom or sign) that is associated with infection with SARS-CoV-2. In some embodiments, the condition is a level of SARS-CoV-2 RNA, protein, or viral particles in sample from a subject (e.g., the subject who is administered a self-assembled polypeptide complex as disclosed herein), which level is indicative of SARS-CoV-2 infection (e.g., because the level satisfies a threshold or exceeds a reference level indicative of SARS-CoV-2 infec-

tion). In some embodiments, the condition is a symptom associated with COVID-19 disease, e.g., fever, cough, tiredness, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, runny nose, headache, chest pain, conjunctivitis, nausea, vomiting, diarrhea, loss of smell, loss of taste, or stroke). In some embodiments, the condition is associated with downstream sequelae of COVID-19 disease and/or is a symptom of long-term COVID-19 disease.

[0302] In some embodiments, the subject is a mammal, e.g., a human.

[0303] Compositions for administration to subjects generally comprise a self-assembled polypeptide complex as disclosed herein. In some embodiments, such compositions further comprise a pharmaceutically acceptable excipient.

[0304] Compositions may be formulated for administration for any of a variety of routes of administration, including systemic routes (e.g., oral, intravenous, intraperitoneal, subcutaneous, or intramuscular administration).

[0305] The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples. These examples are provided for purposes of illustration only, and are not intended to be limiting unless otherwise specified. Thus, the invention should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variations which become evident as a result of the teaching provided herein.

[0306] The following examples do not include detailed descriptions of conventional methods, such as those employed in the construction of vectors and plasmids, the insertion of genes encoding polypeptides into such vectors and plasmids, or the introduction of plasmids into host cells. Such methods are well known to those of ordinary skill in the art and are described in numerous publications including Sambrook, J., Fritsch, E. F. and Maniatis, T. (1989), Molecular Cloning: A Laboratory Manual, 2nd edition, Cold Spring Harbor Laboratory Press, which is incorporated by reference herein.

[0307] Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out the typical aspects of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1: Multivalency Transforms SARS-CoV-2 Antibodies into Ultrapotent Neutralizers

[0308] This example describes the design, expression, purification, and characterization of fusion proteins with apo ferritin. Apoferritin protomers self-assemble into an octahedrally symmetric structure with an ~6 nm hydrodynamic radius (Rh) composed of 24 identical polypeptides. The N-terminus of each apo ferritin subunit points outwards of the spherical nanocage and is therefore accessible for the genetic fusion of proteins of interest. The fusion proteins were designed such that upon folding, apo ferritin protomers act as building blocks that drive the multimerization of the 24 proteins fused to the apo ferritin termini.

Abstract

[0309] SARS-CoV-2, the virus responsible for COVID-19, has caused a global pandemic. Antibodies can be powerful biotherapeutics to fight viral infections. Here, we use the human apoferritin protomer as a modular subunit to drive oligomerization of antibody fragments and transform antibodies targeting SARS-CoV-2 into exceptionally potent neutralizers. Using this platform, half-maximal inhibitory concentration (IC_{50}) values as low as 9×10^{-14} M are achieved as a result of up to 10,000-fold potency enhancements compared to corresponding IgGs. Combination of three different antibody specificities and the fragment crystallizable (Fc) domain on a single multivalent molecule conferred the ability to overcome viral sequence variability together with outstanding potency and IgG-like bioavailability. The MULTi-specific, multi-Affinity antibody (Multabody or MB) platform thus uniquely leverages binding avidity together with multi-specificity to deliver ultra-potent and broad neutralizers against SARS-CoV-2. The modularity of the platform also makes it relevant for rapid evaluation against other infectious diseases of global health importance. Neutralizing antibodies are a promising therapeutic for SARS-CoV-2.

Introduction

[0310] The continuous threat to public health from respiratory viruses such as the novel SARS-CoV-2 underscores the urgent need to rapidly develop and deploy prophylactic and therapeutic interventions to combat pandemics. Monoclonal antibodies (mAbs) have been used effectively for the treatment of infectious diseases as exemplified by palivizumab for the prevention of respiratory syncytial virus in high-risk infants¹ or Zmapp, mAb114, and REGN-EB3 for the treatment of Ebola². Consequently, mAbs targeting the Spike (S) protein of SARS-CoV-2 have been a focus for the development of biomedical countermeasures against COVID-19. To date, several antibodies targeting the S protein have been identified^{3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19}, with bamlanivimab being the first antibody approved in the United States by the Food and Drug Administration (FDA) for the emergency treatment of SARS-CoV-2 in November 2020. Receptor binding domain (RBD)-directed mAbs that interfere with binding to angiotensin converting enzyme 2 (ACE2), the receptor for cell entry²⁰, are usually associated with the highest neutralization potencies^{6,18,19}.

[0311] mAbs can be isolated by B-cell sorting from infected donors, immunized animals, or by identifying binders in preassembled libraries. Despite these methodologies being robust and reliable for the discovery of virus-specific mAbs, identification of the best antibody clone is usually associated with a time-cost penalty. In addition, RNA viruses have higher mutation rates than DNA viruses and such mutations can significantly alter the potency of neutralizing antibodies. Indeed, several studies have already shown a reduction in neutralization potency from convalescent serum and resistance of certain mAbs^{21,22,23} to the more recent B.1.1.7²⁴, B.1.351²⁵, and B.1.1.28^{26,27} variants of SARS-CoV-2. Hence, there is an unmet need for the development of a platform that bridges antibody discovery and the rapid identification and deployment of highly potent neutralizers less susceptible to viral sequence variability.

[0312] The potency of an antibody is greatly affected by its ability to simultaneously interact multiple times with its

epitope^{28,29,30}. This enhanced apparent affinity, known as avidity, has been previously reported to increase the neutralization potency of nanobodies^{31,32} and of IgGs over Fab^{8,10,16} against SARS-CoV-2. To leverage the full power of binding avidity, we have developed an antibody-scaffold technology using the human apoferritin protomer as a modular subunit to multimerize antibody fragments and propel mAbs into ultrapotent neutralizers against SARS-CoV-2. Indeed, the resulting Multabody molecules can increase potency by up to four orders of magnitude over corresponding IgGs. In addition, we demonstrate the ability of this technology to combine three different Fab specificities to better overcome point mutations in the Spike. The Multabody offers a versatile IgG-like “plug-and-play” platform to enhance antiviral characteristics of mAbs against SARS-CoV-2, and demonstrates the power of avidity as a mechanism to be leveraged against viral pathogens.

Materials and Methods

Protein Expression and Purification

[0313] Genes encoding VHH-human apoferritin fusion, Fc fusions, Fabs, IgG, and RBD mutants were synthesized and cloned by GeneArt (Life Technologies) into the pcDNA3.4 expression vector. All constructs were expressed transiently in HEK 293F cells (Thermo Fisher Scientific) at a density of 0.8×10^6 cells/mL with 50 µg of DNA per 200 mL of cells using FectoPRO (Polyplus Transfections) in a 1:1 ratio unless specified otherwise. After 6-7 days of incubation at 125 rpm oscillation at 37° C., 8% CO₂, and 70% humidity in a Multitron Pro shaker (Infors HT), cell suspensions were harvested by centrifugation at 5000×g for 15 min and supernatants were filtered through a 0.22 µm Steritop filter (EMD Millipore). Fabs and IgGs were transiently expressed by co-transfected 90 µg of the LC and the HC in a 1:2 ratio and purified using KappaSelect affinity column (GE Healthcare) and HiTrap Protein A HP column (GE Healthcare), respectively with 100 mM glycine pH 2.2 as the elution buffer. Eluted fractions were immediately neutralized with 1 M Tris-HCl, pH 9.0, and further purified using a Superdex 200 Increase size exclusion column (GE Healthcare). Fc fusions of ACE2 and VHH-72 were purified the same way as IgGs. The VHH-72 apoferritin fusion was purified by hydrophobic interaction chromatography using a HiTrap Phenyl HP column and the eluted fraction was loaded onto a Superose 6 10/300 GL size exclusion column (GE Healthcare) in 20 mM sodium phosphate pH 8.0, 150 mM NaCl. Wild type (BEI NR52309) and mutant RBDs, the prefusion S ectodomain (BEI NR52394) and Fc receptors (FcRn and FcγRI) from mouse and human were purified using a His-Trap Ni-NTA column (GE Healthcare). Ni-NTA purification was followed by Superose 6 in the case of the S trimer and Superdex 200 Increase size exclusion columns (GE Healthcare) in the case of the RBD and Fc receptors, in all cases in 20 mM phosphate pH 8.0, 150 mM NaCl buffer.

Design, Expression and Purification of Multabodies

[0314] All molecules referred herein as Multabodies contain scFab and scFc fragments. The scFabs and scFc polypeptide constructs were generated using a 70 amino acid flexible linker [(GGGGS)_{x14}] to generate heterodimers and homodimer fragments, respectively. Specifically, the C terminus of the Fab light chain is fused, through the linker, to

the N terminus of the Fab heavy chain. In the case of the scFc, the two single Fc chains that form the functional homodimer Fc were fused in tandem. The individual domains are fused to apo ferritin monomers with a 25 amino acid linker: (GGGGS)_{x5}. Genes encoding scFab and scFc fragments linked to half apo ferritin were generated by deletion of residues 1 to 90 (C-Ferritin) and 91 to 175 (N-Ferritin) of the light chain of human apo ferritin. Transient transfection of the Multabodies in HEK 293F cells were obtained by mixing 66 µg of the plasmids scFab-human apo ferritin:scFc-human N-Ferritin:scFab-C-Ferritin in a 2:1:1 ratio. Addition of scFab-human apo ferritin allowed efficient Multobody assembly and increased the number of Fab's compared to Fc's in the final molecule, thus favoring Fab avidity over Fc avidity. In the case of multi-specific Multabodies, a 4:2:1:1 ratio of scFab1-human apo ferritin:scFc-human N-Ferritin:scFab2-C-Ferritin:scFab3-C-Ferritin was used. The DNA mixture was filtered and incubated at room temperature (RT) with 66 µl of FectoPRO before adding to the cell culture. Split Multabodies were purified by affinity chromatography using a HiTrap Protein A HP column (GE Healthcare) with 20 mM Tris pH 8.0, 3 M MgCl₂ and 10% glycerol elution buffer. Fractions containing the protein were concentrated and further purified by gel filtration on a Superose 6 10/300 GL column (GE Healthcare).

Negative-Stain Electron Microscopy

[0315] Three microliters of Multabody at a concentration approximately of 0.02 mg/mL was placed on the surface of a carbon-coated copper grid that had previously been glow-discharged in air for 15 s, allowed to adsorb for 30 s, and stained with 3 µL of 2% uranyl formate. Excess stain was removed immediately from the grid using Whatman No. 1 filter paper and an additional 3 µL of 2% uranyl formate was added for 20 s. Grids were imaged with a FEI Tecnai T20 electron microscope operating at 200 kV and equipped with an Orius charge-coupled device (CCD) camera (Gatan Inc.).

Biolayer Interferometry

[0316] Direct binding kinetics measurements were conducted using an Octet RED96 BLI system (Sartorius ForteBio) in PBS pH 7.4, 0.01% BSA, and 0.002% Tween at 25° C. His-tagged RBD, SARS-CoV-2 Spike was loaded onto Ni-NTA (NTA) biosensors (Sartorius ForteBio) to reach a BLI signal response of 0.8 nm. Association rates were measured by transferring the loaded biosensors to wells containing a two-fold dilution series from 250 to 8 nM (Fabs), 125 to 4 nM (IgG), and 16 to 0.5 nM (MB). Dissociation rates were measured by dipping the biosensors into buffer-containing wells. The duration of each step was 180 s. Fc characterization in the split Multabody design was assessed by measuring binding to hFcγRI and hFcRn loaded onto Ni-NTA (NTA) biosensors following the experimental conditions and concentration ranges indicated above. To probe the theoretical capacity of the Multabodies to undergo endosomal recycling, binding to the hFcRn p2-microglobulin complex was measured at physiological (7.4) and endosomal (5.6) pH. Similarly, Fc characterization of the mouse surrogate MB was assessed by measuring binding to mFcγRI and mFcRn, pre-immobilized onto Ni-NTA (NTA) biosensors. Two-fold dilution series from 100 to 3 nM (IgG) and 10 to 0.3 nM (MB) were used. Analysis of the sensograms

was performed using the Octet software, with a 1:1 fit model. Competition assays were performed in a two-step binding process. Ni-NTA biosensors preloaded with His-tagged RBD were first dipped into wells containing the primary antibody at 50 µg/mL for 180 s. After a 30 s baseline period, the sensors were dipped into wells containing the second antibody at 50 µg/ml for an additional 300 s. All incubation steps were performed in PBS pH 7.4, 0.01% BSA, and 0.002% Tween at 25° C. ACE2-Fc was used to map mAb binding to the receptor binding site.

Dynamic Light Scattering

[0317] The Rh of the Multabody was determined by dynamic light scattering (DLS) using a DynaPro Plate Reader III (Wyatt Technology). About 20 µL of the Multabody at a concentration of 1 mg/mL was added to a 384-well black, clear bottom plate (Corning) and measured at a fixed temperature of 25° C. with a duration of 5 s per read. Particle size determination and polydispersity were obtained from the accumulation of five reads using the Dynamics software (Wyatt Technology).

Aggregation Temperature

[0318] Aggregation temperature (T_{agg}) of the Multabodies and parental IgGs were determined using a UNit instrument (Unchained Labs). Samples were concentrated to 1.0 mg/mL and subjected to a thermal ramp from 25 to 95° C. with 1° C. increments. T_{agg} was determined as the temperature at which 50% increase in the static light scattering at a 266 nm wavelength relative to baseline was observed (i.e., the maximum value of the differential curve). The average and the standard error of two independent measurements were calculated using the UNit analysis software.

Pharmacokinetics and Immunogenicity

[0319] A surrogate Multabody composed of the scFab and scFc fragments of mouse HD37 (anti-hCD19) IgG2a fused to the N-terminus of the light chain of mouse apo ferritin (mFerritin) was used for the study. HD37 scFab-mFerritin:Fc-mFerritin:mFerritin in a 2:1:1 ratio was transfected and purified following the procedure described above. L234A, L235A, and P329G (LALAP) mutations were introduced in the mouse IgG2a Fc-construct to silence effector functions of the Multabody⁴⁸. In vivo studies were performed using 12-week-old male C57BL/6 mice purchased from Charles River (Strain code: 027), housed in individually-ventilated cages under 12 h light/dark cycle (7 a.m./7 p.m.) at a temperature of 21–23° C. and a humidity of 40–55%. All procedures were approved by the Local Animal Care Committee at the University of Toronto Scarborough. A single injection of ~5 mg/kg of Multabodies or control samples (HD37 single chain IgG-IgG1 or IgG2a subtypes) and *Helicobacter pylori* ferritin (HpFerritin)-PfCSP malaria peptide in 200 µL of PBS (pH 7.5) were subcutaneously injected. Blood samples were collected at multiple time points and serum samples were assessed for levels of circulating antibodies and anti-drug antibodies by ELISA. Briefly, 96-well Pierce Nickel Coated Plates (Thermo Fisher) were coated with 50 µL at 0.5 µg/ml of the His_{6x}-tagged antigen hCD19 to determine circulating HD37-specific concentrations using reagent-specific standard curves for IgGs and Multabodies. HRP-ProteinA (Invitrogen) was used to detect the levels of IgG/MBs bound (dilution 1:10,

000). For anti-drug-antibody determination, Nunc MaxiSorp plates (Biolegend) were coated with a 12-mer HD37 scFab-mFerritin or with the HpFerritin-PfCSP malaria peptide. 1:100 sera dilution was incubated for 1 h at RT and further develop using HRP-ProteinA (Invitrogen) as a secondary molecule (dilution 1:10,000). The chemiluminescence signal at 450 nm was quantified using a Synergy Neo2 Multi-Mode Assay Microplate Reader (Biotek Instruments).

Biodistribution

[0320] Eight-week-old male BALB/c mice were purchased from The Jackson Laboratory and housed in individually-vented caging. Mice were housed 14 h of light/10 h dark with phased in dawn to dusk intensity, maximum at noon at a temperature of 20-21° C. and a humidity of 40-60%. All procedures were approved by the Local Animal Care Committee at the University of Toronto. Multabodies composed of the scFab and scFc fragments of mouse HD37 IgG2a fused to the N-terminus of mouse apoferitin light chain was used for this study. HD37 IgG2a Multabody or control samples (HD37 single chain IgG2a) were fluorescently conjugated with Alexa-647 using Alexa Fluor™ 647 Antibody Labeling kit (Invitrogen) as per the manufacturer's instruction. The 15 nm gold nanoparticles labeled with Alexa Fluor™ 647 were purchased from Creative Diagnostics (GFLV-15). PerkinElmer IVIS Spectrum (PerkinElmer) was used to conduct noninvasive biodistribution experiments. BALB/c mice were injected subcutaneously into the loose skin over the shoulders with ~5 mg/kg of the MB, HD37 IgG2a, or gold nanoparticles in 200 µL of PBS (pH 7.5) and imaged at time 0, 1 h, 6 h, 24 h, 2, 3, 4, 8, and 11 days following injection. Prior to imaging, mice were placed in an anesthesia induction chamber containing a mixture of isoflurane and oxygen for 1 min. Anesthetized mice were then placed in the prone position at the center of a built-in heated docking system within the IVIS imaging system (maintained at 37° C. and supplied with a mixture of isoflurane and oxygen). For whole body 2D imaging, mice were imaged for 1-2 s (excitation 640 nm and emission 680 nm) inside the imaging system. Data were analyzed using the IVIS software (Living Image Software for IVIS). After confirming the fluorescent signal from 2D epi-illumination images, 3D transilluminating fluorescence imaging tomography (FLIT) was performed on regions of interest using a built-in scan field of 3x3 or 3x4 transillumination positions. A series of 2D fluorescent surface radiance images were taken at various transillumination positions using an excitation of 640 and 680 nm emission. A series of CT scans were also taken at the corresponding positions. A 3D distribution map of the fluorescent signal was reconstructed by combining fluorescent signal and CT scans. Resulting 3D fluorescent images were thresholded based on the 3D images of PBS injected mice taken at the corresponding body positions. Images were mapped to the rainbow LUT in the IVIS software, with the upper end of the color scale set to 50 pmol M⁻¹ cm⁻¹ for mice injected with gold nanoparticles, and 1000 pmol M⁻¹ cm⁻¹ for MB and IgG2a injected mice, to allow for better visualization of biodistribution over the time course. A mouse organ registration feature of the IVIS software was used as a general guideline for assessing the sample body locations from 3D images.

[0321] Panning of Phage libraries against the RBD of SARS-CoV-2 The commercial SuperHuman 2.0 Phage library (Distributed Bio/Charles River Laboratories) was

used to identify monoclonal antibody binders to the SARS-CoV-2 RBD. For this purpose, an RBD-Fc-Avi tag construct of the SARS-CoV-2 was expressed in the EXPi-293 mammalian expression system. This protein was subsequently purified by protein G Dynabeads, biotinylated and quality-controlled for biotinylation and binding to ACE2 recombinant protein (Sino Biologics Inc). The SuperHuman 2.0 Phage library (5×10^{12}) was heated for 10 min at 72° C. and de-selected against Protein G Dynabeads™ (Invitrogen), M-280 Streptavidin Dynabeads™ (Invitrogen), Histone from Calf Thymus (Sigma), Human IgG (Sigma) and ssDNA-Biotin NNK from Integrated DNA Technologies and DNA-Biotin NNK from Integrated DNA Technologies. Next, the library was panned against the RBD-captured by M-280 Streptavidin Dynabeads™ using an automated protocol on Kingfisher FLEX (ThermoFisher). Selected phages were acid eluted from the beads and neutralized using Tris-HCl pH 7.9 (Teknova). ER2738 cells were infected with the neutralized phage pools at OD₆₀₀=0.5 at a 1:10 ratio and after 40 min incubation at 37° C. and 100 rpm, the phage pools were centrifuged and incubated on agar with antibiotic selection overnight at 30° C. The rescued phages were precipitated by PEG and subjected to three additional rounds of soluble-phase automated panning. PBST/1% BSA buffer and/or PBS/1% BSA was used in the de-selection, washes and selection rounds.

Screening of Anti-SARS-CoV-2 scFvs in Bacterial PPE with SARS-CoV-2 RBD

[0322] Anti-SARS-CoV-2 RBD scFvs selected from phage display were expressed and screened using high-throughput surface plasmon resonance (SPR) on Carterra LSA Array SPR instrument (Carterra) equipped with HC200M sensor chip (Carterra) at 25° C. A V5 epitope tag was added to the scFv to enable capture via immobilized anti-V5 antibody (Abcam, Cambridge, MA) that was pre-immobilized on the chip surface by standard amine-coupling. Briefly: the chip surface was first activated by 10 min injection of a 1:1:1 (v/v/v) mixture of 0.4 M 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), 0.1 M N-hydroxysulfosuccinimide (sNHS) and 0.1 M 2-(N-morpholino) ethanesulfonic acid (MES) pH 5.5. Then, 50 µg/ml of anti-V5 tag antibody prepared in 10 mM sodium acetate pH 4.3 was coupled for 14 min and the excess reactive esters were blocked with 1 M ethanolamine HCl pH 8.5 during a 10 min injection. For screening, a 384-ligand array comprising of crude bacterial periplasmic extracts (PPE) containing the scFvs (one spot per scFv) was prepared. Each extract was prepared at a twofold dilution in running buffer (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, and 0.01% (v/v) Tween-20 (HBSTE)) and printed on the anti-V5 surface for 15 min. SARS-CoV-2 RBD Avi Tev His tagged was then prepared at 0, 3.7, 11.1, 33.3, 100, 37, and 300 nM in 10 mM HEPES pH 7.4, 150 mM NaCl, and 0.01% (v/v) Tween-20 (HBST) supplemented with 0.5 mg/ml BSA and injected as analyte for 5 min with a 15 min dissociation time. Samples were injected in ascending concentration without any regeneration step. Binding data from the local reference spots was used to subtracted signal from the active spots and the nearest buffer blank analyte responses were subtracted to double-reference the data. The double-referenced data were fitted to a simple 1:1 Langmuir binding model in Carterra's Kinetic Inspec-

tion Tool (version October 2019). Twenty medium-affinity binders from phage display screening were selected for the present study.

Pseudovirus Production and Neutralization

[0323] SARS-CoV-2 pseudotyped viruses (PsV) were generated using an HIV-based lentiviral system⁴⁹ with few modifications. Briefly, 293T cells were co-transfected with a lentiviral backbone encoding the luciferase reporter gene (BEI NR52516), a plasmid expressing the Spike (BEI NR52310) and plasmids encoding the HIV structural and regulatory proteins Tat (BEI NR52518), Gag-pol (BEI NR52517), and Rev (BEI NR52519) using Biotransfection reagent (Bioland Scientific) and following the manufacturer's instructions. 24 h post transfection at 37° C., 5 mM sodium butyrate was added to the media and the cells were incubated for an additional 24-30 h at 30° C. SARS-CoV-2 Spike mutant D614G was kindly provided by D. R. Burton (The Scripps Research Institute), SARS-CoV-2 PsV variant B.1.351 was kindly provided by D. D. Ho (Columbia University) and the rest of the PsV mutants were generated using the KOD-Plus mutagenesis kit (Toyobo, Osaka, Japan) using primers described in Table 1. PsV particles were harvested, passed through 0.45 µm pore sterile filters and finally concentrated using a 100 K Amicon (Merck Millipore Amicon-Ultra 2.0 Centrifugal Filter Units).

TABLE 1

Primer Sequences	
Primer name	Primer
N2340_fwd	CAGATCACCGGGTTTCAGACACTGCTGGCC
N2340_rev	GATCCGTAGGGCAGATCCACCAAGGGG
L452R_fwd	CGGTACCGGCTGTTCCGGAAGTCCAATCTG
L452_rev	GTAATTGTAGTTGCCCGCGACTTTGG
A475V_fwd	GTGGGCAGCACCCCTTGTAACGGCGTGGAAAG
A475V_rev	CTGATAGATCTCGGTGGAGATGTCCOC
V483A_fwd	GCCGAAGGCTTCAACTGCTACTTOCCACTGC
V483A_rev	GCCGTTACAAGGGGTGCTGCCGGCC
N439K_fwd	AAGAACCTGGACTCCAAAGTCGGCGGCAACTAC
N439K_rev	GCTGTCCAGGCAATCACAGCCGGTG

[0324] Neutralization was determined in a single-cycle neutralization assay using 293T-ACE2 cells (BEI NR52511) and HeLa-ACE2 cells (kindly provided by D. R. Burton; The Scripps Research Institute). Cells were seeded the day before the experiment at a density of 10,000 cells/well in a 100 µl volume. In the case of 293T cells, plates where pre-coated with poly-L-lysine (Sigma-Aldrich). The day of the experiment, 50 µl of serially diluted IgGs and MB samples were incubated with 50 µl of PsV for 1 h at 37° C. After 1 h incubation, the incubated volume was added to the cells and incubated for 48 h. PsV neutralization was monitored by adding 50 µl Britelite plus reagent (PerkinElmer) to 50 µl of the cells and after 2 min incubation, the volume was transferred to a 96-well white plate (Sigma-Aldrich) and the luminescence in relative light units (RLUs) was measured using a Synergy Neo2 Multi-Mode Assay Microplate Reader (Biotek Instruments). Two to three biological replicates with

two technical replicates each were performed. IC₅₀ fold increase was calculated as:

$$\text{IgG IC}_{50} \text{ (\mu g/mL)} / \text{MB IC}_{50} \text{ (\mu g/mL)}$$

Authentic Virus Neutralization

[0325] VeroE6 cells were seeded in a 96 F plate at a concentration of 30,000/well in DMEM supplemented with 100 U Penicillin, 100 U Streptomycin, and 10% FBS. Cells were allowed to adhere to the plate and rest overnight. After 24 h, fivefold serial dilutions of the IgG and MB samples were prepared in DMEM supplemented with 100 U Penicillin and 100 U Streptomycin in a 96 R plate in quadruplicates (25 µL/well). About 25 µL of SARS-CoV-2/SB2-P4-PB⁵⁰ Clone 1 was added to each well at 100 TCID/well and incubated for 1 h at 37° C. with shaking every 15 min. After co-culturing, the media from the VeroE6 plate was removed, and 50 µL antibody-virus sample was used to inoculate VeroE6 cells in quadruples for 1 h at 37° C., 5% CO₂, shaking every 15 min. After 1 h inoculation, the inoculum was removed and 200 µL of fresh DMEM supplemented with 100 U Penicillin, 100 U Streptomycin, and 2% FBS was added to each well. The plates were further incubated for 5 days. The cytopathic effect (CPE) was monitored and PRISM was used to calculate IC₅₀ values. Three biological replicates with four technical replicates each were performed.

Cross-Linking of Spike Protein with Fabs 80, 298 and 324

[0326] About 100 µg of Spike trimer was mixed with 2x molar excess of Fab 80, 298, or 324 in 20 mM HEPES pH 7.0 and 150 mM NaCl. Proteins were crosslinked by addition of 0.075% (v/v) glutaraldehyde (Sigma Aldrich) and incubated at RT for 120 min. Complexes were purified via size exclusion chromatography (Superose6 Increase 10/300 GL, GE Healthcare), concentrated to 0.5 mg/mL and directly used for cryo-EM grid preparation.

Cross-Linking of Fab 46-RBD Complex

[0327] About 100 µg of Fab 46 was mixed with 2x molar excess of RBD in 20 mM HEPES pH 7.0 and 150 mM NaCl. The complex was crosslinked by addition of 0.05% (v/v) glutaraldehyde (Sigma Aldrich) and incubated at RT for 45 min. The cross-linked complex was purified via size exclusion chromatography (Superdex 200 Increase 10/300 GL, GE Healthcare), concentrated to 2.0 mg/ml and directly used for cryo-EM grid preparation.

Cryo-EM Data Collection and Image Processing

[0328] Three microliters of sample was deposited on holey gold grids prepared in-house⁵¹, which were glow-discharged in air for 15 s with a PELCO easiGlow (Ted Pella) before use. Sample was blotted for 6 s with a modified FEI Mark III Vitrobot (maintained at 4° C. and 100% humidity) using an offset of ~5, and subsequently plunge-frozen in a mixture of liquid ethane and propane. Data were acquired at 300 kV with a Thermo Fisher Scientific Titan Krios G3 electron microscope and prototype Falcon 4 camera operating in electron counting mode at 250 frames/s. Movies were collected for 9.6 s with 29 exposure fractions, a camera exposure rate of ~5 e⁻/pix/s, and total specimen exposure of ~44 e⁻/Å². No objective aperture was used. The pixel size was calibrated at 1.03 Å/pixel from a gold diffraction standard. The microscope was automated with the EPU software package and data collection were monitored with cryoSPARC Live⁵².

[0329] To overcome preferred orientation encountered with some of the samples, tilted data collection was employed⁵³. For the Spike-Fab 80 complex, 820 0° tilted movies and 2790 400 tilted movies were collected. For the Spike-Fab 298 complex, 4259 0° tilted movies and 3513 40° tilted movies were collected. For the Spike-Fab 324 complex, 1098 0° tilted movies and 3380 40° tilted movies were collected. For the RBD-Fab 46 complex, 4722 0° tilted movies were collected. For 0° tilted movies, cryoSPARC patch motion correction was performed. For 40° tilted movies, Relion MotionCorr^{54,55} was used. Micrographs were then imported into cryoSPARC and patch CTF estimation was performed. Templates generated from 2D classification during the cryoSPARC Live session were used for template selection of particles. 2D classification was used to remove junk particle images, resulting in a dataset of 80,951 particle images for the Spike-Fab 80 complex, 203,138 particle images for the Spike-Fab 298 complex, 64,365 particle images for the Spike-Fab 324 complex, and 2,143,629 particle images for the RBD-Fab 46 complex. Multiple rounds of multi-class ab initio refinement were used to clean up the particle image stacks, and homogeneous refinement was used to obtain consensus structures. For tilted particles, particle polishing was done within Relion at this stage and reimported back into cryoSPARC. For the Spike-Fab complexes, extensive flexibility was observed. 3D variability analysis was performed⁵⁶ and together with heterogeneous refinement used to classify out the different states present. Nonuniform refinement was then performed on the final set of particle images⁵⁷. For the RBD-Fab 46 complex, cryoSPARC ab initio refinement with three classes was used iteratively to clean up the particle image stack. Thereafter, the particle image stack with refined Euler angles was brought into cisTEM for reconstruction⁵⁸ to produce a 4.0 Å resolution map. Transfer of data between Relion and cryoSPARC was done with pyem⁵⁹.

Crystallization and Structure Determination

[0330] A ternary complex of 52 Fab-298 Fab-RBD was obtained by mixing 200 µg of RBD with 2x molar excess of each Fab in 20 mM Tris pH 8.0, 150 mM NaCl, and

subsequently purified via size exclusion chromatography (Superdex 200 Increase 10/300 GL, GE Healthcare). Fractions containing the complex were concentrated to 7.3 mg/ml and mixed in a 1:1 ratio with 20% (w/v) 2-propanol, 20% (w/v) PEG 4000, and 0.1 M sodium citrate pH 5.6. Crystals appeared after ~1 day and were cryoprotected in 10% (v/v) ethylene glycol before being flash-frozen in liquid nitrogen.

[0331] Data were collected on the 23-ID-D beamline at the Argonne National Laboratory Advanced Photon Source. The dataset was processed using XDS⁶⁰ and XPREP. Phases were determined by molecular replacement using Phaser⁶¹ with CNT088 Fab as a model for 52 Fab (PDB ID: 4DN3), 20358 Fab as a model for 298 Fab (PDB ID: 5CZX), and PDB ID: 6XDG as a search model for the RBD. Refinement of the structure was performed using phenix.refine⁶² and iterations of manual building in Coot⁶³. PyMOL was utilized for structure analysis and figure rendering⁶⁴. Access to all software was supported through SBGrid⁶⁵. Representative electron density for the two Fab-RBD interfaces is shown in FIG. 2e, f.

Materials Availability

[0332] The electron microscopy maps have been deposited in the Electron Microscopy Data Bank (EMDB) with accession codes EMD-22738, EMD-22739, EMD-22740, and EMD-22741 (Table 2). The crystal structure of the 298-52-RBD complex (Table 3) is available from the Protein Data Bank under accession PDB ID: 7K9Z. The sequences of the monoclonal antibodies used are provided with this paper (Table 4). Additional PDB/EMDB entries were used throughout the manuscript to perform a comparative analysis of the different epitope bins targeted by mAbs. The entries used in this analysis are: REGN10933 (PDB ID: 6XDG), CV30 (PDB ID: 6XE1), C105 (PDB ID: 6XCM), COVA2-04 (PDB ID: 7JMO), COVA2-39 (PDB ID: 7JMP), CC12.1 (PDB ID: 6XC2), BD23 (PDB ID: 7BYR), B38 (PDB ID: 7BZ5), P2C-1F11 (PDB ID: 7BWJ), 2-4 (PDB ID: 6XEY), CB6 (PDB ID: 7C01), REGN10987 (PDB ID: 6XDG), S309 (PDB ID: 6WPS, 6WPPT), EY6A (PDB ID: 6ZCZ), CR3022 (PDB ID: 6YLA), H014 (PDB ID: 7CAH), 4-8 (EMDB ID: 22159), 4A8 (PDB ID: 7C2L), and 2-43 (EMDB ID: 22275).

TABLE 2

Cryo-EM data collection and image processing				
EMDB ID	Fab 80-Spike EMD-22739	Fab 298-Spike EMD-22740	Fab 324-Spike EMD-22741	Fab 46-RBD EMD-22738
<u>Data Collection</u>				
Electron microscope	Titan Krios G3	Titan Krios G3	Titan Krios G3	Titan Krios G3
Camera	Falcon 4EC	Falcon 4EC	Falcon 4EC	Falcon 4EC
Voltage (kV)	300	300	300	300
Nominal magnification	75,000	75,000	75,000	75,000
Calibrated physical pixel size (Å)	1.03	1.03	1.03	1.03
Total exposure (e-/Å ²)	44	44	44	44
Number of frames	29	29	29	29

TABLE 2-continued

Cryo-EM data collection and image processing				
EMDB ID	Fab 80-Spike EMD-22739	Fab 298-Spike EMD-22740	Fab 324-Spike EMD-22741	Fab 46-RBD EMD-22738
<u>Image Processing</u>				
Motion correction software	cryoSPARC v2, Relion MotionCorr	cryoSPARC v2, Relion MotionCorr	cryoSPARC v2, Relion MotionCorr	cryoSPARCv2
CTF estimation software	cryoSPARCv2	cryoSPARCv2	cryoSPARCv2	cryoSPARCv2
Particle selection software	cryoSPARCv2	cryoSPARCv2	cryoSPARCv2	cryoSPARCv2
3D map classification and refinement software	cryoSPARCv2	cryoSPARCv2	cryoSPARCv2	cisTEM
Micrographs used (total)	3610	7772	4478	4722
0° tilt	820	4259	1098	4722
40° tilt	2790	3513	3380	0
Global resolution (Å)	6.2	6.2	6	4
Particles in final maps	7,525	26,972	18,595	32,283

TABLE 3

X-ray crystallography data collection and refinement statistics	
	Fab 52- Fab 298- SARS-CoV-2 RBD
PDB ID	7K9Z
Data Collection	
Wavelength (Å)	1.03317
Space group	P 3 ₂ 2 1
Cell dimensions	
a, b, c (Å)	87.6, 87.6, 325.1
α, β, γ (°)	90.0, 90.0, 120.0
Resolution (Å)	39.66-2.95 (3.05-2.95)
No. Molecules in ASU	1
No. Total observations	496,550 (43,958)
No unique observations	31,545 (3,060)
Multiplicity	15.7 (14.3)
R _{merge} (%)	16.8 (74.2)
R _{free} (%)	4.3 (20.1)
<I/σI>	12.3 (1.4)
CC _{1/2}	99.8 (86.3)
Completeness (%)	99.9 (99.9)

TABLE 3-continued

X-ray crystallography data collection and refinement statistics	
	Fab 52- Fab 298- SARS-CoV-2 RBD
<u>Refinement</u>	
Non-hydrogen atoms	8061
Macromolecule	8047
Glycan	14
R _{work} /R _{free}	0.259/0.286
Rms deviations	
Bond lengths (Å)	0.002
Bond angles (°)	0.53
Ramachandran plot	
Favored regions (%)	95.6
Allowed regions (%)	4.1
Outliers (%)	0.3
Rotamer Outliers (%)	2.6
B-factors (Å ²)	
Wilson B-factor	78.6
Average B-factors	103.9
Average macromolecule	103.9
Average glycans	114.3

TABLE 4

mAb	RBD	IC50 SARS-CoV2 PsV			Variable Heavy Chain	Variable Light Chain		
		KD	CoV2/SB2 (μg/mL)	-P4-PB (μg/mL)				
		(nM)	MB	IgG	MB	IgG	sequence	sequence
56	IGHV1- VK	23	>50	>50	n. d.	n. d.	QVOLVQSG	DIQMTOESP
	46	39					AEVKKKPGA	SSL SASVG
							SVKVSKCA	DRV TITCR

TABLE 4-continued

mAb	RBD KD	IC50 SARS- CoV2/SB2 (μg/mL)		IC50 SARS- CoV2 PsV -P4-PB (μg/mL)		Variable Heavy Chain	Variable Light Chain			
		ID	VH	VK	(nM)	MB	IgG	MB	IgG	sequence
349 IGHV3 - 23	IGKV1 - 39	74	>50	>50	n.d.	n.d.	SGYTFTSY GISWRQAA PGQGLEW MGWISAYN GNTNYAQK LQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC ARDIGPIDY WGQGTLVT VSS	EVQLLESG GGLVQPQGG SLRLSCAAS GFTFSNYG MHWRQAA PGKGLEWV SGISSAGSI TNYADSVK GRFTISRDN SKNTLYLQ MNSLRAED TAVYYCAG NHAGTTVT SEYFQHWG QGTLVTVS S	ASQGISSY LAWYQQKP GKAPKLLI YDASNLOS GVPSRFSG SGSGTDFT LTISSSLQPE DFATYYCQ QANSFPST FGQGTKVE IKR	DIQMTQSP SSLSASVG DRVITITCR ASQSISSW LAWYQQK PGKAPKLLI YDTSNLET GVPSRFSG SGSGTDFT LTISSSLQPE DFATYYCQ QSYTTPWT FGQGTRLE IKR
178 IGHV1 - 46	IGKV3 - 15	72	1.7	>50	n.d.	n.d.	QVQLVQSG AEVKKGAA SVKVSCKA SGYTFTDY HMHWVRQ APGQGLEW MGWINPNS GGTNYAQK FQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC ARDISSWY EITKFDPWG QGTLVTVS S	EIVMTQSP ATLSVSPG ERATLSCK ASQSVSGT YLAWYQQ KPGQAPRL LIYGASTRA TGIPARFS GSGSGTEF TTLTISSLQS EDFAVYYC LQTHSYPP TFGQGTKV EIKR		
108 IGHV1 - 46	IGKV1 - 39	72	0.37	>50	n.d.	n.d.	QVQLVQSG AEVKKGAA SVKVSCKA SGYIFSRYA IHWRQAP GQGLEWM GWMPNISG NTDYAPNF QGRVTMTR DTSTSTVY MELSSLRS EDTAVYYC AKDGSQLA YLVEYFQH WGQGTLVT VSS	DIQMTQSP SSLSASVG DRVITITCR ASQVITNNL AWYQQKP GKAPKLLIY DASTLETG VPSRFSGS GSGTDFTL TISSLOPED FATYYCQQ SYTFPYTF GQGTKVEI KR		
128 IGHV1 - 46	IGKV1 - 39	57	3.5	>50	n.d.	n.d.	QVQLVQSG AEVKKGAA SVKVSCKA SGYTFTHY YMHWRQ APGQGLEW	DIQMTQSP SSLSASVG DRVITITCR ASQNISRY LNWYQQK PGKAPKLLI		

TABLE 4-continued

mAb	RBD KD	IC50 SARS- CoV2/SB2 (μg/mL)		IC50 SARS- CoV2 PsV -P4-PB (μg/mL)		Variable Heavy Chain	Variable Light Chain			
		ID	VH	VK	(nM)	MB	IgG	MB	IgG	sequence
160 IGHV3- 23	IGKV1- 39	7.7	0.22	>50	n.d.	n.d.	QVQLVQSG AEVKPG SVKVSCKA SGYTFGTGH DMHWVRQ APGQGLEW MGIINPSGG STSYAQKF QGRVTMTR DTSTSTVY MELSSLRS EDTAVYYC ARDGRYGS GSYPFDYW GQGTLVTV SS	MGIINPSGG SASYSQKF QGRVTMTR DTSTSTVY MELSSLRS EDTAVYYC ARDGRYGS GSYPFDYW GQGTLVTV SS	YDASNLET GVPSRFSG SGSGTDFT LTIISSLOPE DFATYYCQ QANGFPPT FGQGTKLE IKR	DIQMTQSP SSLSASVG DRVTTITCR ASQSVSS WLAWYQQ KPGKAPKL LTYAASSLQ SGVPSRFS GSGSGTDFT TLTISSLOP EDFATYYC QQGYTPPY TFGQGTKL
368 IGHV1- 69	IGKV2- 28	nb	0.073	>50	n.d.	n.d.	QVQLVQSG AEVKPGS SVKVSCKA SGYTFTSY DINWVRQA PGQGLEW MGAIMPMPF GTANYAQK FQGRVTITA DESTSTAY MELSSLRS EDTAVYYC ARGSSGYY YWGQQGTL VTVSS	QVQLVQSG AEVKPGS SVKVSCKA SGYTFTSY DINWVRQA PGQGLEW MGAIMPMPF GTANYAQK FQGRVTITA DESTSTAY MELSSLRS EDTAVYYC ARGSSGYY YWGQQGTL VTVSS	EIKR DIVMTQSP LSLPVTPG EPASISCR SSQSLLHS NGYNYLD WYLQKPG QSPQLLIYL GSNRASGV PDRFSGSG SGTDFTLKI SRVEAEDV GVYYCMQ ALQTPATF GP GTKVDI KR	
192 IGHV1- 69	IGKV2- 28	nb	0.79	>50	n.d.	n.d.	QVQLVQSG AEVKPGS SVKVSCKA SGGTFSYY AISWVRQA PGQGLEW MGWINPNS GGANYAQK FQGRVTITA DESTSTAY MELSSLRS EDTAVYYC STYYYYDSS GSTYDYWG QGTLVTVS S	QVQLVQSG AEVKPGS SVKVSCKA SGGTFSYY AISWVRQA PGQGLEW MGWINPNS GGANYAQK FQGRVTITA DESTSTAY MELSSLRS EDTAVYYC STYYYYDSS GSTYDYWG QGTLVTVS S	DIVMTQSP LSLPVTPG EPASISCR SSQSLLHS NGYNYLD WYLQKPG SPQLLIYA ASSLQSGV PDRFSGSG SGTDFTLKI SRVEAEDV GVYYCMQ ALQTPYTF GQGTKLEI KR	
158 IGHV1- 46	IGKV1- 39	172	0.1	>50	n.d.	n.d.	QVQLVQSG AEVKPG SVKVSCKA SGYTFGTGY YMHWVRQ APGQGLEW MGWINPLN GGTNFAPK	QVQLVQSG AEVKPG SVKVSCKA SGYTFGTGY YMHWVRQ APGQGLEW MGWINPLN GGTNFAPK	DIQMTQSP SSLSASVG DRVTTITCR ASQSISRYL NWYQQKP GKAPKLLIY DASNLESG VPSRFSGS	

TABLE 4-continued

mAb	RBD KD	IC50 SARS- CoV2/SB2 (μg/mL)		IC50 SARS- CoV2 PsV -P4-PB (μg/mL)		Variable Heavy Chain	Variable Light Chain				
		ID	VH	VK	(nM)	MB	IgG	MB	IgG	sequence	sequence
180	IGHV1- 69	IGKV2- 28	nb		0.89	>50	n.d.	n.d.		FQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC ARDPGGSY SNDAFDIW GQGTLVTV SS	GSGTDFTL TISSLQPED FATYYCQQ ANSFPLTF GGGTKVDI KR
254	IGHV3- 23	IGKV1- 39	127		9.3	>50	n.d.	n.d.		QVQLVQSG AEVKKPGS SVKVSCKA SGYTFTSY AMHWRQQA PGQGLEW MGRISPRS GGTKYAQR FQGRVTIT ADESTSTA YMELESSLR SEDTAVYY CAREAVAG THPQAGDF DLWGRGTL TVSS	DIVMTQSP LSLPVTPG EPASISCR SSQSLLHS NGYNYLD WYLQKPGQ SPOLLIA ASSLQSGV PDRFSGSG SGTDFTLK ISRVEAED VGVYYCQQ YYSSPYTF GGGTTKLEI KR
120	IGHV1- 46	IGKV3- 15	24		7.2	>50	n.d.	n.d.		EVQLLESG GGLVQPGG SLRLSCAA SGFTFSSS AMHWRQQA PGKGLEWV SAIGTGGD TYYADSVK RGFTISRD NSKNLTYL QMNLSRAE DTAVYYCA REGDGYNF YFDYWQGQ TLVTVSS	DIQMTQSP SSLSASVG DRVТИТCR ASQGISSY LAWYQQKP GKAPKLLI YDASSLQI GVPSRFSG SGSGTDFT LTISILOPE DFATYYCL QSYSTPPW TRFGQGTKV EIKR
64	IGHV3- 23	IGKV1- 39	97		14	>50	n.d.	n.d.		QVQLVQSG AEVKKPGA SVKVSCKA SGYTFTSY DINWVRQQA PGQGLEW MGMDIPSG GSTSYAQK FQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC AKDFGGT RYDYWYFD LWGRTLV TVSS	EIVMTQSP ATLSVSPG ERATLSCR ASQSVSSR YLAWSQQK PGQAPRLL IYGASTRA TGIPARFS GSGSGTEP TLTISSLQ SEDFAVYY CQQYYTTP RTFGQGTR ELIKR

TABLE 4-continued

mAb	RBD KD	IC50 SARS- CoV2/SB2 (μg/mL)		IC50 SARS- CoV2 PsV -P4-PB (μg/mL)		Variable Heavy Chain	Variable Light Chain			
		ID	VH	VK	(nM)	MB	IgG	MB	IgG	sequence
298	IGHV1- 46	IGKV4- 1	24	0.00011	2.8	0.0057	2.2	QVQLVQSG AEVKPG SVKVSCKA SGGTFS GISWVRQA PGQGLEWM GWISPN GGTDLAQK FQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC ASDPRDDIA GGYWGQG TLTVSS	AVYYCARD TYGGKV FDYWGQGT LTVSS	QQTYSTPW TFIGQGTKV EIKR
82	IGHV1- 46	IGKV1- 39	206	0.0022	1.6	0.21	19	QVQLVQSG AEVKPG SVKVSCKA SGGSFSTS AFYWVRQA PGQGLEW MGWINPYT GGTNYAQK FQGRVTMT RDTSTSTVY MELSSLRS EDTAVYYC ARSRALYG SGSYFDY GQGTLVTV SS	DIVMTQSP DSLAVSLG ERATINCK SSQSVLYS SNKNYLA WYQQKPGQ PPKLLIY WASTRESG VPDRFSGS GSGTDFTL TISSLQAE DVAVYYCQ QYYSTPPT FGQGTKLE IKR	
46	IGHV3- 23	IGKV1- 39	83	0.0024	2.1	0.027	19	EVQLLESG GGLVQPGR SLRLSCAAS GFTFSSYA MSWVRQAP GKGLEWVS TIYSGGSTY YADSVKGR FTISRDN NTLYLQMN SLRAEDTAV YYCARGDS RDADPIWG QGTMTV S	DIQMTQSP SSLSASVG DRV TITCR ASQVISNY LAWYQQKP GKAPKLLIY DASNLETG VPSRFSGS GSGTDFTL TISSLQPED FATYYCQ SFSPPTF GQGTRLEI KR	
324	IGHV1- 69	IGKV1- 39	111	0.0009	0.78	0.024	21	QVQLVQSG AEVKPG SVKVSCKA SGGTFS GISWVRQA PGQGLEW MGWN SGNTGYAQ KFQGRVTM TRDTSTSTV YME LSSLR SE DTAVYY CARVGDY DYIVSPF DL WGRGTLV T VSS	DIQMTQSP SSLSASVG DRV TITCR ASQSITTYL NWYQQKP KAPKLLIY DASNLETG VPSRFSGS GSGTDFTL TISSLQPED FATYYCQ SFSPPTF GQGTRKEI KR	

TABLE 4-continued

mAb	ID	VH	VK	(nM)	RBD	IC50 SARS-CoV2/SB2 (μg/mL)	SARS-CoV2 PsV -P4-PB (μg/mL)	Variable Heavy Chain	Variable Light Chain
					KD				
236	IGHV1-69	IGKV2-28		145	0.00047	0.057	0.028	5.5	QVQLVQSG AEVKPG SVKVSCKA SGGTFTSY GINWVRQA PGQGLEW MGWMNPN SGNTGYAQ KFQGRVTM TRDTSTSTV YMELSSLR SEDTAVYY CASRGIQLL PRGMDVW GQGTTVTV SS
52	IGHV1-69	IGKV1-39		12	0.0002	0.55	0.27	6.2	QVQLVQSG AEVKPGS SVKVSCKA SGYIFTSY GISWVRQA PGQGLEW MGGIIPMFG TTNYAQKF QGRVTITAD KSTSTAYM ELSSLRSED TAVYYCAR DRGDTIDY WGQGTLVT VSS
80	IGHV1-69	IGKV4-1		142	0.0013	0.1	0.32	12.7	QVQLVQSG AEVKPGS SVKVSCKA SGGTFNRY AFSWSVRQA PGQGLEWM GGIIPIFGT ANYAQKFQ GRVTITADE STSTAYMEL SSLRSEDTA VYYCARST RELPEVVD WYFDLWGR GTLVTVSS

MATERIALS AND METHODS REFERENCES

- [0333] 46. Kabsch, W. et al. XDS. *Acta Crystallogr. Sect. D Biol. Crystallogr.* 66, 125-132 (2010).
- [0334] 47. McCoy, A. J. et al. Phaser crystallographic software. *J. Appl. Crystallogr.* 40, 658-674 (2007).
- [0335] 48. Adams, P. D. et al. PHENIX: A comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr. Sect. D Biol. Crystallogr.* 66, 213-221 (2010).
- [0336] 49. Emsley, P., Lohkamp, B., Scott, W. G. & Cowtan, K. Features and development of Coot. *Acta Crystallogr. Sect. D Biol. Crystallogr.* 66, 486-501 (2010).
- [0337] 50. Morin, A. et al. Collaboration gets the most out of software. *Elife* 2, (2013).
- [0338] 51. Marr, C. R., Benlekbir, S. & Rubinstein, J. L. Fabrication of carbon films with ~500 nm holes for cryo-EM with a direct detector device. *J. Struct. Biol.* 185, 42-47 (2014).
- [0339] 52. Punjani, A., Rubinstein, J. L., Fleet, D. J. & Brubaker, M. A. CryoSPARC: Algorithms for rapid unsupervised cryo-EM structure determination. *Nat. Methods* 14, 290-296 (2017).
- [0340] 53. Zi Tan, Y. et al. Addressing preferred specimen orientation in single-particle cryo-EM through tilting. *Nat. Methods* 14, (2017).
- [0341] 54. Zivanov, J. et al. New tools for automated high-resolution cryo-EM structure determination in RELION-3. *Elife* 9, e42166 (2018).
- [0342] 55. Scheres, S. H. W. RELION: Implementation of a Bayesian approach to cryo-EM structure determination. *J. Struct. Biol.* 180, 519-530 (2012).

- [0343] 56. Punjani, A. & Fleet, D. 3D Variability Analysis: Directly resolving continuous flexibility and discrete heterogeneity from single particle cryo-EM images. *bioRxiv* (2020).
- [0344] 57. Punjani, A., Zhang, H. & Fleet, D. Non-uniform refinement: Adaptive regularization improves single particle cryo-EM reconstruction. *bioRxiv* (2019).
- [0345] 58. Grant, T., Rohou, A. & Grigorieff, N. CisTEM, user-friendly software for single-particle image processing. *Elife* 7, e35383 (2018).
- [0346] 59. Asarnow, D., Palovcak, E. & Cheng, Y. asarnow/pyem: UCSF pyem v0. 5. (2019).

Results

Avidity Enhances Neutralization Potency

[0347] We used the self-assembly of the light chain of human apoferritin to multimerize antigen binding moieties targeting the SARS-CoV-2 S glycoprotein. Apoferritin protomers self-assemble into an octahedrally symmetric structure with an ~6 nm hydrodynamic radius (Rh) composed of 24 identical polypeptides³³. The N terminus of each apoferritin subunit points outwards of the spherical nanocage and is therefore accessible for the genetic fusion of proteins of interest. Upon folding, apoferritin protomers act as building blocks that drive the multimerization of the 24 proteins fused to their N termini (FIG. 1a).

[0348] First, we investigated the impact of multivalency on the ability of the single chain variable domain VHH-72 to block viral infection. VHH-72 has been previously described to neutralize SARS-CoV-2 when fused to a Fc domain, but not in its monovalent format³¹. The light chain of human apoferritin displaying 24 copies of VHH-72 assembled into monodisperse, well-formed spherical particles (FIG. 1b, c) and showed an enhanced binding avidity to the S glycoprotein (FIG. 1d) in comparison to bivalent VHH-72-Fc. Strikingly, display of VHH-72 on the light chain of human apoferritin achieved a ~10,000-fold increase in neutralization potency against SARS-CoV-2 pseudovirus (PsV) compared to the conventional Fc fusion (FIG. 1e), demonstrating the power of avidity to transform binding moieties into potent neutralizers.

Multabodies have IgG-Like Properties

[0349] The Fc confers IgGs in vivo half-life and effector functions through interaction with neonatal Fc receptor (FcRn) and Fc gamma receptors (FcγR), respectively. To confer these IgG-like properties to our multimeric scaffold, we next sought to incorporate both binding moieties and Fc domains. Because a Fab is a hetero-dimer consisting of a light and a heavy chain, and the Fc is a homodimer, we created single-chain Fab (scFab) and single-chain Fc (scFc) polypeptide constructs. scFab and scFc domains were directly fused to the N terminus of the apoferritin protomer. For in vivo proof-of-principle experiments, we generated a species-matched surrogate molecule that consists of mouse light chain apoferritin fusions to a mouse scFab and a mouse scFc (IgG2a subtype). Binding kinetics showed that the resulting MB molecule binds mouse FcRn in a pH dependent manner-binding at endosomal pH (5.6) and no binding at physiological pH (7.4)—similar to the parental IgG (FIG. 3a). Expectedly, binding to the high-affinity mouse FcγR1 was enhanced through avidity effects in comparison to the parental IgG. Hence, we generated a modified mouse scFc version that includes the FcγR-silencing mutations LALAP

to lower Fc binding in a multimeric context (FIG. 3a). Subcutaneous administration of MBs in C57BL/6 or BALB/c mice was well tolerated with no decrease in body weight or visible adverse events. The MB showed favorable IgG-like serum half-life (FIG. 3b), with a prolonged detectable titer in the sera for the lower FcγR-binding MB (LALAP Fc sequence) compared to the WT MB, indicative of a role for the Fc in dictating in vivo bioavailability. Live 2D and 3D-imaging revealed that the fluorescently-labeled MB biodistributed systemically like the corresponding IgG, without accumulation in any specific tissue (FIG. 3c and FIG. 4). In contrast, 15 nm gold nanoparticles (GNP), which have a similar Rh as MBs, rapidly disseminated from the site of injection (FIG. 3c and FIG. 4). Presumably because all sequences derived from the host, the surrogate mouse MB did not induce an anti-drug antibody response in mice (FIG. 3d), thus further highlighting the IgG-like properties of the MB platform.

Protein Engineering to Achieve Higher Valency

[0350] In view of these favorable results for a mouse MB surrogate, we aimed to generate fully-human MBs derived from the previously reported IgG BD23¹² and IgG 4A8¹³ that target the SARS-CoV-2 spike RBD and N-terminal domain (NTD), respectively. Addition of scFc to the MB reduces the number of scFabs that can be multimerized. In order to endow the MB platform with Fc without compromising Fab avidity and hence neutralization potency, we engineered the apoferritin protomer to accommodate more than 24 components per particle. Based on its four-helical bundle fold, the human apoferritin protomer was split into two halves: the two N-terminal α helices (N-Ferritin) and the two C-terminal α helices (C-Ferritin). In this configuration, the scFc fragment of human IgG1 and the scFab of anti-SARS-CoV-2 IgGs were genetically fused at the N terminus of each apoferritin half, respectively. Split apoferritin complementation led to hetero-dimerization of the two halves and consequently resulted in a very efficient hetero-dimerization process of the fused proteins. Co-expression of the scFab-C-Ferritin and scFc-N-Ferritin genes together with the scFab-Ferritin gene in excess resulted in a full apoferritin self-assembly that displays high numbers of scFab and low numbers of scFc on the nanocage periphery (FIG. 5a and Materials and Methods). Conveniently, this design allows for the straightforward purification of the MB using Protein A akin to IgG purification.

[0351] This split MB design forms 16 nm Rh spherical particles with an uninterrupted ring of density and regularly spaced protruding scFabs and scFc (FIG. 5b, c). Hence, the MB is on the lower size range of natural IgMs³⁴, but packs more weight on a similar size to achieve high multi-valency. Binding kinetics experiments demonstrated that high binding avidity of the MB for the Spike was preserved upon addition of Fc fragments (FIG. 5d and Table 5). Binding to human FcγR1 and FcRn at both pH 5.6 and 7.4 confirmed that scFc was properly folded in the split MB design (Tables 6 and 7). In addition, the LALAP mutations in the scFc lowered the binding affinity to human FcγR1 (FIG. 5e), as previously observed with the surrogate mouse MB (FIG. 3a). SARS-CoV-2 PsV neutralization assays with the split design MBs showed that enhanced binding affinity for the Spike translates into an improved neutralization potency in comparison to their IgG counterparts, with a ~1600-fold and >2000-fold increase for BD23 and 4A8, respectively (FIG.

5f). Combined, this data supported the further exploration of the MB as an IgG-like platform that confers exquisite binding avidity and PsV neutralization across epitopes on different Spike domains.

TABLE 5

Kinetic constants and affinities to SARS-CoV-2 Spike antigen of Multabodies determined by BLI.			
Multabody	SARS-CoV-2 Spike		
	k_{on} [M ⁻¹ × s ⁻¹]	K_{off} [s ⁻¹]	K_D [M]
4A8 MB	1.08E+05	<1.0E-07	<1.0E-12
4A8 IgG	1.33E+05	1.91E-04	1.42E-09
BD23 MB	9.57E+05	<1.0E-07	<1.0E-12
BD23 IgG	2.17E+05	9.37E-04	4.33E-09

[0352] Fc mutations of IgG1 backbone evaluated in Multabodies include: LALAP (L234A, L235A and P329G) and I235A, and combinations thereof that decrease antibody binding to FcγR. (Numberings are according to the EU numbering scheme.)

[0353] The values determined for k_{on} , k_{off} and the resulting equilibrium dissociation constant (K_D) for the Multabodies are summarized in Tables 6-10. Binding kinetics showed that the resulting mouse MB molecule binds mouse FcRn in a pH dependent manner—binding at endosomal pH (5.6) and no binding at physiological pH (7.4)—similar to the parental IgG (FIG. 3A). Binding to the high-affinity mouse FcγR1 was enhanced through avidity effects in comparison to the parental IgG. Binding of human MB to human FcγRI and FcRn at endosomal pH confirmed that scFc was properly folded in the split MB design and that LALAP and I253A mutations lowered binding affinities to FcγR1 and FcRn, respectively.

TABLE 6

Kinetic constants and affinities to human FcRn of human Ferritin Multabodies derived from BD23 Antibody (IgG1) targeting SARS-CoV-2.						
Multabody	FcRn, pH 5.6			FcRn, pH 7.5		
	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K_D [M]	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K_D [M]
IgG1 control	5.03E+05	3.86E-03	7.67E-09	—	—	No binding
WT MB	2.18E+05	<1.0E-07	<1.0E-12	—	—	No binding
LALAP MB	2.69E+05	<1.0E-07	<1.0E-12	—	—	No binding
I253A MB	2.00E+05	4.28E-04	2.15E-09	—	—	No binding
LALAP + I253A MB	4.34E+05	6.10E-04	1.41E-09	—	—	No binding

TABLE 7

Kinetic constants and affinities to human FcγRI of human Ferritin Multabodies derived from BD23 Antibody (IgG1) targeting SARS-CoV-2					
Multabody	FcγRI				
	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K_D [M]		
IgG1 control	1.27E+05	1.34E-04	1.06E-09		
WT MB	7.21E+05	<1.0E-07	<1.0E-12		
LALAP MB	—	—	No binding		
I253A MB	5.01E+05	<1.0E-07	<1.0E-12		
LALAP I253A MB	—	—	No binding		

TABLE 8

Kinetic constants and affinities to mouse FcRn of mouse Ferritin Multabodies derived from HD37 Antibody (IgG2a) targeting CD19 determined by BLI.						
Multabody	mFcRn, pH 5.6			mFcRn, pH 7.4		
	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K_D [M]	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K_D [M]
mIgG2a control	1.16E+05	1.23E-04	1.06E-09	—	—	No binding
mWT MB	6.82E+05	<1.0E-07	<1.0E-12	—	—	No binding
gLALAP MB	2.40E+06	<1.0E-07	<1.0E-12	—	—	No binding

TABLE 9

Kinetic constants and affinities to mouse FcγRI of mouse Ferritin Multabodies derived from HD37 Antibody (IgG2) targeting CD19 determined by BLI.

Multabody	mFcγRI		
	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K _D [M]
mIgG2a control	5.22E+04	4.51E-04	8.63E-09
mWT MB	9.39E+05	<1.0E-07	<1.0E-12
mLALAP MB	—	—	No binding

against authentic virus in comparison to PsV is also in agreement with previous reports^{5,8,9,12}.

TABLE 11

human mAb binders of SARS-CoV-2 RBD.			
mAb ID	VH	VK	RBD KD (nM)
56	IGHV1-46	IGKV1-39	23
349	IGHV3-23	IGKV1-39	74
178	IGHV1-46	IGKV3-15	72

TABLE 10

Kinetic constants and affinities to human FcRn of human Ferritin Multabodies derived from BD23 Antibody (IgG1) targeting SARS-CoV-2.

Multabody	mFcRn, pH 5.6			mFcRn, pH 7.5		
	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K _D [M]	k_{on} [M ⁻¹ × s ⁻¹]	k_{off} [s ⁻¹]	K _D [M]
IgG1 control	5.03E+05	3.86E-03	7.67E-09	—	—	No binding
WT MB	2.18E+05	<1.0E-07	<1.0E-12	—	—	No binding
LALAP MB	2.69E+05	<1.0E-07	<1.0E-12	—	—	No binding
1253A MB	2.00E+05	4.28E-04	2.15E-09	—	—	No binding
LALAP +1253A MB	4.34E+05	6.10E-04	1.41E-09	—	—	No binding

From Antibody Discovery to Ultrapotent Neutralizers

[0354] We next assessed the ability of the MB platform to transform mAb binders identified from initial phage display screens into potent neutralizers against SARS-CoV-2 (FIG. 6a). Following standard biopanning protocols against the RBD of SARS-CoV-2, 20 human mAb binders with moderate affinities that range from 10⁻⁶ to 10⁻⁸ M were selected (Table 4; Table 11). These mAbs were produced as full-length IgGs and MBs and their capacity to block viral infection was compared in a neutralization assay against SARS-CoV-2 PsV (FIG. 6b and FIG. 7a). Notably, MB expression yields, homogeneity and thermostability was similar to those of the parental IgG (FIG. 8 and Table 12) and the MB enhanced the potency of 18 out of 20 (90%) IgGs by up to four orders of magnitude (Table 13). The largest increment was observed for mAb 298 which went from a mean VK₅₀ of ~0.3 µg/mL as an IgG to 0.0001 µg/mL as a MB. Strikingly, 11 mAbs were converted from non-neutralizing IgGs to neutralizing MBs in the tested concentration ranges. Seven MBs displayed exceptional potency with IC₅₀ values between 0.2-2 ng/mL against SARS-CoV-2 PsV using two different target cells (293T-ACE2 and HeLa-ACE2 cells; FIG. 6b and FIG. 7b). PsV neutralization assays using recombinant mAbs REGN10933 and REGN10987 as benchmark showed similar IC₅₀ values (0.0044 and 0.030 µg/mL, respectively) to those previously reported⁸, and thus confirmed the extraordinary potency of the MBs observed in our assays. The enhanced neutralization potency of the MB was further confirmed with authentic SARS-CoV-2 virus for the mAbs with the highest potency (FIG. 6c and FIG. 7c), as also benchmarked with the two recombinant REGN mAbs. The less sensitive neutralization phenotype we observed

TABLE 11-continued

human mAb binders of SARS-CoV-2 RBD.			
mAb ID	VH	VK	RBD KD (nM)
108	IGHV1-46	IGKV1-39	72
128	IGHV1-46	IGKV1-39	57
160	IGHV3-23	IGKV1-39	7.7
368	IGHV1-69	IGKV2-28	nb
192	IGHV1-69	IGKV2-28	nb
158	IGHV1-46	IGKV1-39	172
180	IGHV1-69	IGKV2-28	nb
254	IGHV3-23	IGKV1-39	127
120	IGHV1-46	IGKV3-15	24
64	IGHV3-23	IGKV1-39	97
298	IGHV1-46	IGKV4-1	24
82	IGHV1-46	IGKV1-39	206
46	IGHV3-23	IGKV1-39	83
324	IGHV1-69	IGKV1-39	111
236	IGHV1-69	IGKV2-28	145
52	IGHV1-69	IGKV1-39	12
80	IGHV1-69	IGKV4-1	142

nb = binding below the limit of detection

TABLE 12

Aggregation temperature (T _{agg}) of Multabodies and related Antibodies.	
Multabody/Antibody	T _{agg} [° C.]
MB 298	73
MB 82	81
MB 46	69
MB 324	71
MB 236	71

TABLE 12-continued

Multabody/Antibody	T _{agg} [° C.]
MB 52	74
MB 80	85
IgG 298	74
IgG 82	75
IgG 46	75
IgG 324	70
IgG 236	70
IgG 52	73
IgG 80	81

TABLE 13

Multabody	Median IC ₅₀
MB 178	1.7 µg/mL (0.74 nM)
IgG 178	>50 µg/mL (>333 nM)
MB 108	0.37 µg/mL (161 pM)
IgG 108	>50 µg/mL (>333 nM)
MB 128	3.5 µg/mL (1.5 nM)
IgG 128	>50 µg/mL (>333 nM)
MB 160	0.22 µg/mL (96 pM)
IgG 160	>50 µg/mL (>333 nM)
MB 368	0.073 µg/mL (32 pM)
IgG 368	>50 µg/mL (>0333 nM)
MB 192	0.79 µg/mL (343 PM)
IgG 192	>50 µg/mL (>333 nM)
MB 158	0.10 µg/mL (43 pM)
IgG 158	>50 µg/mL (>333 nM)
MB 180	0.89 µg/mL (387 pM)
IgG 180	>50 µg/mL (>333 nM)
MB 254	9.3 µg/mL (4.0 nM)
IgG 254	>50 µg/mL (>333 nM)
MB 120	7.2 µg/mL (3.1 nM)
IgG 120	>50 µg/mL (>333 nM)
MB 64	14 µg/mL (6.1 nM)
IgG 64	>50 µg/mL (>333 nM)
MB 56	>50 µg/mL (>0.33 µM)
IgG 56	>50 µg/mL (>333 nM)
MB 349	>50 µg/mL (>0.33 µM)
IgG 349	>50 µg/mL (>333 nM)
MB 298	0.00011 µg/mL (0.048 pM)
IgG 298	0.28 µg/mL (1.9 nM)
MB 82	0.0022 µg/mL (0.95 pM)
IgG 82	1.6 µg/mL (11 nM)
MB 46	0.0024 µg/mL (1.0 pM)
IgG 46	2.1 µg/mL (14 nM)
MB 324	0.0009 µg/mL (0.39 pM)
IgG 324	0.78 µg/mL (5.2 nM)
MB 236	0.00047 µg/mL (0.20 pM)
IgG 236	0.057 µg/mL (0.38 nM)
MB 52	0.0002 µg/mL (0.087 pM)
IgG 52	0.61 µg/mL (4.1 nM)
MB 80	0.0013 µg/mL (0.56 pM)
IgG 80	0.1 µg/mL (0.67 nM)
Reference IgG (REGN 10933)	0.0044 µg/mL (29 pM)
Reference IgG (REGN 10987)	0.030 µg/mL (0.20 nM)

[0355] Retrospectively, all IgGs and MBs were tested for their ability to bind to the Spike glycoprotein and the RBD of SARS-CoV-2 (FIG. 9). Increased avidity resulted in higher apparent binding affinities with no detectable off-rates against the Spike glycoprotein, most likely due to inter-spike crosslinking that translates into high neutraliza-

tion potency (FIG. 6b-d and FIG. 9). Overall, the data show that the MB platform is compatible with rapid delivery of ultrapotent IgG-like molecules even when starting with mAbs of modest neutralization characteristics.

Epitope Mapping

[0356] Based on their neutralization potency, seven mAbs were selected for further characterization: 298 (IGHV1-46/IGKV4-1), 82 (IGHV1-46/IGKV1-39), 46 (IGHV3-23/IGKV1-39), 324 (IGHV1-69/IGKV1-39), 236 (IGHV1-69/IGKV2-28), 52 (IGHV1-69/IGKV1-39), and 80 (IGHV1-69/IGKV4-1) (FIG. 6b and Table 4). Epitope binning experiments showed that these mAbs target two main sites on the RBD, with one of these bins overlapping with the ACE2 binding site (FIG. 10a and FIG. 11). Cryo-EM structures of Fab-SARS-CoV-2 S complexes at a global resolution of ~6-7 Å confirmed that mAbs 324, 298, and 80 bind overlapping epitopes (FIG. 10b, FIG. 12a-c, and Table 2). To gain insight into the binding of mAbs targeting the other bin, we obtained the cryo-EM structure of Fab 46 in complex with the RBD at a global resolution of 4.0 Å (FIG. 10c, FIG. 12d, and Table 2), and the crystal structure of Fabs 298 and 52 as a ternary complex with the RBD at 2.95 Å resolution (FIG. 10d, FIG. 2, and Table 3).

[0357] The crystal structure shows that Fab 298 binds almost exclusively to the ACE2 receptor binding motif (RBM) of the RBD (residues 438-506). In fact, out of 16 RBD residues involved in binding Fab 298, 12 are also involved in ACE2-RBD binding (FIG. 2a-c and Table 14). The RBM is stabilized by 11 hydrogen bonds from heavy and light chain residues of Fab 298. In addition, RBM Phe486 is contacted by 11 Fab 298 residues burying ~170 Å² (24% of the total buried surface area on RBD) and hence is central to the antibody-antigen interaction (FIG. 2a and Table 14).

[0358] Detailed analysis of the RBD-52 Fab interface reveals that the epitope of mAb 52 is shifted towards the core of the RBD encompassing 20 residues of the RBM and seven residues in the core domain (FIG. 10c, FIG. 2b, and Table 14). In agreement with the competition data, antibody 52 and antibody 46 share a similar binding site, although they approach the RBD with slightly different angles (FIG. 10c, d and FIG. 2d). Inspection of previously reported structures of RBD-antibody complexes reveal that antibodies 46 and 52 target a site of vulnerability on the SARS-CoV-2 spike that has not been described previously (FIG. 10e). The epitope targeted by these antibodies is partially occluded by the NTD in the S “closed” conformation, suggesting that the mechanism of action for this class of antibodies could involve Spike destabilization. Together, these data demonstrate that the enhanced neutralization potency observed for the MB platform through avidity is associated with mAbs that can target distinct epitope bins on the RBD.

TABLE 14

RBD-298 and RBD-52 contacting residues identified by PISA			
RBD	Residue	BSA (Å ²)	Fab 298 Interaction (H—HC, K—KC)
453	Tyr	2	vdW H-Thr31, H-Ile100
455	Leu	20	vdW H-Thr31, H-Ile100
456	Phe	30	vdW H-Thr31, H-Tyr32

TABLE 14-continued

RBD-298 and RBD-52 contacting residues identified by PISA				
458	Lys	1	vdW	K-Ser27F
474	Gln	12	vdW	K-Tyr27D
	Gln ^⑦		HB	K-Tyr27D ^{OH}
475	Ala	45	vdW	K-Tyr27D, H-Tyr32, H-Arg97
	Ala ^O		HB	K-Tyr32 ^{OH}
476	Gly	23	vdW	K-Tyr27D, K-Tyr32, K-Tyr91, K-Tyr92, K-Ser93, H-Arg97
477	Ser	75	vdW	K-Tyr27D, K-Tyr92, K-Ser93, K-Thr94
	Ser ^N		HB	K-Tyr92 ^O
	Ser ^{OG}		HB	K-Tyr92 ^O
478	Thr	41	vdW	K-Tyr27D, K-Tyr92, K-Ser93, K-Thr94
	Thr ^{OG} ^⑦		HB	K-Tyr94 ^{OG} ^⑦
484	Glu	74	vdW	H-Trp50, H-Ser52, H-Ser54, H-Gly55, H-Gly56, H-Thr57, H-Asp58
	Glu ^{OE2}		HB	H-Ser54 ^{OG}
485	Gly	28	vdW	H-Trp50, H-Thr57, H-Asp58
486	Phe	169	vdW	K-Gln89, K-Tyr91, K-Ser93, K-Tyr94, K-Pro96, H-Ser35, H-Trp47, H-Trp50, H-Asp58, H-Asp95, H-Arg97
	Phe ^N		HB	H-Asp58 ^⑦
	Phe ^O		HB	K-Thr94 ^{OG} ^⑦
487	Asn	41	vdW	K-Tyr32, K-Tyr91, K-Ser93, K-Thr94, H-Asp95, H-Arg97
	Asn ^{OD1}		HB	H-Arg97 ^{NHZ}
	Asn ^{ND2}		HB	K-Tyr91 ^O , K-Tyr92 ^O
488	Cys	1	vdW	H-Trp50
489	Tyr	84	vdW	H-Ser30, H-Thr31, H-Tyr32, H-Trp50, H-Asp95, H-Srg97, H-Arg97 ^{NHZ} , H-Asp95 ^{OD2}
	Tyr ^{OH}		HB	H-Ser30, H-Thr31, H-Ile100
Total BSA (Å ²):		691		

RBD	Residue	BSA (Å ²)	Interaction	Fab 298 (H—HC, K—KC)
346	Arg	45	vdW	H-Gln64
351	Tyr	29	vdW	K-Phe94, H-Ile52, H-Thr56, H-Asn58
352	Ala	19	vdW	K-Gly93, K-Phe94
354	Asn	6	vdW	K-Phe94
355	Arg	36	vdW	K-Ser0, K-Gln27
	Arg ^O		HB	K-Ser0 ^{OG}
356	Lys	13	vdW	K-Ser0
357	Arg	66	vdW	K-Ser0, K-Gln27
	Arg ^N		HB	K-Ser0 ^{OG}
	Arg ^{NHZ}		HB	K-Gln27 ^{OE1}
449	Tyr	13	bdW	H-Phe54, H-Thr56
450	Asn	38	vdW	H-Phe54, H-Thr56
452	Leu	47	vdW	H-Ile52, H-Phe54, H-Gly55, H-Thr56
462	Lys	1	vdW	K-Ser30
465	Glu	28	vdW	K-Ser30, K-Asn31, K-Asn32, K-Asn92
	Glu ^{OE2}		HB	K-Ser30 ^{OG}
466	Arg	70	vdW	K-Asn32, K-Asn92, K-93Gly, K-Phe94
	Arg ^O		HB	K-Asn32 ^{NHZ}
	Arg ^{NH} ^⑦		HB	K-Asn92 ^O
467	Asp	12	vdW	K-Asn32, K-Asn92, H-Asp98

TABLE 14-continued

RBD-298 and RBD-52 contacting residues identified by PISA				
468	Ile	102	vdW	K-Asn32, K-Gly91, K-Asn92, K-93Gly, K-Phe94, K-Leu96, H-Arg96, H-Gly97, H-Asp98
469	Ser	37	vdW	K-Asn32, H-Arg96, H-Gly97, H-Asp98
	Ser ^{OG}		HB	H-Asp98 ^{OD1}
470	Thr	67	vdW	Hp-Ser31, H-Tyr32, H-Gly33, H-Ile52, H-Asp95, H-Arg96, H-Gly97, H-Asp98
	Thr ^{OG1}		HB	H-Gly97 ^N
471	Glu	39	vdW	H-Tyr32, H-Arg96, H-Gly97, H-Asp98
	Glu ^{OE1}		SB	H-Arg96NH3
	Glu ^{OE2}		SB	H-Arg96NH2
472	Ile	7	vdW	H-Ser31, H-Tyr32, H-Arg96
481	Asn	1	vdW	H-Tyr32
482	Gly	42	vdW	H-Ser31, H-Tyr32
	Gly ^O		HB	H-Tyr ^{OH}
483	Val	12	vdW	H-Thr28, H-Ser31, H-Tyr32
484	Glu	53	vdW	H-Thr28, H-Phe29, H-Thr30, H-Ser31, H-Met54
490	Phe	87	vdW	H-Thr30, H-Ser31, H-Tyr32, H-Gly33, H-Ile52, H-Met54, H-Phe554
Total BSA (Å ²):		904		
Fab 298	Residue-Chain	BSA (Å ²)	Interaction	RBD
30	Ser-H	9	vdW	Tyr489, Gln493
31	Thr-H	68	vdW	Tyr453, Leu455, Phe456, Tyr489, Gln493
32	Tyr-H	57	vdW	Phe456, Ala475, Tyr489
35	Ser-H	8	vdW	Phe486
47	Trp-H	23	vdW	Phe486
50	Trp-H	79	vdW	Glu484, Gly485, Phe486, Cys488, Tyr489
52	Ser-H	8	vdW	Glu484
54	Ser-H	17	vdW	Glu484
	Ser ^{OG} -H		HB	Glu484 ^{OE2}
55	Gly-H	7	vdW	Glu484
56	Gly-H	7	vdW	Glu484
57	Thr-H	10	vdW	Glu484, Gly485
58	Asp-H	28	vdW	Glu484, Gly485, Phe486
	Asp ^{OD2} -H		HB	Phe486 ^N
95	Asp-H	15	vdW	Phe486, Asn487, Tyr489
	Asp ^{OD2} -H		HB	Tyr489 ^{OE}
97	Arg-H	61	vdW	Asn487, Tyr489
	Arg ^{NHZ} -H		HB	Asn487 ^{OD1} , Tyr489 ^{OH}
100	Ile-H	7	vdW	Tyr453, Leu455, Gln493
27D	Tyr-K	59	vdW	Gln474, Ala475, Gly476, Ser477, Thr478
	Tyr ^{OH} -K		HB	Gln474 ^{NE2}
27F	Ser-K	1	vdW	Lys458
32	Tyr-K	28	vdW	Ala475, Gly476, Asn487
	Tyr ^{OB} -K		HB	Ala475 ^O
89	Gln-K	1	vdW	Phe486
91	Tyr-K	30	vdW	GLy476, Phe486, Asn487
	Tyr ^O -K		HB	Asn487 ^{ND2}
92	Tyr-K	40	vdW	Gly476, Ser477, Thr478
	Tyr ^O -K		HB	Asn487 ^{ND2}
	Tyr ^O -K		HB	Ser477 ^N , Ser477 ^{OG}

TABLE 14-continued

RBD-298 and RBD-52 contacting residues identified by PISA				
93	Ser-K	26	vdW	Gly476, Ser477, Thr478, Phe486, Ser487
94	Thr-K	57	vdW	Ser477, Thr478, Phe486, Asn487
	Thr ^{OG1} -K		HB	Thr478 ^{OG1} , Phe486 ^O
96	Pro-K	23	vdW	Phe486
Total BSA (Å ²):				669
Fab 52	Residue-Chain	BSA (Å ²)	Interaction	RBD
28	Thr-H	24	vdW	Val483, Glu484
30	Thr-H	3	vdW	Glu484, Phe490
31	Ser-H	66	vdW	Glu471, Gly482, Val483, Glu484, Phe490
32	Tyr-H	51	vdW	Thr470, Glu471, Ile472, Asn481, Gly482, Val483, Phe490
	Tyr ^{OH} -H		HB	Gly482 ^O
33	Gly-H	7	vdW	Thr470, Phe490
52	Ile-H	62	vdW	Tyr351, Leu452, Thr470, Phe490, Leu492
53	Met-H	38	vdW	Glu484, Phe490, Leu492
54	Phe-H	110	vdW	Tyr449, Asn450, Leu452, Phe490, Leu492, Gln493, Ser494
55	Gly-H	4	vdW	Leu452
56	Thr-H	57	vdW	Tyr351, Tyr449, Asn450, Leu452
58	Asn-H	10	vdW	Tyr351
64	Gln-H	43	vdW	Arg346
95	Asp-H	2	vdW	Thr470
96	Arg-H	64	vdW	Ile468, Ser469, Thr470, Glu471, Ile472
	Arg ^{NHD} -H		SB	Glu471 ^{OE1} , Glu471 ^{OE2}
97	Gly-H	64	vdW	Ile468, Ser469, Thr470, Glu471
	Gly ^N -H		HB	Thr70 ^{OG1}
98	Asp-H	28	vdW	Asp467, Ile468, Ser469, Thr470, Glu471
	Asp ^{OD1} -H		HB	Ser469 ^{OG}
0	Ser-K	77	vdW	Arg355, Lys356, Arg357
	Ser ^{OG} -K		HB	Arg355 ^O , Arg357 ^N
27	Gln-H	60	vdW	Arg355, Arg357
	Gln ^{OE3} -K		HB	Arg357 ^{NHZ}
30	Ser-K	28	vdW	Lys462, Glu465
	Ser ^{OG} -K		HB	Glu465 ^{OE2}
32	Asn-K	19	vdW	Glu465, Arg466, Asp467, Ile468, Ser469
	Asn ^{ND2} -K		HB	Arg466 ^O
91	Gly-K	18	vdW	Ile468
92	Asn-K	56	vdW	Glu465, Arg466, Asp467, Ile468
	Asn-O-K		HB	Arg466NH1
93	Gly-K	22	vdW	Ala352, Arg466, Ile468
94	Phe-K	56	vdW	Tyr351, Ala352, Asn354, Arg466, Ile468
96	Leu-K	5	vdW	Ile468
Total BSA (Å ²):				974

vdW: van der Waals interaction (5.0 Å cut-off)

HB: hydrogen bond (3.8 Å cut-off)

SB: salt bridge (4.0 Å cut-off)

② indicates text missing or illegible when filed

Multabodies Overcome Spike Sequence Variability

[0359] To explore whether MBs could potentially resist viral escape via their enhanced binding avidity, we tested the

effect of four naturally occurring RBD mutations³⁵ on the binding and neutralization of the seven human mAbs of highest potency: L452R—located within the epitope of antibodies 46 and 52 (bin 1), A475V and V483A—located within the ACE2 binding site (bin 2), and the circulating RBD variant N439K³⁶ (FIG. 13a-c). In addition, the impact of mutating Asn234—an N-linked glycosylation site—to Gln was also assessed because the absence of glycosylation at this site has been previously reported to decrease sensitivity to neutralizing antibodies targeting the RBD³⁵. The more infectious PsV variant D614G³⁷ was also included in the panel. As expected, mutation L452R significantly decreased binding and potency of mAbs 52 and 46, while antibody 298 was sensitive to mutation A475V (FIG. 13b, c). Deletion of the N-linked glycan at position Asn234 increased viral resistance to the majority of the antibodies, especially mAbs 46, 80, and 324, emphasizing the importance of glycans in viral antigenicity (FIG. 13c). Strikingly, the following antibody specificities in the MB format were minimally impacted in their exceptional neutralization potency by any S mutation: 298, 80, 324, and 236 (FIG. 13d). Mutation L452R decreased the sensitivity of the 46-MB and 52-MB but in contrast to their parental IgGs, they remained neutralizing against this PsV variant (FIG. 13d). The more infectious SARS-CoV-2 PsV variant D614G was neutralized with similar potency as the WT PsV for both IgGs and MBs (FIG. 13c and FIG. 14a).

[0360] MB cocktails consisting of three monospecific MBs resulted in pan-neutralization across all PsV variants without a significant loss in potency and hence achieved a 100-1000-fold higher potency compared to the corresponding IgG cocktails (FIG. 13e and FIG. 14c, d). In order to achieve breadth within a single molecule, we next generated tri-specific MBs by combining multimerization subunits displaying three different Fabs in the same MB assembly (FIG. 14b). Notably, the resulting tri-specific MBs exhibited pan-neutralization while preserving the exceptional neutralization potency of the monospecific versions including against the B.1.351 PsV variant (FIG. 13e, f and FIG. 14c, d). The highest potency was observed for the 298-324-46 combination (FIG. 14c, e), where the tri-specific MB achieved exceptional potency beyond that observed for some of the most potent IgGs reported to date and that we generated recombinantly from available sequences (FIG. 13g). In addition, the MB format was able to increase the potency of these previously reported highly potent IgGs by a further one to two orders of magnitude against PsV and live replicating SARS-CoV-2 virus (FIG. 13h), thus highlighting the plug-and-play nature of the MB and the ability of multivalency to enhance the neutralization capacity of mAbs across a range of potencies.

[0361] The values determined for median IC₅₀ of neutralization are summarized in Table 13 and Table 15.

TABLE 15

SARS-CoV-2 Neutralization by Multabodies	
Multabody	Median IC ₅₀
VHH-hFerr	0.00011 µg/mL (0.13 pM)
VHH-Fc	1.3 µg/mL (16 nM)
BD23 MB	0.008 µg/mL (3.5 pM)

TABLE 15-continued

SARS-CoV-2 Neutralization by Multabodies	
Multobody	Median IC ₅₀
BD23 IgG	13 µg/mL (87 nM)
4A8 MB	0.052 µg/mL (23 pM)
4A8 IgG	>100 g/mL (> 0.66 µM)

Discussion

[0362] In this study, we reveal how binding avidity can be leveraged as an effective mechanism to propel antibody neutralization potency and resistance from viral mutations. To this effect, we used protein engineering to develop a plug-and-play antibody-multimerization platform that increases avidity of mAbs targeting SARS-CoV-2. The seven most potent MBs have IC₅₀ values of 0.2 to 2 ng/mL (9×10⁻¹⁴ to 9×10⁻¹³ M) against SARS-CoV-2 PsVs and therefore are, to our knowledge, within the most potent antibody-like molecules reported to date against SARS-CoV-2.

[0363] The MB platform was designed to include key favorable attributes from a developability perspective. First, the ability to augment antibody potency is independent of antibody sequence, format or epitope targeted. The modularity and flexibility of the platform was exemplified by enhancing the potency of a VHH and multiple Fabs that target non-overlapping regions on two SARS-CoV-2 S sub-domains (RBD and NTD). Using the MB to enhance the potency of VHH domains could provide particular value to this class of molecules since its small size allows highly efficient multimerization. Second, in contrast to other approaches that enhance avidity through tandem fusions of single chain variable fragments^{38,39}, MBs do not suffer from low stability and in fact self-assemble into highly stable particles with aggregation temperatures similar to those of their parental IgGs. Third, alternative multimerization strategies like streptavidin⁴⁰, verotoxin B subunit scaffolds⁴¹, or viral-like nanoparticles⁴² face immunogenicity challenges and/or poor bioavailability because of the absence of a Fc fragment and therefore the inability to undergo FcRn-mediated recycling. The light chain of apoferritin is fully human, biologically inactive, has been engineered to include Fc domains, and despite multimerization of >24 Fab/Fc fragments, has a Rh similar to an IgM. As such, a surrogate mouse MB did not elicit antidrug antibodies in mice and similar to its parental IgG was detectable in the sera for over a week. However, in vivo bioavailability of the MB was dependent on its binding affinity to FcγRs, suggesting that Fc avidity will need to be carefully fine-tuned for efficient translation of the MB to the clinic. In addition, further studies will be needed to evaluate how the MB distributes at anatomical sites of interest, such as the lungs in the case of SARS-CoV-2 infection. The plug-and-play nature of the Multabody also lends itself to exploring alternate half-life extending moieties other than the Fc if bioavailability is the only desired trait absent of effector functions e.g., human serum albumin⁴³, or binding moieties that bind human serum albumin^{44,45}.

[0364] Different increases in neutralization potency were observed for different mAb sequences tested on the MB against SARS-CoV-2. This suggests that the ability of the MB to enhance potency may depend on epitope location on

the Spike, or the geometry of how the Fabs engage the antigen to achieve neutralization. The fact that the neutralization of two out of 20 SARS-CoV-2 RBD binders were not rescued by the MB platform suggests limitations based on mAb sequences and binding properties alone. Nevertheless, the capacity of the MB to transform avidity into neutralization potency across a range of epitope specificities on the SARS-CoV-2 Spike highlights the potential for using this technology broadly. It will be interesting to explore the potency-enhancement capacity of the MB platform against viruses with low surface spike density like HIV-1⁴⁶, or against other targets like the tumor necrosis factor receptor superfamily, where bivalency of conventional antibodies limits their efficient activation⁴⁷.

[0365] Virus escape can arise in response to selective pressure from treatments or during natural selection. A conventional approach to combat escape mutants is the use of antibody cocktails targeting different epitopes. MBs showed a lower susceptibility to S mutations in comparison to their parental IgGs, presumably because the loss in affinity was compensated by enhanced binding avidity. Hence, when used in cocktails, the MB overcame viral sequence variability with exceptional potency. In addition, the split MB design allows combination of multiple antibody specificities within a single multimerized molecule resulting in similar potency and breadth as the MB cocktails. Importantly, the B.1.351 variant of concern that can escape the neutralization of several mAbs^{21,22,23} is neutralized with high potency by a tri-specific Multabody, thus further highlighting the capacity of these molecules to resist viral escape. Multi-specificity within the same particle could offer additional advantages such as intra-S avidity and synergy for the right combination of mAbs, setting the stage for further investigation of different combinations of mAb specificities on the MB. Avidity and multi-specificity could also be leveraged to deliver a single molecule that neutralizes potently across viral genera, such as betacoronaviruses.

[0366] Overall, the MB platform provides a tool to surpass antibody affinity limits and generate broad and potent neutralizing molecules while by-passing extensive antibody discovery or engineering efforts. This platform is an example of how binding avidity can be leveraged to accelerate the timeline to discovery of the most potent biologics against infectious diseases of global health importance.

REFERENCES

- [0367] 1. Connor, E. M. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 102, 531-537 (1998).
- [0368] 2. Mulangu, S. et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N. Engl. J. Med.* 381, 2293-2303 (2019).
- [0369] 3. Ju, B. et al. Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature* 584, 115-119 (2020).
- [0370] 4. Liu, L. et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. *Nature* 584, 450-456 (2020).
- [0371] 5. Wang, C. et al. A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat. Commun.* 11, 2251 (2020).

- [0372] 6. Zost, S. J. et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. *Nature* 584, 443-449 (2020).
- [0373] 7. Baum, A. et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science* 369, 1014-1018 (2020).
- [0374] 8. Hansen, J. et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* 369, 1010-1014 (2020).
- [0375] 9. Lv, Z. et al. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. *Science* 369, 1505-1509 (2020).
- [0376] 10. Tortorici, M. A. et al. Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms. *Science* 370, 950-957 (2020).
- [0377] 11. Zhou, D. et al. Structural basis for the neutralization of SARS-CoV-2 by an antibody from a convalescent patient. *Nat. Struct. Mol. Biol.* 27, 950-958 (2020).
- [0378] 12. Cao, Y. et al. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. *Cell* 182, 73-84 (2020).
- [0379] 13. Chi, X. et al. A neutralizing human antibody binds to the N-terminal domain of the Spike protein of SARS-CoV-2. *Science* 369, 650-655 (2020).
- [0380] 14. Seydoux, E. et al. Analysis of a SARS-CoV-2-infected individual reveals development of potent neutralizing antibodies with limited somatic mutation. *Immunity* 53, 98-105 (2020).
- [0381] 15. Pinto, D. et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature* 583, 290-295 (2020).
- [0382] 16. Barnes, C. O. et al. Structures of human antibodies bound to SARS-CoV-2 spike reveal common epitopes and recurrent features of antibodies. *Cell* 182, 828-842.e16 (2020).
- [0383] 17. Shi, R. et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. *Nature* 584, 120-124 (2020).
- [0384] 18. Rogers, T. F. et al. Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model. *Science* 369, 956-963 (2020).
- [0385] 19. Brouwer, P. J. M. et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. *Science* 369, 643-650 (2020).
- [0386] 20. Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 181, 271-280 (2020).
- [0387] 21. Wang, P. et al. Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization. *Cell Host Microbe*. 29, 747-751.e4 (2021).
- [0388] 22. Wu, K. et al. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. Preprint at *bioRxiv* (2021).
- [0389] 23. Wibmer, C. K. et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nat. Med.* 27, 622-625 (2021).
- [0390] 24. Rambaut, A. et al. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. Preprint at <https://virological.org/t/preliminarygenomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-ofspike-mutations/563> (2020).
- [0391] 25. Tegally, H. et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. Preprint at *medRxiv* <https://doi.org/10.1101/2020.12.21.20248640> (2020).
- [0392] 26. Faria, N. R. et al. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. *Science* 372, 815-821 (2021).
- [0393] 27. Naveca, F. et al. Phylogenetic relationship of SARS-CoV-2 sequences from Amazonas with emerging Brazilian variants harboring mutations E484K and N501Y in the spike protein. Preprint at <https://virological.org/t/phylogenetic-relationship-of-sars-cov-2-sequences-from-amazonas-with-emerging-brazilian-variants-harboring-mutations-e484k-and-n501y-in-the-spoke-protein/585> (2021).
- [0394] 28. Wu, H. et al. Ultra-potent antibodies against respiratory syncytial virus: effects of binding kinetics and binding valence on viral neutralization. *J. Mol. Biol.* 350, 126-144 (2005).
- [0395] 29. Icenogle, J. et al. Neutralization of poliovirus by a monoclonal antibody: kinetics and stoichiometry. *Virology* 127, 412-425 (1983).
- [0396] 30. Cavacini, L. A., Emes, C. L., Power, J., Duval, M. & Posner, M. R. Effect of antibody valency on interaction with cell-surface expressed HIV-1 and viral neutralization. *J. Immunol.* 152, 2538-2545 (1994).
- [0397] 31. Wrapp, D. et al. Structural basis for potent neutralization of betacoronaviruses by single-domain camelid antibodies. *Cell* 181, 1004-1015.e15 (2020).
- [0398] 32. Li, W. et al. High potency of a bivalent human VH domain in SARS-CoV-2 animal models. *Cell* 183, 1-13 (2020).
- [0399] 33. Lawson, D. M. et al. Solving the structure of human H ferritin by genetically engineering intermolecular crystal contacts. *Nature* 349, 541-544 (1991).
- [0400] 34. Radomsky, M. L., Whaley, K. J., Cone, R. A. & Saltzman, W. M. Macromolecules released from polymers: diffusion into unstirred fluids. *Biomaterials* 11, 619-624 (1990).
- [0401] 35. Li, Q. et al. The impact of mutations in SARS-CoV-2 spike on viral infectivity and antigenicity. *Cell* 182, 1284-1294 (2020).
- [0402] 36. Thomson, E. C. et al. Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity. *Cell*. 185, 1171-1187.e20 (2021).
- [0403] 37. Korber, B. et al. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. *Cell* 182, 812-827 (2020).
- [0404] 38. Miller, K. et al. Design, construction, and in vitro analyses of multivalent antibodies. *J. Immunol.* 170, 4854-4861 (2003).
- [0405] 39. Kipriyanov, S. M. et al. Bispecific tandem diabody for tumor therapy with improved antigen binding and pharmacokinetics. *J. Mol. Biol.* 293, 41-56 (1999).
- [0406] 40. Kipriyanov, S. M. et al. Affinity enhancement of a recombinant antibody: formation of complexes with multiple valency by a single-chain Fv fragment-core streptavidin fusion. *Protein Eng.* 9, 203-211 (1996).
- [0407] 41. Zhang, J. et al. Pentamerization of single-domain antibodies from phage libraries: a novel strategy

- for the rapid generation of high-avidity antibody reagents. *J. Mol. Biol.* 335, 49-56 (2004).
- [0408] 42. Hoffmann, M. A. G. et al. Nanoparticles presenting clusters of CD4 expose a universal vulnerability of HIV-1 by mimicking target cells. *Proc. —Natl Acad. Sci. USA* 117, 18719-18728 (2020).
- [0409] 43. Sleep, D., Cameron, J. & Evans, L. R. Albumin as a versatile platform for drug half-life extension. *Biochim. Biophys. Acta* 1830, 5526-5534 (2013).
- [0410] 44. van Faassen, H. et al. Serum albumin-binding VHJs with variable pH sensitivities enable tailored half-life extension of biologics. *FASEB J.* 34, 8155-8171 (2020).
- [0411] 45. Adams, R. et al. Extending the half-life of a fab fragment through generation of a humanized anti-human serum albumin Fv domain: an investigation into the correlation between affinity and serum half-life. *MAbs* 8, 1336-1346 (2016).
- [0412] 46. Zhu, P. et al. Electron tomography analysis of envelope glycoprotein trimers on HIV and simian immunodeficiency virus virions. *Proc. Natl Acad. Sci. USA* 100, 15812-15817 (2003).
- [0413] 47. Wajant, H. Principles of antibody-mediated TNF receptor activation. *Cell Death Differ.* 22, 1727-1741 (2015).
- [0414] 48. Schlothauer, T. et al. Novel human IgG1 and IgG4 Fc-engineered antibodies with completely abolished immune effector functions. *Protein Eng. Des. Sel.* 29, 457-466 (2016).
- [0415] 49. Crawford, K. H. D. et al. Protocol and reagents for pseudotyping lentiviral particles with SARS-CoV-2 spike protein for neutralization assays. *Viruses* 12, 513 (2020).
- [0416] 50. Banerjee, A. et al. Isolation, sequence, infectivity, and replication kinetics of severe acute respiratory syndrome coronavirus 2. *Emerg. Infect. Dis.* 26, 2054-2063 (2020).
- [0417] 51. Marr, C. R., Benlekbir, S. & Rubinstein, J. L. Fabrication of carbon films with ~500 nm holes for cryo-EM with a direct detector device. *J. Struct. Biol.* 185, 42-47 (2014).
- [0418] 52. Punjani, A., Rubinstein, J. L., Fleet, D. J. & Brubaker, M. A. CryoSPARC: algorithms for rapid unsupervised cryo-EM structure determination. *Nat. Methods* 14, 290-296 (2017).
- [0419] 53. Zi Tan, Y. et al. Addressing preferred specimen orientation in single-particle cryo-EM through tilting. *Nat. Methods* 14, 793-796 (2017).
- [0420] 54. Zivanov, J. et al. New tools for automated high-resolution cryo-EM structure determination in RELION-3. *Elife* 9, e42166 (2018).
- [0421] 55. Scheres, S. H. W. RELION: implementation of a Bayesian approach to cryo-EM structure determination. *J. Struct. Biol.* 180, 519-530 (2012).
- [0422] 56. Punjani, A. & Fleet, D. J. 3D variability analysis: Resolving continuous flexibility and discrete heterogeneity from single particle cryo-EM. *J. Struct. Biol.* 213, 107702 (2021).
- [0423] 57. Punjani, A., Zhang, H. & Fleet, D. J. Non-uniform refinement: adaptive regularization improves single-particle cryo-EM reconstruction. *Nat. Methods.* 17, 1214-1221 (2020).
- [0424] 58. Grant, T., Rohou, A. & Grigorieff, N. CisTEM, user-friendly software for single-particle image processing. *Elife* 7, e35383 (2018).
- [0425] 59. Asarnow, D., Palovcak, E. & Cheng, Y. asarnow/pyem: UCSF pyem v0. 5 (Zenodo, 2019).
- [0426] 60. Kabsch, W. et al. XDS. *Acta Crystallogr. D Biol. Crystallogr.* 66, 125-132 (2010).
- [0427] 61. McCoy, A. J. et al. Phaser crystallographic software. *J. Appl. Crystallogr.* 40, 658-674 (2007).
- [0428] 62. Adams, P. D. et al. PHENIX: a comprehensive Python-based system for macromolecular structure solution. *Acta Crystallogr. D Biol. Crystallogr.* 66, 213-221 (2010).
- [0429] 63. Emsley, P., Lohkamp, B., Scott, W. G. & Cowtan, K. Features and development of Coot. *Acta Crystallogr. Sect. D Biol. Crystallogr.* 66, 486-501 (2010).
- [0430] 64. The PyMol Molecular Graphics System, Versión 1.8 (Schrödinger, LLC., 2015).
- [0431] 65. Morin, A. et al. Collaboration gets the most out of software. *Elife* 2, e01456 (2013).
- [0432] 66. Lan, J. et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature* 581, 215-220 (2020).
- [0433] 67. Yuan, M. et al. A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV. *Science* 368, 630-633 (2020).
- [0434] 68. Piccoli, L. et al. Mapping neutralizing and immunodominant sites on the SARS-CoV-2 spike receptor-binding domain by structure-guided high-resolution serology. *Cell* 183, 1024-1042.e21 (2020).
- [0435] 69. Hurlburt, N. K. et al. Structural basis for potent neutralization of SARS-CoV-2 and role of antibody affinity maturation. *Nat. Commun.* 11, 5413 (2020).
- [0436] 70. Barnes, C. O. et al. SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies. *Nature* 588, 682-687 (2020).
- [0437] 71. Yuan, M. et al. Structural basis of a shared antibody response to SARS-CoV-2. *Science* 369, 1119-1123 (2020).
- [0438] 72. Hansen, J. et al. Studies in humanized mice and convalescent humans yield a SARS-CoV-2 antibody cocktail. *Science* 369, 1010-1014 (2020).

Example 2

Virus Production and Pseudovirus Neutralization Assays

- [0439] SARS-CoV-2 pseudotyped viruses (PsV) were generated using an HIV-based lentiviral system as previously described⁴⁴ with few modifications. Briefly, 293T cells were co-transfected with a lentiviral backbone encoding the luciferase reporter gene (BEI NR52516), a plasmid expressing the Spike (BEI NR52310) and plasmids encoding the HIV structural and regulatory proteins Tat (BEI NR52518), Gag-pol (BEI NR52517) and Rev (BEI NR52519). 24 h post transfection at 37° C., 5 mM sodium butyrate was added to the media and the cells were incubated for an additional 24-30 h at 30° C. PsV mutants were generated using the KOD-Plus mutagenesis kit (Toyobo, Osaka, Japan). SARS-CoV-2 spike variants of concern B.1.117, B.1.351, P.1 and B.1.617.2 were kindly provided by David Ho (Columbia). Neutralization was determined in a single-cycle neutralization assay using 293T-ACE2 cells (BEI NR52511). PsV neutralization was monitored by adding Britelite plus reagent (PerkinElmer) to the cells and measuring lumines-

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SKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGGGGGGGGGGGGGGGGGGGGGSEVQLVESGAEVKKPGASVKVS
CKVSGYTLTELSMHWRQAPGKGLEWMGGFDPEGETMYAQKFQGRVTMTEDTSTDTAYMEL
SSLRSEDTAVYYCATSTAVAGTPDLDFYFPEPVTVWSNGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TSGGTAALGCLVDYFPEPVTVWSNGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCGGGGGGGGGGGGGGGGGGGGGGGGGGGSS**QQIRQNYSTD**
VEAAVNSLVNLQASYTYLSLGFYFDRDDVALEGVSHFFRELAEKREGYERLLKMQNQRG
GRALFQDIKKPAEDEWGKTPDAMKAAMALEKEKKLNQALLDLHALGSARTDPHLCDFLETHFLD
EVKLIKKMDHLTLHRLGGPEAGLGEYLFERLTLRHD

V_K for 4A8

SEQ ID NO:17
EIVMTQSPLSSPVTLGQPAISCRSSQSLVHSDGNTYLSWLQQRPGQPPRLLIYKISNRFSG
VPDRFSGSGAGTDFTLKISRVEAEDVGVYYCTQATQFPYTFGQGTVDIK

V_H for 4A8

SEQ ID NO:18
EVQLVESGAEVKKPGASVKVCKVSGYTLTELSMHWRQAPGKGLEWMGGFDPEGETMYAQ
KFQGRVTMTEDTSTDTAYMELSSLRSEDTAVYYCATSTAVAGTPDLDFYFPEPVTV
WSS

4A8-scFab C hFerritinLC

(Underlining indicates linker sequence; bolding indicates
C_hFerritinLC)
SEQ ID NO:19

EIVMTQSPLSSPVTLGQPAISCRSSQSLVHSDGNTYLSWLQQRPGQPPRLLIYKISNRFSG
VPDRFSGSGAGTDFTLKISRVEAEDVGVYYCTQATQFPYTFGQGTVDIKRTVAAPSVFIFP
PSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGGGGGGGGGGGGGGGGGGGGGGGGGGGSEVQLVESGAEVKKPGASVKVS
CKVSGYTLTELSMHWRQAPGKGLEWMGGFDPEGETMYAQKFQGRVTMTEDTSTDTAYMEL
SSLRSEDTAVYYCATSTAVAGTPDLDFYFPEPVTVWSNGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TSGGTAALGCLVDYFPEPVTVWSNGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQ
TYICNVNHKPSNTKVDKKVEPKSCGGGGGGGGGGGGGGGGGGGGGGGGGGGKTPDAMKAAM
ALEKKLNQALLDLHALGSARTDPHLCDFLETHFLDEEVKLIKKMDHLTLHRLGGPEAGL
G
EYLFERLTLRHD

mFerritin

SEQ ID NO:20
MTSQIRQNYSTEVEAANRLVLNHLRASYTYLSLGFFFFDRDDVALEGVGHFFRELAEKREG
AERLLEFQNDRGGRALPQDVQKPSQDEWGKTQEAMEAALAMEKLNQALLDLHALGSARTDP
HLCDFFLESHYLDKEVKLIKKMGNHLTNLRRVAGPQPAQTGAPQGSLGEYLFERLTLKH

HD37-scIgG

(underlining indicates linker sequence)
SEQ ID NO:21
DILLTQTPASLAVSLQRATISCKASQSVDYDGDSYLNWYQQIPGQPPKLLIYDASNLVSGI
PPRFSGSGSGTDFTLNIHPVEKDAATYHCQQSTEDPWTFGGTKLEIKRADAAPTVSIUFFF
SSEQLTSGGASVVCFLNNFYPUDKINVWKIDGSERQNGVLNUSTWDQDSKDSTYSMSSTLTL
KDEYERHNSYTCEATHKTSTSPIVKSFNRNECGGSSGSGSGTGTSSSGTGTSAGTTGTSAS
TSGSGSGGGGGGGGGGGAGGTATAGASSGSGSSGSSSSGGTGQVQLQQSGAELVRPGSSV

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KISCKASGYAFSSYWMNWVKQRPGQGLEWIGQIWPGDGTNTYNGFKGKATLTADESSSTAY
MQLSSLASEDSAVYFCARRETTVGRYYAMDYWGQGTSVTSSQSFPNVPLVSCESPS
DKNLVAMGCLARDFLPSTISFTWNQNNTTEVIQGIRTFPTLRTGGKYLATSQVLLSPKSILE
GSDEYLVCKIHGGKNRDLHVPIPSKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISSPI
VTCVVVDVSEDDPDVQISWFVNNEVHTAQTQTHREDYNSTLRVVSALPIQHODWMMSGKEFK
CKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEMTKQVTLTCMVTDMPEDIYVWT
NNKGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNNWVERNSYCSVVHEGLHNHHTTKSFURT
PGK

(underlining indicates linker sequence; bolding indicates mFerritin)

SEQ ID NO:22

KPCPPCKCPAPNLLGGPSV**F**IFPPPKIKDVLMI**L**SPIVTCVVVDVSEDDPDVQISWFVNNE
VHTAQ**T**QTHREDYNSTLRVVSALPI**Q**HQDWMSG**K**EFKCKVNNKDL**P**API**E**RTISKPKGSVRA
PQVYVLPPPEEEMKKQVTLTCMVTDFMPED**I**Y**V**EWTNNGKTELNYKNTEPVLDSDGSYPMY
SKLRVEKKNNVERNSYSCSVVHEGLHNHHTTKSFSRTPGKGSSGSGSGSTGTSSSGTGTSA
GTTGTSASTSGSGSGGGGGSGGGGSAGGTATAGASSGSGSSGSSSSGGT**G**KPCPPCKCPAPN
LLGGPSV**F**IFPPKIKDVLMI**L**SPIVTCVVVDVSEDDPDVQISWFVNNEVHTAQ**T**QTHRED
YNSTLRVVSALPI**Q**HQDWMSG**K**EFKCKVNNKDL**P**API**E**RTISKPKGSVRA**P**QVYVLPPPEEE
MTKKQVTLTCMVTDFMPED**I**Y**V**EWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNNVWE
RNSYSCSVVHEGLHNHHTTKSFSRTPGKSRASTASSASSGGGGGSGGGSGMS**T**QS**I**RQ
NYSTEVEAAVNRLVNLHLRASYTYL**S**LGFFDRDDVALEGVGHF**R**ELAEKREGA**E**RL**L**LE
QNDRGGRALFQDVQKPSQDEWGKTQEAMEAALAMEKNLNQALLDLHALGSARTDPHLCDFLE
SHYLDKEVKLI**K**MGNHNLTRRVAGPQPAQTGAPQGSLGEYL**F**ERLT**L**KHD

scFc-N-hFerr LALAP I253A
(Underlining indicates linker sequence; bolding indicates hFerritinLC; boxes indicate residues that are mutated relative to wild type IgG1 Fc)

- continued

wild type human IgG1 Fc

SEQ ID NO:24

DKTHTCPPCPAPELLGGPSVFLPPKPDTLMISRTPEVTCVVVDVSHDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLLTCLVKGFYPSDIAVEWESNGOPENNYKTPPVLDSDGSFFL
YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Antibody 56 light chain

SEQ ID NO:25

DIQMTQSPSSLSASVGDRVTITCRASQGISSYLAWYQQKPGKAPKLLIYDASNLQSGVPSRF
SGSGSGTDFTLTISLQPEDFATYYCQQANSFPSTPGQGTTKVEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKADY
EHKVYACEVTHQGLSSPVTKSFNRGEC

Antibody 56 heavy chain

SEQ ID NO:26

QVQLVQSGAEVKKPGASVKVKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQ
KLQGRVTMTRDTSTVYMELSSLRSEDTAVYYCARDIGPIDIYWGQGTLVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVWNMGALTSVHFTPAVLQSSGLYSLSSWVT
VPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

Antibody 349 light chain

SEQ ID NO:27

DIQMTQSPSSLSASVGDRVTITCRASQSISSWLAWYQQKPGKAPKLLIYDTSNLETGVPSRF
SGSGSGTDFTLTISLQPEDFATYYCQQSYTTPWTFGQGTRLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKADY
EHKVYACEVTHQGLSSPVTKSFNRGEC

Antibody 349 heavy chain

SEQ ID NO:28

EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSGISSAGSITNYAD
SVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAGNHAGTTVTS EYFQHWGQGTLVTVSSA
STKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVWNMGALTSVHFTPAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

Antibody 178 light chain

SEQ ID NO:29

EIVMTQSPATLSVSPGERATLSCAKASQSVSGTLYAWYQQKPGQAPRLLIYGA STRATGIPAR
FSGSGSGTEFTLTISLQSEDFAVYYCLQTHSYPPTFGQGTTKVEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKAD
YEHKVYACEVTHQGLSSPVTKSFNRGEC

Antibody 178 heavy chain

SEQ ID NO:30

QVQLVQSGAEVKKPGASVKVKASGYTFTDYHMHWVRQAPGQGLEWMGWINPNSGGTNYAQ
KFQGRVTMTRDTSTVYMELSSLRSEDTAVYYCARDI SSWYEITKFDPWGQGTLVTVSSAS
TKGPSVFP LAPSSKSTSGGTAALGCLVKDYFPEPVTVWNMGALTSVHFTPAVLQSSGLY
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC

- continued

Antibody 108 light chain

SEQ ID NO:31

```
DIQMTQSPSSLSASVGDRVTITCRASQVITNNLAWYQQKPGKAPKLLIYDASTLETGVPSRF
SGSGSGTDFLTISLQPEDFATYYCQQSYTFPYTFQGQGTKEIKRTVAAPSVDIFPPSDEQ
LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKADY
EIKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 108 heavy chain

SEQ ID NO:32

```
QVQLVQSGAEVKPGASVKVKASGYIFSRYAIHWVRQAPGQGLEWMGMNPISGNTDYAP
NFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAKDGSQLAYLVEYFQHWGQGTLTVSSA
STKGPSVPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAAVLQSSGLY
SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
```

Antibody 128 light chain

SEQ ID NO:33

```
DIQMTQSPSSLSASVGDRVTITCRASQNISRYLNWYQQKPGKAPKLLIYDASNLETGVPSRF
SGSGSGTDFLTISLQPEDFATYYCQQANGFPPTFGQGTKEIKRTVAAPSVDIFPPSDEQ
LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKADY
EIKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 128 heavy chain

SEQ ID NO:34

```
QVQLVQSGAEVKPGASVKVKASGYTFTHYYMHWVRQAPGQGLEWMGIINPSSSSASYSQ
KFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDGRYGSGSYPFDYWQGTLTVSSAS
TKGPSVPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAAVLQSSGLYS
LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
```

Antibody 160 light chain

SEQ ID NO:35

```
DIQMTQSPSSLSASVGDRVTITCRASQSVSSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRF
SGSGSGTDFLTISLQPEDFATYYCQQGYTPYTFQGQGTKEIKRTVAAPSVDIFPPSDEQ
LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTTLSKADY
EIKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 160 heavy chain

SEQ ID NO:36

```
QVQLVQSGAEVKPGASVKVKASGYTFTGHDMHWVRQAPGQGLEWMGIINPSGGSTSQAQ
KFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARANSLRYYYGMDVWGQGTMVTVSSAST
KGPSVPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSWNSGALTSGVHTFPAAVLQSSGLYSL
SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC
```

Antibody 368 light chain

SEQ ID NO:37

```
DIVMTQSPSLPVTPGEPAS1CRSSQSLLHNGNYLDWYLQKPGQSPQLLIYLGSNRASG
VPDRFSGSGSGTDFTLKISRVEADVGVYYCMQALQTPATFPGPTKVDIKRTVAAPSVDIFP
PSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 368 heavy chain

SEQ ID NO:38

```
QVQLVQSGAEVKPGSSVKVKASGYTFTSYDINWVRQAPGQGLEWMGAIMPMFGTANYAQ
KFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARGSSGYYYGWGQGTLTVSSASTKGPS
```

- continued

VFP LAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFP A VLQSSGLYSL SVVS

TVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSC

Antibody 192 light chain

SEQ ID NO:39

DIVMTQSPLSLPVTPGEPASISCRSSQSLHSNGNYLDWYLQKPGQSPQLLIYAASSLQSG

V PDR FSGSGSGTDF TLKISR VEA DVGVYYCMQALQTPYTF QG T KLEIKRTVAAPSVFIFP

PSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTL

SKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC

Antibody 192 heavy chain

SEQ ID NO:40

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAI SWVRQAPGQGLEWMGWINPNSSGANYAQ

KFQGRVTITADESTSTAYMELSSLRSEDTAVYYCSTYYDSSGYSTDYWGQGTLTVSSA ST

KGPSPVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFP A VLQSSGLYSL

SSWTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSC

Antibody 158 light chain

SEQ ID NO:41

DIQMTQSPSSLSASVGDRVTITCRASQSI SRYLNWYQQKPGKAPKLLIYDASNLESGVPSRF

SGSGSGTDF TLTISSLQPEDFATYYCQ QANSFPLTFGGGTKV DIKRTVAAPSVFIFPPSDEQ

LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLKADY

EKH KVYACEVTHQGLSSPVTKSFNR GEC

Antibody 158 heavy chain

SEQ ID NO:42

QVQLVQSGAEVKKPGASVKVSCKASGYTFTGYYMH WVRQAPGQGLEWMGWINPLNGGTNFAP

KFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARDPGGSYSNDAFDI WGQGTLTVSSA S

TKGPSPVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFP A VLQSSGLYS

LSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSC

Antibody 180 light chain

SEQ ID NO:43

DIQMTQSPSSLSASVGDRVTITCRASQSI SRYLNWYQQKPGKAPKLLIYDASNLESGVPSRF

V PDR FSGSGSGTDF TLKISR VEA DVGVYYCQYYSPYTF QG T KLEIKRTVAAPSVFIFP

PSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTL

SKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC

Antibody 180 heavy chain

SEQ ID NO:44

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYAMH WVRQAPGQGLEWMGRISPRSGGTKYAQ

RFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAREAVGTHPQAGDFDLWGRGTLTVSS

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWSNSGALTSGVHTFP A VLQSSGL

YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV DKKVEPKSC

Antibody 254 light chain

SEQ ID NO:45

DIQMTQSPSSLSASVGDRVTITCRASQGISSYLA WYQQKPGKAPKLLIYDASSLQIGVPSRF

SGSGSGTDF TLTISSLQPEDFATYYCLOSYSTPPWTFGQG T KVEIKRTVAAPSVFIFPPSDE

QLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLKAD

YEKH KVYACEVTHQGLSSPVTKSFNR GEC

- continued

Antibody 254 heavy chain

SEQ ID NO:46

```
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSSAMHWRQAPGKGLEWVSAIGTGGDTYYADS
VKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREGDGYNFYFDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC
```

Antibody 120 light chain

SEQ ID NO:47

```
EIVMTQSPATLSVSPGERATLSCRASQSVSSRYLAQQKPGQAPRLLIYGASTRATGIPAR
FSGSGSGTEFTLTISLQSEDFAVYYCQQYTTPRTRFGQGTRLEIKRTVAAPSIFFPPSDE
QLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTTLSKAD
YEHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 120 heavy chain

SEQ ID NO:48

```
QVQLVQSGAEVKPGASVKVKASGYTFTSYDINWVRQAPGQGLEWMGMIDPSGGSTSQAQ
KFQGRVTMTRDTSTVYMELSSLRSEDTAVYYCAKDFGGGTRYDYWYFDLWGRGLTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVTVPPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC
```

Antibody 64 light chain

SEQ ID NO:49

```
DIQMTQSPSSLSASVGDRVITICRASQGSISSHAWYQQKPGKAPKLLIYDASNLETGVPSRF
SGSGSGTDFTLTISLQPEDFATYYCQQTYPWTFGQGTRKVEIKRTVAAPSIFFPPSDEQ
LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTTLSKADY
EYHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 64 heavy chain

SEQ ID NO:50

```
EVQLLESGGGLVQPGGSLRLSCAASGFPFSQHGMHWVRQAPGKGLEWVSAIDRSGSYIYYAD
SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDTYGGKTYFDYWGQGTLVTVSSAST
KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL
SSVTVPPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC
```

Antibody 298 light chain

SEQ ID NO:51

```
DIVMTQSPDSLAVSLGERATINCKSSQSVLSSNNKNYLAWYQQKPGQPPKLLIYWASTRES
GPVDRFSGSGSGTDFTLTISLQAEDVAVYYCQQYYPPTFGQGTRKLEIKRTVAAPSIF
PPSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEYHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 298 heavy chain

SEQ ID NO:52

```
QVQLVQSGAEVKPGASVKVKASGGTFSTYGISWVRQAPGQGLEWMGIISPNSGGTDLAQ
KFQGRVTMTRDTSTVYMELSSLRSEDTAVYYCASDPRDDIAGGYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC
```

Antibody 82 light chain

SEQ ID NO:53

```
DIQMTQSPSSLSASVGDRVITICRASQVISNYLAWYQQKPGKAPKLLIYDASNLETGVPSRF
SGSGSGTDFTLTISLQPEDFATYYCQQSFSPPPTRFGQGTRLEIKRTVAAPSIFFPPSDEQ
```

- continued

LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLKADY

EHKHVYACEVTHQGLSSPVTKSFNRGEC

Antibody 82 heavy chain

SEQ ID NO:54

QVQLVQSGAEVKPGASVKVSCKASGGFSTSAYWVRQAPGQGLEWMGWNPYTGTTNYAQ

KFQGRVTMTRDTSTTVYMEMLSSLRSEDTAVYYCARSLALYGGSYFDYWQGTLTVSSAS

TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS

LSSWVTPPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKC

Antibody 46 light chain

SEQ ID NO:55

DIQMTQSPSSLSASVGDRVTITCRASQSISWWLAWYQQKPGKAPKLLIYDASNLETGVPSRF

SGSGSGTDFTLTISSLQPEDFATYYCQOSYSTPFTFGPGTKVDIKRTVAAPSVFIFPPSDEQ

LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLKADY

EHKHVYACEVTHQGLSSPVTKSFNRGEC

Antibody 46 heavy chain

SEQ ID NO:56

EVQLLESGGGLVQPGRSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSTIYSGGSTYYADS

VKGRTFISRDNKNTLYLQMNSLRAEDTAVYYCARGDSRDAFIWGQGTMVTVSSASTKGPS

VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSVV

TVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKC

Antibody 324 light chain

SEQ ID NO:57

DIQMTQSPSSLSASVGDRVTITCRASQSITTYLNWYQQKPGKAPKLLIYDASNLETGVPSRF

SGSGSGTDFTLTISSLQPEDFATYYCQOSYSTPPTFGQGKVEIKRTVAAPSVFIFPPSDEQ

LKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLKADY

EHKHVYACEVTHQGLSSPVTKSFNRGEC

Antibody 324 heavy chain

SEQ ID NO:58

QVQLVQSGAEVKPGASVKVSCKASGGTFNNYGIWVRQAPGQGLEWMGWNPNSGNTGYAQ

KFQGRVTMTRDTSTTVYMEMLSSLRSEDTAVYYCARVGDYGDYIVSPFDLWGRGTLTVSSA

STKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY

SLSSWVTPPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKC

Antibody 236 light chain

SEQ ID NO:59

DIVMTQSPLSLPVTPGEPASI CRSSQSLLHNGNYLDWYLQKPGQSPQLIYLGSNRASG

VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTTPPTFGQGTRLEIKRTVAAPSVFIFP

PSDEQLKSGTASVVCLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL

KADYEHKHVYACEVTHQGLSSPVTKSFNRGEC

Antibody 236 heavy chain

SEQ ID NO:60

QVQLVQSGAEVKPGASVKVSCKASGGFTSYGINWVRQAPGQGLEWMGWNPNSGNTGYAQ

KFQGRVTMTRDTSTTVYMEMLSSLRSEDTAVYYCASRGIQLLPRGMDWGGTTVSSAST

KGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL

SSVVTVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKC

- continued

Antibody 52 light chain

SEQ ID NO: 61

```
DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPKLLIYAASSLESGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQQGNGFPLTPGP GTKVDIKRTVAAPS VFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTSKADY
EIKHKVYACEVTHQGLSSPVTKSFNRGEC

Antibody 52 light chain N92T
```

SEQ ID NO: 62

```
DIQMTQSPSSLSASVGDRVTITCRASQGISNNLNWYQQKPGKAPKLLIYAASSLESGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQQG[ ]GFPLTFGP GTKVDIKRTVAAPS VFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTSKA
DYE EIKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 52 heavy chain

SEQ ID NO: 63

```
QVQLVQSGAEVKPGSSVKVSKASGYTFTSYG ISWVRQAPGQGLEWMGGIIPMFGTTNYAQ
KFQGRVTITADKSTSTAYMELSSLRSEDTAVYYCARDRGDTIDYWQGTLTVSSASTKGPS
VFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC
```

Antibody 80 light chain

SEQ ID NO: 64

```
DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPGQPPKLLIYWA STRES
GV PDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYY SAPLTFGGGTKVEIKRTVAAPS VFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL
LSKADY EIKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Antibody 80 heavy chain

SEQ ID NO: 65

```
QVQLVQSGAEVKPGSSVKVSKASGGTFNRYAF SWVRQAPGQGLEWMGGIIPIFGTANYAQ
KFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARSTRELPEVVDWYFDLWGRGLTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFP AVLQSSGL
YSLSSWTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSC
```

EQUIVALENTS/OTHER EMBODIMENTS

[0442] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of

the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features herein before set forth.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 118

<210> SEQ ID NO 1
<211> LENGTH: 175
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

Met Ser Ser Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala		
1	5	10
		15

-continued

Val Asn Ser Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu
20 25 30

Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val
35 40 45

Ser His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu
50 55 60

Arg Leu Leu Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln
65 70 75 80

Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp Gly Lys Thr Pro Asp Ala
85 90 95

Met Lys Ala Ala Met Ala Leu Glu Lys Lys Leu Asn Gln Ala Leu Leu
100 105 110

Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp
115 120 125

Phe Leu Glu Thr His Phe Leu Asp Glu Glu Val Lys Leu Ile Lys Lys
130 135 140

Met Gly Asp His Leu Thr Asn Leu His Arg Leu Gly Gly Pro Glu Ala
145 150 155 160

Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu Thr Leu Arg His Asp
165 170 175

<210> SEQ ID NO 2

<211> LENGTH: 27

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Linker

<400> SEQUENCE: 2

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Ser Gly Gly
20 25

<210> SEQ ID NO 3

<211> LENGTH: 326

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VHH-hFerr

<400> SEQUENCE: 3

Gln Val Gln Leu Gln Glu Ser Gly Gly Leu Val Gln Ala Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Glu Tyr
20 25 30

Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
35 40 45

Ala Thr Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Thr Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ala Ala Gly Leu Gly Thr Val Val Ser Glu Trp Asp Tyr Asp Tyr
100 105 110

-continued

Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Gly Gly Gly
 115 120 125
 Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser
 130 135 140
 Gly Gly Gly Ser Gly Gly Ser Ser Gln Ile Arg Gln Asn Tyr
 145 150 155 160
 Ser Thr Asp Val Glu Ala Ala Val Asn Ser Leu Val Asn Leu Tyr Leu
 165 170 175
 Gln Ala Ser Tyr Thr Tyr Leu Ser Leu Gly Phe Tyr Phe Asp Arg Asp
 180 185 190
 Asp Val Ala Leu Glu Gly Val Ser His Phe Phe Arg Glu Leu Ala Glu
 195 200 205
 Glu Lys Arg Glu Gly Tyr Glu Arg Leu Leu Lys Met Gln Asn Gln Arg
 210 215 220
 Gly Gly Arg Ala Leu Phe Gln Asp Ile Lys Lys Pro Ala Glu Asp Glu
 225 230 235 240
 Trp Gly Lys Thr Pro Asp Ala Met Lys Ala Ala Met Ala Leu Glu Lys
 245 250 255
 Lys Leu Asn Gln Ala Leu Leu Asp Leu His Ala Leu Gly Ser Ala Arg
 260 265 270
 Thr Asp Pro His Leu Cys Asp Phe Leu Glu Thr His Phe Leu Asp Glu
 275 280 285
 Glu Val Lys Leu Ile Lys Lys Met Gly Asp His Leu Thr Asn Leu His
 290 295 300
 Arg Leu Gly Gly Pro Glu Ala Gly Leu Gly Glu Tyr Leu Phe Glu Arg
 305 310 315 320
 Leu Thr Leu Arg His Asp
 325

<210> SEQ ID NO 4
 <211> LENGTH: 354
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: VHH-Fc

<400> SEQUENCE: 4

Gln Val Gln Leu Gln Glu Ser Gly Gly Leu Val Gln Ala Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Arg Thr Phe Ser Glu Tyr
 20 25 30
 Ala Met Gly Trp Phe Arg Gln Ala Pro Gly Lys Glu Arg Glu Phe Val
 35 40 45
 Ala Thr Ile Ser Trp Ser Gly Gly Ser Thr Tyr Tyr Thr Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Val Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Lys Pro Asp Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Ala Ala Gly Leu Gly Thr Val Val Ser Glu Trp Asp Tyr Asp Tyr
 100 105 110
 Asp Tyr Trp Gly Gln Gly Thr Gln Val Thr Val Ser Ser Gly Ser Asp
 115 120 125

-continued

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
130 135 140

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
145 150 155 160

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
165 170 175

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
180 185 190

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
195 200 205

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
210 215 220

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
225 230 235 240

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
245 250 255

Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu
260 265 270

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
275 280 285

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
290 295 300

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
305 310 315 320

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
325 330 335

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
340 345 350

Gly Lys

<210> SEQ ID NO 5
<211> LENGTH: 90
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-hFerritinLC

<400> SEQUENCE: 5

Met Ser Ser Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala
1 5 10 15

Val Asn Ser Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu
20 25 30

Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val
35 40 45

Ser His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu
50 55 60

Arg Leu Leu Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln
65 70 75 80

Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp
85 90

<210> SEQ ID NO 6
<211> LENGTH: 85

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C-hFerritinLC

<400> SEQUENCE: 6

Gly Lys Thr Pro Asp Ala Met Lys Ala Ala Met Ala Leu Glu Lys Lys
1 5 10 15

Leu Asn Gln Ala Leu Leu Asp Leu His Ala Leu Gly Ser Ala Arg Thr
20 25 30

Asp Pro His Leu Cys Asp Phe Leu Glu Thr His Phe Leu Asp Glu Glu
35 40 45

Val Lys Leu Ile Lys Lys Met Gly Asp His Leu Thr Asn Leu His Arg
50 55 60

Leu Gly Gly Pro Glu Ala Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu
65 70 75 80

Thr Leu Arg His Asp
85

<210> SEQ ID NO 7
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Signal sequence

<400> SEQUENCE: 7

Met Gly Ile Leu Pro Ser Pro Gly Met Pro Ala Leu Leu Ser Leu Val
1 5 10 15

Ser Leu Leu Ser Val Leu Leu Met Gly Cys Val Ala Glu
20 25

<210> SEQ ID NO 8
<211> LENGTH: 70
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Linker

<400> SEQUENCE: 8

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly
20 25 30

Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
35 40 45

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
50 55 60

Ser Gly Gly Gly Ser
65 70

<210> SEQ ID NO 9
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Linker

<400> SEQUENCE: 9

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Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
20 25

<210> SEQ ID NO 10
<211> LENGTH: 714
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BD23-scFab-hFerritinLC

<400> SEQUENCE: 10

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys Gly Gly Ser Gly Gly Ser Gly Gly Ser
210 215 220

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly
225 230 235 240

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
245 250 255

Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
260 265 270

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Gln Leu
275 280 285

Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val Lys Val
290 295 300

Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Ala Met Asn Trp
305 310 315 320

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

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<210> SEQ ID NO 11
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VK for BD23

<400> SEQUENCE: 11

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
1           5          10          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20          25          30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45

Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50          55          60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Tyr
85          90          95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100         105

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<210> SEQ ID NO 12
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: VH for BD23

<400> SEQUENCE: 12

Gln Val Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala
1           5          10          15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20          25          30

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35          40          45

Gly Trp Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe
50          55          60

Thr Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65          70          75          80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95

Ala Arg Pro Gln Gly Gly Ser Ser Trp Tyr Arg Asp Tyr Tyr Gly
100         105         110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115         120         125

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<210> SEQ ID NO 13
<211> LENGTH: 627
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: BD23-scFab-C_hFerritinLC

<400> SEQUENCE: 13

Leu Glu Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser
1           5          10          15

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Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser
20 25 30

Ser Trp Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Lys Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe
50 55 60

Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu
65 70 75 80

Gln Pro Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr
85 90 95

Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val
100 105 110

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
115 120 125

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
130 135 140

Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn
145 150 155 160

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
165 170 175

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
180 185 190

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
195 200 205

Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Ser Gly Gly Gly
210 215 220

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
225 230 235 240

Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser
245 250 255

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly
260 265 270

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Val
275 280 285

Gln Leu Val Gln Ser Gly Ser Glu Leu Lys Lys Pro Gly Ala Ser Val
290 295 300

Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr Ala Met
305 310 315 320

Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Trp
325 330 335

Ile Asn Thr Asn Thr Gly Asn Pro Thr Tyr Ala Gln Gly Phe Thr Gly
340 345 350

Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr Leu Gln
355 360 365

Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
370 375 380

Pro Gln Gly Gly Ser Ser Trp Tyr Arg Asp Tyr Tyr Tyr Gly Met Asp
385 390 395 400

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys
405 410 415

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Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
 420 425 430
 Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 435 440 445
 Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 450 455 460
 Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 465 470 475 480
 Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 485 490 495
 Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
 500 505 510
 Lys Ser Cys Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
 515 520 525
 Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Lys
 530 535 540
 Thr Pro Asp Ala Met Lys Ala Ala Met Ala Leu Glu Lys Lys Leu Asn
 545 550 555 560
 Gln Ala Leu Leu Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro
 565 570 575
 His Leu Cys Asp Phe Leu Glu Thr His Phe Leu Asp Glu Glu Val Lys
 580 585 590
 Leu Ile Lys Lys Met Gly Asp His Leu Thr Asn Leu His Arg Leu Gly
 595 600 605
 Gly Pro Glu Ala Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu Thr Leu
 610 615 620
 Arg His Asp
 625

<210> SEQ ID NO 14
<211> LENGTH: 640
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFc-N_hFerritinLC

<400> SEQUENCE: 14

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
1 5 10 15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65 70 75 80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85 90 95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
100 105 110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115 120 125

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Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser
130							135				140				
Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu
145							150			155					160
Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro
	165						170				175				
Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val
	180						185				190				
Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met
	195						200				205				
His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser
	210						215				220				
Pro	Gly	Lys	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
	225						230				235				240
Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
	245						250				255				
Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser		
	260						265				270				
Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly		
	275						280				285				
Gly	Gly	Gly	Ser	Gly	Gly	Ser	Asp	Lys	Thr	His	Thr	Cys	Pro		
	290						295				300				
Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe
	305						310				315				320
Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val
	325						330				335				
Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe
	340						345				350				
Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro
	355						360				365				
Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr
	370						375				380				
Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val
	385						390				395				400
Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala
	405						410				415				
Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg
	420						425				430				
Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly
	435						440				445				
Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro
	450						455				460				
Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser
	465						470				475				480
Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln
	485						490				495				
Gly	Asn	Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
	500						505				510				
Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	Gly	Gly	Gly	Gly
	515						520				525				
Ser	Gly	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Ser

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530	535	540
Gly Gly Gly Ser Gly Gly Ser Ser Gln Ile Arg Gln Asn Tyr Ser		
545	550	560
Thr Asp Val Glu Ala Ala Val Asn Ser Leu Val Asn Leu Tyr Tyr Leu Gln		
565	570	575
Ala Ser Tyr Thr Tyr Leu Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp		
580	585	590
Val Ala Leu Glu Gly Val Ser His Phe Phe Arg Glu Leu Ala Glu Glu		
595	600	605
Lys Arg Glu Gly Tyr Glu Arg Leu Leu Lys Met Gln Asn Gln Arg Gly		
610	615	620
Gly Arg Ala Leu Phe Gln Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp		
625	630	635
<210> SEQ ID NO 15		
<211> LENGTH: 227		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: scFc(LALAP)		
 <400> SEQUENCE: 15		
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly		
1	5	10
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met		
20	25	30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His		
35	40	45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val		
50	55	60
His Asn Ala Lys Thr Lys Pro Arg Glu Gln Tyr Asn Ser Thr Tyr		
65	70	75
Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly		
85	90	95
Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile		
100	105	110
Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val		
115	120	125
Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser		
130	135	140
Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu		
145	150	155
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro		
165	170	175
Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val		
180	185	190
Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met		
195	200	205
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser		
210	215	220
Pro Gly Lys		
225		

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<210> SEQ ID NO 16
<211> LENGTH: 721
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4A8-scFab-hFerritinLC

<400> SEQUENCE: 16

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Thr Leu Gly
1           5          10          15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20          25          30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35          40          45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50          55          60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Ala
85          90          95

Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100         105         110

Arg Thr Val Ala Ala Pro Ser Val Phe Pro Pro Ser Asp Glu
115         120         125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130         135         140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145         150         155         160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165         170         175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180         185         190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195         200         205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Ser
210         215         220

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly
225         230         235         240

Gly Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly
245         250         255

Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly
260         265         270

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly
275         280         285

Ser Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly
290         295         300

Ala Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu
305         310         315         320

Leu Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
325         330         335

Met Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Met Tyr Ala Gln Lys
340         345         350

Phe Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala

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

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<210> SEQ ID NO 17
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: VK for 4A8

<400> SEQUENCE: 17

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Ala
85 90 95

Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105 110

<210> SEQ ID NO 18

<211> LENGTH: 128

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: VH for 4A8

<400> SEQUENCE: 18

Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu Leu
20 25 30

Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Met Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Thr Ser Thr Ala Val Ala Gly Thr Pro Asp Leu Phe Asp Tyr Tyr
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 19

<211> LENGTH: 632

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4A8-scFab C_hFerritinLC

<400> SEQUENCE: 19

Glu Ile Val Met Thr Gln Ser Pro Leu Ser Ser Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro

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35	40	45
Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro		
50	55	60
Asp Arg Phe Ser Gly Ser Gly Ala Gly Thr Asp Phe Thr Leu Lys Ile		
65	70	75
		80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Thr Gln Ala		
85	90	95
Thr Gln Phe Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Asp Ile Lys		
100	105	110
Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu		
115	120	125
Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe		
130	135	140
Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln		
145	150	155
		160
Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser		
165	170	175
Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu		
180	185	190
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser		
195	200	205
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Ser		
210	215	220
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser Gly		
225	230	235
		240
Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		
245	250	255
Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly		
260	265	270
Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly		
275	280	285
Ser Glu Val Gln Leu Val Glu Ser Gly Ala Glu Val Lys Lys Pro Gly		
290	295	300
Ala Ser Val Lys Val Ser Cys Lys Val Ser Gly Tyr Thr Leu Thr Glu		
305	310	315
		320
Leu Ser Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp		
325	330	335
Met Gly Gly Phe Asp Pro Glu Asp Gly Glu Thr Met Tyr Ala Gln Lys		
340	345	350
Phe Gln Gly Arg Val Thr Met Thr Glu Asp Thr Ser Thr Asp Thr Ala		
355	360	365
Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr		
370	375	380
Cys Ala Thr Ser Thr Ala Val Ala Gly Thr Pro Asp Leu Phe Asp Tyr		
385	390	395
		400
Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser		
405	410	415
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser		
420	425	430
Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp		
435	440	445

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Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
450 455 460

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
465 470 475 480

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
485 490 495

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
500 505 510

Lys Lys Val Pro Lys Ser Cys Gly Gly Gly Ser Gly Gly Gly
515 520 525

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly
530 535 540

Ser Gly Gly Lys Thr Pro Asp Ala Met Lys Ala Ala Met Ala Leu
545 550 555 560

Glu Lys Lys Leu Asn Gln Ala Leu Leu Asp Leu His Ala Leu Gly Ser
565 570 575

Ala Arg Thr Asp Pro His Leu Cys Asp Phe Leu Glu Thr His Phe Leu
580 585 590

Asp Glu Glu Val Lys Leu Ile Lys Lys Met Gly Asp His Leu Thr Asn
595 600 605

Leu His Arg Leu Gly Gly Pro Glu Ala Gly Leu Gly Glu Tyr Leu Phe
610 615 620

Glu Arg Leu Thr Leu Arg His Asp
625 630

<210> SEQ ID NO 20
<211> LENGTH: 183
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: mFerritin

<400> SEQUENCE: 20

Met Thr Ser Gln Ile Arg Gln Asn Tyr Ser Thr Glu Val Glu Ala Ala
1 5 10 15

Val Asn Arg Leu Val Asn Leu His Leu Arg Ala Ser Tyr Thr Tyr Leu
20 25 30

Ser Leu Gly Phe Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val
35 40 45

Gly His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Ala Glu
50 55 60

Arg Leu Leu Glu Phe Gln Asn Asp Arg Gly Gly Arg Ala Leu Phe Gln
65 70 75 80

Asp Val Gln Lys Pro Ser Gln Asp Glu Trp Gly Lys Thr Gln Glu Ala
85 90 95

Met Glu Ala Ala Leu Ala Met Glu Lys Asn Leu Asn Gln Ala Leu Leu
100 105 110

Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp
115 120 125

Phe Leu Glu Ser His Tyr Leu Asp Lys Glu Val Lys Leu Ile Lys Lys
130 135 140

Met Gly Asn His Leu Thr Asn Leu Arg Arg Val Ala Gly Pro Gln Pro
145 150 155 160

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Ala Gln Thr Gly Ala Pro Gln Gly Ser Leu Gly Glu Tyr Leu Phe Glu
165 170 175

Arg Leu Thr Leu Lys His Asp
180

<210> SEQ ID NO 21
<211> LENGTH: 747
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Anti-CD19 single chain immunoglobulin

<400> SEQUENCE: 21

Asp Ile Leu Leu Thr Gln Thr Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Gln Arg Ala Thr Ile Ser Cys Lys Ala Ser Gln Ser Val Asp Tyr Asp
20 25 30

Gly Asp Ser Tyr Leu Asn Trp Tyr Gln Gln Ile Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Asp Ala Ser Asn Leu Val Ser Gly Ile Pro Pro
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80

Pro Val Glu Lys Val Asp Ala Ala Thr Tyr His Cys Gln Gln Ser Thr
85 90 95

Glu Asp Pro Trp Thr Phe Gly Gly Thr Lys Leu Glu Ile Lys Arg
100 105 110

Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln
115 120 125

Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr
130 135 140

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
145 150 155 160

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
165 170 175

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
180 185 190

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
195 200 205

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys Gly Gly Ser Ser Gly Ser
210 215 220

Gly Ser Gly Ser Thr Gly Thr Ser Ser Gly Thr Gly Thr Ser Ala
225 230 235 240

Gly Thr Thr Gly Thr Ser Ala Ser Thr Ser Gly Ser Gly Ser Gly
245 250 255

Gly Gly Gly Ser Gly Gly Gly Ser Ala Gly Gly Thr Ala Thr Ala
260 265 270

Gly Ala Ser Ser Gly Ser Gly Ser Ser Gly Ser Ser Ser Gly Gly
275 280 285

Thr Gly Thr Gly Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val
290 295 300

Arg Pro Gly Ser Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala
305 310 315 320

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

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Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu His Asn His His
725 730 735

Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys
740 745

<210> SEQ ID NO 22
<211> LENGTH: 734
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: IgG2a Fc_mFerr

<400> SEQUENCE: 22

Lys Pro Cys Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly
1 5 10 15

Pro Ser Val Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile
20 25 30

Ser Leu Ser Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp
35 40 45

Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His
50 55 60

Thr Ala Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg
65 70 75 80

Val Val Ser Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys
85 90 95

Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu
100 105 110

Arg Thr Ile Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr
115 120 125

Val Leu Pro Pro Pro Glu Glu Met Thr Lys Lys Gln Val Thr Leu
130 135 140

Thr Cys Met Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp
145 150 155 160

Thr Asn Asn Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val
165 170 175

Leu Asp Ser Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu
180 185 190

Lys Lys Asn Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His
195 200 205

Glu Gly Leu His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro
210 215 220

Gly Lys Gly Gly Ser Ser Gly Ser Gly Ser Thr Gly Thr Ser
225 230 235 240

Ser Ser Gly Thr Gly Thr Ser Ala Gly Thr Thr Gly Thr Ser Ala Ser
245 250 255

Thr Ser Gly Ser Gly Ser Gly Gly Ser Gly Gly Gly Gly
260 265 270

Ser Ala Gly Gly Thr Ala Thr Ala Gly Ala Ser Ser Gly Ser Gly Ser
275 280 285

Ser Gly Ser Ser Ser Ser Gly Gly Thr Gly Lys Pro Cys Pro Pro Cys
290 295 300

Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val Phe Ile Phe
305 310 315 320

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

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725

730

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<210> SEQ ID NO 23
<211> LENGTH: 640
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: scFc-N-hFerr LALAP I253A

<400> SEQUENCE: 23

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly
1           5          10          15

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20          25          30

Ala Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35          40          45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50          55          60

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
65          70          75          80

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
85          90          95

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Gly Ala Pro Ile
100         105         110

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
115         120         125

Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
130         135         140

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
145         150         155         160

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
165         170         175

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
180         185         190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
195         200         205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
210         215         220

Pro Gly Lys Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
225         230         235         240

Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly
245         250         255

Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser
260         265         270

Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly
275         280         285

Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Asp Lys Thr His Thr Cys Pro
290         295         300

Pro Cys Pro Ala Pro Glu Ala Ala Gly Pro Ser Val Phe Leu Phe
305         310         315         320

Pro Pro Lys Pro Lys Asp Thr Leu Met Ala Ser Arg Thr Pro Glu Val
325         330         335

Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe

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340	345	350
Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro		
355	360	365
Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr		
370	375	380
Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val		
385	390	395 400
Ser Asn Lys Ala Leu Gly Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala		
405	410	415
Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg		
420	425	430
Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly		
435	440	445
Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro		
450	455	460
Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser		
465	470	475 480
Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln		
485	490	495
Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His		
500	505	510
Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly		
515	520	525
Ser Gly Gly Gly Ser Gly Gly Ser Gly Gly Ser Gly Gly Ser		
530	535	540
Gly Gly Gly Ser Gly Gly Ser Ser Gln Ile Arg Gln Asn Tyr Ser		
545	550	555 560
Thr Asp Val Glu Ala Ala Val Asn Ser Leu Val Asn Leu Tyr Leu Gln		
565	570	575
Ala Ser Tyr Thr Tyr Leu Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp		
580	585	590
Val Ala Leu Glu Gly Val Ser His Phe Phe Arg Glu Leu Ala Glu Glu		
595	600	605
Lys Arg Glu Gly Tyr Glu Arg Leu Leu Lys Met Gln Asn Gln Arg Gly		
610	615	620
Gly Arg Ala Leu Phe Gln Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp		
625	630	635 640
<210> SEQ ID NO: 24		
<211> LENGTH: 227		
<212> TYPE: PRT		
<213> ORGANISM: Homo sapiens		
<400> SEQUENCE: 24		
Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly		
1	5	10 15
Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met		
20	25	30
Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His		
35	40	45
Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val		
50	55	60

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<210> SEQ ID NO 25
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody 56 light chain

<400> SEQUENCE: 25

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1					5					10					15

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Tyr
	20					25						30			

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35			40						45			

Tyr	Asp	Ala	Ser	Asn	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50				55					60					

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
	65				70			75						80	

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ala	Asn	Ser	Phe	Pro	Ser
	85						90						95		

Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
	100					105						110			

Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
	115					120						125			

Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130				135						140				

Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
	145				150					155					160

Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
	165						170						175		

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Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 26

<211> LENGTH: 219

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 56 heavy chain

<400> SEQUENCE: 26

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ile Gly Pro Ile Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
115 120 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
130 135 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145 150 155 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
165 170 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
180 185 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
195 200 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215

<210> SEQ ID NO 27

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 349 light chain

<400> SEQUENCE: 27

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Asp Thr Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Trp
 85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 28
 <211> LENGTH: 226
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody 349 heavy chain

<400> SEQUENCE: 28

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
 20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Gly Ile Ser Ser Ala Gly Ser Ile Thr Asn Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Gly Asn His Ala Gly Thr Thr Val Thr Ser Glu Tyr Phe Gln His
 100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
 115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
 130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
 145 150 155 160

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Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

Ser Cys
225

<210> SEQ ID NO 29

<211> LENGTH: 215

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 178 light chain

<400> SEQUENCE: 29

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Ser Gly Thr
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Thr His Ser Tyr Pro
85 90 95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 30

<211> LENGTH: 225

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 178 heavy chain

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<400> SEQUENCE: 30

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1           5          10          15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20          25          30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35          40          45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50          55          60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65          70          75          80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95

Ala Arg Asp Ile Ser Ser Trp Tyr Glu Ile Thr Lys Phe Asp Pro Trp
100         105         110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115         120         125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
130         135         140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145         150         155         160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
165         170         175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
180         185         190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
195         200         205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
210         215         220

Cys
225

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<210> SEQ ID NO 31

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 108 light chain

<400> SEQUENCE: 31

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5          10          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Thr Asn Asn
20          25          30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45

Tyr Asp Ala Ser Thr Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Phe Pro Tyr
85          90          95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala

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100	105	110	
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly			
115	120	125	
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala			
130	135	140	
Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln			
145	150	155	160
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser			
165	170	175	
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr			
180	185	190	
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser			
195	200	205	
Phe Asn Arg Gly Glu Cys			
210			

<210> SEQ ID NO 32
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 108 heavy chain

<400> SEQUENCE: 32

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Arg Tyr			
20	25	30	
Ala Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Trp Met Asn Pro Ile Ser Gly Asn Thr Asp Tyr Ala Pro Asn Phe			
50	55	60	
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Lys Asp Gly Ser Gln Leu Ala Tyr Leu Val Glu Tyr Phe Gln His			
100	105	110	
Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly			
115	120	125	
Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly			
130	135	140	
Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val			
145	150	155	160
Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe			
165	170	175	
Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val			
180	185	190	
Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val			
195	200	205	
Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys			
210	215	220	
Ser Cys			

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225

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<210> SEQ ID NO 33
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 128 light chain

<400> SEQUENCE: 33

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5          10          15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Ser Arg Tyr
20          25          30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Gly Phe Pro Pro
85          90          95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100         105         110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115         120         125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130         135         140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145         150         155         160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165         170         175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180         185         190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195         200         205

Phe Asn Arg Gly Glu Cys
210

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<210> SEQ ID NO 34
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 128 heavy chain

<400> SEQUENCE: 34

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1           5          10          15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20          25          30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35          40          45

Gly Ile Ile Asn Pro Ser Ser Ser Ala Ser Tyr Ser Gln Lys Phe
50          55          60

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Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
65					70				75					80	
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
								85	90				95		
Ala	Arg	Asp	Gly	Arg	Tyr	Gly	Ser	Gly	Ser	Tyr	Pro	Phe	Asp	Tyr	Trp
					100				105			110			
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
							115	120				125			
Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
							130	135			140				
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
							145	150			155			160	
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
							165	170			175				
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
							180	185			190				
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
							195	200			205				
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
							210	215			220				

Cys
225

<210>	SEQ_ID_NO	35													
<211>	LENGTH:	214													
<212>	TYPE:	PRT													
<213>	ORGANISM:	Artificial Sequence													
<220>	FEATURE:														
<223>	OTHER_INFORMATION:	Antibody 160 light chain													
<400>	SEQUENCE:	35													
Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1							5	10				15			
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Val	Ser	Ser	Trp
							20	25				30			
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
							35	40			45				
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
							50	55			60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
							65	70			75		80		
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Tyr	Thr	Thr	Pro	Tyr
							85	90			95				
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
							100	105			110				
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
							115	120			125				
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
							130	135			140				
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
							145	150			155		160		
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
							165	170			175				

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Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 36

<211> LENGTH: 224

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 160 heavy chain

<400> SEQUENCE: 36

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly His
20 25 30

Asp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ala Asn Ser Leu Arg Tyr Tyr Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
115 120 125

Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala
130 135 140

Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val
145 150 155 160

Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala
165 170 175

Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
180 185 190

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His
195 200 205

Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> SEQ ID NO 37

<211> LENGTH: 219

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 368 light chain

<400> SEQUENCE: 37

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

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Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Ser
35							40					45			
Pro	Gln	Leu	Leu	Ile	Tyr	Leu	Gly	Ser	Asn	Arg	Ala	Ser	Gly	Val	Pro
50						55					60				
Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Lys	Ile
65					70					75					80
Ser	Arg	Val	Glu	Ala	Glu	Asp	Val	Gly	Val	Tyr	Tyr	Cys	Met	Gln	Ala
						85			90					95	
Leu	Gln	Thr	Pro	Ala	Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys
						100			105				110		
Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu
							115		120				125		
Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe
						130			135			140			
Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln
							145		150			155			160
Ser	Gly	Asn	Ser	Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser
							165		170				175		
Thr	Tyr	Ser	Leu	Ser	Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glut
							180		185				190		
Lys	His	Lys	Val	Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser
							195		200			205			
Pro	Val	Thr	Lys	Ser	Phe	Asn	Arg	Gly	Glu	Cys					
						210			215						

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Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> SEQ ID NO 39

<211> LENGTH: 219

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 192 light chain

<400> SEQUENCE: 39

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 40

<211> LENGTH: 224

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 192 heavy chain

<400> SEQUENCE: 40

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser

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1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr			
20	25	30	
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Trp Ile Asn Pro Asn Ser Gly Gly Ala Asn Tyr Ala Gln Lys Phe			
50	55	60	
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ser Thr Tyr Tyr Asp Ser Ser Gly Tyr Ser Thr Asp Tyr Trp Gly			
100	105	110	
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
115	120	125	
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
130	135	140	
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val			
145	150	155	160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala			
165	170	175	
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
180	185	190	
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			
195	200	205	
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys			
210	215	220	

<210> SEQ ID NO 41
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 158 light chain

<400> SEQUENCE: 41			
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr			
20	25	30	
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
35	40	45	
Tyr Asp Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu			
85	90	95	
Thr Phe Gly Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala			
100	105	110	
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly			
115	120	125	
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala			

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130	135	140
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Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln 145 150 155 160		
Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 165 170 175		
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr 180 185 190		
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser 195 200 205		
Phe Asn Arg Gly Glu Cys 210		

<210> SEQ ID NO 42

<211> LENGTH: 225

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 158 heavy chain

<400> SEQUENCE: 42

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala 1 5 10 15		
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr 20 25 30		
Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met 35 40 45		
Gly Trp Ile Asn Pro Leu Asn Gly Gly Thr Asn Phe Ala Pro Lys Phe 50 55 60		
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr 65 70 75 80		
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys 85 90 95		
Ala Arg Asp Pro Gly Gly Ser Tyr Ser Asn Asp Ala Phe Asp Ile Trp 100 105 110		
Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro 115 120 125		
Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr 130 135 140		
Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr 145 150 155 160		
Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro 165 170 175		
Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr 180 185 190		
Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn 195 200 205		
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser 210 215 220		

Cys
225

<210> SEQ ID NO 43

<211> LENGTH: 219

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 180 light chain

<400> SEQUENCE: 43

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1           5           10          15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20          25          30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35          40          45

Pro Gln Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
50          55          60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65          70          75          80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
85          90          95

Tyr Ser Ser Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100         105         110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115         120         125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130         135         140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145         150         155         160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165         170         175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180         185         190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195         200         205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210         215

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<210> SEQ ID NO 44
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 180 heavy chain

<400> SEQUENCE: 44

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1           5           10          15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20          25          30

Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35          40          45

Gly Arg Ile Ser Pro Arg Ser Gly Gly Thr Lys Tyr Ala Gln Arg Phe
50          55          60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65          70          75          80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95

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Ala Arg Glu Ala Val Ala Gly Thr His Pro Gln Ala Gly Asp Phe Asp
 100 105 110
 Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
 115 120 125
 Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
 130 135 140
 Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
 145 150 155 160
 Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
 165 170 175
 Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
 180 185 190
 Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
 195 200 205
 Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
 210 215 220
 Lys Ser Cys
 225

<210> SEQ ID NO 45
 <211> LENGTH: 215
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Antibody 254 light chain

 <400> SEQUENCE: 45

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1			5			10				15					

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
 20 25 30

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Ile
35				40					45					

Tyr Asp Ala Ser Ser Leu Gln Ile Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70				75		80					

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Tyr Ser Thr Pro Pro
 85 90 95

Trp	Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala
100						105			110						

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
 115 120 125

Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu
130						135			140						

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
 145 150 155 160

Gln	Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu
165				170				175							

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
 180 185 190

Tyr	Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys
195					200				205						

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Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 46
<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 254 heavy chain

<400> SEQUENCE: 46

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Ser
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Gly Thr Gly Asp Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Glu Gly Asp Gly Tyr Asn Phe Tyr Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

<210> SEQ ID NO 47
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 120 light chain

<400> SEQUENCE: 47

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Arg
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

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Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Thr Thr Pro
85 90 95

Arg Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg Thr Val Ala
100 105 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
115 120 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
130 135 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145 150 155 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
165 170 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
180 185 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
195 200 205

Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ_ID NO 48
<211> LENGTH: 227
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 120 heavy chain

<400> SEQUENCE: 48

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Met Ile Asp Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Phe Gly Gly Thr Arg Tyr Asp Tyr Trp Tyr Phe Asp
100 105 110

Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

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Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys
225

<210> SEQ ID NO 49
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 64 light chain

<400> SEQUENCE: 49

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 50
<211> LENGTH: 224
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 64 heavy chain

<400> SEQUENCE: 50

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Pro Phe Ser Gln His

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20	25	30	
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val			
35	40	45	
Ser Ala Ile Asp Arg Ser Gly Ser Tyr Ile Tyr Tyr Ala Asp Ser Val			
50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr			
65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Arg Asp Thr Tyr Gly Gly Lys Val Thr Tyr Phe Asp Tyr Trp Gly			
100	105	110	
Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser			
115	120	125	
Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala			
130	135	140	
Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val			
145	150	155	160
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala			
165	170	175	
Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val			
180	185	190	
Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His			
195	200	205	
Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys			
210	215	220	

<210> SEQ ID NO 51
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 298 light chain

<400> SEQUENCE: 51

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly			
1	5	10	15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser			
20	25	30	
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln			
35	40	45	
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val			
50	55	60	
Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr			
65	70	75	80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln			
85	90	95	
Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile			
100	105	110	
Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp			
115	120	125	
Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn			
130	135	140	
Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu			

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145	150	155	160
Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp			
165	170	175	
Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr			
180	185	190	
Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser			
195	200	205	
Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys			
210	215	220	

<210> SEQ ID NO 52
<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 298 heavy chain
<400> SEQUENCE: 52

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala			
1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Thr Tyr			
20	25	30	
Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Trp Ile Ser Pro Asn Ser Gly Gly Thr Asp Leu Ala Gln Lys Phe			
50	55	60	
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Ser Asp Pro Arg Asp Asp Ile Ala Gly Gly Tyr Trp Gly Gln Gly			
100	105	110	
Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe			
115	120	125	
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu			
130	135	140	
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp			
145	150	155	160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu			
165	170	175	
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser			
180	185	190	
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro			
195	200	205	
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys			
210	215	220	

<210> SEQ ID NO 53
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 82 light chain
<400> SEQUENCE: 53

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Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1															
			5					10							15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Val	Ile	Ser	Asn	Tyr
			20					25							30
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
			35					40							45
Tyr	Asp	Ala	Ser	Asn	Leu	Glu	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
			50					55							60
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
			65					70							80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Phe	Ser	Pro	Pro	Pro
			85					90							95
Thr	Phe	Gly	Gln	Gly	Thr	Arg	Leu	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
			100					105							110
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
			115					120							125
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
			130					135							140
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
			145					150							160
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
			165					170							175
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
			180					185							190
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
			195					200							205
Phe	Asn	Arg	Gly	Glu	Cys										
			210												

<210> SEQ ID NO 54
<211> LENGTH: 225
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 82 heavy chain

<400> SEQUENCE: 54

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1															
				5				10							15
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Gly	Ser	Phe	Ser	Thr	Ser
			20					25							30
Ala	Phe	Tyr	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
			35					40							45
Gly	Trp	Ile	Asn	Pro	Tyr	Thr	Gly	Gly	Thr	Asn	Tyr	Ala	Gln	Lys	Phe
			50					55							60
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
			65					70							80
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
			85					90							95
Ala	Arg	Ser	Arg	Ala	Leu	Tyr	Gly	Ser	Gly	Ser	Tyr	Phe	Asp	Tyr	Trp
			100					105							110
Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
			115					120							125

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Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
130							135				140				

Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
145							150			155			160		

Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
							165		170		175				

Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
							180		185		190				

Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
	195					200			205						

His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
	210						215			220					

Cys
225

<210> SEQ ID NO 55

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 46 light chain

<400> SEQUENCE: 55

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1							5		10			15			

Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Trp
				20				25			30				

Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
				35		40			45						

Tyr	Asp	Ala	Ser	Asn	Leu	Glu	Thr	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55			60						

Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70			75		80					

Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Tyr	Ser	Thr	Pro	Phe
				85				90			95				

Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys	Arg	Thr	Val	Ala	Ala
					100		105			110					

Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
	115					120				125					

Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130				135				140						

Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
145					150				155			160			

Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
				165				170			175				

Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
				180		185			190						

Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
	195					200				205					

Phe	Asn	Arg	Gly	Glu	Cys										
	210														

<210> SEQ ID NO 56

<211> LENGTH: 220

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 46 heavy chain

<400> SEQUENCE: 56

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Asp Ser Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
115 120 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
130 135 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145 150 155 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
165 170 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
180 185 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
195 200 205

Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys
210 215 220

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<210> SEQ ID NO 57
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 324 light chain

<400> SEQUENCE: 57

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 58
<211> LENGTH: 226
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 324 heavy chain
<400> SEQUENCE: 58

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Asn Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Asp Tyr Gly Asp Tyr Ile Val Ser Pro Phe Asp Leu
100 105 110

Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly
115 120 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
130 135 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
165 170 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
180 185 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
195 200 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
210 215 220

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Ser Cys
225

<210> SEQ ID NO 59
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 236 light chain

<400> SEQUENCE: 59

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
115 120 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
130 135 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145 150 155 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
165 170 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
180 185 190

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> SEQ ID NO 60
<211> LENGTH: 224
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 236 heavy chain

<400> SEQUENCE: 60

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe

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50	55	60														
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr	
65					70				75					80		
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	
														85	90	95
Ala	Ser	Arg	Gly	Ile	Gln	Leu	Leu	Pro	Arg	Gly	Met	Asp	Val	Trp	Gly	
					100				105				110			
Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	
					115			120			125					
Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	
					130			135			140					
Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	
					145			150			155			160		
Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	
					165			170			175					
Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	
					180			185			190					
Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	
					195			200			205					
Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	
					210			215			220					

<210> SEQ ID NO 61
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Antibody 52 light chain

<400> SEQUENCE: 61

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	
1					5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Asn	Asn	
					20			25			30					
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile	
					35			40			45					
Tyr	Ala	Ala	Ser	Ser	Leu	Glu	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	
					50			55			60					
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro	
					65			70			75			80		
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Gly	Phe	Pro	Leu	
					85			90			95					
Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile	Lys	Arg	Thr	Val	Ala	Ala	
					100			105			110					
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	
					115			120			125					
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	
					130			135			140					
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln	
					145			150			155			160		
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser	
					165			170			175					
Ser	Thr	Leu	Thr	Leu	Ser	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr	

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180	185	190
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Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	195	200
	200	205
Phe Asn Arg Gly Glu Cys		
	210	

<210> SEQ ID NO 62

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 52 light chain N92T

<400> SEQUENCE: 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	1	5
	10	15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn	20	25
	30	

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40
	45	

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55
	60	

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70
	75	80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Thr Gly Phe Pro Leu	85	90
	95	

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala	100	105
	110	

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly	115	120
	125	

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala	130	135
	140	

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln	145	150
	155	160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser	165	170
	175	

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr	180	185
	190	

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser	195	200
	205	

Phe Asn Arg Gly Glu Cys	210	
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<210> SEQ ID NO 63

<211> LENGTH: 220

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 52 heavy chain

<400> SEQUENCE: 63

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser	1	5
	10	15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr	20	25
	30	

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Gly	Ile	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
35				40					45						
Gly	Gly	Ile	Ile	Pro	Met	Phe	Gly	Thr	Thr	Asn	Tyr	Ala	Gln	Lys	Phe
50				55				60							
Gln	Gly	Arg	Val	Thr	Ile	Thr	Ala	Asp	Lys	Ser	Thr	Ser	Thr	Ala	Tyr
65				70				75			80				
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	85				90				95						
Ala	Arg	Asp	Arg	Gly	Asp	Thr	Ile	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu
	100				105				110						
Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu
	115				120				125						
Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys
	130				135				140						
Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser
	145				150				155			160			
Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser
	165					170			175						
Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser
	180					185			190						
Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn
	195					200			205						
Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys				
	210					215			220						

<210> SEQ_ID NO 64															
<211> LENGTH: 220															
<212> TYPE: PRT															
<213> ORGANISM: Artificial Sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: Antibody 80 light chain															
<400> SEQUENCE: 64															
Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Asp	Ser	Leu	Ala	Val	Ser	Leu	Gly
1				5				10			15				
Glu	Arg	Ala	Thr	Ile	Asn	Cys	Lys	Ser	Ser	Gln	Ser	Val	Leu	Tyr	Ser
	20				25				30						
Ser	Asn	Asn	Lys	Asn	Tyr	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Gln
	35				40				45						
Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
	50				55				60						
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
	65				70				75			80			
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	Gln
	85					90			95						
Tyr	Tyr	Ser	Ala	Pro	Leu	Thr	Phe	Gly	Gly	Thr	Lys	Val	Glu	Ile	
	100				105				110						
Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp
	115					120			125						
Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn
	130				135				140						
Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu
	145				150				155			160			

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Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
165 170 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
180 185 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
195 200 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215 220

<210> SEQ ID NO 65

<211> LENGTH: 227

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Antibody 80 heavy chain

<400> SEQUENCE: 65

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Arg Tyr
20 25 30

Ala Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Arg Glu Leu Pro Glu Val Val Asp Trp Tyr Phe Asp
100 105 110

Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys
225

<210> SEQ ID NO 66

<211> LENGTH: 85

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Cferritin

<400> SEQUENCE: 66

-continued

Gly Lys Thr Pro Asp Ala Met Lys Ala Ala Met Ala Leu Glu Lys Lys
1 5 10 15

Leu Asn Gln Ala Leu Leu Asp Leu His Ala Leu Gly Ser Ala Arg Thr
20 25 30

Asp Pro His Leu Cys Asp Phe Leu Glu Thr His Phe Leu Asp Glu Glu
35 40 45

Val Lys Leu Ile Lys Lys Met Gly Asp His Leu Thr Asn Leu His Arg
50 55 60

Leu Gly Gly Pro Glu Ala Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu
65 70 75 80

Thr Leu Lys His Asp
85

<210> SEQ ID NO 67

<211> LENGTH: 26

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Linker

<400> SEQUENCE: 67

Gly Gly Ser Gly Gly Ser Gly Ser Gly Gly Ser Gly Gly Ser
1 5 10 15

Gly Gly Ser Gly Gly Ser Gly Ser Gly
20 25

<210> SEQ ID NO 68

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 68

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ile Gly Pro Ile Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 69

<211> LENGTH: 123

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

-continued

<400> SEQUENCE: 69

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Ser Ala Gly Ser Ile Thr Asn Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Gly Asn His Ala Gly Thr Thr Val Thr Ser Glu Tyr Phe Gln His
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 70

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 70

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

His Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ile Ser Ser Trp Tyr Glu Ile Thr Lys Phe Asp Pro Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 71

<211> LENGTH: 123

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 71

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Ser Arg Tyr
20 25 30

-continued

Ala Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Ile Ser Gly Asn Thr Asp Tyr Ala Pro Asn Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Gly Ser Gln Leu Ala Tyr Leu Val Glu Tyr Phe Gln His
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 72

<211> LENGTH: 122

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 72

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr His Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Ser Ser Ala Ser Tyr Ser Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gly Arg Tyr Gly Ser Gly Ser Tyr Pro Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 73

<211> LENGTH: 121

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 73

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly His
20 25 30

Asp Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Ile Ile Asn Pro Ser Gly Gly Ser Thr Ser Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr

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65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Arg Ala Asn Ser Leu Arg Tyr Tyr Gly Met Asp Val Trp Gly			
100	105	110	
Gln Gly Thr Met Val Thr Val Ser Ser			
115	120		

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<210> SEQ ID NO 74
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

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<400> SEQUENCE: 74			
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser			
1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr			
20	25	30	
Asp Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Ala Ile Met Pro Met Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe			
50	55	60	
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ala Arg Gly Ser Ser Gly Tyr Tyr Gly Trp Gly Gln Gly Thr Leu			
100	105	110	
Val Thr Val Ser Ser			
115			

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<210> SEQ ID NO 75
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

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<400> SEQUENCE: 75			
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser			
1	5	10	15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr			
20	25	30	
Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met			
35	40	45	
Gly Trp Ile Asn Pro Asn Ser Gly Gly Ala Asn Tyr Ala Gln Lys Phe			
50	55	60	
Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr			
65	70	75	80
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys			
85	90	95	
Ser Thr Tyr Tyr Asp Ser Ser Gly Tyr Ser Thr Asp Tyr Trp Gly			
100	105	110	

-continued

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 76
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 76

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Leu Asn Gly Gly Thr Asn Phe Ala Pro Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Pro Gly Gly Ser Tyr Ser Asn Asp Ala Phe Asp Ile Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 77
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 77

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Ser Pro Arg Ser Gly Gly Thr Lys Tyr Ala Gln Arg Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Ala Val Ala Gly Thr His Pro Gln Ala Gly Asp Phe Asp
100 105 110

Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 78
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 78

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1				5			10						15		
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Ser
	20				25								30		
Ala	Met	His	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
	35				40							45			
Ser	Ala	Ile	Gly	Thr	Gly	Asp	Thr	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	
	50				55							60			
Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu
	65				70					75			80		
Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala
	85				90							95			
Arg	Glu	Gly	Asp	Gly	Tyr	Asn	Phe	Phe	Asp	Tyr	Trp	Gly	Gln	Gly	
	100				105							110			
Thr	Leu	Val	Thr	Val	Ser	Ser									
	115														

<210> SEQ ID NO 79

<211> LENGTH: 124

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 79

Gln	Val	Gln	Leu	Val	Gln	Ser	Gly	Ala	Glu	Val	Lys	Lys	Pro	Gly	Ala
1					5			10			15				
Ser	Val	Lys	Val	Ser	Cys	Lys	Ala	Ser	Gly	Tyr	Thr	Phe	Thr	Ser	Tyr
	20				25							30			
Asp	Ile	Asn	Trp	Val	Arg	Gln	Ala	Pro	Gly	Gln	Gly	Leu	Glu	Trp	Met
	35				40							45			
Gly	Met	Ile	Asp	Pro	Ser	Gly	Gly	Ser	Thr	Ser	Tyr	Ala	Gln	Lys	Phe
	50				55							60			
Gln	Gly	Arg	Val	Thr	Met	Thr	Arg	Asp	Thr	Ser	Thr	Ser	Thr	Val	Tyr
	65				70					75			80		
Met	Glu	Leu	Ser	Ser	Leu	Arg	Ser	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
	85				90							95			
Ala	Lys	Asp	Phe	Gly	Gly	Thr	Arg	Tyr	Asp	Tyr	Trp	Tyr	Phe	Asp	
	100				105							110			
Leu	Trp	Gly	Arg	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser				
	115				120										

<210> SEQ ID NO 80

<211> LENGTH: 121

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 80

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1					5			10			15				

-continued

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Pro Phe Ser Gln His
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Asp Arg Ser Gly Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Thr Tyr Gly Gly Lys Val Thr Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 81
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 81

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Thr Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Ser Pro Asn Ser Gly Gly Thr Asp Leu Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Asp Pro Arg Asp Asp Ile Ala Gly Gly Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 82
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 82

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Ser Phe Ser Thr Ser
20 25 30

Ala Phe Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Tyr Thr Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

-continued

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Arg Ala Leu Tyr Gly Ser Gly Ser Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 83

<211> LENGTH: 117

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 83

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Tyr Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Gly Asp Ser Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Met
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 84

<211> LENGTH: 123

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 84

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Asn Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Asp Tyr Gly Asp Tyr Ile Val Ser Pro Phe Asp Leu

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100	105	110
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Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 85
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 85

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Ser Arg Gly Ile Gln Leu Leu Pro Arg Gly Met Asp Val Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 86
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 86

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Met Phe Gly Thr Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Asp Thr Ile Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 87
<211> LENGTH: 124

-continued

<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 87

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Asn Arg Tyr
20 25 30

Ala Phe Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Thr Arg Glu Leu Pro Glu Val Val Asp Trp Tyr Phe Asp
100 105 110

Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 88
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 88

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Ser
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 89
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 89

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp

-continued

20	25	30
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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile		
35	40	45

Tyr Asp Thr Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Thr Pro Trp		
85	90	95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg		
100	105	

<210> SEQ ID NO 90

<211> LENGTH: 109

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 90

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly			
1	5	10	15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Gln Ser Val Ser Gly Thr		
20	25	30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu		
35	40	45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser		
50	55	60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln			
65	70	75	80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Leu Gln Thr His Ser Tyr Pro		
85	90	95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg		
100	105	

<210> SEQ ID NO 91

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 91

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Thr Asn Asn		
20	25	30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Ile		
35	40	45

Tyr Asp Ala Ser Thr Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly		
50	55	60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Thr Phe Pro Tyr		
85	90	95

-continued

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 92
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 92

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Ser Arg Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Gly Phe Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> SEQ ID NO 93
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 93

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Val Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Tyr Thr Thr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> SEQ ID NO 94
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 94

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly

-continued

1	5	10	15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser			
20	25	30	
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser			
35	40	45	
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro			
50	55	60	
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
65	70	75	80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala			
85	90	95	
Leu Gln Thr Pro Ala Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys			
100	105	110	

Arg

<210> SEQ ID NO 95			
<211> LENGTH: 113			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Polypeptide			
 <400> SEQUENCE: 95			
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly			
1	5	10	15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser			
20	25	30	
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser			
35	40	45	
Pro Gln Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro			
50	55	60	
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile			
65	70	75	80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala			
85	90	95	
Leu Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys			
100	105	110	

Arg

<210> SEQ ID NO 96			
<211> LENGTH: 108			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Polypeptide			
 <400> SEQUENCE: 96			
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly			
1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Tyr			
20	25	30	
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile			
35	40	45	
Tyr Asp Ala Ser Asn Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly			
50	55	60	

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> SEQ ID NO 97

<211> LENGTH: 113

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 97

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln Tyr
85 90 95

Tyr Ser Ser Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 98

<211> LENGTH: 109

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 98

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Gln Ile Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 99

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<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 99

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Arg
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Ser Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Tyr Thr Thr Pro
85 90 95

Arg Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
100 105

<210> SEQ ID NO 100
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 100

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser His
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Tyr Ser Thr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 101
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 101

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

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-continued

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys Arg

<210> SEQ ID NO 102

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 102

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Ser Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Phe Ser Pro Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys Arg
100 105

<210> SEQ ID NO 103

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 103

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
85 90 95

-continued

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> SEQ ID NO 104
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 104

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Thr Thr Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 105
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 105

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Pro Pro Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 106
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 106

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Asn
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Gly Phe Pro Leu
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
100 105

<210> SEQ ID NO 107

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Polypeptide

<400> SEQUENCE: 107

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Ala Pro Leu Thr Phe Gly Gly Thr Lys Val Glu Ile
100 105 110

Lys Arg

<210> SEQ ID NO 108

<211> LENGTH: 227

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Fc Chain 1

<400> SEQUENCE: 108

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
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Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
20 25 30

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
35 40 45

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
50 55 60

-continued

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
 65 70 75 80
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
 85 90 95
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
 100 105 110
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
 115 120 125
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser
 130 135 140
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
 145 150 155 160
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
 165 170 175
 Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
 180 185 190
 Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Leu
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 His Glu Ala Leu His Ser His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
 210 215 220
 Pro Gly Lys
 225

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 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 109

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30

<210> SEQ ID NO 110
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 <220> FEATURE:
 <223> OTHER INFORMATION: Primer

<400> SEQUENCE: 110

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27

<210> SEQ ID NO 111
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 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
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<400> SEQUENCE: 111

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30

<210> SEQ ID NO 112
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 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

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<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 112

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Cys Gly Ala Cys Thr Thr Gly Gly
20 25

<210> SEQ ID NO 113

<211> LENGTH: 31

<212> TYPE: DNA

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<220> FEATURE:

<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 113

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<220> FEATURE:

<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 114

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26

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<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Primer

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<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 116

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<210> SEQ ID NO 117

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 117

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33

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<211> LENGTH: 28

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Primer

<400> SEQUENCE: 118

gctgttccag gcaatcacac agccggtg

28

1. A fusion protein comprising a nanocage monomer linked to a SARS-CoV-2 binding moiety, wherein a plurality of the fusion proteins self-assemble to form a nanocage.
2. The fusion protein of claim 1, wherein the SARS-CoV-2 binding moiety targets the SARS-CoV-2 S glycoprotein.
3. (canceled)
4. The fusion protein of claim 1, wherein the SARS-CoV-2 binding moiety comprises an antibody or fragment thereof.
5. The fusion protein of claim 4, wherein the antibody or fragment thereof comprises a Fab fragment.
6. The fusion protein of claim 4, wherein the antibody or fragment thereof comprises a scFab fragment, a scFv fragment, a sdAb fragment, a VH domain or a combination thereof.
7. The fusion protein of claim 4, wherein the antibody or fragment thereof comprises a heavy and/or light chain of a Fab fragment.
8. The fusion protein of claim 4, wherein the SARS-CoV-2 binding moiety comprises single chain variable domain VHH-72, BD23 and/or 4A8.
9. The fusion protein of claim 4, wherein the SARS-CoV-2 binding moiety comprises an mAb listed in Table 4.
10. The fusion protein of claim 9, wherein the SARS-CoV-2 binding moiety comprises mAb 298, 324, 46, 80, 52, 82, or 236 from Table 4, or variants thereof.
11. The fusion protein of claim 1, wherein the SARS-CoV-2 binding moiety is linked at the N- or C-terminus of the nanocage monomer, or wherein there is a first SARS-CoV-2 binding moiety linked at the N-terminus and a second SARS-CoV-2 binding moiety linked at the C-terminus of the nanocage monomer, wherein the first and second SARS-CoV-2 binding moieties are the same or different.
12. The fusion protein of claim 1, wherein the nanocage monomer comprises a first nanocage monomer subunit linked to the SARS-CoV-2 binding moiety; wherein the first nanocage monomer subunit self-assembles with a second nanocage monomer subunit to form the nanocage monomer.
- 13-20. (canceled)
21. The fusion protein of claim 1, wherein the nanocage monomer is selected from ferritin, apoferritin, encapsulin, SOR, lumazine synthase, pyruvate dehydrogenase, carboxysome, vault proteins, GroEL, heat shock protein, E2P, MS2 coat protein, fragments thereof, and variants thereof.
22. The fusion protein of claim 21, wherein the nanocage monomer is apoferritin.
23. The fusion protein of claim 22, wherein the first and second nanocage monomer subunits interchangeably comprise the "N" and "C" regions of apoferritin.
- 24.-25. (canceled)
26. The fusion protein of claim 1, further comprising a linker between the nanocage monomer subunit and the bioactive moiety.
27. The fusion protein of claim 26, wherein the linker is flexible or rigid and comprises from about 1 to about 30 amino acid residues.
28. The fusion protein of claim 26, wherein the linker comprises at least one GGS repeat.
29. (canceled)
30. The fusion protein of claim 1, further comprising a C-terminal linker.
31. (canceled)
32. A nanocage comprising at least one fusion protein of claim 1 and at least one second nanocage monomer subunit that self-assembles with the fusion protein to form a nanocage monomer.
33. The nanocage of claim 32, wherein each nanocage monomer comprises the fusion protein of claim 1.
34. (canceled)
35. The nanocage of claim 32, comprising at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 different SARS-CoV-2 binding moieties.
36. The nanocage of claim 32, wherein the nanocage is multivalent and/or multispecific.
37. The nanocage of claim 32, comprising one of more mAbs from Table 4.
38. The nanocage of claim 37, comprising 3 mAbs from Table 4.
39. The nanocage of claim 37 comprising mAbs 298, 324, 46, 52, 80, 82 and/or 236 from Table 4.
40. The nanocage of claim 32, comprising a 4:2:1:1 ratio of scFab1-human apoferitin:scFc-human N-Ferritin:scFab2-C-Ferritin:scFab3-C-Ferritin.
41. The nanocage of claim 32, carrying a cargo molecule selected from the group consisting of a pharmaceutical agent, a diagnostic agent, and an imaging agent.
- 42-44. (canceled)
45. A tri-specific antibody construct targeting SARS-CoV-2.
46. A SARS-CoV-2 therapeutic or prophylactic composition comprising the nanocage of claim 32.
47. A nucleic acid molecule encoding the fusion protein of claim 1.
48. A vector comprising the nucleic acid molecule of claim 47.
49. A host cell comprising the vector of claim 48.
50. A method for treating and/or preventing SARS-CoV-2 in a subject in need thereof, the method comprising administering to the subject the nanocage of claim 32.
- 51.-52. (canceled)
53. A polypeptide comprising an amino acid sequence having at least

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AYNGNTNYAQKQLQGRVTMTRDTST VYMEPLLRSRSEDAVYYCARDIGPIDY WGQGTLVTVSS (SEQ ID NO: 68)	SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQQANSFPSTFGQGTTKEIKR (SEQ ID NO: 88)
EVQLLESGGGLVQPGGSRLSCAASGF TFSNYGMHWVRQAPGKGLEWVGII AGSITNYADSVKGRFTISRDNSKNTLY LQMNSLRAEDTAVYYCAGNHAGTTV TSEYFQHVGQGTLVTVSS (SEQ ID NO: 69)	DIQMTQSPSSLSASVGDRVITTCRASQS ISWLAWYQQKPGKAPKLLIYDTSNLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYTTPWTFGQGTRLEIKR (SEQ ID NO: 89)
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QVQLVQSGAEVKKPGASVKVSCKASG YIFSRYIAHWVRQAPGQGLEWMGW NPISGNTDYQPNFQGRVTMTRDTSTS VYMEPLLRSRSEDAVYYCAKDGSOLA YIVEYFQHVGQGTLVTVSS (SEQ ID NO: 71)	DIQMTQSPSSLSASVGDRVITTCRASQV ITNNLAWYQQKPGKAPKLLIYDASTLE TGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQSYTFFPYTFGQGTTKEIKR (SEQ ID NO: 91)
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QVQLVQSGAEVKKPGASVKVSCKASG YTFTGHDMHWVRQAPGQGLEWMGII NPSSGGSTSAYAQKFQGRVTMTRDTSTS VYMEPLLRSRSEDAVYYCARANSLRY YYGMDVWQGQGTMVTVSS (SEQ ID NO: 73)	DIQMTQSPSSLSASVGDRVITTCRASQS VSWSLAWYQQKPGKAPKLLIYASSL QSGVPSRFSGSGSGTDFTLTISSLQPEDF ATYYCQQGYTTPYTFGQGTTKEIKR (SEQ ID NO: 93)
QVQLVQSGAEVKKPGSSVKVSCKASG YTFTSYIDINWVQAPGQGLEWMGAIM PMFGTANYAQKFQGRVTITADESTSTA YMEPLLRSRSEDAVYYCARGSSYYY GWGQGTLVTVSS (SEQ ID NO: 74)	DIVMTQSPPLSLPVTGEPASISCRSSQL LHSNGYNYLDWYLQKPGQSPQLLIYL GSNRASGPDRFSGSGSGTDFTLKISR EAEDVGVYYCMQALQTPATFGPGTKV DI KR (SEQ ID NO: 94)
QVQLVQSGAEVKKPGSSVKVSCKASG GTSSSYAISWVQAPGQGLEWMGIN PNSGGANYAQKFQGRVTITADESTSTA YMEPLLRSRSEDAVYYCSTYYDSSG YSTDYWQGQGTLVTVSS (SEQ ID NO: 75)	DIVMTQSPPLSLPVTGEPASISCRSSQL LHSNGYNYLDWYLQKPGQSPQLLIYA ASSLQSGVPDRFSGSGSGTDFTLKISR EAEDVGVYYCMQALQTPYTFGQGTTKL EI KR (SEQ ID NO: 95)
QVQLVQSGAEVKKPGASVKVSCKASG YTFTGYYMMHWVRQAPGQGLEWMGWI NPPLNGGTNFAPKFOGRVTMTRDTSTS VYMEPLLRSRSEDAVYYCARDPGGSY SNDAFD1WGQGTLVTVSS (SEQ ID NO: 76)	DIQMTQSPSSLSASVGDRVITTCRASQS ISRYLNWYQQKPGKAPKLLIYDASNLE SGVPSRFSGSGSGTDFTLTISSLQPEDFA TYYCQQQANSFPLTFGGGTTKEIKR (SEQ ID NO: 96)
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QVQLVQSGAEVKKPGASVKVSCKASG YTFTSYDINWVRQAPGQGLEWMGMID PSGGSTSYAQKPGQGRVTMTRDTSTTV YMELESSLRSEDTAVYYCAKDFGGGTR YDWFYFDLWGRGLTVTVSS (SEQ ID NO: 79)	EIVMTQSPATLSVSPGERATLSCRASQS VSSRYLAWYQQKPGQAPRLIYGAST RATGTPARFSGSGSGTEFTLTISLQSED FAVYYCQYYTTPRTFGQGTRLEIKR (SEQ ID NO: 99)
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QVQLVQSGAEVKKPGASVKVSCKASG GSFSTSAYWVQAPGQGLEWMGWIS PYTGGTNYAQKPGQGRVTMTRDTST VYMELESSLRSEDTAVYYCARSRALY SGSYFDIWQGQTLTVTVSS (SEQ ID NO: 82)	DIQMTQSPSSLSASVGDRVITTCRASQV ISNYLAWYQQKPGKAPKLLIYDASNLE TGVPSPRSFGSGSGTDFTLTISLQPEDF ATYYCQSFSPPTFGQGTRLEIKR (SEQ ID NO: 102)
EVQLLESGGGLVQPGGRSLRLSCKASGF TFSSYAMSWVRQAPGKLEWVSTIYS GGSTYYADSVKGRFTISRDNSKNTLY QMNLSLRSEDTAVYYCARGDSDRAFDI WGQGTMVTVSS (SEQ ID NO: 83)	DIQMTQSPSSLSASVGDRVITTCRASQS ISSHLAWYQQKPGKAPKLLIYDASNLE TGVPSPRSFGSGSGTDFTLTISLQPEDF ATYYCQSYSTPPTFGPGTKVDIKR (SEQ ID NO: 103)
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QVQLVQSGAEVKKPGSSVKVSCKASG GTPNRYAFSWVRQAPGQGLEWMGGII PIFGTANYAQKPGQGRVTIADESTSTA YMELESSLRSEDTAVYYCARSTRELPEV VDWFYFDLWGRGLTVTVSS (SEQ ID NO: 87)	DIVMTQSPDSLAVSLGERATINCKSSQS VLYSSNNKNYLAWYQQKPGQPPKLLI YWASTRESGPDRFSGSGSGTDFTLTIS SLQAEDVAVYYCQYYSAPLTFGGGT KVEIKR (SEQ ID NO: 107)

or a functional fragment thereof.

54.-56. (canceled)

57. A fusion polypeptide comprising (1) a fragment crystallizable (Fc) region linked to (2) a nanocage monomer or subunit thereof, wherein the Fc region comprises the I253A mutation, wherein numbering is according to the EU index.

58.-66. (canceled)

67. A self-assembled polypeptide complex comprising:

- (a) a plurality of first fusion polypeptides, each first fusion polypeptide comprising (1) an Fc region linked to (2) a nanocage monomer or subunit thereof, and
- (b) a plurality of second fusion polypeptides, each second fusion polypeptide comprising (1) a SARS-CoV-2-binding antibody fragment linked to (2) a nanocage monomer or subunit thereof.

68. The self-assembled polypeptide complex of claim **67**, wherein the nanocage monomer is a ferritin monomer.

69. The self-assembled polypeptide complex of claim **68**, wherein the nanocage monomer is a ferritin light chain.

70. The self-assembled polypeptide complex of claim **69**, which does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.

71.-82. (canceled)

83. A self-assembled polypeptide complex comprising:

- (a) a plurality of first fusion polypeptides, each first fusion polypeptide comprising (1) an IgG1 Fc region linked to (2) a human ferritin monomer or subunit thereof, wherein the IgG1 Fc region comprises the LALAP (L234A/L235A/P329G) and I253A mutations, wherein numbering is according to the EU index, and
- (b) a plurality of second fusion polypeptides, each second fusion polypeptide comprising (1) a Fab fragment of an antibody that is capable of binding to a SARS-CoV-2 protein, the Fab fragment being linked to (2) a human ferritin monomer or subunit thereof.

84-99. (canceled)

100. A method of treating, ameliorating, or preventing a SARS-CoV-2-related condition, the method comprising administering to a subject a composition comprising the self-assembled polypeptide complex of claim **67**.

101.-102. (canceled)

103. The fusion protein of claim **10**, wherein the SARS-CoV-2 binding moiety comprises mAb 298, 80, and 52 from Table 4, or variants thereof.

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