



US012384837B2

(12) **United States Patent**
Cady et al.

(10) **Patent No.:** US 12,384,837 B2
(b4) **Date of Patent:** *Aug. 12, 2025

(54) **TREATMENT OF MOST BOthersome SYMPTOM (MBS) ASSOCIATED WITH MIGRAINE USING ANTI-CGRP ANTIBODIES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/182,822**

(22) Filed: **Mar. 13, 2023**

(65) **Prior Publication Data**

US 2024/0101653 A1 Mar. 28, 2024

Related U.S. Application Data

(63) Continuation of application No. 16/860,239, filed on Apr. 28, 2020, now abandoned.

(60) Provisional application No. 63/005,950, filed on Apr. 6, 2020.

(51) **Int. Cl.**

C07K 16/18 (2006.01)
A61K 9/00 (2006.01)
A61K 39/00 (2006.01)
A61P 25/06 (2006.01)

(52) **U.S. Cl.**

CPC **C07K 16/18** (2013.01); **A61K 9/0019** (2013.01); **A61P 25/06** (2018.01); **A61K 2039/545** (2013.01)

(58) **Field of Classification Search**

CPC C07K 16/18; C07K 2317/565; C07K 2317/76; A61K 9/0019; A61K 2039/545; A61K 39/39591; A61K 2039/505; A61P 25/06

See application file for complete search history.

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(57) **ABSTRACT**

Methods for treatment of most bothersome symptom (MBS) associated with migraine are provided. Exemplary methods provide improvement in MBS associated with migraine within 1 month of administration of anti-CGRP antibodies of the invention. Also provided are methods for improvement of patient impression of change (PGIC) associated with migraine. Exemplary methods comprise administration of an anti-CGRP antagonistic antibody to a patient in need thereof.

12 Claims, 23 Drawing Sheets

Specification includes a Sequence Listing.

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Figure 1 - Heavy Chain Protein Sequence

Sequence Name: Ab6

FR1	EVQLVESGGGLVQPGGSLRLSCAVSGIDLS	SEQ ID NO: 203
CDR1	GYYMN	SEQ ID NO: 204
FR2	WVRQAPGKGLEWVG	SEQ ID NO: 205
CDR2	VIGINGATYYASWAKG	SEQ ID NO: 206
FR3	RFTISRDNSKTTVYLQMNSLRAEDTAVYFCAR	SEQ ID NO: 207
CDR3	GDI	SEQ ID NO: 208
FR4	WGQGTLVTVSS	SEQ ID NO: 209
Variable Region	EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWV RQAPGKGLEWVGIVIGINGATYYASWAKGRFTISRDNS KTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSS	SEQ ID NO: 202
Constant Region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAPVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHPKSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDLMISRTPETCVVVD VSHEDEPVKFNWYVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKA KGQPREPVQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVD KSRWQQGNVFCSVMHEALHNHYTQKSLSLSPKG	SEQ ID NO: 564
Alternative constant region	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAPVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHPKSNTKVDKRVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDLMISRTPETCVVVD VSHEDEPVKFNWYVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKA KGQPREPVQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVD KSRWQQGNVFCSVMHEALHNHYTQKSLSLSPKG	SEQ ID NO: 565
Full length Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWV RQAPGKGLEWVGIVIGINGATYYASWAKGRFTISRDNS KTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAPVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHPKSNTKVDARVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDLMISRTPETCVVVD VSHEDEPVKFNWYVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKA KGQPREPVQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVD KSRWQQGNVFCSVMHEALHNHYTQKSLSLSPKG	SEQ ID NO: 201
Alternative Full length Heavy Chain	EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMNWV RQAPGKGLEWVGIVIGINGATYYASWAKGRFTISRDNS KTTVYLQMNSLRAEDTAVYFCARGDIWGQGTLVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAPVLQSSGLYSLSSVVTVPSS SLGTQTYICNVNHPKSNTKVDARVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDLMISRTPETCVVVD VSHEDEPVKFNWYVDGVEVHNAKTKPREEQYASTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKA KGQPREPVQVYTLPPSREEMTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTPVLDSDGSFFLYSKLTVD KSRWQQGNVFCSVMHEALHNHYTQKSLSLSPKG	SEQ ID NO: 566

Figure 2 - Light Chain Protein Sequence

Sequence Name: Ab6

FR1	QVLTQSPSSLSASVGDRVTINC	SEQ ID NO: 223
CDR1	QASQSVYHNTYLA	SEQ ID NO: 224
FR2	WYQQKPGKVKPQLIY	SEQ ID NO: 225
CDR2	DASTLAS	SEQ ID NO: 226
FR3	GVPSRFGSGSGTDFTLTISLQPEDVATYYC	SEQ ID NO: 227
CDR3	LGSYDCTNGDCFV	SEQ ID NO: 228
FR4	FGGGTTKVEIKR	SEQ ID NO: 229
Variable Region	QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLA WYQQKPGKVKPQLIYDASTLASGVPSRFGSGSGTDFTL TISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEI KR	SEQ ID NO: 222
Constant Region	TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTTLS KADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 563
Full length light Chain	QVLTQSPSSLSASVGDRVTINCQASQSVYHNTYLA WYQQKPGKVKPQLIYDASTLASGVPSRFGSGSGTDFTL TISSLQPEDVATYYCLGSYDCTNGDCFVFGGGTKVEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	SEQ ID NO: 221

Figure 3A - Heavy Chain DNA Sequence

Sequence Name: Ab6

FR1	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCC AGCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTC TGGAAATCGACCTCAGT	SEQ ID NO: 213
CDR1	GGCTACTACATGAAC	SEQ ID NO: 214
FR2	TGGGTCCGTCAAGGCTCCAGGGAAAGGGGCTGGAGTGGG TCGGA	SEQ ID NO: 215
CDR2	GTCATTGGTATTAATGGTGCCACATACTACGCGAGCT GGCGAAGGGC	SEQ ID NO: 216
FR3	CGATTCAACCCTCTCCAGAGACAATTCCAAGACCACGG TGTATCTCAAATGAACAGCCTGAGAGCTGAGGACAC TGCTGTGTATTCGTGCTAGA	SEQ ID NO: 217
CDR3	GGGGACATC	SEQ ID NO: 218
FR4	TGGGGCCAAGGGACCCCTCGTCACCGTCTCGAGC	SEQ ID NO: 219
Variable Region	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCC AGCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTC TGGAAATCGACCTCAGTGGCTACTACATGAACACTGGTC CGTCAGGCTCCAGGGAAAGGGGCTGGAGTGGGTGGAG TCATTGGTATTAATGGTGCCACATACTACGCGAGCTG GGCGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGACCACGGTGTATCTCAAATGAACAGCCTGAGAG CTGAGGACACTGCTGTGTATTCGTGCTAGAGGGGA CATCTGGGGCCAAGGGACCCCTCGTCACCGTCTCGAGC	SEQ ID NO: 212
Full length Heavy Chain	GAGGTGCAGCTTGTGGAGTCTGGGGGAGGCTTGGTCC AGCTGGGGGGTCCCTGAGACTCTCCTGTGCAGTC TGGAAATCGACCTCAGTGGCTACTACATGAACACTGGTC CGTCAGGCTCCAGGGAAAGGGGCTGGAGTGGGTGGAG TCATTGGTATTAATGGTGCCACATACTACGCGAGCTG GGCGAAGGGCCGATTCACCATCTCCAGAGACAATTCC AAGACCACGGTGTATCTCAAATGAACAGCCTGAGAG CTGAGGACACTGCTGTGTATTCGTGCTAGAGGGGA CATCTGGGGCCAAGGGACCCCTCGTCACCGTCTCGAGC GCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCAC CCTCCCTCCAAGAGCACCTCTGGGGCACAGGGCCCT GGGCTGCCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTGTTGGAAACTCAGGCGCCCTGACCAGGGCG TGCACACCTTCCCAGGTGTCTACAGTCTCAGGACT CTACTCCCTCAGCAGGGTGGTACCGTCCCCCTCAGC AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATC ACAAGCCCAGCAACACCAAGGTGGACCGCGAGAGTTGA GCCCAATCTGTGACAAAACCTCACACATGCCAACCG TGCCCAGCACCTGAACTCTGGGGGACCGTCAAGTCT TCCCTCTCCCCCAAAACCAAGGACACCCCTCATGAT CTCCCGGACCCCTGAGGTCAAGTCAACTGGT GTGAGGCCACGAAGACCCCTGAGGTCAAGTCAACTGGT ACGTGGACGGGGTGGAGGTGATAATGCCAAGACAAA GCCCGGGAGGAGCAGTACGCCAGCACGTACCGTGTG GTCAGCGTCCTCACCGTCTGCACCAGGACTGGCTGA ATGGCAAGGAGTACAAGTGCAGGTCTCCAACAAAGC CCTCCCAGCCCCCATCGAGAAAACCATCTCAAAGCC AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCCTGC CCCCATCCCAGGGAGGAGATGACCAAGAACCCAGGTGAC CCTGACACTGCCCTGGTCAAAGGCTTCTATCCCAGCGAC	SEQ ID NO: 211

Figure 3B - Heavy Chain DNA Sequence

Sequence Name: Abc

	ATCGCCGTGGAGTGGGAGAGCAATGGCAGCCGGAGA ACAAC TACAAGACCACGCCTCCCGTGTGGACTCCGA CGGCTCCTCTTCCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACTACACGCA GAAGAGCCTCTCCCTGTCTCCGGTAAATGA	
Alternative Full length Heavy Chain	GAGGTGCAGCTGTGGAGTCTGGGGGAGGCTTGGTCC AGCCTGGGGGGTCCCTGAGACTCTCTGTGCAGTCTC TGGAAATCGACCTCAGTGGTACTACATGAACCTGGTC CGTCAGGCTCAGGGAAAGGGCTGGAGTGGTGGAG TCATTGGTATTAAATGGTGCCACATACTACCGCAGGCTG GGCGAAAGGCCGATTCACCATCTCCAGAGACAATTCC AAGACCACGGTGTATCTTCAAATGAACAGCCTGAGAG CTGAGGACACTGCTGTATTTCTGTGCTAGAGGGGA CATCTGGGCAAGGGACCCCTCGTACCCGTCTCGAGC GCCTCCACCAAGGGCCATCGGTCTTCCCCCTGGCAC CCTCCTCCAAGAGCACCTCTGGGGCACAGCGGGCCT GGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTG ACGGTGTGTTGAACCTCAGGCGCCCTGACCAGGGCG TGCACACCTTCCCAGCTGTCTACAGTCTCAGGACT CTACTCCCTCAGCAGCGTGGTGACCGTGCCTCCAGC AGCTTGGGCAACCCAGACCTACATCTGCAACGTGAATC ACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGA GCCCAAATCTTGTGACAAAACCTCACACATGCCAACCG TGCCCAGCACCTGAECTCTGGGGGACCGTCAGTCT TCCCTTCCCCCAAAACCAAGGACACCCCTCATGAT CTCCCGGACCCCTGAGGTACATGCGTGGTGGAC GTGAGCCACGAAGACCTGAGGTCAAGTTCAACTGGT ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAA GCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTG GTCAGCGTCTCACCCTGTCACATGCGTGGTGGAC ATGGCAAGGAGTACAAGTGCACAGGTCTCCAACAAAGC CCTCCCAGCCCCCATCGAGAAAACCATCTCAAAGCC AAAGGGCAGCCCCGAGAACCCACAGGTGTACACCCCTGC CCCCATCCUGGGAGGAGATGACCAAGAACCAAGGTCAG CCTGACCTGCCCTGGTCAAAGGCTTCTATCCCAGCGAC ATCGCCGTGGAGTGGGAGAGCAATGGCAGCCGGAGA ACAAC TACAAGACCACGCCTCCCGTGTGGACTCCGA CGGCTCCTCTTCCTCTACAGCAAGCTCACCGTGGAC AAGAGCAGGTGGCAGCAGGGAACGTCTTCTCATGCT CCGTGATGCATGAGGCTCTGCACAACCACTACACGCA GAAGAGCCTCTCCCTGTCTCCGGTGA	SEQ ID NO: 567

Figure 4 - Light Chain DNA Sequence

Sequence Name: Ab6

FR1	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCAATTGC	SEQ ID NO: 233
CDR1	CAGGCCAGTCAGAGTGTATCATAACACCTACCTGG CC	SEQ ID NO: 234
FR2	TGGTATCAGCAGAAACCAGGGAAAGTTCTAAGAAC TGATCTAT	SEQ ID NO: 235
CDR2	GATGCATCCACTCTGGCATCT	SEQ ID NO: 236
FR3	GGGGTCCCCTCTCGTTCTAGTGGCAGTGGATCTGGGA CAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGA AGATGTTGCAACTTATTACTGT	SEQ ID NO: 237
CDR3	CTGGGCAGTTATGATTGACTAATGGTGATTGTTTG TT	SEQ ID NO: 238
FR4	TTCCGGCGGAGGAACCAAGGTGGAAATCAAACGT	SEQ ID NO: 239
Variable Region	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCAATTGCCAGGGCAG TCAGAGTGTATCATAACACCTACCTGGCCTGGTAT CAGCAGAAACCAGGGAAAGTTCTAAGCAACTGATCT ATGATGCATCCACTCTGGCATCTGGGATCTGGGACAGATTC TTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCATCAGCAGCCTGCAGCCTGAAGAGTGTGCAACTT ATTACTGTCTGGCAGTTATGATTGACTAATGGTGA TTGTTTGTGTTCTGGCGAGGAACCAAGGTGGAAATC AAACGTACGGTGGCTGCACCCTGTCTTCATCTCC CGCCATCTGATGAGCAGTGAAGATCTGGAACGCTC TGTGTTGCTGCTGCTGAATAACTCTATCCCAGAGAG GCCAAAGTACAGTGGAAAGGTGGATAACGCCCTCCAAT CGGTAACCTCCAGGAGAGTGTACAGAGCAGGACAG CAAGGACAGCACCTACAGCCTCAGCAGCACCTGACG CTGAGCAAAGCAGACTACAGAGAAACACAAAGTCTACG CCTGCGAAGTCACCCATCAGGGCTGAGCTCGCCCGT CACAAAGAGCTTCAACAGGGAGAGTGTAG	SEQ ID NO: 232
Full length light Chain	CAAGTGCTGACCCAGTCTCCATCCTCCCTGTCTGCAT CTGTAGGAGACAGAGTCACCATCAATTGCCAGGGCAG TCAGAGTGTATCATAACACCTACCTGGCCTGGTAT CAGCAGAAACCAGGGAAAGTTCTAAGCAACTGATCT ATGATGCATCCACTCTGGCATCTGGGATCTGGGACAGATTC TTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTC ACCATCAGCAGCCTGCAGCCTGAAGAGTGTGCAACTT ATTACTGTCTGGCAGTTATGATTGACTAATGGTGA TTGTTTGTGTTCTGGCGAGGAACCAAGGTGGAAATC AAACGTACGGTGGCTGCACCCTGTCTTCATCTCC CGCCATCTGATGAGCAGTGAAGATCTGGAACGCTC TGTGTTGCTGCTGCTGAATAACTCTATCCCAGAGAG GCCAAAGTACAGTGGAAAGGTGGATAACGCCCTCCAAT CGGTAACCTCCAGGAGAGTGTACAGAGCAGGACAG CAAGGACAGCACCTACAGCCTCAGCAGCACCTGACG CTGAGCAAAGCAGACTACAGAGAAACACAAAGTCTACG CCTGCGAAGTCACCCATCAGGGCTGAGCTCGCCCGT CACAAAGAGCTTCAACAGGGAGAGTGTAG	SEQ ID NO: 231

Figure 5

Heavy Chain Protein Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab6	1-111	202	31-35	204	50-65	206	98-100	208

Figure 6

Heavy Chain Protein Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab6	1-30	203	36-49	205	66-97	207	101-111	209	112-441	564
									112-440	565

Figure 7

Light Chain Protein Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab6	1-113	222	23-35	224	51-57	226	90-102	228

Figure 8

Light Chain Protein Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:	Constant Region Coordinates	SEQ ID NO:
Ab6	1-22	223	36-50	225	58-89	227	103-113	229	114-219	563

Figure 9

Heavy Chain DNA Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab6	1-333	212	91-105	214	148-195	216	292-300	218

Figure 10

Heavy Chain DNA Sequence Features

Antibody	FR1 Coordin ates	SEQ ID NO:	FR2 Coordin ates	SEQ ID NO:	FR3 Coordin ates	SEQ ID NO:	FR4 Coordin ates	SEQ ID NO:
Ab6	1-90	213	106-147	215	196-291	217	301-333	219

Figure 11

Light Chain DNA Sequence Features

Antibody	Variable Region Coordinates	SEQ ID NO:	CDR1 Coordinates	SEQ ID NO:	CDR2 Coordinates	SEQ ID NO:	CDR3 Coordinates	SEQ ID NO:
Ab6	1-339	232	67-105	234	151-171	236	268-306	238

Figure 12

Light Chain DNA Sequence Features

Antibody	FR1 Coordinates	SEQ ID NO:	FR2 Coordinates	SEQ ID NO:	FR3 Coordinates	SEQ ID NO:	FR4 Coordinates	SEQ ID NO:
Ab6	1-66	233	106-150	235	172-267	237	307-339	239

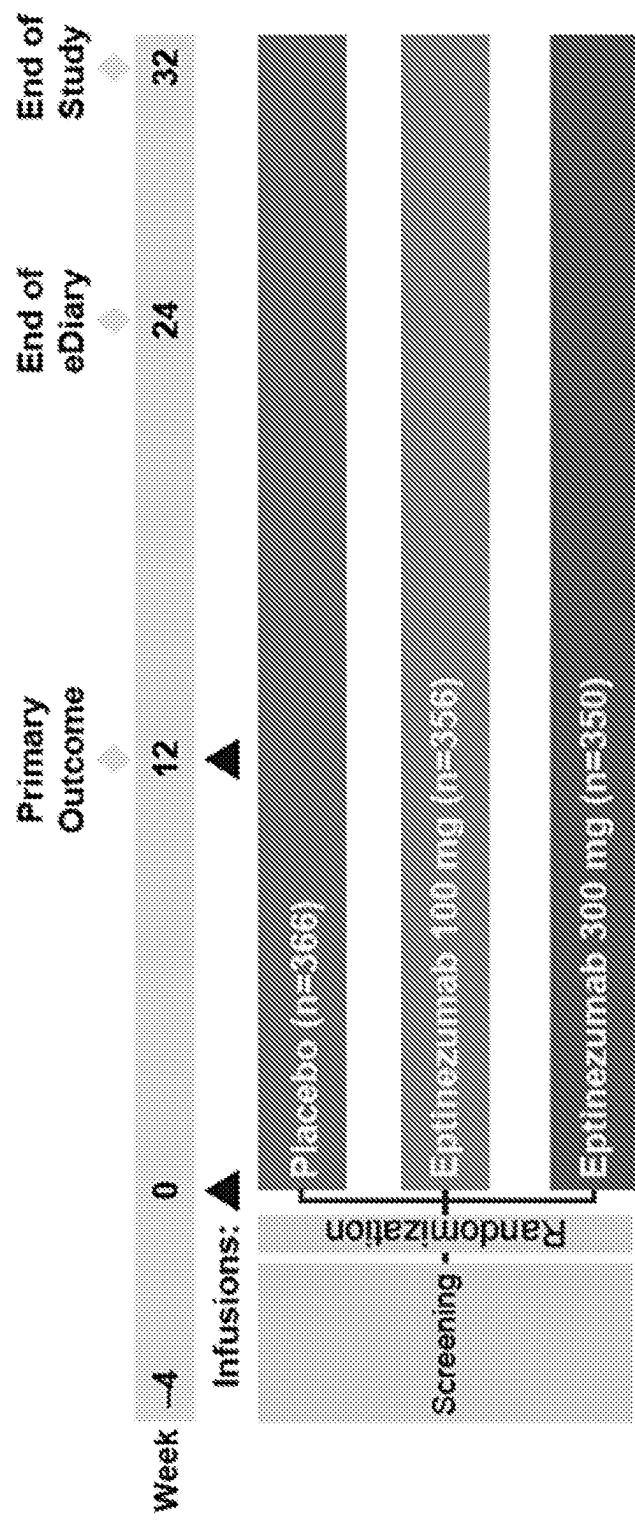


Fig 13 - Study design of clinical trial of example 2

Fig 14 - Mean Monthly migraine days

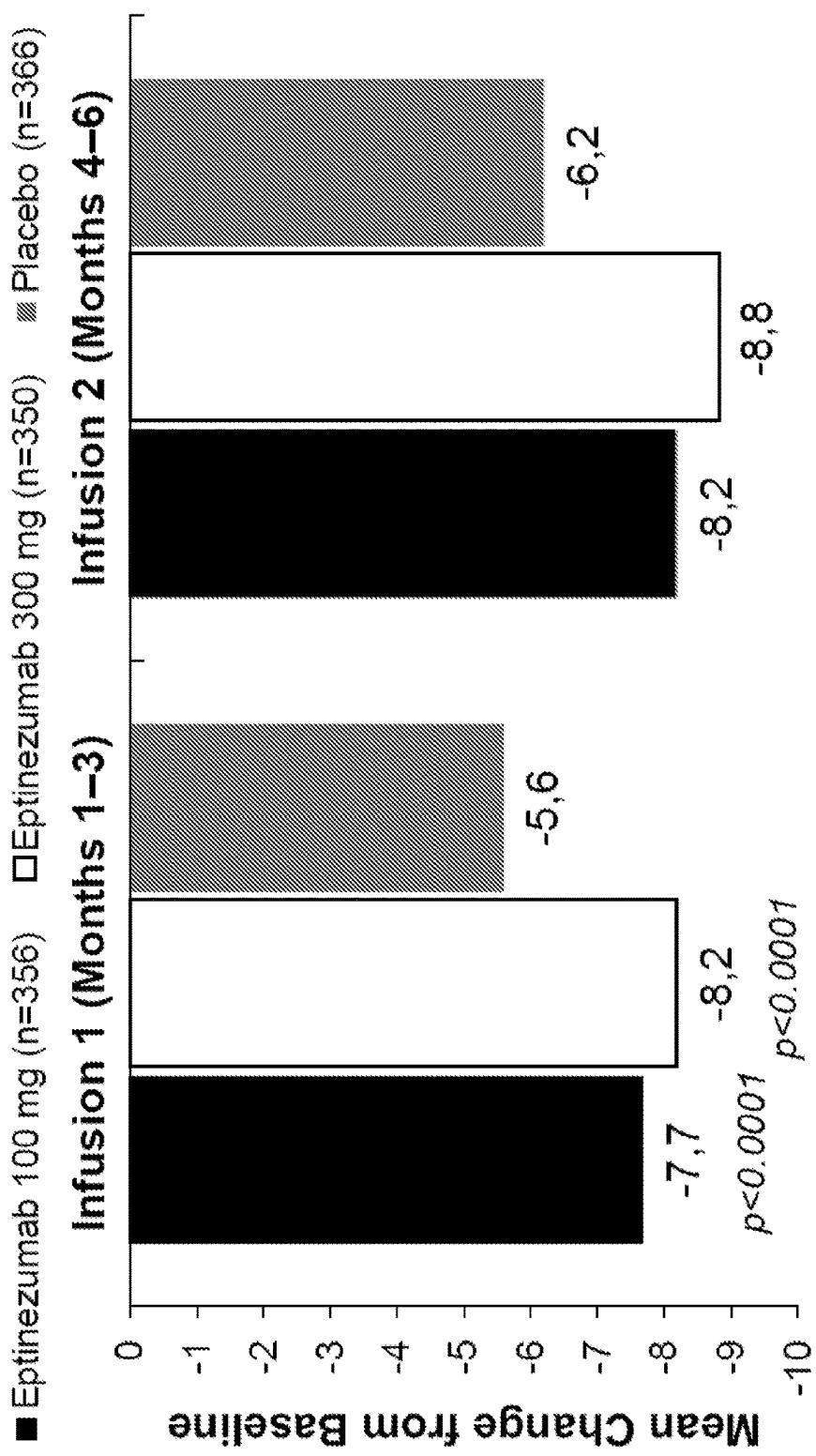


Fig. 15.—Most Bothersome Symptoms Across the Course of the Migraine

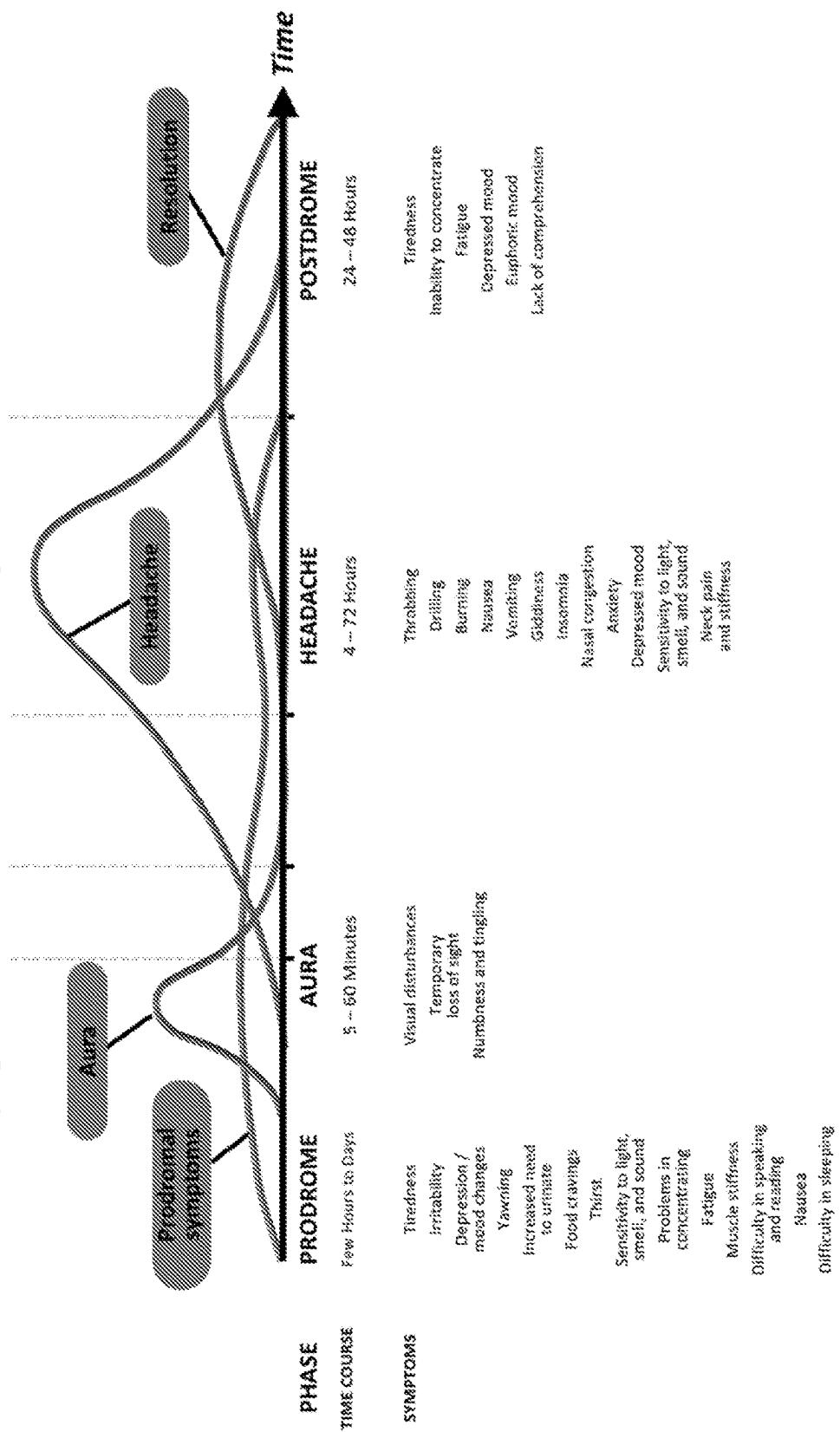


Fig 16 – MBS change from baseline during the 28 day screening period – i.e. before the first infusion of Ab6

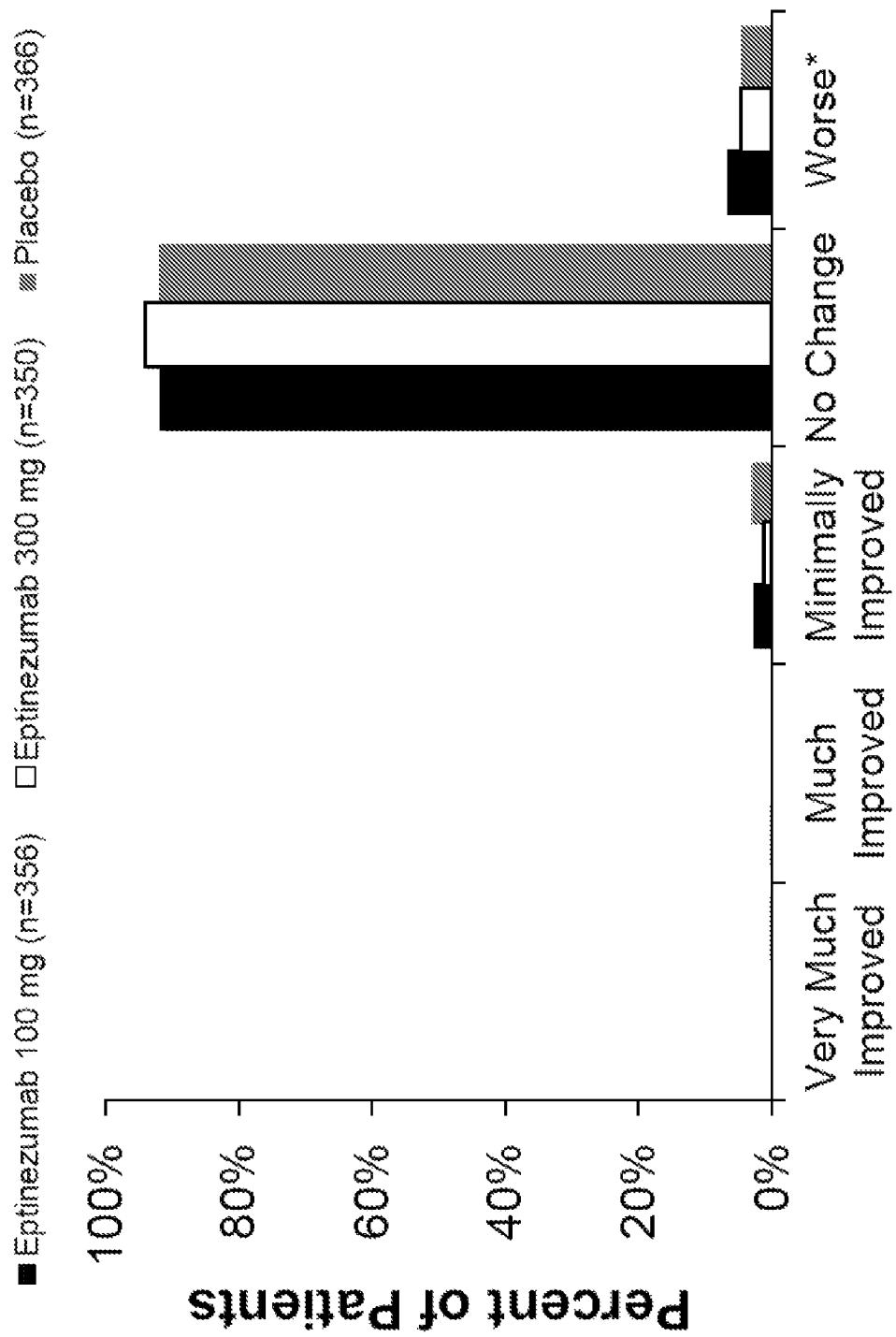


Fig 17 – MBS change from baseline 1 month after first infusion

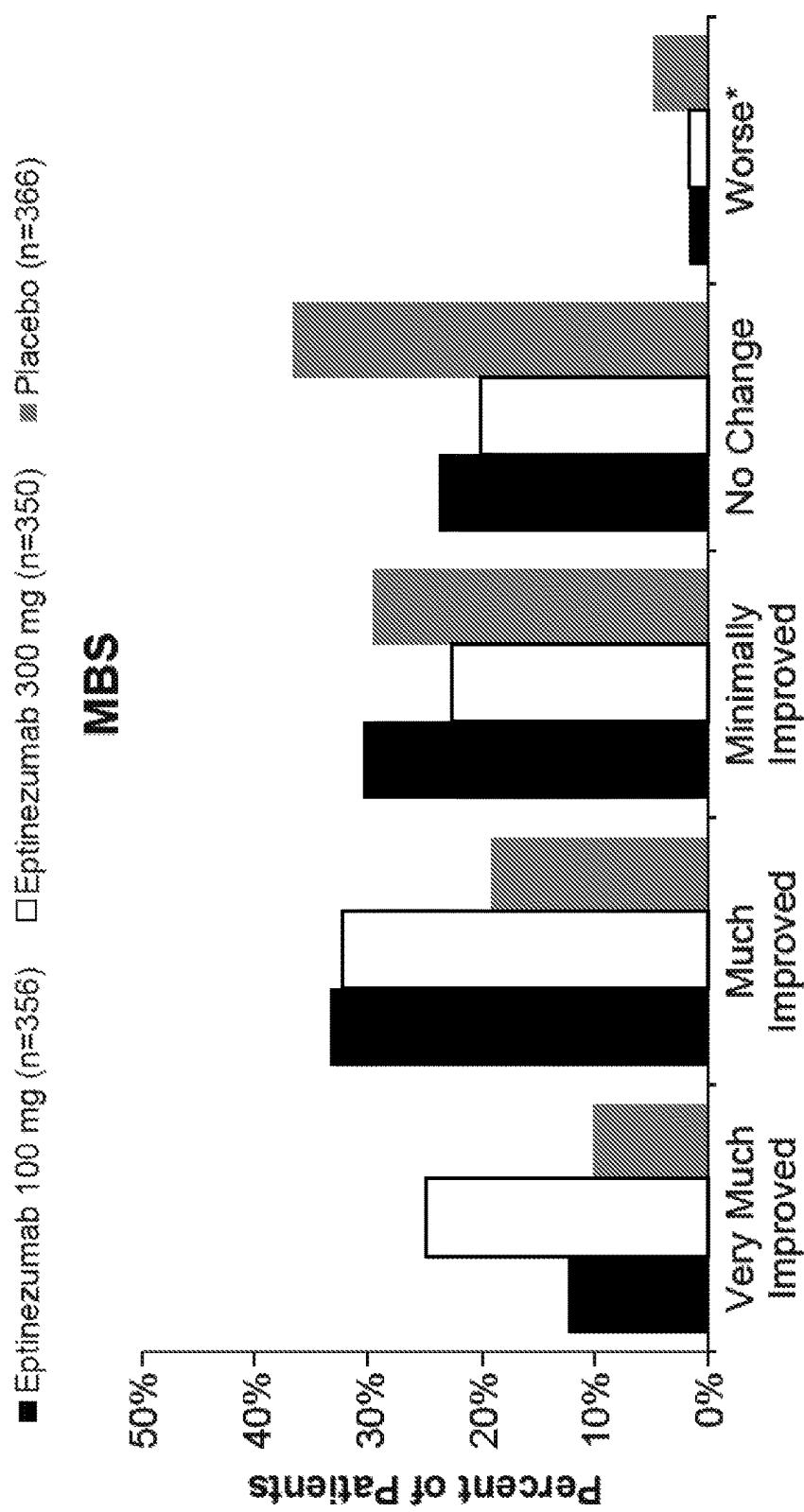


Fig 18 – PGIC from baseline 1 month after first infusion

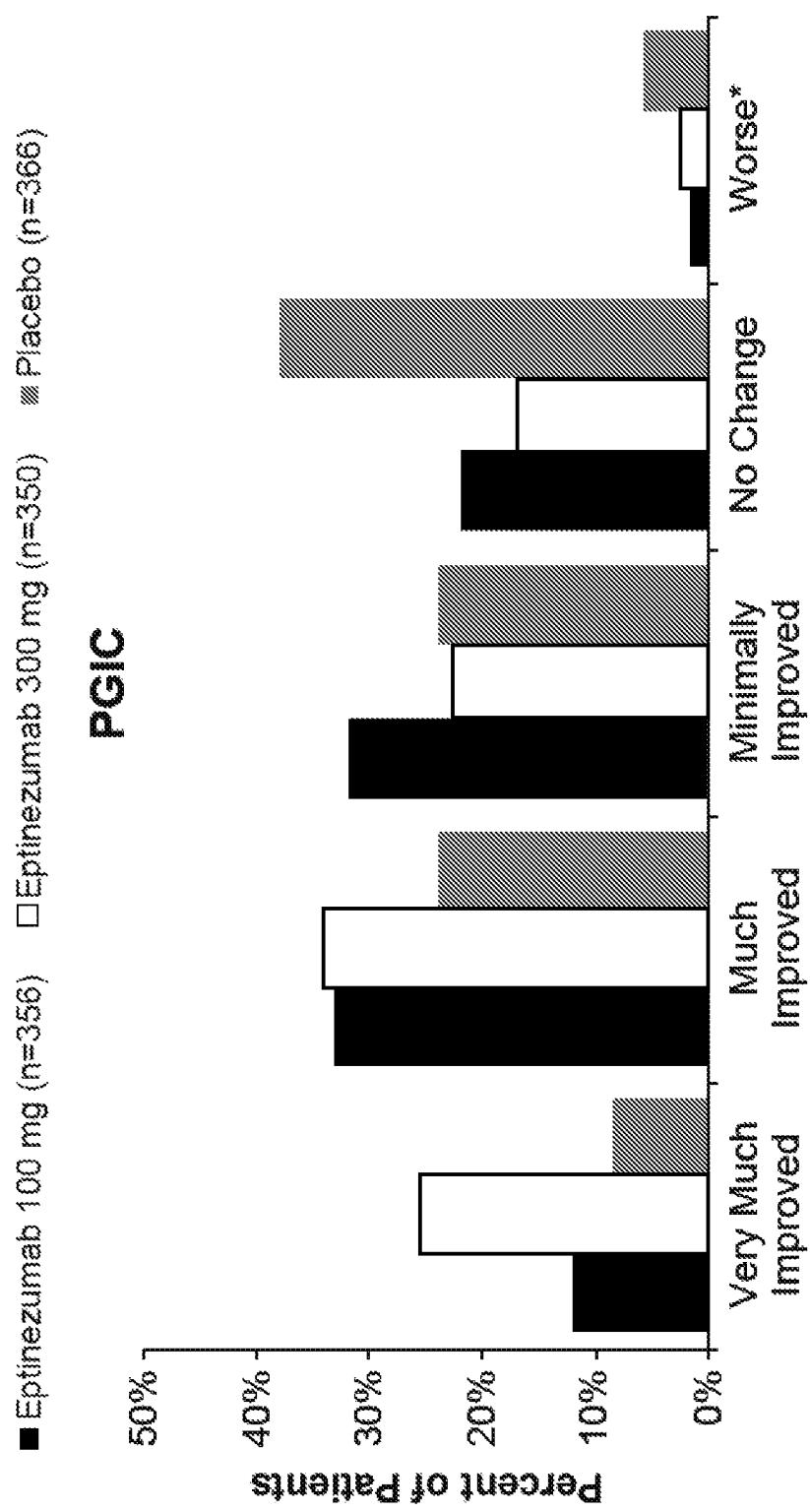


Fig 19 – MBS change from baseline 3 month after first infusion

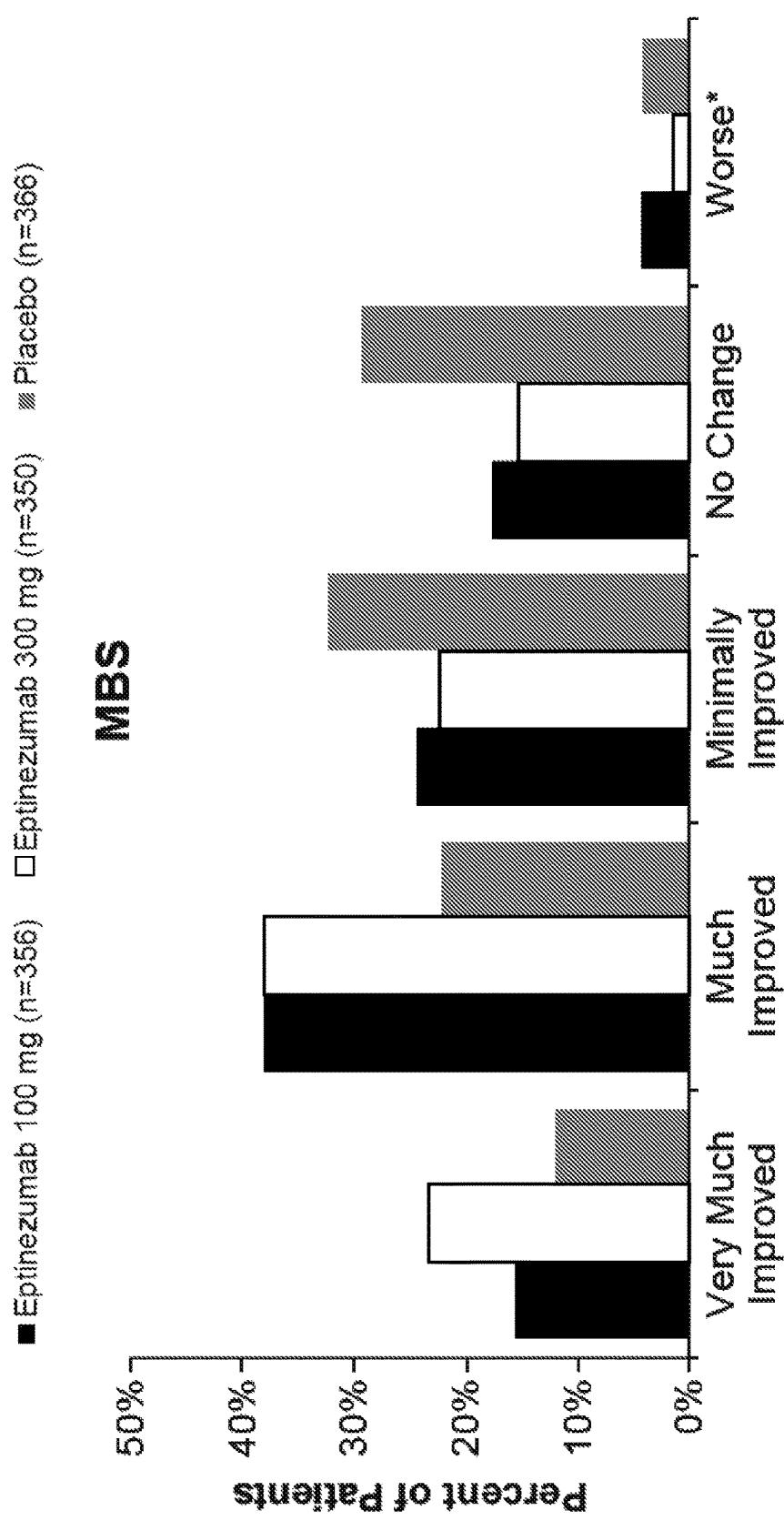


Fig 20 – PGIC from baseline 3 month after first infusion

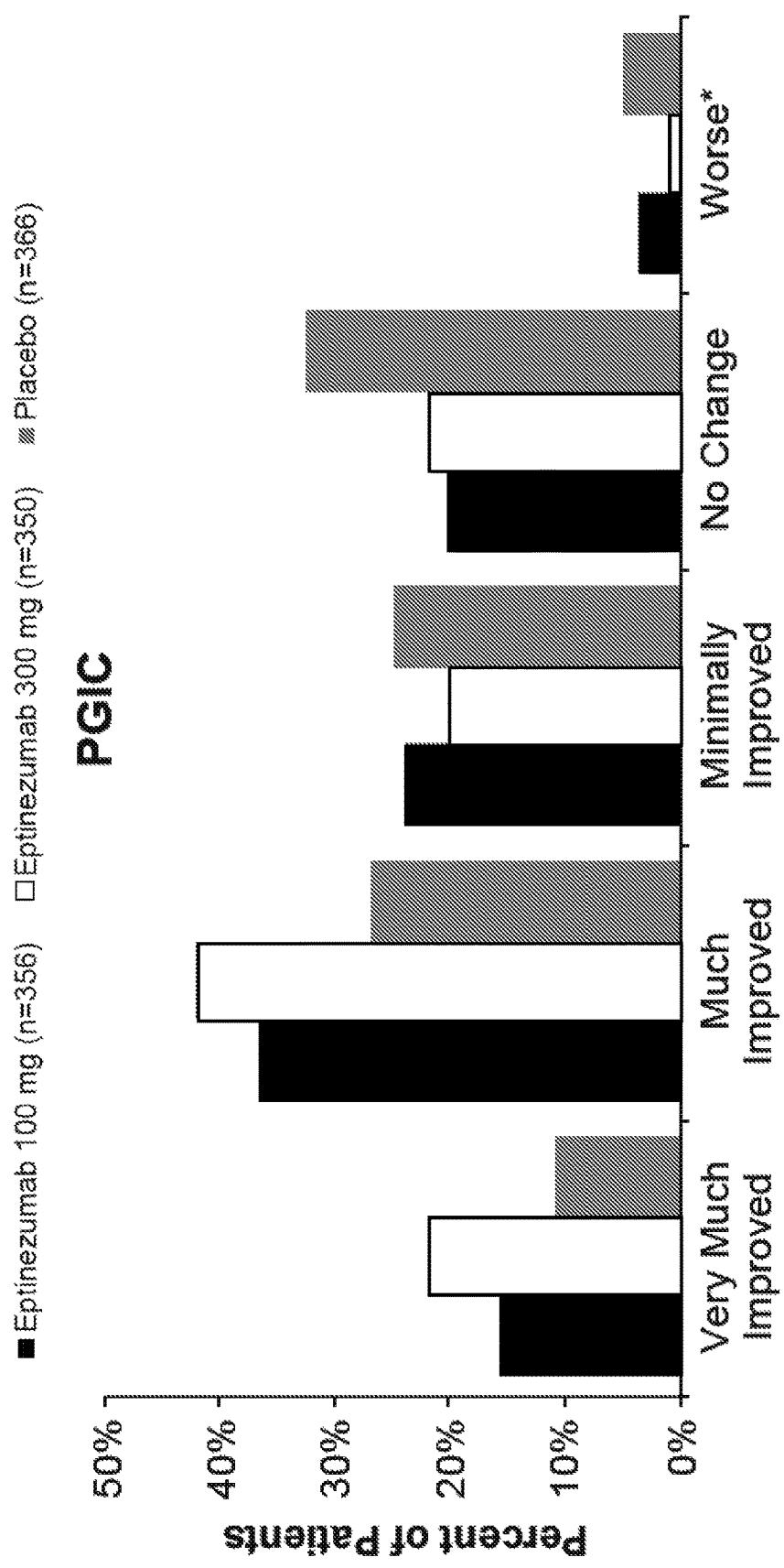


Fig 21 – MBS change from baseline 6 month after first infusion

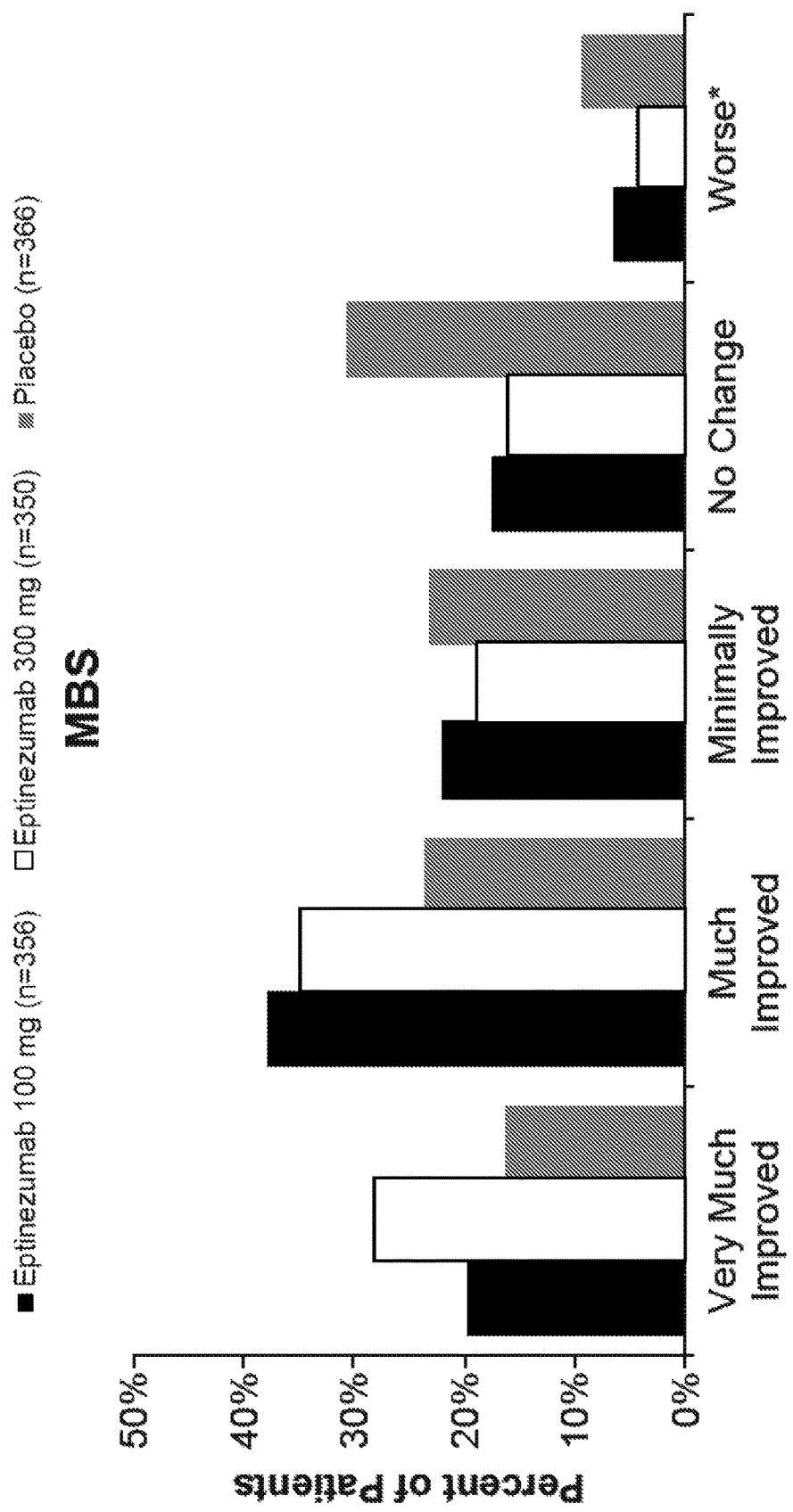
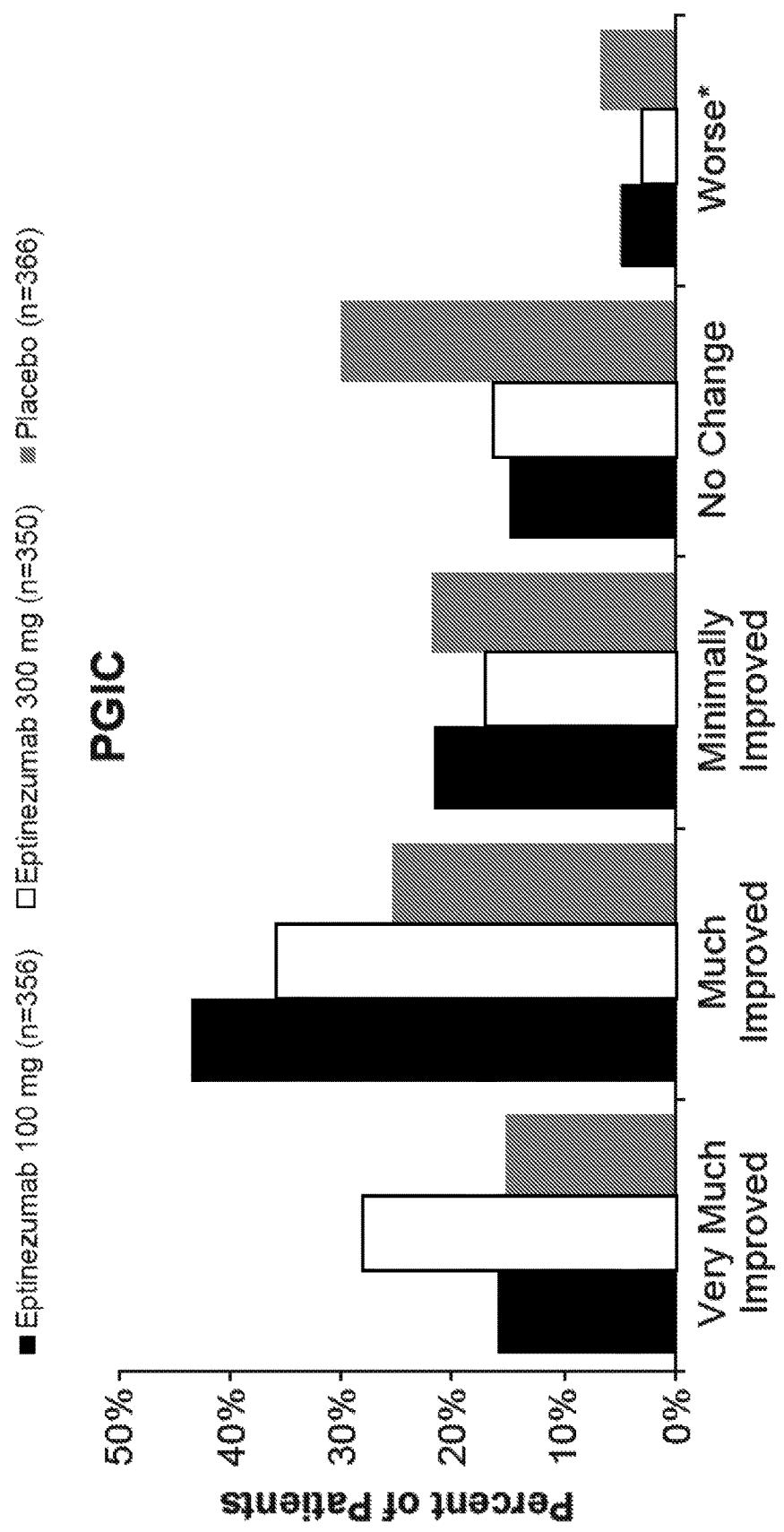


Fig 22 – PGIC from baseline 6 month after first infusion



**TREATMENT OF MOST BOthersome
SYMPTOM (MBS) ASSOCIATED WITH
MIGRAINE USING ANTI-CGRP ANTIBODIES**

SEQUENCE LISTING DISCLOSURE

This application is a continuation of U.S. application Ser. No. 16/860,239 filed Apr. 28, 2020, which claims priority to U.S. Provisional Appl. No. 63/005,950, filed Apr. 6, 2020, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING DISCLOSURE

This application includes as part of its disclosure an electronic sequence listing text file named "1143257o009402.xml", having a size of 771,211 bytes and created on Mar. 13, 2023, which is hereby incorporated by reference in its entirety.

**SEQUENCES NOT PERMITTED TO BE
ENTERED IN ST.26 XML FILE DUE TO
SEQUENCE LENGTH**

Table A below lists sequences present in the U.S. priority application Ser. No. 16/860,239 and 63/244,466 (identified above, which are both herein incorporated by reference in their entirety) but cannot be included in the "1143257o009402.xml" file submitted herewith due to the length of the sequences.

TABLE A

Sequence	Previous SEQ ID NO: #	Length	Type	Organism	Other Information
Gly Asp Ile	8	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	18	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	48	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	58	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	88	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	98	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	128	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	138	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	168	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	178	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	208	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	218	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	248	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	258	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	288	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	298	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	328	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	338	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	368	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	378	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	408	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	418	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	448	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	458	9	DNA	Artificial	Engineered antibody sequence
Gly Asp Ile	528	3	Protein	Artificial	Engineered antibody sequence
ggggacatc	538	9	DNA	Artificial	Engineered antibody sequence

BACKGROUND OF THE INVENTION

Field of the Invention

This invention pertains to methods of treatment of most bothersome symptom associated with migraine, using antibodies and fragments thereof (including Fab fragments) that specifically bind to human Calcitonin Gene Related Peptide (hereinafter "CGRP").

Description of Related Art

Calcitonin Gene Related Peptide (CGRP) is produced as a multifunctional neuropeptide of 37 amino acids in length. 5 Two forms of CGRP, the CGRP-alpha and CGRP-beta forms, exist in humans and have similar activities. CGRP-alpha and CGRP-beta differ by three amino acids in humans, and are derived from different genes. CGRP is released from numerous tissues such as trigeminal nerves, which when activated release neuropeptides within the meninges, mediating neurogenic inflammation that is characterized by vasodilation, vessel leakage, and mast-cell degradation. Durham, P. L., *New Eng. J. Med.*, 350 (11):1073-75 (2004). Biological effects of CGRP are mediated via the CGRP receptor (CGRP-R), which consists of a seven-transmembrane component, in conjunction with receptor-associated membrane protein (RAMP). CGRP-R further requires the activity of the receptor component protein (RCP), which is essential for 10 an efficient coupling to adenylate cyclase through G proteins and the production of cAMP. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

Migraines are neurovascular disorder affecting approximately 10% of the adult population in the U.S., and are typically accompanied by intense headaches. CGRP is believed to play a prominent role in the development of migraines. In fact, several companies, i.e., Amgen, Eli Lilly, Teva and Alder Biopharmaceuticals (recently acquired by Lundbeck A/S) have developed anti-CGRP and anti-

CGRP-R antibodies for use in treating or preventing migraine headaches. The present assignee has previously 60 filed patent applications related to anti-CGRP antibodies and uses thereof including published PCT Application WO/2012/162243 filed May 21, 2012 entitled "ANTI-CGRP COMPOSITIONS AND USE THEREOF", published PCT Application WO/2012/162257 filed May 21, 65 2012, entitled "USE OF ANTI-CGRP ANTIBODIES AND ANTIBODY FRAGMENTS TO PREVENT OR INHIBIT PHOTOPHOBIA OR LIGHT AVERSIÓN IN SUBJECTS

IN NEED THEREOF, ESPECIALLY MIGRAINE SUFFERERS" published PCT Application WO/2012/162253, filed May 21, 2012, entitled "USE OF ANTI-CGRP OR ANTI-CGRP-R ANTIBODIES OR ANTIBODY FRAGMENTS TO TREAT OR PREVENT CHRONIC AND ACUTE FORMS OF DIARRHEA" and published PCT Application WO/2015/003122, filed Jul. 3, 2014, entitled "REGULATION OF GLUCOSE METABOLISM USING ANTI-CGRP ANTIBODIES" all of which applications are incorporated by reference in their entirety.

BRIEF SUMMARY

The present disclosure provides methods of treatment of most bothersome symptom (MBS) associated with migraine in patient suffering from chronic migraine, comprising administering to a patient in need an effective amount of at least one anti-CGRP antibody or antibody fragment thereof or an anti-CGRP-R antibody or antibody fragment thereof or one or more formulations comprising said antibody or antibody fragment as disclosed herein. Said antibody treatment may be initiated in the interictal period, i.e. in between migraine attacks or in the ictal phase, i.e. during the migraine episode. Said migraine may comprise e.g. chronic migraine or episodic migraine, in a specific aspect of the present invention the patient suffers from chronic migraine. In the present invention, said anti-CGRP antibody or antibody fragment is denoted Ab6. Ab6 is an anti-CGRP antibody or antibody fragment thereof having the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208; or having the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively. Said anti-CGRP antibody may comprise the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202. Said anti-CGRP antibody may comprise the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212. Said anti-CGRP antibody may comprise the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may comprise the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells. Said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia*

pastoris or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions. Any of the aforementioned anti-CGRP antibodies or antibody fragments, preferably 5 Ab6, may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, 10 having a pH of about 5.8. The administered dosage of said antibody may be between about 100 mg and about 300 mg, such as about 100 mg, about 300 mg, 100 mg, or 300 mg. The dosage may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL

Said patient may exhibit less than 25 headache days per month, less than 20 headache days per month, less than 15 headache days per month, or less than 10 headache days per month. For example, said patient may exhibit less than 14 20 headache days, less than 13 headache days, less than 12 headache days, less than headache 11 days, less than 10 headache days, less than 9 headache days, less than 8 headache days, less than 7 headache days, or less than 6 headache days per month. Said patient may exhibit between 25 2-15 headache days, e.g., 3-14 headache days, 4-13 headache days, 5-12 headache days, 6-11 headache days, or 7-10 headache days/month.

Said patient may exhibit less than 10 migraines per month, such as between 1-9 migraines per month, such as 30 between 2-8 migraines per month, between 3-7 migraine per month, between 4-6 migraine per month, or about 5 migraines per month. Said patient may exhibit fewer than 1 migraine per month on average, e.g., on average one migraine every 2 months, one every 3 months, one every 4 or 6 months, or intermediate values such as 2 every 3 months, etc. Said migraine may be diagnosed in accord with the ICHD-3 guidelines.

In addition to headache and associated symptoms as described in the diagnostic criteria of the International 40 Classification of Headache Disorders (ICHD-3) for migraine with or without aura, migraine patients experience a variety of autonomic, cognitive, sensory and motor symptoms during migraine, these symptoms are experienced uniquely by individual patients. In the present invention, the patients 45 were allowed to self-identify a specific symptom associated with chronic migraine that they considered to be most bothersome. In the present application these symptoms will be referred to at the most bothersome symptom (MBS) associated with migraine. In the present invention the patient could identify their MBS without limitation, which provides a unique patient-centered approach for identifying and measuring the efficacy of antibodies of the invention as treatment of these most bothersome migraine-associated symptoms and hence is expected to have a meaningful impact on the 50 patients ability to function during migraine. Although nausea, vomiting, photophobia, and phonophobia are migraine-associated symptoms included in ICDH-3 diagnostic criteria, many other symptoms may be observed to occur prior to, after, and even between days with diagnosable migraine. 55 Over the duration of a migraine attack, these can include cognitive symptoms (e.g. memory, executive function, attention deficit), affective symptoms (e.g. mood changes, depression, anxiety, irritability), other sensory symptoms (e.g. osmophobia, taste abnormalities), as well as blurry vision, nasal congestion, rhinorrhea, lacrimation, sweating, 60 ptosis, yawning, polyuria, abdominal cramps, diarrhea, dizziness, and neck pain. The MBS associated with migraine 65

reported by the patients enrolled in the clinical trial described in Example 2 is summarized in Table 1. Although nausea/vomiting, photophobia, and phonophobia were common in the patient population in Example 2, less than half of these patients named one of these 3 symptoms included in ICDH-3 diagnostic criteria as their patient-identified MBS.

Migraine is a complex disorder of the brain associated with multifaceted symptomatology yet expressed in a personalized unique manner. Often persisting over multiple days, the peri-ictal period of migraine can be classified into four distinct phases—prodrome/premonitory, preictal/aura, 10 ictal/headache, postdrome/postictal—with overlapping symptoms occurring during each phase of migraine. The various types and timing of MBS across the course of the migraine is illustrated in FIG. 15. It is highly relevant to assess MBS in migraine patients during clinical trials, since it is recognized that headache pain alone is not considered sufficient to adequately eliminate the impact of migraine on the patients daily living and health status. The reduction in mean monthly migraine days (MMDs) or a similar endpoints in clinical trials do not fully capture the burden of migraine and the associated symptoms that are affected by therapeutic intervention. The inventors of the present invention found that in addition to reducing MMDs Ab6, an anti-CGRP antibody, was also effective in improving MBS in migraine patients. Improvements in these symptoms associated with treatment were correlated with improved patients' perception of disease status and indirectly with satisfaction with treatment response. It is known that migraine patients often continue to seek treatment for their migraine because of the burden of their MBS, thus supporting the clinical value of treating both the primary migraine pathology and the MBS associated with said migraine.

The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to improve the MBS associated with migraine in patients suffering from migraine, such as chronic or episodic migraine. The MBS parameter rates the patient's assessment of change (improvement or worsening since the start of the study) in this symptom.

The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to improve the patient global impression of change (PGIC) associated with migraine treatment in patients impacted by migraine, such as chronic or episodic migraine. The patient global impression of change (PGIC) associated with migraine parameter comprises a single question concerning the patient's impression of the overall change (improvement or worsening since the start of the study) in their disease status evaluated on a 7 point Likert scale anchored by very much improved and very much worse.

The present invention provides anti-CGRP antibodies or antibody fragments thereof, which are able to reduce MMDs as well as improve the patient's most bothersome symptom (MBS) associated with migraine in a manner that is highly correlated with positive change in the patient's global impression of change (PGIC) of migraine treatment. This dual action constitutes an improved treatment option for patient suffering from migraine, which goes beyond treating the migraine headache, and provides treatment for the collective migraine burden experienced by the patient comprising both migraine headache as well as MBS associated with migraine.

The present invention provides methods of improving most bothersome symptom (MBS) associated with migraine, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an

anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

5 The present invention provides methods of improving patient global impression of change (PGIC), comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and simultaneously reduce the MMDs, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

15 In another aspect, the invention provides methods of improving patient global impression of change (PGIC) associated with migraine and simultaneously reduce the MMDs, comprising intravenously administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

20 In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and patient global impression of change (PGIC) associated with migraine, comprising intravenously 25 administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

30 In another aspect, the invention provides methods of improving most bothersome symptom (MBS) associated with migraine and/or patient global impression of change (PGIC) associated with migraine and simultaneously reduce the MMDs, comprising intravenously 35 administering to a patient in need thereof between about 100 mg and about 300 mg of an anti-CGRP antibody, wherein said anti-CGRP antibody preferably comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or 566.

40 In some exemplary embodiments the dosage of said anti-CGRP antibody may be 100 mg.

In other exemplary embodiments the dosage of said anti-CGRP antibody may be 300 mg.

45 The method may further comprise intravenously administering 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

The method may further comprise intravenously administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

50 The antibody may be provided or administered in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

Prior to first dosage, the patient may exhibit between about 10 and about 22 migraine days per month, such as between about 13 and about 19 migraine days per month, such as about 16 migraine days per month.

Prior to first dosage, the patient may exhibit between about 14 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

Said patient may have been diagnosed with migraine at least 10 years prior to said first dosage, such as at least 15 years prior to said first dosage, such as at least 18 or at least 19 years prior to said first dosage.

Said patient may have been diagnosed with chronic migraine at least 5 years prior to said first dosage, such as at least 8 years prior to said first dosage, such as at least 11 or at least 12 years prior to said first dosage.

The patient may have a headache when administered the anti-CGRP antibody or fragments thereof of the invention.

The patient may have a migraine, such as a migraine with aura, when administered anti-CGRP antibody or fragments thereof of the invention.

Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said first dose relative to the baseline number of migraine days experienced by that patient prior to said first dose.

Said patient may experience an improvement in their MBS associated with migraine in the one month period after being administered said first dose measured as the change from the baseline MBS.

Said patient may experience an improvement in their MBS associated with migraine in the 3 month period after being administered said first dose measured as the change from the baseline MBS.

Said patient may experience an improvement in their MBS associated with migraine in the 6 month period after being administered said first dose measured as the change from the baseline MBS.

Said patient may experience an improvement in their PGIC associated with migraine in the one month period after being administered said first dose measured as the change from the baseline.

Said patient may experience an improvement in their PGIC associated with migraine in the 3 month period after being administered said first dose measured as the change from the baseline.

Said patient may experience an improvement in their PGIC associated with migraine in the 6 month period after being administered said first dose measured as the change from the baseline.

The method may further comprise administering, e.g., intravenously, a second dose of an anti-CGRP antibody of the invention to said patient within about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said first dose.

Said first dose may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

Prior to said administration, the patient may exhibit between about 15 and about 30 migraine days per month, such as between about 16 and about 28 migraine days per month, such as between about 17 and about 26 migraine days per month, such as about 16 migraine days per month.

Prior to said administration, the patient may exhibit between about 15 and about 27 headache days per month, such as between about 17 and about 24 headache days per month, such as about 20 or about 21 headache days per month.

Said patient may have been diagnosed with migraine at least 10 years prior to said administration, such as at least 15 years prior to said administration, such as at least 18 or at least 19 years prior to said administration.

Said patient may have been diagnosed with chronic migraine at least 5 years prior to said administration, such as at least 8 years prior to said administration, such as at least 11 or at least 12 years prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

Said patient may have a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to said administration.

The method may further comprise administering, e.g., intravenously, a second dose of said anti-CGRP antibody to

said patient within about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months, after said administration.

Said administration may comprise about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

Said anti-CGRP antibody may be aglycosylated or if glycosylated only may contain only mannose residues.

Said anti-CGRP antibody may consist of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566. Said anti-CGRP antibody may consist of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain of SEQ ID NO: 222 and/or the variable heavy chain of SEQ ID NO: 202. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the variable light chain encoded by SEQ ID NO: 232 and/or the variable heavy chain encoded by SEQ ID NO: 212.

In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain of SEQ ID NO: 221 and/or the heavy chain of SEQ ID NO: 201 or SEQ ID NO: 566. In some embodiments, said anti-human CGRP antibody or antibody fragment comprises the light chain encoded by SEQ ID NO: 231 and/or the heavy chain encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the VL polypeptide of SEQ ID NO: 222 and the VH polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

In some embodiments, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

In some embodiments any of the aforementioned anti-CGRP antibodies or antibody fragments may be comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8. The antibody or fragment may be administered by different means, e.g., intravenously, e.g., in a saline solution such as 0.9% sodium chloride in a suitable volume, such as 100 mL.

In some embodiments, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

In other embodiments, about 100 mg of said anti-CGRP antibody or antibody fragment is administered.

In other embodiments, about 300 mg of said anti-CGRP antibody or antibody fragment is administered, e.g., intravenously.

In exemplary embodiments, the anti-human CGRP antibody or antibody fragment is administered, e.g., intravenously at a frequency which is at most every 10-14 weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks, wherein the antibody dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10-14 weeks, preferably every 11-13 weeks, more preferably every 3 months or every 12 weeks. The phrase "the antibody dosage is administered in a single formulation or divided into different formulations" refers to the administration of the recited amount of antibody within a relatively short period of time, e.g., within a period of several hours, e.g., 1 to 8 hours, about one day, within about two days, or within about one week, which may be by the same or different routes (e.g., i.v., i.m., and/or s.c.), sites of administration. The term "different formulations" in this context refers to antibody dosages that are administered at different times and/or at different sites and/or different routes, irrespective of whether the dosages are the same or different with respect to the chemical composition of the pharmaceutical formulation in which each dosage is administered; for example, the concentration, excipients, carriers, pH, and the like may be the same or different between the different administered dosages.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 8 weeks or every 2 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks or every 3 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 16 weeks or every 4 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 20 weeks or every 5 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 24 weeks or every 6 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 28 weeks or every 7 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 32 weeks or every 8 months.

11

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 36 weeks or every 9 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 40 weeks or every 8 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 44 weeks or every 9 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 48 weeks or every 10 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 52 weeks or every 11 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 56 weeks or every 12 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 15-18 months.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment dosage is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 18-21 months.

In other exemplary embodiments, the anti-human CGRP antibody dosage or antibody fragment used in the afore-mentioned methods is administered in a single formulation or divided into different formulations which are administered at a frequency of approximately every 2 years.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods is administered systemically.

In other exemplary embodiments, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered by a mode of administration is selected from intravenous, intramuscular, intravenous, intrathecal, intracranial, topical, intranasal, and oral. In a preferred embodiment, the anti-human CGRP antibody or antibody fragment used in the afore-mentioned methods is administered intravenously.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 10 days.

In other exemplary embodiments, the anti-human CGRP antibody has an in vivo half-life of at least 15 days.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 20 days.

In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods has an in vivo half-life of at least 20-30 days.

12

In other exemplary embodiments, the anti-human CGRP antibody is administered at a dosage of between about 100 mg and about 300 mg has an in vivo half-life of ±20% of at least about (284±44 hours).

⁵ In other exemplary embodiments, the anti-human CGRP antibody used in the afore-mentioned methods binds to human α- and β-CGRP.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ¹⁰ vasodilation induced by topically applied capsaicin at least 30 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ¹⁵ vasodilation induced by topically applied capsaicin at least 60 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in inhibition of ²⁰ vasodilation induced by topically applied capsaicin at least 90 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ²⁵ vasodilation induced by topically applied capsaicin at least 120 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ³⁰ vasodilation induced by topically applied capsaicin at least 150 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ³⁵ vasodilation induced by topically applied capsaicin at least 180 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in the inhibition of ⁴⁰ vasodilation induced by topically applied capsaicin more than 180 days after antibody administration.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity, within 5% of the maximal ⁴⁵ response (Imax) (as compared to lower antibody doses).

In other exemplary embodiments, the administered anti-human CGRP antibody dosage results in sustained pharmacodynamic (PK) activity which is maintained for at least 2-3 months after antibody administration, wherein PK analysis ⁵⁰ of the anti-human CGRP antibody is derived from plasma concentrations.

In other exemplary embodiments, the administered anti-human CGRP antibody dosage is between about 100 mg and about 300 mg or more which is administered no more ⁵⁵ frequently than every 2 months.

The present invention is additionally directed to the use of specific antibodies and fragments thereof having binding specificity for CGRP, in particular antibodies having desired epitopic specificity, high affinity or avidity and/or functional ⁶⁰ properties. A preferred embodiment of the invention is directed to usage of chimeric or humanized antibodies and fragments thereof (including Fab fragments) capable of binding to CGRP and/or inhibiting the biological activities mediated by the binding of CGRP to the CGRP receptor (“CGRP-R”) e.g., wherein such antibodies optionally are derived from recombinant cells engineered to express same, optionally yeast or mammalian cells, further optionally *Pichia pastoris* and CHO cells.

In another preferred embodiment of the invention, full ⁶⁵ length antibodies and Fab fragments thereof are contemplated that inhibit the CGRP-alpha-, CGRP-beta-, and rat CGRP-driven production of cAMP. In a further preferred

13

embodiment of the invention, full length and Fab fragments thereof are contemplated that reduce vasodilation in a recipient following administration.

The invention also contemplates usage of conjugates of anti-CGRP antibodies and binding fragments thereof conjugated to one or more functional or detectable moieties. The invention also contemplates usage of chimeric or humanized anti-CGRP or anti-CGRP/CGRP-R complex antibodies and binding fragments thereof. In one embodiment, binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv, scFv fragments, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provide the polypeptide sequences of the full-length heavy chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

FIG. 2 provide the polypeptide sequences of the full-length light chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and constant region sequences delimited.

FIGS. 3A and 3B provide exemplary polynucleotide sequences encoding the full-length heavy chain for antibody Ab6 with framework regions (FR), complementarity determining regions (CDRs), and variable region coding sequences delimited.

FIG. 4 provide exemplary polynucleotide sequences encoding the full-length light chain for antibody Ab6 with their framework regions (FR), complementarity determining regions (CDRs), and variable region coding sequences delimited.

FIG. 5 provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibodies Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 6 provides the polypeptide sequence coordinates within the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 7 provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 8 provides the polypeptide sequence coordinates within the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 9 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 10 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length heavy chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 11 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding

14

the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the variable region and complementarity determining regions (CDRs), and the SEQ ID NO of each individual feature.

FIG. 12 provides the polynucleotide sequence coordinates within the exemplary polynucleotide sequences encoding the full-length light chain polypeptide sequences of antibody Ab6 of sequence features including the framework regions (FRs) and constant region, and the SEQ ID NO of each individual feature.

FIG. 13 Study design of the clinical trial protocol as summarized in Example 2.

FIG. 14 displays the efficacy of Ab6 on Mean Monthly Migraine Days (MMDs) in the clinical trial described in Example 2.

FIG. 15 Illustrates the types and timing of Most Bothersome Symptoms (MBS) across the course of the migraine

FIG. 16 Illustrates the MBS change from baseline during the 28 day screening period of the clinical trial described in Example 2—i.e. before the first infusion of Ab6.

FIG. 17 Illustrates the MBS change from baseline 1 month after the first infusion of Ab6 in the clinical trial described in Example 2.

FIG. 18 Illustrates the PGIC from baseline 1 month after the first infusion of Ab6 in the clinical trial described in Example 2.

FIG. 19 Illustrates the MBS change from baseline 3 month after the first infusion of Ab6 in the clinical trial described in Example 2.

FIG. 20 Illustrates the PGIC from baseline 3 month after the first infusion of Ab6 in the clinical trial described in Example 2.

FIG. 21 Illustrates the MBS change from baseline 6 month after the first infusion of Ab6 in the clinical trial described in Example 2.

FIG. 22 Illustrates the PGIC from baseline 6 month after the first infusion of Ab6 in the clinical trial described in Example 2.

DETAILED DESCRIPTION

Use of anti-CGRP antibodies for treatment of MBS and/or PGIC associated with migraine, such as chronic migraine or episodic migraine is described herein. Additionally, anti-CGRP antibodies are demonstrated herein to be effective for treatment of MMDs. The treatment efficacy on both MBS and PGIC are shown to be effective in providing relief of MBS and PGIC at 1 month, 3 months and 6 months following the first infusion of an anti-CGRP antibody or fragments thereof of the invention.

Definitions

It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms “a”, “and”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a cell” includes a plurality of such cells and reference to “the protein” includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as

15

commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

As used herein, the term “most bothersome symptom associated with migraine” refers to symptoms which is identified by an individual patient to be the most bothersome symptom they associate with their migraine. In the present invention the “most bothersome symptom associated with migraine” is specified in Table 1. The “most bothersome symptom associated with migraine” of the present invention described by the patient to the study investigator who assists in medical interpretation of the patients symptom. The investigator in the clinical study was able to with the patient consultation selected from the group of known migraine symptoms consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty. A patient’s “most bothersome symptom associated with migraine” as used in the present invention refers to the self-identified “most bothersome symptom associated with migraine”, which may be one or more of the symptoms described herein above or may be classified as “other”

As used herein, the term “improvement of” or “improving” most bothersome symptom associated with migraine refers the change in the patient’s assessment of the MBS compared to baseline (i.e the MBS prior to the first dosing with anti-CGRP antibodies or fragments thereof of the invention). An improvement is characterized as ≥ 1 categorical change in the patients assesment of the MBS compared to baseline on the 7 point Likert scale described in Example 2.

As used herein, the term “improvement of” or “improving” patient global impression of change associated with migraine refers the change in the patient’s assessment of their disease status compared to baseline (i.e the disease status prior to the first dosing with anti-CGRP antibodies or fragments thereof of the invention). An improvement is characterized as ≥ 1 categorical change in the patients assesment of the PGIC compared to baseline on the 7-step scale described in Example 2.

As used herein, the term “chronic migraine” refers to a condition wherein a patient exhibits, on average, at least 15 headache per month with a subset of these headache days fulling the ICHD-3 criteria for migraine with or without aura. The term “episodic migraine” refers to a condition wherein a patient exhibits, on average, less than 15 day a month of headache with typically 4-15 being a migraine phenotype meeting the ICHD-3 definition of migraine with or without aura.

As used herein, the term “diagnosed with chronic migraine” refers to a patient meeting the clinical criteria for chronic migraine, whether or not a formal diagnosis of that patient was performed.

As used herein, the term “intravenously administering” refers to a mode of administration wherein a substance, e.g., an antibody, is introduced directly into the circulation of that patient, most typically into the venous circulation. The substance may be introduced in a carrier fluid, such as an aqueous solution, e.g., normal saline. The substance may be administered in a single formulation or in multiple formulations, as long as the administration is completed over a

16

short period of time (e.g., within 1 day, preferably within 12 hours, more preferably within 6 hours, and most preferably within 1-2 hours).

As used herein, the term “the baseline number of migraine days” refers to the number of migraine days exhibited by a patient in a specified time period, e.g., prior to treatment. For example, the baseline number of migraine days may be determined over a period of one month, or longer, e.g., by recording each day whether or not a migraine occurred.

As used herein, the term “migraine days per month” refers to the number of days per month on which a patient has a migraine, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of migraine. The number of migraine days per month may be determined by recording each day whether or not a migraine occurred.

As used herein, the term “headache days per month” refers to the number of days per month on which a patient has a headache, i.e., at any time during that day, the patient has symptoms that meet the clinical definition of a headache. The number of headache days per month may be determined by recording each day whether or not a headache occurred.

Calcitonin Gene Related Peptide (CGRP): As used herein, CGRP encompasses not only the following *Homo sapiens* 25 CGRP-alpha and *Homo sapiens* CGRP-beta amino acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA):

CGRP-alpha: ACDTATCVTHRLAGLLSRSGGVVKNFVPTNVGSKAF-NH₂ (SEQ ID NO: 561), wherein the terminal phenylalanine is amidated;

CGRP-beta: ACNTATCVTHRLAGLLSRSGGMVKNSNFVPTNVGSKAF-NH₂ (SEQ ID NO: 562), wherein the terminal phenylalanine is amidated; but also any membrane-bound forms of these CGRP amino acid sequences, as well as mutants (mutiens), splice variants, isoforms, orthologs, homologues and variants of this sequence.

Expression Vector: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell, e.g., a yeast or mammalian cell such as *Pichia pastoris* or CHO cells. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, e.g. *E. coli*, and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Steams, T. (2000). Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

Expression vectors for use in yeast or mammalian cells 60 will generally further include yeast or mammalian specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains or transformed mammalian cells. A drug marker may further be used to amplify copy number of the vector in the host cell.

The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in

host cells, e.g., *Pichia pastoris* or CHO cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, e.g. a signal sequence, and the like. A yeast or mammalian origin of replication is optional, as expression vectors are often integrated into the host cell genome. In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway® Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, e.g., the presence or absence of a nutrient or a change in temperature.

The promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the host genome; alternatively a selectable marker is used as the site for homologous recombination. Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg et al. (1989) *Mol. Cell. Biol.* 9:1316-1323); ICL1 promoter (Menendez et al. (2003) *Yeast* 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham et al. (1997) *Gene* 186(1):37-44); and FLD1 promoter (Shen et al. (1998) *Gene* 216(1):93-102). The GAP promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention such as mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

Examples of mammalian promoters include cytomegalovirus (CMV) derived promoters, chicken 3-actin (CBM) derived promoters, adenomatous polyposis coli (APC) derived promoters, leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) promoters, CAG promoter, Beta actin promoter, elongation factor-1 (EF1) promoter, early

growth response 1 (EGR-1) promoter, eukaryotic initiation factor 4A (EIF4A1) promoter, simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters such as, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter, among others. Combinations of two or more of the foregoing promoters may also be used. Further, inducible promoters may be used. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionein promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

The polypeptides of interest may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, e.g. a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Secretion signals for use in mammalian as well as yeast cells include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, e.g., K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto et. al. *Protein Eng* 11(2) 75 (1998); and Kobayashi et. al. *Therapeutic Apheresis* 2(4) 257 (1998).

Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs

or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann. Rev. Biochem.* 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli*-encoded recombination proteins. Recombination occurs between specific attachment (att) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed. (Cold Spring Harbor, NY: Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the att sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

Att sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing att B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing att sites; and the like.

Folding, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. Proper folding is typically the arrangement of a polypeptide that results in optimal biological activity, and in the case of antibodies can conveniently be monitored by assays for activity, e.g. antigen binding.

The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, i.e. foldases, chaperonins, etc. Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, etc. as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, e.g. one strain may express BIP, and the other strain may express PDI or combinations thereof.

The terms "desired protein" or "desired antibody" are used interchangeably and refer generally to a parent anti-

body specific to a target, i.e., CGRP or a chimeric or humanized antibody or a binding portion thereof derived therefrom as described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and in particular IgG_{tc}, from all sources, e.g. human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, etc., are considered to be "antibodies." A preferred source for producing antibodies useful as starting material according to the invention is rabbits. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camel bodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fab's, Fab', F(ab')₂ and the like. See Streltsov V A, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, *Protein Sci.* 2005 November; 14(11):2901-9. Epub 2005 Sep. 30; Greenberg A S, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, *Nature*. 1995 Mar. 9; 374(6518): 168-73; Nuttall S D, et al., Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, *Mol Immunol.* 2001 August; 38(4):313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, *Nature*. 1993 Jun. 3; 363(6428):446-8; Gill D S, et al., Biopharmaceutical drug discovery using novel protein scaffolds, *Curr Opin Biotechnol.* 2006 December; 17(6):653-8. Epub 2006 Oct. 19.

For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine

residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (e.g., a functional domain, catalytic amino acid residues, etc). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for in vitro mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, e.g., in U.S. Pat. No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, and IgG4 constant regions.

Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. See, e.g., U.S. Pat. No. 6,187,287, incorporated fully herein by reference.

In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (e.g., Fab', F(ab')₂, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest, e.g. diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

Immunoglobulins and fragments thereof may be modified post-translationally, e.g. to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided infra.

A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (i.e., the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory molecules (e.g., transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence.

"Amplification" of polynucleotide sequences is the in vitro production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, *Bio Technol.*, 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., *Ann. N.Y. Acad. Sci.*, 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 daltons (the "light chain"), and two identical heavy chains of

23

molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the Fc region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (i.e., the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ , μ , α , δ , and ϵ (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., Structural Concepts in Immunology and Immunochemistry, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., et al., *Clinical Immunobiology*, pp 1-18, W. B. Sanders (1980); Kohl, S., et al., *Immunology*, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or, (λ lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat et al. ("Sequences of Proteins of Immunological Interest," Kabat E., et al., US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, *J Mol. Biol.* 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., Methods, 36:25-34 (2005)). In the present invention when

24

specific antibody amino acid or nucleic acid residues are referenced by number this generally refers to its position within a specified amino acid or nucleic acid sequence (i.e., particular sequence identifier) and/or in accordance with Kabat et al numbering.

The expressions "framework region" or "FR" refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (See Kabat, E. A. et al., Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

"C_{max}" refers to the maximum (or peak) concentration that an antibody or other compound achieves in tested area (e.g., in the serum or another compartment such as cerebrospinal fluid) after the drug has been administered. For example, serum C_{max} may be measured from serum, e.g., prepared by collecting a blood sample, allowing it to clot and separating solid components by centrifugation or other means to yield serum (blood containing neither blood cells nor clotting factors), and then detecting the concentration of the analyte in the serum by ELISA or other means known in the art.

"AUC" refers to the area under the concentration-time curve which is expressed in units of mg/mL*hr (or equivalently mg*hr/ml) unless otherwise specified. "AUC_{0-t}" refers to the area under the concentration-time curve from time=0 to last quantifiable concentration. "AUC_{0-inf}" refers to the area under the concentration-time curve from time=0 extrapolated to infinity.

"I_{max}" refers to the maximal pharmacodynamic response elicited by an anti-CGRP antibody dosage, preferably a dosage of 350 mg or more, more typically at least 750 or 1000 mg, as compared to the response elicited by a lower anti-CGRP antibody doses, e.g., wherein such response may be detected by the inhibition of vasodilation after topical application of capsaicin.

Anti-CGRP Antibodies and Binding Fragments Thereof Having Binding Specificity for CGRP

The invention specifically includes the use of Ab6, which is a specific anti-CGRP antibody or antibody fragment, which comprises or consists of the CDR, VL, VH, CL, CH polypeptides sequences identified in FIGS. 1-12. The polypeptides comprised in the anti-CGRP antibody, Ab6 is further described below.

Antibody Ab6

(SEQ ID NO: 222)
QVLTQSPSSLASAVGDRVTINCQASQSVHNTYLAWYQQKPGKVPKQLI
YDASTLASGVPSRFSGSQSGTDFTLTISSLQPEDVATYYCLGSYDCTNG
DCFVFGGGTKVEIKR.

The invention also includes humanized antibodies having binding specificity to CGRP and possessing a light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 221)
QVLTQSPSSLASAVGDRVTINCQASQSVHNTYLAWYQQKPGKVPKQLI
YDASTLASGVPSRFSGSQSGTDFTLTISSLQPEDVATYYCLGSYDCTNG
DCFVFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR

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EAKVQWKVDNALQSGNSQESVTEQDSKDSTYSSLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC.

The invention further includes humanized antibodies having binding specificity to CGRP and possessing a variable heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 202)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMWVRQAPGKGLEWVG
VIGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARG
DIWGQGTLVTVV.

The invention also includes humanized antibodies having binding specificity to CGRP and possessing a heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 201)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMWVRQAPGKGLEWVG
VIGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARG
DIWGQGTLVTVVSSASTKGPSVPPLAPSSKSTSGGTAAALGCLVKDYPPEP
VTVSWNSGALTSGVHTPPAVLQSSGLYSLSSVTVPVSSSLGTQTYICNV
NHKPSNTKVDARVEPKSCDKTHCPCPAPEELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPREEQYASTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVY
TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
DSDGSFFLYSKLTVDKSRWQQGNFSCSVHEALHNHYTQKSLSLSPGK.

Alternatively, the heavy chain of Ab6 may lack the C-terminal lysine of SEQ ID NO: 201, i.e., a heavy chain sequence comprising the sequence set forth below:

(SEQ ID NO: 566)
EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYMMWVRQAPGKGLEWVG
VIGINGATYYASWAKGRFTISRDNSKTTVYLQMNSLRAEDTAVYFCARG
DIWGQGTLVTVVSSASTKGPSVPPLAPSSKSTSGGTAAALGCLVKDYPPEP
VTVSWNSGALTSGVHTPPAVLQSSGLYSLSSVTVPVSSSLGTQTYICNV
NHKPSNTKVDARVEPKSCDKTHCPCPAPEELLGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPREEQYASTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVY
TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
DSDGSFFLYSKLTVDKSRWQQGNFSCSVHEALHNHYTQKSLSLSPG.

The invention further contemplates antibodies comprising one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221, and/or one or more of the polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the

26

variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566, or combinations of these polypeptide sequences. In another embodiment of the invention, the antibodies of the invention or fragments thereof comprise, or alternatively consist of, combinations of one or more of the CDRs, the variable heavy and variable light chain sequences, and the heavy and light chain sequences set forth above, including all of them.

10 The invention also contemplates fragments of the antibody having binding specificity to CGRP. In one embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 222 or SEQ ID NO: 221. In another embodiment of the invention, antibody fragments of the invention comprise, or alternatively consist of, the polypeptide sequence of SEQ ID NO: 202 or SEQ ID NO: 201 or SEQ ID NO: 566.

In a further embodiment of the invention, fragments of the 20 antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the 25 variable light chain sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

In a further embodiment of the invention, fragments of the antibody having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polypeptide 30 sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208 which correspond to the complementarity-determining regions (CDRs, or hypervariable regions) of the variable heavy chain sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

The invention also contemplates antibody fragments which include one or more of the antibody fragments described herein. In one embodiment of the invention, fragments of the antibodies having binding specificity to 40 CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following antibody fragments: the variable light chain region of SEQ ID NO: 222; the variable heavy chain region of SEQ ID NO: 202; the complementarity-determining regions (SEQ ID NO: 224; 45 SEQ ID NO: 226; and SEQ ID NO: 228) of the variable light chain region of SEQ ID NO: 222; and the complementarity-determining regions (SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208) of the variable heavy chain region of SEQ ID NO: 202.

50 In a particularly preferred embodiment of the invention, the humanized anti-CGRP antibody is Ab6, comprising, or alternatively consisting of, SEQ ID NO: 221 and SEQ ID NO: 201 or SEQ ID NO: 566, and having at least one of the biological activities set forth herein.

55 In a further particularly preferred embodiment of the invention, antibody fragments comprise, or alternatively consist of, Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the Fab fragment includes the variable light chain sequence 60 of SEQ ID NO: 222 and the variable heavy chain sequence of SEQ ID NO: 202. This embodiment of the invention further contemplates additions, deletions, and variants of SEQ ID NO: 222 and/or SEQ ID NO: 202 in said Fab while retaining binding specificity for CGRP.

65 In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells

which express nucleic acid sequences encoding the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202, which polypeptides optionally are respectively linked to human light and heavy constant region polypeptides, e.g., human IgG1, IgG2, IgG3 or IgG4 constant regions, which constant regions optionally may be modified to alter glycosylation or proteolysis, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells.

In another particularly preferred embodiment of the invention, said anti-CGRP antibody may comprise the antibody expression product isolated from recombinant cells which express nucleic acid sequences encoding the light chain of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566, wherein said recombinant cells optionally comprise yeast or mammalian cells, e.g., *Pichia pastoris* or CHO cells, wherein the constant regions thereof optionally may be modified to alter glycosylation or proteolysis or other effector functions.

In another particularly preferred embodiment of the invention, any of the aforementioned anti-CGRP antibodies or antibody fragments may be optionally comprised in a formulation as disclosed herein, e.g., comprising histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg anti-CGRP antibody, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8.

In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

In another embodiment, antibody fragments may be present in one or more of the following non-limiting forms: Fab, Fab', F(ab')₂, Fv and single chain Fv antibody forms. In a preferred embodiment, the anti-CGRP antibodies described herein further comprises the kappa constant light chain sequence comprising the sequence set forth below:

(SEQ ID NO: 563)

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TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKDSTYLSSTTLSKADYEKHKVYACEVTHQGLSSPV
KSFNRGEC.
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In another preferred embodiment, the anti-CGRP antibodies described herein further comprises the gamma-1 constant heavy chain polypeptide sequence comprising the sequence set forth below or the same sequence lacking the carboxy terminal lysine residue (SEQ ID NO: 564 and SEQ ID NO: 565, respectively):

(SEQ ID NO: 564)

```
ASTKGPSVFPLAPSSKSTGGTAALGCLVKDYFPEPVTVWSWNSGALTSG
VHTFPAVLQSSGLYSLSSVTVPPSSLGTQTYICNVNHPNSNTKVDKRV
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDW
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LNGKEYKCKVSNKALPAPIEKTIASKAGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
5 VDKSRWQQGNVFCSVMEALHNHYTQKSLSLSPGK.
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(SEQ ID NO: 565)

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ASTKGPSVFPLAPSSKSTGGTAALGCLVKDYFPEPVTVWSWNSGALTSG
10 VHTFPAVLQSSGLYSLSSVTVPPSSLGTQTYICNVNHPNSNTKVDKRV
EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDW
15 LNGKEYKCKVSNKALPAPIEKTIASKAGQPREPQVYTLPPSREEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFCSVMEALHNHYTQKSLSLSPGK.
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For clarity, any antibody disclosed herein is intended to include any variant of the disclosed constant region variant sequences, e.g., Ab6 may comprise the constant region of SEQ ID NO: 564 containing the C-terminal lysine or may comprise the constant region of SEQ ID NO: 565 lacking the C-terminal lysine. Thus, every disclosure herein of the heavy chain of SEQ ID NO: 201 also includes a variant lacking the C-terminal lysine residue thereof, i.e., having the heavy chain variable region sequence of Ab6 (SEQ ID NO: 202) and the constant region sequence of SEQ ID NO: 565.

30 For example, the sequence encoding an antibody comprising a C-terminal lysine in the heavy chain may, when expressed in cell lines such as CHO cells, produce an antibody lacking said C-terminal lysine due to proteolysis, or a mixture of heavy chains containing or lacking said C-terminal lysine.

35 In one embodiment of the invention, the antibodies or V_H or V_L polypeptides originate or are selected from one or more rabbit B cell populations prior to initiation of the humanization process referenced herein.

In another embodiment of the invention, the anti-CGRP antibodies and fragments thereof do not have binding specificity for CGRP-R. In a further embodiment of the invention, the anti-CGRP antibodies and fragments thereof inhibit the association of CGRP with CGRP-R. In another embodiment of the invention, the anti-CGRP antibodies and fragments 45 thereof inhibit the association of CGRP with CGRP-R and/or additional proteins and/or multimers thereof, and/or antagonizes the biological effects thereof.

As stated herein, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as 50 chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

Antibodies or fragments thereof may also be chemically modified to provide additional advantages such as increased solubility, stability and circulating time (in vivo half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. 60 No. 4,179,337). The chemical moieties for derivatization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be 65 modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

There are a number of attachment methods available to those skilled in the art. See e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF). See also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

Alternatively, antibodies or fragments thereof may have increased in vivo half-lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (See, e.g., U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1-585 of human serum albumin as shown in FIGS. 1

and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

- 5 Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, 10 fluorescein isothiocyanate, umbelliflone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. 15 Further exemplary radioactive materials include, but are not limited to, Iodine 125 (¹²⁵I), Carbon 14 (¹⁴C), Sulfur 35 (³⁵S), Tritium (H) and Phosphorus 32 (³²P).

Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, amonopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone 20 and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimyotic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, pseudomonas exotoxin, 25 gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, teniposide, colchicine, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, 30 mytotoxin (O,P'-DDD), interferons, and mixtures of these cytotoxic agents.

Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and *Pseudomonas* toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., *Proc. Nat'l Acad. Sci. USA* 77:5483 (1980); Gilliland, et al., *Proc. Nat'l Acad. Sci. USA* 77:4539 (1980); Krolick, et al., *Proc. Nat'l Acad. Sci. USA* 77:5419 (1980)).

Other cytotoxic agents include cytotoxic ribonucleases as 35 described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (³²P), Scandium-47 (⁴⁷Sc), Copper-67 (⁶⁷Cu), Gallium-67 (⁶⁷Ga), Yttrium-88 (⁸⁸Y), Yttrium-90 (⁹⁰Y), Iodine-125 (¹²⁵I) Iodine-131 (¹³¹I), Samarium-153 (¹⁵³Sm), Lutetium-177 (¹⁷⁷Lu), Rhenium-186 (¹⁸⁶Re) or 40 Rhenium-188 (¹⁸⁸Re), and alpha-emitters such as Astatine-211 (²¹¹At), Lead-212 (²¹²Pb), Bismuth-212 (²¹²Bi) or -213 (²¹³Bi) or Actinium-225 (²²⁵Ac).

31

Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, *Nature* 144:945 (1962); David et al, *Biochemistry* 13:1014 (1974); Pain et al, *J Immunol. Meth.* 40:219 (1981); and Nygren, *J. Histochem. and Cytochem.* 30:407 (1982).

Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camel-bodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, e.g., conservative substitution mutations, (i.e., the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, e.g., one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

In another embodiment, the invention further contemplates the above-recited polypeptide homologs of the antibody fragments, variable regions and CDRs set forth herein further having anti-CGRP activity. Non-limiting examples of anti-CGRP activity are set forth herein.

The invention further contemplates treatment methods wherein the one or more anti-human CGRP antibodies discussed above are aglycosylated or if glycosylated are only mannosylated; that contain an Fc region that has been modified to alter effector function, half-life, proteolysis, and/or glycosylation; are human, humanized, single chain or chimeric; and are a humanized antibody derived from a rabbit (parent) anti-human CGRP antibody. An exemplary mutation which impairs glycosylation comprises the mutation of the Asn residue at position 297 of an IgG heavy chain constant region such as IgG1 to another amino acid, such as Ala as described in U.S. Pat. No. 5,624,821, which is incorporated by reference in its entirety.

The invention further contemplates one or more anti-human CGRP antibodies wherein the framework regions (FRs) in the variable light region and the variable heavy regions of said antibody respectively are human FRs which are unmodified or which have been modified by the substitution of one or more human FR residues in the variable light or heavy chain region with the corresponding FR residues of the parent rabbit antibody, and wherein said human FRs have been derived from human variable heavy and light chain antibody sequences which have been selected from a library of human germline antibody sequences based on their high level of homology to the corresponding rabbit variable heavy or light chain regions relative to other human germline antibody sequences contained in the library.

The invention also contemplates that the treatment method may involve the administration of two or more

32

anti-CGRP antibodies or fragments thereof and disclosed herein. If more than one antibody is administered to the patient, the multiple antibodies may be administered simultaneously or concurrently, or may be staggered in their administration. The anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, may also be described by their strength of binding or their affinity for CGRP. In one embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with a dissociation constant (K_D) of less than or equal to 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-9} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-11} M, 5×10^{-11} M, 10^{-12} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, or 10^{-13} M. Preferably, the anti-CGRP antibodies and fragments thereof bind CGRP with a dissociation constant of less than or equal to 10^{-1} M, 5×10^{-2} M, or 10^{-12} M. In a specific embodiment of the invention the anti-CGRP antibody is Ab6 having a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM when measured using surface plasmon resonance (Misura, K et al, July 2019, Poster P220LB, AHS 61st annual scientific meeting). In another embodiment of the invention, the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to a linear or conformational CGRP epitope.

In another embodiment of the invention, the anti-CGRP activity of the anti-CGRP antibodies of the present invention, and fragments thereof having binding specificity to CGRP, bind to CGRP with an off-rate of less than or equal to 10^{-4} S⁻¹, 5×10^{-5} S⁻¹, 10^{-5} S⁻¹, 5×10^{-6} S⁻¹, 10^{-6} S⁻¹, 5×10^{-7} S⁻¹, or 10^{-7} S⁻¹. In a specific embodiment of the invention the anti-CGRP antibody is Ab6 having an off-rate of less than or equal to 5×10^{-6} S⁻¹, such as less than or equal to 4×10^{-6} S⁻¹, such as less than or equal to 3×10^{-6} S⁻¹, such as less than or equal to 2×10^{-6} S⁻¹, such as less than or equal to 1×10^{-6} S⁻¹ when measured using surface plasmon resonance.

40 Polynucleotides Encoding Anti-CGRP Antibody Polypeptides

As aforementioned the invention specifically includes the use of specific anti-CGRP antibody or antibody fragment referred to herein as Ab6, which comprises or consists of the 45 CDR, VL, VH, CL, and CH polypeptides having the sequences identified in FIGS. 1-12. The nucleic acid sequences encoding the foregoing VL, VH, CL, and CH polypeptides comprised in Ab6 are also comprised in FIGS. 1-12. The nucleic acid sequences which encode the CDR, VL, VH, CL, and CH polypeptides of an especially preferred anti-CGRP antibody, Ab6, are further described below.

Polynucleotides Encoding Antibody Ab6

The invention is further directed to polynucleotides 55 encoding antibody polypeptides having binding specificity to CGRP. In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable light chain polypeptide sequence of SEQ ID NO: 222:

60
 (SEQ ID NO: 232)
 CAAGTGCTGaccaggatctccatccctccgtctgcacatctgttaggagaca
 gagtcaccatcATTtgccAGGCCAGTCAGAGTGTATTCAAAACACCTA
 65 CCTGGCCTggtatcagcagaaaaccaggaaagtccctaagCAActgatc

33

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tatGATGCATCCACTTGGCATCTgggtccatctcgttcagtggca
gtggatctggacagattcactctcaccatcagcagccgcgctga
agatgttcaacttattactgtCTGGGCAGTTATGATTGTACTAATGGT
GATTGTTTGTtccggcgaggaaccaagggtggaaatcaaactgt .

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the light chain polypeptide sequence of SEQ ID NO: 221:

(SEQ ID NO: 231)
CAAGTGCTGaccaggatctccatcctccctgtgcattgttaggagaca
gagt caccatcAAttgcCAGGCCAGTCAGAGTGTATCATAACACCTA
CTGGCCtggatcagcagaaaccaggaaagttcttaagCAActgatc
tatGATGCATCCACTTGGCATCTgggtccatctcgttcagtggca
gtggatctggacagattcactctcaccatcagcagccgcgctga
agatgttcaacttattactgtCTGGGCAGTTATGATTGTACTAATGGT
GATTGTTTGTtccggcgaggaaccaagggtggaaatcaaactgtACGG
TGGCTGCACCACATGTCTTCATCTTCCGCATCTGATGAGCAGTGAA
ATCTGGAACTGCCTCTGTTGTGCGCTGCTGAATAACTTCTATCCAGA
GAGGCCAAAGTACAGTGGAAAGGTGGATAACGCCCTCCAATGGGTACT
CCCAGGAGAGTGTACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT
CAGCAGCACCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTC
TACGCCCTGCGAAGTCACCCATAGGGCTGAGCTCGCCGTACAAAAGA
GCTTCAACAGGGAGAGTGTAG .

In another embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the variable heavy chain polypeptide sequence of SEQ ID NO: 202:

(SEQ ID NO: 212)
gaggtgcagctTgtggagtctggggaggcttggccagctgggggggt
ccctgagactctctgtcaGTCTctggaATCGACCTCagtgGCTACTA
CATGAACTgggtccgtcaggccaggaaaggggctggagtggtcGGA
GTCATTGGTATTAATGGTGCACATACAGCAGCTGGCGAAAGGCC
gattcaccatctccagagacaattccaagACCACGGTGTatcttcaat
gaacagcctgagagctgaggacactgtgttatTTCTgtGCTAGAGGG
GACATCtggggccaaggggaccctcgtcaccgtcTCGAGC .

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 201:

(SEQ ID NO: 211)
gaggtgcagctTgtggagtctggggaggcttggccagctgggggggt
ccctgagactctctgtcaGTCTctggaATCGACCTCagtgGCTACTA
CATGAACTgggtccgtcaggccaggaaaggggctggagtggtcGGA

34

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GTCATTGGTATTAATGGTGCACATACAGCAGCTGGCGAAAGGCC
gattcaccatctccagagacaattccaagACCACGGTGTatcttcaat
5 gaacagcctgagagctgaggacactgtgttatTTCTgtGCTAGAGGG
GACATCtggggccaaggggaccctcgtcaccgtcTCGAGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCACCTCCTCCaAGAGCACCTCTGG
10 GGGCACAGCGGCCTGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTGGAACTCAGGCCTGACCAGCGGTGACACCT
TCCCGGTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
15 GACCGTGCCCTCAGCAGCTTGGCACCCAGACCTACATCTGCAACGTG
AATCACAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGCCAAAT
CTTGTGACAAAACCTACACATGCCACCGTGCCAGCACCTGAACTCCT
20 GGGGGGACCGTCAGTCTCCCTTCCCCC AAAACCCAAGGACACCCCTC
ATGaTCTCCGACCCCTGAGGTACATGCGTGGTGGACGTGAGCC
ACGAAGACCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGT
25 GCATAATGCCAACAGCAAAGCCGGAGGAGCAGTACGCCAGCACGTAC
CGTGTGGTCAGCCTCTCACCGTCCTGCACCAAGGACTGGCTGAATGCCA
AGGAGTACAAGTGCACAGGTCTCAACAAAGCCCTCCAGCCCCATCGA
30 GAAAACCATCTCAAAGCCAAGGGCAGCCCCGAGAACACCACAGGTGTAC
ACCCCTGCCCTACCCGGAGGAGATGACCAAGAACCGAGTCAGCCTGA
CCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATGCCGTGGAGTGGGA
GAGCAATGGGAGCCGGAGAACAAACTACAAGACCACGCCCTCCCGTGTG
35 35 GACTCCGACGGCTCCTCTCTACAGCAAGCTCACCGTGGACAAGA
GCAGGGTGGCAGGGAAACGTCTCATGCTCCGTGATGCGATGAGGC
TCTGCACAACCAACTACACCGAGAACAGGCTCTCCCTGTCTCCGGTAAA
40 TGA.

In one embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, the following polynucleotide sequence encoding the heavy chain polypeptide sequence of SEQ ID NO: 566:

(SEQ ID NO: 567)
gaggtgcagctTgtggagtctggggaggcttggccagctgggggggt
50 ccctgagactctctgtcaGTCTctggaATCGACCTCagtgGCTACTA
CATGAACTgggtccgtcaggccaggaaaggggctggagtggtcGGA
GTCATTGGTATTAATGGTGCACATACAGCAGCTGGCGAAAGGCC
55 gattcaccatctccagagacaattccaagACCACGGTGTatcttcaat
gaacagcctgagagctgaggacactgtgttatTTCTgtGCTAGAGGG
GACATCtggggccaaggggaccctcgtcaccgtcTCGAGCCTCCACCA
AGGGCCCATCGGTCTTCCCCCTGGCACCTCCTCCaAGAGCACCTCTGG
60 GGGCACAGCGGCCTGGCTGCCTGGTCAAGGACTACTTCCCCGAACCG
GTGACGGTGTGGAACTCAGGCCTGACCAGCGGTGACACCT
TCCCGGTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGT
65 GACCGTGCCCTCAGCAGCTTGGCACCCAGACCTACATCTGCAACGTG

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AATCACAAAGCCCAGCAACACCAAGGTGGACGCGAGAGTTGAGGCCAAAT
CTTGTGACAAAACCTCACACATGCCAACCGTGCCCCAGCACCTGAACCTC
GGGGGGACCGTCAGTCTCCCTTCCCCAAAACCCAAGGACACCCCTC
ATGaTCTCCCgGACCCCTGAGGTCAACATGCGTGGTGGTGACCGTGAGCC
ACGAAGACCCCTGAGGTCAAGTTCAACTGGTACCTGGACGGCGTGGAGGT
GCATAATGCCAACAGCAAAGCCGCGGGAGGAGCAGTACGCCAGCGACGTAC
CGTGTGGTCAGCGCCTCACCGTCCCTGCACCAGGACTGGCTGAATGGCA
AGGAGTACAAGTCAAGGTCTCAACAAAGCCCTCCAGCCCCCATCGA
GAAAACCATCTCAAAGCCAAGGGCAGCCCCGAGAACCCACAGGTGTAC
ACCCCTGCCCATCCCGGGAGGAGATGACCAAGAACCCAGGTGAGCCTGA
CCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATGCCGTGGAGTGGGA
GAGCAATGGGAGCCGGAGAACAAACTACAAGACCACGCCCTCCCGTGTG
GACTCCGACGGCTCCCTCTCTACAGCAAGCTCACCGTGGACAAGA
GCAGGGTGGCAGCAGGGGAACGTCTCTCATGCTCCGTGATGCATGAGGC
TCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGTTGA.

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In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221.

In a further embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one or more of the polynucleotide sequences of SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218 which correspond to polynucleotides encoding the complementarity-determining regions (CDRs, or hypervariable regions) of the heavy chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

The invention also contemplates polynucleotide sequences including one or more of the polynucleotide sequences encoding antibody fragments described herein. In one embodiment of the invention, polynucleotides encoding antibody fragments having binding specificity to CGRP comprise, or alternatively consist of, one, two, three or more, including all of the following polynucleotides encoding antibody fragments: the polynucleotide SEQ ID NO: 232 encoding the light chain variable sequence of SEQ ID NO: 222; the polynucleotide SEQ ID NO: 231 encoding the light chain sequence of SEQ ID NO: 221; the polynucleotide SEQ ID NO: 212 encoding the heavy chain variable sequence of SEQ ID NO: 202; the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201; the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566; polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238) of the light chain variable sequence of SEQ ID NO: 222 or the light chain sequence of SEQ ID NO: 221; and polynucleotides encoding the complementarity-determining regions (SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218) of the heavy

chain variable sequence of SEQ ID NO: 202 or the heavy chain sequence of SEQ ID NO: 201 or SEQ ID NO: 566.

In a preferred embodiment of the invention, polynucleotides of the invention comprise, or alternatively consist of, 5 polynucleotides encoding Fab (fragment antigen binding) fragments having binding specificity for CGRP. With respect to antibody Ab6, the polynucleotides encoding the full length Ab6 antibody comprise, or alternatively consist of, the polynucleotide SEQ ID NO: 231 encoding the light 10 chain sequence of SEQ ID NO: 221 and the polynucleotide SEQ ID NO: 211 encoding the heavy chain sequence of SEQ ID NO: 201 or the polynucleotide SEQ ID NO: 567 encoding the heavy chain sequence of SEQ ID NO: 566.

Another embodiment of the invention contemplates these 15 polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast *Pichia*. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*. In one 20 embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (e.g., papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab 25 fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but 30 are not limited to, *Pichia pastoris*.

Host cells and vectors comprising said polynucleotides are also contemplated.

The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy 35 and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another 40 embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

Methods of Producing Antibodies and Fragments Thereof

In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and 45 fragments thereof. Methods for producing antibodies and fragments thereof secreted from polyploidal, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. Pat. No. 7,935,340 to Garcia-Martinez et al., the disclosures of each 50 of which are herein incorporated by reference in their entireties. Methods for producing antibodies and fragments thereof in mammalian cells, e.g., CHO cells are further well known in the art.

Other methods of producing antibodies are also well 55 known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (See, for example, U.S. Pat. No. 4,816,567 to Cabilly et al.; Morrison et al., *P.N.A.S. USA*, 81:8651-55 (1984); Neuberger, M. S. et al., *Nature*, 314:268-270 (1985); Boulianne, G. L. et al., *Nature*, 312:643-46 (1984), the 60 disclosures of each of which are herein incorporated by reference in their entireties).

Likewise, other methods of producing humanized anti-65 bodies are now well known in the art (See, for example, U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen et al; U.S. Pat. Nos. 5,225,539 and 6,548,640 to

Winter; U.S. Pat. Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al; U.S. Pat. No. 6,632,927 to Adair; Jones, P. T. et al, *Nature*, 321:522-525 (1986); Reichmann, L., et al, *Nature*, 332:323-327 (1988); Verhoeven, M, et al, *Science*, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

The present invention further includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of most bothersome symptom associated with migraine.

Administration

In one embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of between about 0.1 and 100.0 mg/kg of body weight of recipient subject. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject at a concentration of about 0.4 mg/kg of body weight of recipient subject and/or at a dosage of 100 or 300 mg. In a preferred embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a recipient subject with a frequency of once every twenty-six weeks or six months or less, such as once every sixteen weeks or four months or less, once every eight weeks or two months or less, once every four weeks or monthly or less, once every two weeks or bimonthly or less, once every week or less, or once daily or less. In general the administration of sequential doses may vary by plus or minus a few days from the aforementioned schedule, e.g., administration every 3 months or every 12 weeks includes administration of a dose varying from the schedule day by plus or minus 1, 2, 3, 4, 5, 5, or 7 days.

Fab fragments may be administered every two weeks or less, every week or less, once daily or less, multiple times per day, and/or every few hours. In one embodiment of the invention, a patient receives Fab fragments of 0.1 mg/kg to 40 mg/kg per day given in divided doses of 1 to 6 times a day, or in a sustained release form, effective to obtain desired results.

It is to be understood that the concentration of the antibody or Fab administered to a given patient may be greater or lower than the exemplary administration concentrations set forth above.

A person of skill in the art would be able to determine an effective dosage and frequency of administration through routine experimentation, for example guided by the disclosure herein and the teachings in Goodman, L. S., Gilman, A., Brunton, L. L., Lazo, J. S., & Parker, K. L. (2006). Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; Howland, R. D., Mycek, M. J., Harvey, R. A., Champe, P. C., & Mycek, M. J. (2006). Pharmacology. Lippincott's illustrated reviews. Philadelphia: Lippincott Williams & Wilkins; and Golan, D. E. (2008). Principles of pharmacology: the pathophysiologic basis of drug therapy. Philadelphia, Pa., [etc.]: Lippincott Williams & Wilkins.

In another embodiment of the invention, the anti-CGRP antibodies described herein, or CGRP binding fragments thereof, as well as combinations of said antibodies or antibody fragments, are administered to a subject in a pharmaceutical formulation.

A "pharmaceutical composition" refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to buccal, epicutaneous, epidural, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal, preferably intravenous. In addition, administration can occur by means of injection, powder, liquid, gel, drops, or other means of administration.

A "pharmaceutical excipient" or a "pharmaceutically acceptable excipient" is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington's Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

As used herein "pharmaceutically acceptable carrier" or "excipient" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated

39

delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

An exemplary composition comprises, consists essentially of Ab6, an excipient such as histidine, an isotonic agent such as sorbitol, and a surfactant such as polysorbate 80 in an aqueous solution. For example, the composition may comprise, consist essentially of, or consist of histidine (L-histidine), sorbitol, polysorbate 80, such as, per 1 mL volume, about 100 mg Ab6, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, having a pH of about 5.8, or approximately that constitution, e.g., within 10% of those values, within 5% of those values, within 1% of those values, within 0.5% of those values, or within 0.1% of those values, and water. For example, the pH value may be within 10% of 5.8, i.e., between 5.22 and 6.38. The Ab6 antibody may comprise or consist of the variable light and heavy chain polypeptides of SEQ ID NO: 222 and SEQ ID NO: 202 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, or the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively. The composition may be in the form of an aqueous solution, or a concentrate (e.g., lyophilized) which when reconstituted, e.g., by addition of water, yields the aforementioned constitution. An exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 201 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.10% of those quantities. Another exemplary composition consists of, per mL, 100 mg of the light and heavy chain polypeptides of SEQ ID NO: 221 and SEQ ID NO: 566 respectively, about 3.1 mg L-Histidine, about 40.5 mg Sorbitol, and about 0.15 mg Polysorbate 80, and water Q.S, or approximately that constitution, e.g., within 10% of those quantities, within 5% of those quantities, within 1% of those quantities, within 0.5% of those quantities, or within 0.10% of those quantities. The composition may be suitable for intravenous or subcutaneous administration, preferably intravenous administration. For example, the composition may be suitable for mixing with an intravenous solution (such as 0.9% sodium chloride) at an amount of between about 100 mg and about 300 mg antibody added to 100 mL of intravenous solution. Preferably the composition may be shelf-stable for at least 1, 3, 6, 12, 18, or 24 months, e.g., showing formation of aggregates of no more than 5% or no more than 10% of the antibody or fragment after storage at room temperature or when refrigerated at 4° C. for the specified duration, or in an accelerated aging test that simulates storage for that duration.

For each of the recited embodiments, the compounds can be administered by a variety of dosage forms. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, reconstitutable powders, elixirs, liquids, solutions, suspensions, emulsions, powders, granules, particles, microparticles, dispersible granules, cachets, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants,

40

injectables (including subcutaneous, intramuscular, intravenous, and intradermal, preferably intravenous), infusions, and combinations thereof.

The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

Certain CGRP antibody polynucleotides and polypeptides are disclosed in the sequence listing accompanying this patent application filing, and the disclosure of said sequence listing is herein incorporated by reference in its entirety.

The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (e.g. amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

Additional Exemplary Embodiments

Additional exemplary embodiments of the invention are provided as follows:

S1. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody.

S2. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said migraine patient suffers from chronic migraine.

S3. Use of an anti-CGRP antibody for the manufacturing of a medicament for treating most bothersome symptom (MBS) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said patient suffers from episodic migraine.

S4. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved

41

at 1-12 hours post-completion of administration or infusion, such as 1-5 hours post-completion of administration or infusion, 1-2 hours post-completion of administration or infusion, or about 2 hours post-completion of administration or infusion.

S5. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 1 month from the first dosing with said anti-CGRP antibody.

S6. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 3 month from the first dosing with said anti-CGRP antibody.

S7. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 6 month from the first dosing with said anti-CGRP antibody.

S8. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

S9. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

S10. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty.

S11. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes and Sensitivity to smell (osmophobia or olfactophobia).

S12. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody.

S13. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said migraine patient suffers from chronic migraine.

S14. Use of an anti-CGRP antibody for the manufacturing of a medicament for improving patient global impression of change (PGIC) associated with migraine, comprising administering to a migraine patient an anti-CGRP antibody, wherein said patient suffers from episodic migraine.

S15. Use of the anti-CGRP antibody of any one of the embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine within 1 month from the first dosing with said anti-CGRP antibody.

S16. Use of the anti-CGRP antibody of any one of the embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change

42

(PGIC) associated with migraine within 3 month from the first dosing with said anti-CGRP antibody.

S17. Use of the anti-CGRP antibody of any one of the embodiments S12-S14, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine within 6 month from the first dosing with said anti-CGRP antibody.

S18. Use of the anti-CGRP antibody of any one of the embodiments S12-S17, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine, and wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

S19. Use of the anti-CGRP antibody of any one of the embodiments S12-S18, wherein the administration of said medicament improves patient global impression of change (PGIC) associated with migraine, and wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

S20. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous or subcutaneous infusion.

S21. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous infusion.

S22. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of administration or infusion.

S23. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

S24. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

S25. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

S26. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

S27. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

S28. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

S29. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

43

S30. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

S31. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

S32. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

S33. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

S34. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

S35. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

S36. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

S37. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

S38. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S39. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S40. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S41. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S42. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

S43. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

S44. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

S45. Use of the anti-CGRP antibody of any one of the embodiments S1-S42, wherein said medicament is for intravenous administration in a dosage of 300 mg of said

44

anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

S46. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

S47. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

S48. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

S49. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

S50. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

S51. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

S52. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein, prior to administration of said medicament, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

S53. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to administration of said medicament.

S54. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to administration of said medicament.

S55. Use of the anti-CGRP antibody of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to administration of said medicament.

S56. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S57. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S58. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S59. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S60. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S61. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said patient further has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to administration of said medicament.

S62. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament is further for administration in a second dose of said anti-CGRP antibody about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after administration of said medicament.

S63. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said medicament comprises about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

S64. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

S65. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

S66. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

S67. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

S68. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

S69. Use of the anti-CGRP antibody of any of any one of embodiments S1-S67, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

S70. Use of the anti-CGRP antibody of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

S71. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

S72. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL

volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

S73. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

S74. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

S75. Use of the anti-CGRP antibody of embodiment S70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

S76. Use of the anti-CGRP antibody of any of any one of the foregoing embodiments, wherein the anti-CGRP antibody has a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM.

Further Exemplary Embodiments

Further exemplary embodiments of the invention are provided as follows:

E1. An anti-CGRP antibody for use in treating most bothersome symptom (MBS) associated with migraine in a patient suffering from migraine.

E2. The anti-CGRP antibody for use of embodiment E1, wherein the patient suffers from chronic migraine.

E3. The anti-CGRP antibody for use of embodiment E1, wherein the patient suffers from episodic migraine.

E4. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved at 1-12 hours post-completion of administration or infusion, such as 1-5 hours post-completion of administration or infusion, 1-2 hours post-completion of administration or infusion, or about 2 hours post-completion of administration or infusion.

E5. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 1 month from the first dosing with said anti-CGRP antibody.

E6. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 3 month from the first dosing with said anti-CGRP antibody.

E7. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the patients most bothersome symptom (MBS) associated with migraine is improved within 6 month from the first dosing with said anti-CGRP antibody.

E8. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the improvement is sustained for at least 3 months from the first dosing with said anti-CGRP antibody.

E9. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the improvement is sustained for at least 6 months from the first dosing with said anti-CGRP antibody.

E10. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes, Sensitivity to smell (osmophobia or olfactophobia), Visual impact, Pressure/tightness, Pain (anatomical), Eye pain, Neck pain, Dizziness, Allodynia, Inactivity, Sensory disturbance, Sleep disturbance and Speech difficulty.

E11. The anti-CGRP antibody for use according to any of the foregoing embodiments, wherein the MBS is selected from the group consisting of: Sensitivity to light (photophobia), Nausea/vomiting, Headache, Sensitivity to sound (phonophobia), Aura, Pain with activity, Pain, Throbbing/pulsation, Cognitive disruption, Fatigue, Mood changes and Sensitivity to smell (osmophobia or olfactophobia).

E12. An anti-CGRP antibody for use in improving patient global impression of change (PGIC) associated with migraine in a patient suffering from migraine.

E13. The anti-CGRP antibody for use of embodiment E12, wherein the patient suffers from chronic migraine.

E14. The anti-CGRP antibody for use of embodiment E12, wherein the patient suffers from episodic migraine.

E15. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 1 month from the first dosing with said anti-CGRP antibody.

E16. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 3 month from the first dosing with said anti-CGRP antibody.

E17. The anti-CGRP antibody for use according to any of embodiments E12-E14, wherein the improvement of patient global impression of change (PGIC) associated with migraine is observed within 6 month from the first dosing with said anti-CGRP antibody.

E18. The anti-CGRP antibody for use according to any of embodiments E12-E17, wherein the improvement of patient global impression of change (PGIC) associated with migraine is sustained for 3 months from the first dosing with said anti-CGRP antibody.

E19. The anti-CGRP antibody for use according to any of embodiments E12-E18, wherein the improvement of patient global impression of change (PGIC) associated with migraine is sustained for 6 months from the first dosing with said anti-CGRP antibody.

E20. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous or subcutaneous infusion.

E21. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous infusion.

E22. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient is headache free 2 hours post-completion of administration or infusion.

E23. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises Ab6.

E24. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody

comprises the light chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively.

E25. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively.

E26. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

E27. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

E28. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224; SEQ ID NO: 226; and SEQ ID NO: 228, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 204; SEQ ID NO: 206; and SEQ ID NO: 208, respectively.

E29. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 234; SEQ ID NO: 236; and SEQ ID NO: 238, respectively and heavy chain CDR 1, 2, and 3 polypeptide sequences encoded by SEQ ID NO: 214; SEQ ID NO: 216; and SEQ ID NO: 218, respectively.

E30. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222.

E31. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232.

E32. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide of SEQ ID NO: 202.

E33. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

E34. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide of SEQ ID NO: 222 and the variable heavy chain polypeptide of SEQ ID NO: 202.

E35. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the variable light chain polypeptide encoded by SEQ ID NO: 232 and the variable heavy chain polypeptide encoded by SEQ ID NO: 212.

E36. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221.

E37. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231.

E38. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E39. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E40. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E41. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody comprises the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E42. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is between about 100 mg and about 300 mg, or is about 100 mg, or is about 300 mg.

E43. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the administered amount of said anti-CGRP antibody is 100 mg.

E44. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is for intravenous administration in a dosage of 100 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

E45. The anti-CGRP antibody for use of any one of the embodiments E1-E42, wherein said anti-CGRP antibody is for intravenous administration in a dosage of administering 300 mg of said anti-CGRP antibody every 10-14 weeks, preferably every 11-13 weeks, more preferably every 12 weeks.

E46. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 1-10 migraine attacks per month in the month or in the 3 months prior to administration.

E47. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 2-8 migraine attacks per month in the month or in the 3 months prior to administration.

E48. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits between 3-7 migraine attacks per month in the month or in the 3 months prior to administration.

E49. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 25 headache days per month in the month or in the 3 months prior to administration.

E50. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 20 headache days per month in the month or in the 3 months prior to administration.

E51. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 15 headache days per month in the month or in the 3 months prior to administration.

E52. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein, prior to administration of said anti-CGRP antibody, the patient exhibits less than 10 headache days per month in the month or in the 3 months prior to administration.

E53. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 10 years prior to the administration of said anti-CGRP antibody.

E54. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 15 years prior to the administration of said anti-CGRP antibody.

E55. The anti-CGRP antibody for use of any one of the foregoing embodiments wherein said patient was diagnosed with migraine at least 18 or at least 19 years prior to the administration of said anti-CGRP antibody.

E56. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E57. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E58. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the one month period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E59. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 50% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E60. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by at least 75% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E61. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said patient has a reduction in the number of migraine days by 100% in the 12 week period after being administered said antibody relative to the baseline number of migraine days experienced by that patient prior to the administration of said anti-CGRP antibody.

E62. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises administering a second dose of said anti-CGRP antibody to said patient about 10-14 weeks, preferably 11-13 weeks, more preferably about 12 weeks or about 3 months after the administration of said anti-CGRP antibody.

E63. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said use comprises admin-

51

istering about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg of said anti-CGRP antibody.

E64. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody is aglycosylated or if glycosylated only contains only mannose residues.

E65. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide of SEQ ID NO: 221 and the heavy chain polypeptide of SEQ ID NO: 201 or SEQ ID NO: 566.

E66. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody consists of the light chain polypeptide encoded by SEQ ID NO: 231 and the heavy chain polypeptide encoded by SEQ ID NO: 211 or SEQ ID NO: 567.

E67. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said headache or said migraine is diagnosed according to the third edition of the International Classification of Headache Disorders.

E68. The anti-CGRP antibody for use of any of any one of the foregoing embodiments, wherein said anti-CGRP antibody is expressed in or obtained by expression in *Pichia pastoris*.

E69. The anti-CGRP antibody for use of any of any one of embodiments E1-E67, wherein said anti-CGRP antibody is expressed in or obtained by expression in CHO cells.

E70. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein said anti-CGRP antibody or anti-CGRP antibody fragment is comprised in a formulation comprising or consisting of histidine (L-histidine), sorbitol, polysorbate 80, and water.

E71. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-10% of said values, and having a pH of 5.8 or within +/-10% of said value.

E72. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-5% of said values, and/or having a pH of 5.8 or within +/-5% of said value.

E73. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-1% of said values, and/or having a pH of 5.8 or within +/-1% of said value.

E74. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or having amounts of each constituent within +/-0.5% of said values, and/or having a pH of 5.8 or within +/-0.5% of said value.

E75. The anti-CGRP antibody for use of embodiment E70, wherein said formulation comprises or consists of, per 1 mL volume, 100 mg anti-CGRP antibody, 3.1 mg L-Histidine, 40.5 mg Sorbitol, and 0.15 mg Polysorbate 80, or

52

having amounts of each constituent within +/-0.1% of said values, and/or having a pH of 5.8 or within +/-0.1% of said value.

E76. The anti-CGRP antibody for use of any one of the foregoing embodiments, wherein the anti-CGRP antibody has a dissociation constant of less than or equal to 10 pM, such as 2-8 pM, such as 3-6 pM, such as less than or equal to about 5 pM.

10

EXAMPLES

The following examples are provided in order to illustrate the invention, but are not to be construed as limiting the scope of the claims in any way.

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Example 1

Preparation of Antibodies that Bind CGRP

The preparation of exemplary anti-CGRP antibody Ab6 having the sequences in FIGS. 1-12 is disclosed in commonly owned PCT Application WO/2012/162243, published on Nov. 29, 2012, the contents of which are incorporated by reference herein. This application exemplifies synthesis of these antibodies in *Pichia pastoris* cells. The present Applicant further contemplates synthesis of anti-CGRP antibody Ab6 particularly in CHO cells.

Example 2

30 Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic Migraine Patients

This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 for chronic migraine prevention. In the study, 35 1,072 patients were randomized to receive Ab6 (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks. The study design is depicted in FIG. 13. To be eligible for the trial, patients must have experienced at least 15 headache days per month, of which at least eight met criteria for migraine. Patients that participated in the trial had an average of 16.1 migraine days per month at baseline. The primary endpoint of the present study was the change from baseline in mean monthly migraine days (MMDs) over weeks 1-12 following the first infusion of Ab6. The change from baseline in mean monthly migraine days (MMDs) following the second infusion at week 12 was also assessed and the results are shown in FIG. 14.

40 Study endpoints further included patient-identified MBS as part of the predefined key secondary endpoints. At screening, patients verbally identified the MBS associated with their migraine, which was pooled across treatment arms for this analysis. The change from baseline of these symptoms were than rated by the patient every month of the study beginning from Day 0.

45 In the present study, patients verbally identified the most bothersome symptom (MBS) associated with their migraine at screening. The MBS associated with their migraine was then categorized by the investigator into a predefined list of 8 symptoms or an "other" option. The predefined list included the terms nausea, vomiting, sensitivity to light, sensitivity to sound, mental cloudiness, fatigue, pain with activity, and mood changes. The "other" option provided investigators the opportunity to identify any migraine-associated symptom without limitation described by the patient as most bothersome but did not easily fit into the check list of symptoms included in the work study checklist. For those patients who selected the "other" category for their MBS,

their “write-in” responses were re-coded post hoc and re-classified to the predefined list or to new symptom classes. At subsequent visits, patients were asked to rate the change from the screening visit in their self-reported MBS on a 7-point scale, which is shown below:

Very Much Improved	Much Improved	Minimally Improved	No Change	Minimally Worse	Much Worse	Very Worse
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In addition to MBS, the patients were also requested to evaluate the efficacy of the treatment on patient global impression of change (PGIC), which is a parameter comprising a single question assessing the patient’s own impression of the overall change in their disease status since the start of the study. This parameter was also rated by the patients at a 7-point scale identical to the one used to assess change in MBS as displayed above and at the same time points in the study. In FIGS. 16-22 the “worse” category includes “minimally worse”, “much worse”, and “very much worse”.

At the screening visit in, patients indicated a wide range of symptoms as their MBS, with the “other” category being the most frequent response (40%-42% across the 3 treatment groups). The patients who selected the “other” category generally provided more details and/or had more than 1 symptom as their MBS, allowing for these symptoms to be recoded. The overall list of MBS is summarized in Table 1 below.

TABLE 1

Symptom, n (%)	Summary of patient-identified MBS in the present study as described in Example 2			
	Eptinezumab 100 mg (n = 356)	Eptinezumab 300 mg (n=350)	Placebo (n = 366)	Total (N = 1072)
ICHD-3 Symptoms				
Sensitivity to light	67 (18.8)	64 (18.3)	69 (18.9)	200 (18.7)
Nausea/vomiting	55 (15.4)	46 (13.1)	61 (16.7)	162 (15.1)
Headache	45 (12.6)	43 (12.3)	32 (8.7)	120 (11.2)
Sensitivity to sound	22 (6.2)	28 (8.0)	28 (7.7)	78 (7.3)
Aura	4 (1.1)	1 (<1)	2 (<1)	7 (0.7)
Additional Symptoms				
Pain with activity	53 (14.9)	45 (12.9)	49 (13.4)	147 (13.7)
Pain	35 (9.8)	45 (12.9)	53 (14.5)	133 (12.4)
Throbbing/pulsation	18 (5.1)	17 (4.9)	15 (4.1)	50 (4.7)
Cognitive disruption	17 (4.8)	14 (4.0)	13 (3.6)	44 (4.1)
Fatigue	7 (2.0)	11 (3.1)	8 (2.2)	26 (2.4)
Mood changes	8 (2.2)	4 (1.1)	4 (1.1)	16 (1.5)
Sensitivity to smell	1 (<1)	1 (<1)	8 (2.2)	10 (0.9)
Visual impact	2 (<1)	3 (<1)	3 (<1)	8 (0.7)
Pressure/tightness	2 (<1)	2 (<1)	3 (<1)	7 (0.7)
Pain, anatomical	3 (<1)	3 (<1)	0	6 (0.6)
Eye pain	4 (1.1)	1 (<1)	1 (<1)	6 (0.6)
Neck pain	1 (<1)	1 (<1)	3 (<1)	5 (0.5)
Dizziness	2 (<1)	2 (<1)	1 (<1)	5 (0.5)
Allodynia	1 (<1)	1 (<1)	1 (<1)	3 (0.3)
Inactivity	0	1 (<1)	1 (<1)	2 (0.2)
Sensory disturbance	1 (<1)	0	0	1 (0.1)
Sleep disturbance	0	0	1 (<1)	1 (0.1)
Speech difficulty	0	0	1 (<1)	1 (0.1)
Multiple*	7 (2.0)	12 (3.4)	8 (2.2)	27 (2.5)
Other	1 (<1)	5 (1.4)	1 (<1)	7 (0.7)

*Patient’s most bothersome symptom included more than 1 symptom type.

ICHD-3 = International Classification of Headache Disorders 3rd edition.

The most commonly reported symptoms were light sensitivity, nausea/vomiting, pain with activity, pain, headache,

sound sensitivity, throbbing/pulsation, cognitive disruption, fatigue, mood changes, and sensitivity to smell, with each category having at least 10 patients reporting these events as their MBS. At the end of the 28-day screening period (i.e., before dosing at the baseline visit), patients were asked to rate the change in their identified MBS from very much worse to very much improved, with >90% reporting no change in their MBS, which is illustrated in FIG. 16. This suggests that the bothersomeness of patient-identified MBS was quite stable among this cohort with chronic migraine during the screening period.

Infusion of Ab6 in doses of 100 mg and 300 mg provided significantly reduction in mean MMDs across months 1-3 of the study, with further reduction after an additional infusion at week 12 of the study. This effect is shown in FIG. 14.

The efficacy of Ab6 on the MBS was demonstrated at 1 month (FIG. 17), 3 months (FIG. 19), and 6 months (FIG. 21), following the first infusion of Ab6 in doses of 100 mg and 300 mg. The efficacy of Ab6 on the PGIC was demonstrated at 1 month (FIG. 18), 3 months (FIG. 20), and 6 months (FIG. 22), following the first infusion of Ab6 in doses of 100 mg and 300 mg. The efficacy on these parameters were sustained or increased through 2 doses of Ab6 over 6 months; at Month 1, 75-82% of Ab6-treated patients indicated some level of improvement compared to 56-59% for the placebo-treated patients; at Month 3 ratings of improvement were similar to those of month 1; at Month 6, ~80% of Ab6-treated patients indicated ≥1 categorical level of improvement in MBS and PGIC. The distribution of ratings for MBS improvement and PGIC were similar across time points, suggesting that the 2 identically rated measures in patients with chronic migraine move in parallel. These data suggest that improvements in patient-identified most bothersome migraine-associated symptoms are highly correlated with the patient’s perception of an improved disease status in patients with chronic migraine.

The administered antibody, Ab6, is an anti-CGRP antibody consisting of the light chain polypeptide of SEQ ID NO: 221 and heavy chain polypeptide of SEQ ID NO: 201.

Patient characteristics are summarized in Table 2 below, with separate columns for patients receiving placebo, 100 mg of the antibody, or 300 mg of the antibody. Patients had a mean number of years from migraine diagnosis of between 17.0 and 19.0 years, a mean duration of suffering from chronic migraine of between 11.5 and 12.4 years, and between 44.3% and 45.2% of patients utilized at least one prophylactic medication. In addition, patients with a dual diagnosis of chronic migraine and medications overuse excluding opioid and butalbital over were included in this study. At baseline, in both antibody treatment groups the mean number of migraine days per month was 16.1, while for the placebo group, the mean number of migraine days per month was 16.2.

TABLE 2

60	Summarizes the characteristics of patients in each treatment group in the clinical trials described in Example 2.			
	Eptinezumab 100 mg n = 356	Eptinezumab 100 mg n = 350	Placebo n = 366	
	Age (years), mean (SD)	41.0 (11.72)	41.0 (10.36)	39.6 (11.28)
Sex, n (%)				
Male	49 (13.8%)	36 (10.3%)	41 (11.2%)	
Female	307 (86.2%)	314 (89.7%)	325 (88.8%)	

US 12,384,837 B2

55

TABLE 2-continued

Summarizes the characteristics of patients in each treatment group in the clinical trials described in Example 2.			
	Eptinezumab 100 mg n = 356	Eptinezumab 100 mg n = 350	Placebo n = 366
Race, n (%)			
White	332 (93.3%)	322 (92.0%)	321 (87.7%)
Black or African American	21 (5.9%)	23 (6.6%)	38 (10.4%)
Other*	3 (0.8%)	5 (1.4%)	7 (1.9%)
BMI (kg/m ²), mean (SD)	26.4 (4.98)	26.3 (7.14)	27.0 (5.56)
Age at migraine diagnosis (years), mean (SD)	22.8 (10.64)	22.0 (9.30)	22.6 (9.98)
Duration of migraine diagnosis (years), mean (SD)	18.3 (12.22)	19.0 (11.50)	17.0 (11.63)

56

TABLE 2-continued

Summarizes the characteristics of patients in each treatment group in the clinical trials described in Example 2.				
	Eptinezumab 100 mg n = 356	Eptinezumab 100 mg n = 350	Placebo n = 366	
5	Duration of chronic migraines (years), mean (SD)	11.6 (11.72)	12.3 (11.15)	11.6 (10.90)
10	Number of migraine days, mean (SD) †	16.1 (4.61)	16.1 (4.77)	16.2 (4.55)
	Medication-overuse headache diagnosis, n (%)‡	139 (39.0%)	147 (42.0%)	145 (39.6%)
15	BMI, body mass index; SD, standard deviation;			
	*Other includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and other.			
	†As reported by the eDiary in the 28-day screening period.			
	‡Based on 3rd edition of the International Classification of Headache Disorders (beta).			

SEQUENCE LISTING

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APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV 180
PSSSLGTQTY ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYAS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKAL PAPIEKTIK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
VKGFYPSDIA VEWESENQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM 420
HEALHNHYTQ KSLSLSPGK 439

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FEATURE           Location/Qualifiers

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PSVFLFPKKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGE EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPSPREE 240
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atgaccaaga accagggttccatgcgttgcacc ctgttcaaa gtttctatcc cagccacatc 780
gcctggaggt gggagagccaa tggcagccg gagaacaactt acaagaccac gcctccctgt 840
ctggactccatccatgcgttgcacc ttcttccatccatgcgttgcacc ccgtggacaa gagcagggttgg 900
cagcaggggaa acgttccatccatgcgttgcacc ttcttccatccatgcgttgcacc ccactacacg 960
cagaagggccatc tcccccgttc tccgggtaaa tga                                993

SEQ ID NO: 21      moltype = AA length = 219
FEATURE          Location/Qualifiers
REGION          1..219
source           note = Engineered antibody sequence
                 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 21
QVLTQTASPV SAAVGSTVTI NCQASQSYVD NNYLAWYQQK PGQPPKQLIY STSTLASGVS  60
SRFKGSGSGT QFTLTISDLE CADAATYYCL GSYDCSSGD C FVFGGGTEVV VKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLASKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC                                219

SEQ ID NO: 22      moltype = AA length = 113
FEATURE          Location/Qualifiers
REGION          1..113
source           note = Engineered antibody sequence
                 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 22
QVLTQTASPV SAAVGSTVTI NCQASQSYVD NNYLAWYQQK PGQPPKQLIY STSTLASGVS  60
SRFKGSGSGT QFTLTISDLE CADAATYYCL GSYDCSSGD C FVFGGGTEVV VKR                                113

SEQ ID NO: 23      moltype = AA length = 22
FEATURE          Location/Qualifiers
REGION          1..22
source           note = Engineered antibody sequence
                 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 23
QVLTQTASPV SAAVGSTVTI NC                                22

SEQ ID NO: 24      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION          1..13
source           note = Engineered antibody sequence
                 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 24

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QASQSVYDNN YLA	13
SEQ ID NO: 25	moltype = AA length = 15
FEATURE	Location/Qualifiers
REGION	1..15
source	note = Engineered antibody sequence 1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 25	
WYQQKPGQPP KQLIY	15
SEQ ID NO: 26	moltype = AA length = 7
FEATURE	Location/Qualifiers
REGION	1..7
source	note = Engineered antibody sequence 1..7
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 26	
STSTLAS	7
SEQ ID NO: 27	moltype = AA length = 32
FEATURE	Location/Qualifiers
REGION	1..32
source	note = Engineered antibody sequence 1..32
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 27	
GVSSRFKGSG SGTQFTLTIS DLECADAATY YC	32
SEQ ID NO: 28	moltype = AA length = 13
FEATURE	Location/Qualifiers
REGION	1..13
source	note = Engineered antibody sequence 1..13
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 28	
LGSYDCSSGD CFV	13
SEQ ID NO: 29	moltype = AA length = 11
FEATURE	Location/Qualifiers
REGION	1..11
source	note = Engineered antibody sequence 1..11
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 29	
FGGGTEVVVK R	11
SEQ ID NO: 30	moltype = AA length = 106
FEATURE	Location/Qualifiers
REGION	1..106
source	note = Engineered antibody sequence 1..106
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 30	
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60
KDSTYSLSSLT LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	106
SEQ ID NO: 31	moltype = DNA length = 660
FEATURE	Location/Qualifiers
misc_feature	1..660
source	note = Engineered antibody sequence 1..660
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 31	
caagtgtcga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc	60
aattgccagg ccagtcatgc tgtttatgtt aacaactaccc tagecctggta tcagcagaaaa	120
ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tgggtctca	180
tgcgggttca aaggcagtgg atctgggaca cagttcactc tcaccatcag cgacctggag	240
tgtgccatgt ctgccactta ctactgtcta ggcagttatg attgttagtag tggtgatgt	300
tttgtttcg gcgaggggac cgaggtgggtg gtcaaacgtt cggtggtgc accatctgtc	360
ttcatcttcc cgccatctga tgagcagtgg aaatctggaa ctgcctctgt tggtgatgt	420
ctgaataact tctatcccaag agaggccaaa gtacagtggaa aggtggataa cggccctcaa	480

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tcgggttaact cccaggagag tggcacagag caggacagca aggacagcac ctacagctc 540
 agcagcaccc tgacgctgag caaaaggagac tacgagaaac acaaagtcta cgccctcgaa 600
 gtcacccatc agggccttagt ctcggccgtc acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 32 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 32
 caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgcagg ccagtcaagag ttgttatgtt aacaactacc tagctggta tcagcagaaa 120
 ccaggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tggggtctca 180
 tcgcggttca aaggcagtgg atctggaca cagttcactt tcaccatcag cgacctggag 240
 tggccgtatc ctggccactta ctactgtcta ggcagttatc attgtatgtt tggtgatgt 300
 tttgttttcg gggggggac cgagggtgtt gtcaaacgt 339

SEQ ID NO: 33 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 33
 caagtgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 34 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 34
 caggccagtc agagtgttta tgataacaac taccttagcc 39

SEQ ID NO: 35 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 35
 tggtatcagg agaaaccagg gcagcctccc aagcaactga tctat 45

SEQ ID NO: 36 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 36
 tctacatcca ctctggcatc t 21

SEQ ID NO: 37 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 37
 ggggtctcat cgccggttcaa aggcaagtggaa tctgggacac agttcactt caccatcagc 60
 gacctggatg gtggccatgc tgccacttac tactgt 96

SEQ ID NO: 38 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 38

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ctaggcagtt atgattttag tagtgggtat tgttttgtt	39
SEQ ID NO: 39	moltype = DNA length = 33
FEATURE	Location/Qualifiers
misc_feature	1..33
	note = Engineered antibody sequence
source	1..33
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 39	
ttcggcgagg ggaccgaggt ggtggtcaaa cgt	33
SEQ ID NO: 40	moltype = DNA length = 321
FEATURE	Location/Qualifiers
misc_feature	1..321
	note = Engineered antibody sequence
source	1..321
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 40	
acggtgtggctt caccatctgt ctccatcttc cccatctgt atgaggcgtt gaaatcttga	60
actgcctctg ttgtgtgcct gcttaataac ttctatccca gagaggccaa agtacagtgg	120
aagggtggata accgcctcca atccggtaac tcccaggaga gtgtcacaga gcaggacac	180
aaggacacga cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa	240
cacaagaatct acgcctgcga agtcacccat cagggcctga gctcgccctg cacaagagc	300
ttcaacacagg gagagtgtta g	321
SEQ ID NO: 41	moltype = AA length = 441
FEATURE	Location/Qualifiers
REGION	1..441
	note = Engineered antibody sequence
source	1..441
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 41	
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA	60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF	120
PLAPSSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV	180
TVPSSSLGTQ TYICNVNHPK SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVLFPPK	240
PDTLMLMSRT PEVTCVVVD SHEDPEVKPN WYVDGVEVHN AKTKPREEQV ASTYRVVSVL	300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT	360
CLVKGFYPSD IAVEWESNGQ PENNYKTTTP VLSDSDGSFFL YSKLTVDKSR WQQGNVFSCS	420
VMHEALHNHY TQKSLSLSPG K	441
SEQ ID NO: 42	moltype = AA length = 111
FEATURE	Location/Qualifiers
REGION	1..111
	note = Engineered antibody sequence
source	1..111
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 42	
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA	60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S	111
SEQ ID NO: 43	moltype = AA length = 30
FEATURE	Location/Qualifiers
REGION	1..30
	note = Engineered antibody sequence
source	1..30
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 43	
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS	30
SEQ ID NO: 44	moltype = AA length = 5
FEATURE	Location/Qualifiers
REGION	1..5
	note = Engineered antibody sequence
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 44	
SYYMQ	5
SEQ ID NO: 45	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
	note = Engineered antibody sequence

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source	1..14	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 45		
WVRQAPGKGL EWVG		14
SEQ ID NO: 46	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
REGION	1..16	
	note = Engineered antibody sequence	
source	1..16	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 46		
VIGINDNTYY ASWAKG		16
SEQ ID NO: 47	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
	note = Engineered antibody sequence	
source	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 47		
RFTISRDNSK TTVYLMQNSL RAEDTAVYFC AR		32
SEQ ID NO: 48	moltype = length =	
SEQUENCE: 48		
000		
SEQ ID NO: 49	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
	note = Engineered antibody sequence	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 49		
WGQGTLVTVS S		11
SEQ ID NO: 50	moltype = AA length = 330	
FEATURE	Location/Qualifiers	
REGION	1..330	
	note = Engineered antibody sequence	
source	1..330	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 50		
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS	60	
GLYSLSVVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG	120	
PSVFLFPPKP KDLMISRTP EVTCVVVDVS HEDPEVKFW VYDGVEVHNA KTKPREEQYA	180	
STYRVSVL VT LHQDWLNKG EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE	240	
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	300	
QQGNVFCSV MHEALHNHYT QKSLSLSPGK	330	
SEQ ID NO: 51	moltype = DNA length = 1326	
FEATURE	Location/Qualifiers	
misc_feature	1..1326	
	note = Engineered antibody sequence	
source	1..1326	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 51		
gagggtcagc ttgtggagtc tgggggaggo ttgttccagc ctggggggtc cctgagactc	60	
tcctgtcagc tctctggact cgacactcagt agctactaca tgcaatgggt ccgtcaggct	120	
ccagggaaagg ggctggagtg ggtcgagtc attggatcatc atgataaacac atactacgcg	180	
agctggacca aaggccgatt caccatctcc agagacaat ccaagaccac ggttatctt	240	
caaataatggaca gcctgagacg gctggactt gctgtgtatt tctgtgttag aggggacatc	300	
tggggccaag ggacctctgt cacccgtctcg agccgcctca ccaaggcccc atccgtcttc	360	
cccccgtggac cctccctccaa gageacctct gggggcacag cggccctggg ctgcctggc	420	
aaggactact tccccgaacc ggtgacgggt tcgtgaaact caggcgccct gaccagccgc	480	
gtgcacaccc tcccggtctgt cctacagttc tcaggactct actccctcag cagcgtggtg	540	
accgtgcacct ccacgttgtt gggcaccctcg acctacatctt gcaacgtgaa tcacaaggccc	600	
agcaacacca aggtggacaa gaggtttag cccaaatctt gtgacaaaac tcacacatgc	660	
ccaccgtgcc cagcacctga actccctgggg ggaccgtcaag tcttcctt ccccccaaaa	720	
cccaaggaca ccctcatgtat cttccggacc cctgagggtca catgcgttgt ggtggacgtg	780	
accgcacgaag accctgaggt caagttcaac tggtaacgtgg acggcgtgga ggtgcataat	840	
gccaagacaa agccgcggga ggacgtac gccagcacgt accgtgttgt cagcgtcctc	900	
accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcacaggt ctccaacaaa	960	

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gcccctccag cccccatcgaaaaaaccatc tccaaagccaaagggcagcc ccgagaacca 1020
 cagggttaca ccctggccc atcccgaggag gagatgacca agaaccagt cagcctgacc 1080
 tgccctggta aaggcttcta tcccgacatcgccgttg agtggggagag caatggcag 1140
 cccgagaaca actacaagac cacgcctccgtgtggact ccgacggctc cttttctc 1200
 tacagcaacgc tcaccgttga caagagcagg tggcagcagg ggaacgttcttcatgctcc 1260
 gtgtatgcattggctctgca caaccactac acgcagaaga gctctccct gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 52 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 52
 gaggtgcagttgtggagtc ttggggaggttgggtccagc ctgggggggtc cctgagactc 60
 tcctgtgcagttctgtggactcgacctcgt agtactaca tgcaatgggt ccgtcaggct 120
 ccaggaaagg ggctggagttgtggatcatggatca atgataaacatatactacqcg 180
 agctgggcga aaggccgatt caccatctcc agagacaatttccaagaccac ggtgtatctt 240
 caaatgaaca ggctgagagtc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaagggaccctcg cacgtctcg agc 333

SEQ ID NO: 53 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 53
 gaggtgcagttgtggagtc ttggggaggttgggtccagc ctgggggggtc cctgagactc 60
 tcctgtgcagttctgtggactcgacctcgt 90

SEQ ID NO: 54 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 54
 agtactaca tgcaa 15

SEQ ID NO: 55 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 55
 tgggtccgtc aggctccagg gaaggggctggatgggtcg ga 42

SEQ ID NO: 56 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 56
 gtcattggta tcaatgataa cacatactac gcgagctggcgaaaggc 48

SEQ ID NO: 57 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 57
 cgattcacca tctccagaga caattccaaag accacgggtatcttcaat gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 58 moltype = length =

SEQUENCE: 58
 000

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SEQ ID NO: 59 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
note = Engineered antibody sequence
source 1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 59 tggggcacaag ggaccctcggt caccgtctcg agc 33

SEQ ID NO: 60 moltype = DNA length = 993
FEATURE Location/Qualifiers
misc_feature 1..993
note = Engineered antibody sequence
source 1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 60 gcctccacca agggcccatc ggttttcccc ctggccacct cctccaagag cacctctggg 60
ggcacagcgg ccctgggtcg cctgttcaag gactacttc cggaaagggt gagcgtgtcg 120
tggaaactca ggcgcctgac cagggcgtcg cacacccctt cggctgtcc acagtccctca 180
ggactctact ccctcagcag cgtgttgacc gtgccctcca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagggcago aacaccaagg tggaaagag agttgagccc 300
aaatcttggt acaaaactca catatggcca ccgtggccag caccgttaact cctggggggg 360
ccgtcagtct tccttcttccc cccaaaaacc aaggacatctc tcatgtatcc cggggccct 420
gaggtcacat gcgtgtgtgtt ggacgtgago cacaagacc ctgaggtaaa gttcaactgg 480
tacgtggacg gcgtggaggt gcataatgcc aagacaaaagg cgccgggggaga gcagtacgcc 540
agcaccgtact gtgtgtgtcg cgttccatcc gtcctgcacc aggactgtgtt gaatggcaag 600
gagtagtcaatg gcaagggttc acaaaaggcc cttccagggcc ecattcgagaa aaccatctcc 660
aaaggccaaag ggcagccccg agaaggacacc ttgtacacc tgccccccat ccgggggggg 720
atgaccaaga accagggtca cctgacccctc ctggtaaaag gcttctatcc cagcgacatc 780
gcgggtggaggt gggagagccaa tggggccggc gagaacaact acaagaccac gcctcccggt 840
ctggactccggc acgggtccctt ctccctctac agcaactca ccgtggacaa gaggcagggtgg 900
caggcgggggaa acgttccctc atgtccgttg atgtatcgagg ctctgcacaa ccactacacg 960
cagaagggcc tctccctgtc tccgggtaaa tga 993

SEQ ID NO: 61 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 61 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPPSDEQL KSGTASVVCL LNNFYPREAK VOWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTTLTSKAD YEHKHVYACE VTHQGLSSPV TKSFRNRREC 219

SEQ ID NO: 62 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 62 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKR 113

SEQ ID NO: 63 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 63 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 64 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 64 QASQSYVDNN YLA 13

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SEQ ID NO: 65      moltype = AA length = 15
FEATURE
REGION
1..15
note = Engineered antibody sequence
1..15
mol_type = protein
organism = synthetic construct
SEQUENCE: 65
WYQQKPGKVP KQLIY                                         15

SEQ ID NO: 66      moltype = AA length = 7
FEATURE
REGION
1..7
note = Engineered antibody sequence
1..7
mol_type = protein
organism = synthetic construct
SEQUENCE: 66
STSTLAS                                                       7

SEQ ID NO: 67      moltype = AA length = 32
FEATURE
REGION
1..32
note = Engineered antibody sequence
1..32
mol_type = protein
organism = synthetic construct
SEQUENCE: 67
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC                         32

SEQ ID NO: 68      moltype = AA length = 13
FEATURE
REGION
1..13
note = Engineered antibody sequence
1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 68
LGSYDCSSGD CFV                                              13

SEQ ID NO: 69      moltype = AA length = 11
FEATURE
REGION
1..11
note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct
SEQUENCE: 69
FGGGTKVEIK R                                               11

SEQ ID NO: 70      moltype = AA length = 106
FEATURE
REGION
1..106
note = Engineered antibody sequence
1..106
mol_type = protein
organism = synthetic construct
SEQUENCE: 70
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC             106

SEQ ID NO: 71      moltype = DNA length = 660
FEATURE
misc_feature
1..660
note = Engineered antibody sequence
1..660
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 71
caagtgtga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
aattgccagg ccagtcagag tgtttatgtt aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaaagca actgatctat tctacatccca ctctggcatc tgggtccca 180
tctcgttcca gtggcagttt atctggaca gatttcactc tcaccatcag cagctgcag 240
cctgaagatg ttgcaactta ttactgtcta ggtagttatg atttgtatgt tggtgtatgt 300
tttggtttcg gcggaggaaac caagggtggaa atcaaacgtt cgggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttt aaatctggaa ctgcctctgt tgggtgcctg 420
ctgaataact tctatcccg agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

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agcagcaccc tgacgcttag caaagcagac tacgagaaaac acaaagtcta cgccctgcgaa 600
gtcacccatc agggccttag ctcgcccgtc acaaagact tcaacagggg agagtgttag 660

SEQ ID NO: 72          moltype = DNA length = 339
FEATURE
misc_feature           Location/Qualifiers
1..339
note = Engineered antibody sequence
source
1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 72
caagtgtga cccaggtctcc atcctccctg tctgcatacg taggagacag agtcaccatc 60
aattggcagg ccagtcaagat tggtttat aacaacttac tagccctggta tcagcagaaa 120
ccaggaaag ttccataagca actgtatcat ttcataatcca ctctggcata tggggtccca 180
tctcggttca gtggcagttgg atctgggaca gatttcaact tcacatcag cagctgcag 240
cctgaagatg ttgcaactta ttactgtcta ggcagttatg attgtatgtatgt 300
tttgtttcg gggggggaaac caagggtggaa atcaaacacgt 339

SEQ ID NO: 73          moltype = DNA length = 66
FEATURE
misc_feature           Location/Qualifiers
1..66
note = Engineered antibody sequence
source
1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 73
caagtgtga cccaggtctcc atcctccctg tctgcatacg taggagacag agtcaccatc 60
aattgc 66

SEQ ID NO: 74          moltype = DNA length = 39
FEATURE
misc_feature           Location/Qualifiers
1..39
note = Engineered antibody sequence
source
1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 74
caggccatc agagtgttta tgataacaac taccttagcc 39

SEQ ID NO: 75          moltype = DNA length = 45
FEATURE
misc_feature           Location/Qualifiers
1..45
note = Engineered antibody sequence
source
1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 75
tggtatcagc agaaaaccagg gaaagttctt aagcaactga tctat 45

SEQ ID NO: 76          moltype = DNA length = 21
FEATURE
misc_feature           Location/Qualifiers
1..21
note = Engineered antibody sequence
source
1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 76
tctacatcca ctctggcata t 21

SEQ ID NO: 77          moltype = DNA length = 96
FEATURE
misc_feature           Location/Qualifiers
1..96
note = Engineered antibody sequence
source
1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 77
ggggtcccat ctgcgttcag tggcagttgg aatccactct caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 78          moltype = DNA length = 39
FEATURE
misc_feature           Location/Qualifiers
1..39
note = Engineered antibody sequence
source
1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 78
ctaggcagtt atgattgttag tagtggtat tgttttgtt 39

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SEQ ID NO: 79      moltype = DNA length = 33
FEATURE          Location/Qualifiers
misc_feature     1..33
source           note = Engineered antibody sequence
                 1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 79
ttcggcggag gaaccaagg gaaaaatcaa cgt                                33

SEQ ID NO: 80      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
source           note = Engineered antibody sequence
                 1..321
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 80
acgggtggctg caccatctgt ctcatcttc cgcgcattctg atgagcaggaaatctgga 60
actgcctcg ttgtgtgcct gctaaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgcctccaa atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacacgca cttacagcct cagcagcacc ctgacgctgaa gcaaaaggcatacggagaaa 240
cacaaggatct acgcctgcga agtcacccat cagggctgtaa gtcgccccgt cacaaggagc 300
ttcaacagggg gagagtgtta g                                321

SEQ ID NO: 81      moltype = AA length = 441
FEATURE          Location/Qualifiers
REGION           1..441
source           note = Engineered antibody sequence
                 1..441
mol_type = protein
organism = synthetic construct
SEQUENCE: 81
EVOLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS CGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
TVPSSSLGTQ TYICCNVNHKP SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMISRT PEVTCVVDV SHEDPEVKFN WYDGVENVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALTHNHY TQKSLSLSPG K                                441

SEQ ID NO: 82      moltype = AA length = 111
FEATURE          Location/Qualifiers
REGION           1..111
source           note = Engineered antibody sequence
                 1..111
mol_type = protein
organism = synthetic construct
SEQUENCE: 82
EVOLVESGGG LVQPGGSLRL SCAVSGLDLS SYYMQWVRQA PGKGLEWVGIGINDNTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S                                111

SEQ ID NO: 83      moltype = AA length = 30
FEATURE          Location/Qualifiers
REGION           1..30
source           note = Engineered antibody sequence
                 1..30
mol_type = protein
organism = synthetic construct
SEQUENCE: 83
EVQLVESGGG LVQPGGSLRL SCAVSGLDLS                                30

SEQ ID NO: 84      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
source           note = Engineered antibody sequence
                 1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 84
SYYMQ                                5

SEQ ID NO: 85      moltype = AA length = 14
FEATURE          Location/Qualifiers
REGION           1..14
source           note = Engineered antibody sequence
                 1..14

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mol_type = protein
organism = synthetic construct

SEQUENCE: 85
WVRQAPGKGL EWVG                                         14

SEQ ID NO: 86      moltype = AA length = 16
FEATURE
REGION           Location/Qualifiers
1..16
note = Engineered antibody sequence
1..16
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 86
VIGINDNTYY ASWAKG                                         16

SEQ ID NO: 87      moltype = AA length = 32
FEATURE
REGION           Location/Qualifiers
1..32
note = Engineered antibody sequence
1..32
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 87
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC AR                         32

SEQ ID NO: 88      moltype = length =
SEQUENCE: 88
000

SEQ ID NO: 89      moltype = AA length = 11
FEATURE
REGION           Location/Qualifiers
1..11
note = Engineered antibody sequence
1..11
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 89
WGQGTLVTVS S                                              11

SEQ ID NO: 90      moltype = AA length = 330
FEATURE
REGION           Location/Qualifiers
1..330
note = Engineered antibody sequence
1..330
source
mol_type = protein
organism = synthetic construct

SEQUENCE: 90
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSVVVT VPSSSLGTQT YICNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLPPKPK KDTLMISRTP EVTCVVVDWS HEDPEVKFPNW YVDGVEVHNA KTKPREEQYA 180
STYRVSVLTL VHLDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPKG                           330

SEQ ID NO: 91      moltype = DNA length = 1326
FEATURE
misc_feature      Location/Qualifiers
1..1326
note = Engineered antibody sequence
1..1326
source
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 91
gaggtgcagc ttgtggatc tggggggaggc ttggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggact cgacctca agctactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggatg ggtcgaggc attggatca atgataacac atactacgc 180
agctggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaataaca gaactggaggc tgactggact gctgtgtatt tctgtgttag agggggacatc 300
tggggccaag gggccctcgat caccgtctcg agccgcctcca ccaaggggccc atcggtttc 360
ccccctggcac cctccctccaa gagccctctt gggggcacaac cggccctggg ctgctgtc 420
aaggactact tcccccaacc ggtgacgggt tcgtggaaact caggcgccct gaccagccgc 480
gtgcacacct tccccggctt cctacagtcc tcaggactct actccctcag cagcgtggc 540
accgtgcctt ccaggcagctt gggcacccag acctacatct gcaacgtgaa tcacaaggcc 600
agcaacacca aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctga actcttgggg ggaccgtca gtttccctt ccccccaaaa 720
cccaaggaca ccctcatgtat ctccccggacc cctgagggtca catgcgtggt ggtggacgtg 780
agccacacaa accctggatgtt caagttaaac tggtagctgg acggcggtgaa ggtgcataat 840
gccaagacaa agcccgccggaa ggagcgtac gccagcacgt accgtgttgtt cagcgtctc 900
accgtcctgc accaggactg gctgaatggc aaggagtaca agtgcaaggt ctccaaacaaa 960
ccccctcccg ccccccattca gaaaaccatc tccaaaggcca aaggcgccgccc ccgagaacca 1020

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cagggtgtaca ccctgcccc atccggag gagatgacca agaaccagg cagcctgacc 1080
 tgcctggta aaggctcta tcccagcgac atccggctgg agtgggagag caatggcag 1140
 cccgagaaca actacaagac cacgcctcc gtgctggact ccgacggctc cttttctc 1200
 tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgttt ctcatgtcc 1260
 gtgatgtcatc aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 92 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 92
 gaggtgcagc ttgtggagtc tgggggaggo ttgtccagc ctggggggc cctgagactc 60
 tccctgtcag tctctggact cgacctcaagt agtactactaca tgcaatgggt ccgtcaggct 120
 ccagggagg ggctggatg ggtcgaggatc attggatatac atgataaacat atactacgc 180
 agctggcgaa aaggccgatt caccatcc agagacaat ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggaccctcgta caccgtctcg agc 333

SEQ ID NO: 93 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 93
 gaggtgcagc ttgtggagtc tgggggaggo ttgtccagc ctggggggc cctgagactc 60
 tccctgtcag tctctggact cgacctcaagt 90

SEQ ID NO: 94 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 94
 agtactaca tgcaa 15

SEQ ID NO: 95 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 95
 tgggtccgtc aggctccagg gaaggggctg gatgggtc ga 42

SEQ ID NO: 96 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 96
 gtcattggta tcaatgataa cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 97 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 97
 cgattcacca tctccagaga caattccaa accacgggtt atcttcaat gaacagctg 60
 agagctgagg acactgttgtt gtatctgt gctaga 96

SEQ ID NO: 98 moltype = length =
 SEQUENCE: 98
 000

SEQ ID NO: 99 moltype = DNA length = 33

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FEATURE Location/Qualifiers
misc_feature
 source 1..33
 note = Engineered antibody sequence
 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 99
 tggggccaag ggaccctcg caccgtctcg agc 33

SEQ ID NO: 100 moltype = DNA length = 993
 FEATURE Location/Qualifiers
misc_feature 1..993
 source note = Engineered antibody sequence
 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 100
 gectccacca agggcccatc ggttccccc ctggcacccct cctccaagag cacctctggg 60
 ggcacagcgg ccctgggtcg cctggtaag gactactcc cggaaacgggt gacgggtgtcg 120
 tggaaactcg ggcggctgac cagcgggtcg cacacccctt cgggttcct acatgcctca 180
 ggacttctact ccctcagcag cgtgtgtgg gtggcccttca gcacgttggg caccggaccc 240
 tacatctgcac acgtgaatca caaaggccgc aacaccaagg tggacgogag agttgagccc 300
 aaatcttggtg aaaaaactca cacatggccca ccgtggcccg cacctgaact cctgggggga 360
 ccgtcgtact tccttcctcc cccaaacccca aaggacacc ctcgtatctc cccggacccct 420
 gaggtcacat gcgtgggtgt ggacgtgago cacagaaagg ctggaggctaa gttcaactgg 480
 taatgtggaccc gcgtgggggtt aataatggcc aagacaaagg cgccggggagg gcaatgtggcc 540
 agcacgtacc gtgtggtcag cgttccatcacc gtcctgcacc aggactggct gaatggcaag 600
 gactacaatgg gcaagggttcc caaacaaaggcc ctccggccccc ccacatctcc 660
 aaaggccaaagg ggcaggccccca agaaccacag gtgtacccatc tggcccccattc cgggaggag 720
 atgaccacaa accagggttcc cctgacccctt cttgttcaaaa gtttcttatcc cagcgtacatc 780
 gccgtggagt gggagagcaa tggcggcccg gagaacaact acaagaccac gcctccctgtg 840
 ctggactcccg acggctccctt ctteccatc agcaagtcga ccgtggacaa gagcagggtgg 900
 cagcaggggaa acgttccctt atgtccctgt atgcatgagg ctctgcacaa ccactacacgg 960
 cagaagagcc ttcctctgtc tccggtaaaa tga 993

SEQ ID NO: 101 moltype = AA length = 219
 FEATURE Location/Qualifiers
REGION
 source 1..219
 note = Engineered antibody sequence
 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 101
 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKRTVAAPSV 120
 FIPPPSDEQL KSGTASVVCV LNNFYFREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 SSTLTLASKD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 102 moltype = AA length = 113
 FEATURE Location/Qualifiers
REGION
 source 1..113
 note = Engineered antibody sequence
 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 102
 QVLTQSPSSL SASVGDRVTI NCQASQSYVD NNYLAWYQQK PGKVPQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSSGDC FVFGGGTKVE IKR 113

SEQ ID NO: 103 moltype = AA length = 22
 FEATURE Location/Qualifiers
REGION
 source 1..22
 note = Engineered antibody sequence
 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 103
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 104 moltype = AA length = 13
 FEATURE Location/Qualifiers
REGION
 source 1..13
 note = Engineered antibody sequence
 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 104
 QASOSVYDNN YLA 13

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SEQ ID NO: 105	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
REGION	1..15	
source	note = Engineered antibody sequence	
	1..15	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 105		
WYQQKPGKVP KQLIY		15
SEQ ID NO: 106	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
source	note = Engineered antibody sequence	
	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 106		
STSTLAS		7
SEQ ID NO: 107	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence	
	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 107		
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC		32
SEQ ID NO: 108	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence	
	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 108		
LGSYDCSSGD CFV		13
SEQ ID NO: 109	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = Engineered antibody sequence	
	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 109		
FGGGTKVEIK R		11
SEQ ID NO: 110	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
source	note = Engineered antibody sequence	
	1..106	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 110		
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS		60
KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		106
SEQ ID NO: 111	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
source	note = Engineered antibody sequence	
	1..660	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 111		
caagtgtcga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc		60
aattggcagg ccagtcagag tgtttatgt aacaactacc tagcctggta tcagcagaaa		120
ccaggaaag ttccctaagca actgatctat tctacatccca ctctggcatc tggggtccca		180
tctcggttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag		240
cctgaagatg ttgcaactta ttactgtcta ggcagttatg atttgtatcg tggtgatgt		300
tttggtttcg gcggaggaac caagggtggaa atcaaacgtg cggtggtgc accatctgc		360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tggtgctg		420
ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa		480
tcgggttaact cccaggagag tgcacagag caggacagca aggacagcac ctacagcctc		540
agcagcaccctc tgacgcttag caaaggacac tacgagaaac acaaagtcta cgcctcgaa		600

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gtcacccatc agggcctgag ctgcggcgta acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 112 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 112
 caaagtgtga cccagtcgtcc atcctccctg tctgcgtatctg taggagacag agtcaccatc 60
 aattgccagg ccagtcaagag tgtttatgtt aacaactacc tagcctggta tcagcagaaa 120
 ccaggaaag ttccataagca actgtatcatc tctacatccatc ctctggcatc tgggtccca 180
 ttccgttca gtggcagtgg atctgggaca gatttcactc tccatcatc cagcctgcag 240
 cctgaagatg ttgcaacttta ttactgtcta ggcagttatg attgtatgtatgtatgt 300
 ttgttttcg gcggaggaac caagggtggaa atcaaacgt 339

SEQ ID NO: 113 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 113
 caaagtgtga cccagtcgtcc atcctccctg tctgcgtatctg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 114 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 114
 caggccagtc agagtttta tgataacaac tacctagcc 39

SEQ ID NO: 115 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 115
 tggttatcagc agaaaaccagg gaaagttcct aagcaactga tctat 45

SEQ ID NO: 116 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 116
 tctacatcca ctctggcatc t 21

SEQ ID NO: 117 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 117
 ggggtcccat ctcgtttcag tggcagtggta tctgggacag atttcactct caccatcagc 60
 agcctgcagc ctgaagatgt tgcaacttta tactgt 96

SEQ ID NO: 118 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 118
 cttaggcagtt atgattgttag tagtggtat tgttttgtt 39

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SEQ ID NO: 119 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 119
 ttccggcggag gaaccaagggt ggaaatcaaaa cgt 33

SEQ ID NO: 120 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 misc_feature 1..321
 note = Engineered antibody sequence
 source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 120
 accggtggctg caccatctgt cttcatcttc ccgcgcattctg atgagcagggt gaaatcttga 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata accgcctccca atccggtaac tcccaggaga gtgtcacaga gcaggacac 180
 aaggacagaca cttacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
 cacaaggatct accgcctgcga agtacccat caggcgcgtga gctcgccctg cacaaggagc 300
 ttcaacacggg gagagtgtta g 321

SEQ ID NO: 121 moltype = AA length = 439
 FEATURE Location/Qualifiers
 REGION 1..439
 note = Engineered antibody sequence
 source 1..439
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 121
 QSLLEESGGRL VTPGTPLTLT CSVSGIDLSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSSA STKGPSVFPL 120
 APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TPPAVLQSSG LYSLSSVTV 180
 PSSSLGTQTY ICNVNHPKSN TKVDRKVEPK SCDKTHTCPP CPAPELLGGP SVFLPPPKPK 240
 DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VGVEVHNAAK TKPREEQYAS TYRVVSVLT 300
 LHODWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
 VKGFYPSDIA VEWESNGQPE NNYKTPPPVLDSDGSFFFLYS KLTVDKSRWQ QGNVFSCVM 420
 HEALHNHYTQ KSLSLSPGK 439

SEQ ID NO: 122 moltype = AA length = 109
 FEATURE Location/Qualifiers
 REGION 1..109
 note = Engineered antibody sequence
 source 1..109
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 122
 QSLLEESGGRL VTPGTPLTLT CSVSGIDLSG YYMNWVRQAP GKGLEWIGVI GINGATYYAS 60
 WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSS 109

SEQ ID NO: 123 moltype = AA length = 29
 FEATURE Location/Qualifiers
 REGION 1..29
 note = Engineered antibody sequence
 source 1..29
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 123
 QSLLEESGGRL VTPGTPLTLT CSVSGIDLS 29

SEQ ID NO: 124 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 124
 GYYMN 5

SEQ ID NO: 125 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein

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organism = synthetic construct

SEQUENCE: 125
WVRQAPGKGL EWIG 14

SEQ ID NO: 126 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
source note = Engineered antibody sequence
1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 126
VIGINGATYY ASWAKG 16

SEQ ID NO: 127 moltype = AA length = 31
FEATURE Location/Qualifiers
REGION 1..31
source note = Engineered antibody sequence
1..31
mol_type = protein
organism = synthetic construct

SEQUENCE: 127
RFTISKTSST TVDLKMTSLT TEDTATYFCA R 31

SEQ ID NO: 128 moltype = length =
SEQUENCE: 128 000

SEQ ID NO: 129 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
source note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 129
WGPGTTLTVVS S 11

SEQ ID NO: 130 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
source note = Engineered antibody sequence
1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 130
ASTKGPSVP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMSIRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVRVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPSPREE 240
MTYNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSPFLY SKLTVDKSRW 300
QQGNVNFCSCV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 131 moltype = DNA length = 1320
FEATURE Location/Qualifiers
misc_feature 1..1320
source note = Engineered antibody sequence
1..1320
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 131
cagtgcgtgg aggagtcggg gggccctggtc acgcacccctt gacactcacc 60
tgttccgtct ctggcatcgaa cctcgtgg tactacatgaa actgggtccg ccaggctcca 120
gggaaggggc tggatggat cgggttcatt ggattaaatg gtgcacata ctacgcgagc 180
tggggcggaaag gccgattcac catctccaaa acctcgtcgaa ccacgggtgaa tctgaaaatg 240
accagtctga caaccgagga cacggccacc tatttctgtg ccagaggggaa catctgggc 300
ccggccaccctt ctcgtccacggg tccaccaagg gcccattcggtt cttccccctg 360
gcacccctctt ccaagagcac ctctggggggc acagcggccac tgggctgcgtt ggtcaaggagc 420
taacttcccccggg aaccgggtgac ggtgtcgtgg aactcgtggcc ctctgaccagc cggcgctgcac 480
accttcccccggg ctgtccataca gtcctcggaa ctctactccctt ctagcgtcggtt ggtgaccgtg 540
ccctcccgaca gtttggggcac ccagacccatc atctgcaacgg tgaatcacaac gccccggcaac 600
accaagggtgg acaagaggtt tgagccaaa ttctgtgacaa aaactcacac atgcccacccg 660
tgccccagcac ctgaactctt cttcccccggggggaccccg tcaacttccctt cttccccccc 720
gacacccctca tgatctcccg gaccccttgcgtt gtcacatcggtt ggtgtggaa cgtgacccac 780
gaagacccctg aggtcaagttt caacttgcgtt gttggacccggc tggagggtgca taatgccaag 840
acaaaggccgc gggaggagca gtacggccacccg acgttaccgtt gttgtcgtcggtt ccttcccg 900
ctgcaccagg actggctgaa tggcaaggag tacaagtgcac aggtctccaa caaaggccctc 960
ccagccccca tcgagaaaac catctccaaa gccaaaggccg agcccccggaga accacagggtt 1020
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcgtcggtt gacccgttcc 1080

US 12,384,837 B2

95

96

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gtcaaaaggct tctatccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag 1140
 aacaactaca agaccacgccc tcccgctg gactccgacg gtccttctt cctctacagc 1200
 aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtatg 1260
 catgaggcgc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaatga 1320

SEQ ID NO: 132 moltype = DNA length = 327
 FEATURE Location/Qualifiers
 misc_feature 1..327
 note = Engineered antibody sequence
 source 1..327
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 132
 cagtgcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
 tgttccgtct ctggcatcga cctcagtgg tactacatga actgggtccg ccaggctcca 120
 gggaaaggccc tggaaatggat cggagtcgg tggattaaatg gtgccacata ctacgcgacg 180
 tgggcgaaag ggcgattcac catctccaaa acctcgtcga ccacgggtggaa tctgaaaatg 240
 accagtcgtga caaccggagc cacggccacc tatttctgtg ccagagggggaa catctggggc 300
 cccggccacc ttcgtaccgt ctcgagc 327

SEQ ID NO: 133 moltype = DNA length = 87
 FEATURE Location/Qualifiers
 misc_feature 1..87
 note = Engineered antibody sequence
 source 1..87
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 133
 cagtgcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacacccct gacactcacc 60
 tgttccgtct ctggcatcga cctcagtgg 87

SEQ ID NO: 134 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 134
 gggtactaca tgaac 15

SEQ ID NO: 135 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 135
 tgggtccggc aggctccagg gaaggggtcg gaatggatcg ga 42

SEQ ID NO: 136 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 136
 gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 137 moltype = DNA length = 93
 FEATURE Location/Qualifiers
 misc_feature 1..93
 note = Engineered antibody sequence
 source 1..93
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 137
 cgattcacca tctccaaaac ctcgtcgacc acgggtggatc tgaaaaatgac cagtctgaca 60
 accgaggaca cggccaccta tttctgtgcc aga 93

SEQ ID NO: 138 moltype = length =
 SEQUENCE: 138
 000

SEQ ID NO: 139 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33

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source          note = Engineered antibody sequence
1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 139
tggggcccg gcaccctcgt caccgtctcg agc                               33

SEQ ID NO: 140      moltype = DNA length = 993
FEATURE
misc_feature       Location/Qualifiers
1..993
note = Engineered antibody sequence
source             1..993
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 140
gcctccacca agggcccatc ggtttcccc ctggcaccc cctccaagag caccctctgg  60
ggcacagccg ccctgggctg cctgttcaag gactacttcc cccgaaccgg gacgggttcg 120
tggaaactcg cgcccttgac cagccgtg cacaaccttcc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtgttgcgtt gttccctca cagacttggg caccaggacc 240
tacatctgca acgtgaatca caagcccg aacaccaagg tggacaagag agttgagccc 300
aaatcttgcg aaaaaactca cacatggccca cctgtcccaag caccctgaactt cctgggggga 360
ccgtcagtcttccccc cccaaaaccc aaggacacccttccatgtatcc ccggaccctt 420
gagggtcacat gctgttgggtt ggacgttgcgcg caccgaagacc ctggaggtaaa gttcaacttgg 480
tacgtggacg cgctggagggt gcataatggc aagacaaaggc cgcggggagg gcaacttggc 540
agcacgttcccg gtgttgcgttcccg cttccgttcccg aggacttgcgtt gaatggcaag 600
gagttacaatggc gcaagggttcccg caacaaggcc cttccgttcccg ccatcgagaa aaccatctcc 660
aaaggccaaagg ggcaggcccg agaaccacacg gtgttacacccttccccc cccggaggag 720
atgaccaaga accagggttcccg cttccgttcccg ctggtaaa gtttctatcc cagcgacatc 780
gcctgttgggtt gggagggccaa tggggcagccg gagaacaaacttcc acaagaccac gcctccctgg 840
ctggacttcccg acgggttcccg cttccgttcccg agcaaggcttcc cctgttggccaa gagcagggttgg 900
caggcaggccaa acgttcccg atgttccgttcccg atgttccgttcc cctgttggccaa ccactacacg 960
cagaaggccaa tttccgttcccg tccggtaaa tggc                               993

SEQ ID NO: 141      moltype = AA length = 219
FEATURE
REGION            Location/Qualifiers
1..219
note = Engineered antibody sequence
source             1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 141
QVLTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP  60
SRFSGSGSGT QFTLTISGVQ CNDAAAYYCL GSYDCTNGDC FVFGGGTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLASKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC                           219

SEQ ID NO: 142      moltype = AA length = 113
FEATURE
REGION            Location/Qualifiers
1..113
note = Engineered antibody sequence
source             1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 142
QVLTQTPSPV SAAVGSTVTI NCQASQSVYH NTYLAWYQQK PGQPPKQLIY DASTLASGVP  60
SRFSGSGSGT QFTLTISGVQ CNDAAAYYCL GSYDCTNGDC FVFGGGTEVV VKR                               113

SEQ ID NO: 143      moltype = AA length = 22
FEATURE
REGION            Location/Qualifiers
1..22
note = Engineered antibody sequence
source             1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 143
QVLTQTPSPV SAAVGSTVTI NC                               22

SEQ ID NO: 144      moltype = AA length = 13
FEATURE
REGION            Location/Qualifiers
1..13
note = Engineered antibody sequence
source             1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 144
QASQSVYHNT YLA                                              13

SEQ ID NO: 145      moltype = AA length = 15
FEATURE

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REGION	1..15 note = Engineered antibody sequence	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 145		
WYQQKPGQPP KQLIY		15
SEQ ID NO: 146	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
source	note = Engineered antibody sequence	
1..7	mol_type = protein	
SEQUENCE: 146	organism = synthetic construct	
DASTLAS		7
SEQ ID NO: 147	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence	
1..32	mol_type = protein	
SEQUENCE: 147	organism = synthetic construct	
GVPSRFSGSG SGTQFTLTIS GVQCNDAAAY YC		32
SEQ ID NO: 148	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence	
1..13	mol_type = protein	
SEQUENCE: 148	organism = synthetic construct	
LGSYDCTNGD CFV		13
SEQ ID NO: 149	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = Engineered antibody sequence	
1..11	mol_type = protein	
SEQUENCE: 149	organism = synthetic construct	
FGGGTEVVVK R		11
SEQ ID NO: 150	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
source	note = Engineered antibody sequence	
1..106	mol_type = protein	
SEQUENCE: 150	organism = synthetic construct	
TVAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60	
KDSTYSLSSLT LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC	106	
SEQ ID NO: 151	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
source	note = Engineered antibody sequence	
1..660	mol_type = other DNA	
SEQUENCE: 151	organism = synthetic construct	
caagtgcgtga ccagactcc atccccctgt tctgcagctg tgggaagcac agtcaccatc	60	
aattgcagg ccagtccagg tgtttatcat aacacctacc tggcctggta tcagcagaaa	120	
ccaggggcagg ctcccaaaca actgatctat gatgcattca ctctggcgcc tgggttccca	180	
tccgcgggtca gcccggatgg atctgggaca cagttcactc tcaccatcag cggcggtcag	240	
tgtaacatgtc ctgcggctta ctactgtctg ggcaatgttggatgttggatgttggatgt	300	
tttgggttcg gcccggggac cgagggttgtc gtcaaaacgtt cgggttgtc accatgttc	360	
ttcatcttcc cggccatcttca tgacgttgtt aaatctggaa ctgccttgt tggatgttgt	420	
ctgaataact ttatccatc agaggccaaa gtacatgttggaa aggtggatata cggccctccaa	480	
tccgggttact cccaggagag tgcacatggag caggacacca aggacacac ctacagctc	540	
agcagcaccc tgacgttgttca caaaggacac tacgagaaac acaaagtcta cgcctgcgaa	600	
gttcacccatc agggccttgat ctcggccgtc acaaagatc tcaacagggg agatgttag	660	

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SEQ ID NO: 152 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 152
 caagtgtga cccagactcc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgccagg ccagtccagg tggatgttac aacacccatca tgccctggta tcagcagaaaa 120
 ccaggcagc ctcccaaaaca actgtatcat gatgcacatca ctctggcgctc tgggttccca 180
 tcgcgggtca gcggcagttg atctgggaca cagtttacttc tcaccatcag cggcgtgcag 240
 tggtaacatgt ctgcggctta ctactgtctg ggcaatgttatttactaa tggtgatgt 300
 ttgttttcg gcggaggac cgagggtggta gtcaaacatc 339

SEQ ID NO: 153 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 153
 caagtgtga cccagactcc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 154 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 154
 caggccagtc agagtgttta tcataaacacc tacctggcc 39

SEQ ID NO: 155 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 155
 tggtatcagg agaaaccagg gcagcctccc aaacaactga tctat 45

SEQ ID NO: 156 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 156
 gatgcacatcca ctctggcgctc t 21

SEQ ID NO: 157 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 157
 ggggtcccat cgccgggttcag cggcagtttgc tctgggacac agtttactt caccatcagc 60
 ggcgtgcagt gtaacatgtc tgccgcttac tactgt 96

SEQ ID NO: 158 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 158
 ctggggcagtttgc atgattgtac taatgggtat tgggtttttt 39

SEQ ID NO: 159 moltype = DNA length = 33
 FEATURE Location/Qualifiers

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misc_feature          1..33
source               note = Engineered antibody sequence
                     1..33
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 159
ttcggcgagg ggaccgaggt ggtggtcaaa cgt                               33

SEQ ID NO: 160           moltype = DNA length = 321
FEATURE              Location/Qualifiers
misc_feature          1..321
source               note = Engineered antibody sequence
                     1..321
                     mol_type = other DNA
                     organism = synthetic construct
SEQUENCE: 160
acggtgttgcg caccatctgt ctcatcttc ccgcacatctg atgagcagtt gaaatctgga   60
actgccttcg ttgtgtgcg gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgcctcca atcgggttaac tcccaggaga gtgtcacaaga gcaggacgc 180
aaggacacga cctacagac cagcagcacc ctgacgctga gcaaagcaga ctacagaaaa 240
cacaacatgt acgcctgcga agtacccat cagggctgta gtcgcggcgt cacaacagc 300
ttcaacacagg gagatgtta g                                         321

SEQ ID NO: 161           moltype = AA length = 441
FEATURE              Location/Qualifiers
REGION              1..441
source               note = Engineered antibody sequence
                     1..441
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 161
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS GYMMNWVRQA PGKGLEWVGV IGINGATYYA   60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSSKTS GGTAALGCLV KDYPFPEVNTS SNNSGALTSG VHTFPVPLQS SGLYSLSSVV 180
TVPSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVLFPPK 240
PKDTLMISRT PEVCTVVDV SHEDPEVKEN WYVDGVVEHVN AKTKPREEQY ASTYRVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGKFYPSD IAVEWESNQG PENNYKTTPP VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K                                         441

SEQ ID NO: 162           moltype = AA length = 111
FEATURE              Location/Qualifiers
REGION              1..111
source               note = Engineered antibody sequence
                     1..111
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 162
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS GYMMNWVRQA PGKGLEWVGV IGINGATYYA   60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S             111

SEQ ID NO: 163           moltype = AA length = 30
FEATURE              Location/Qualifiers
REGION              1..30
source               note = Engineered antibody sequence
                     1..30
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 163
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS                               30

SEQ ID NO: 164           moltype = AA length = 5
FEATURE              Location/Qualifiers
REGION              1..5
source               note = Engineered antibody sequence
                     1..5
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 164
GYMMN                                               5

SEQ ID NO: 165           moltype = AA length = 14
FEATURE              Location/Qualifiers
REGION              1..14
source               note = Engineered antibody sequence
                     1..14
                     mol_type = protein
                     organism = synthetic construct
SEQUENCE: 165

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WVRQAPGKGL EWVG	14
SEQ ID NO: 166	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
source	note = Engineered antibody sequence 1..16 mol_type = protein organism = synthetic construct
SEQUENCE: 166	
VIGINGATYY ASWAKG	16
SEQ ID NO: 167	moltype = AA length = 32
FEATURE	Location/Qualifiers
REGION	1..32
source	note = Engineered antibody sequence 1..32 mol_type = protein organism = synthetic construct
SEQUENCE: 167	
RFTISRDNSK TTVYIQLMNSL RAEDTAVYFC AR	32
SEQ ID NO: 168	moltype = length =
SEQUENCE: 168	
000	
SEQ ID NO: 169	moltype = AA length = 11
FEATURE	Location/Qualifiers
REGION	1..11
source	note = Engineered antibody sequence 1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 169	
WGGTTLVTVS S	11
SEQ ID NO: 170	moltype = AA length = 330
FEATURE	Location/Qualifiers
REGION	1..330
source	note = Engineered antibody sequence 1..330 mol_type = protein organism = synthetic construct
SEQUENCE: 170	
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60 GLYSLSVVVT VPSSSLQTQ YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120 PSVFLFPPKPK KDTLMSRTP EYTCVVVDVS HEDPEVKFVN VYDGVEVHNA KTKPREEQYA 180 STYRVSVLVT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPSPREE 240 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330	
SEQ ID NO: 171	moltype = DNA length = 1326
FEATURE	Location/Qualifiers
misc_feature	1..1326
source	note = Engineered antibody sequence 1..1326 mol_type = other DNA organism = synthetic construct
SEQUENCE: 171	
gagggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60 tcctgtcgag tctctggaaat cgacctca ggcatactaca tgaactgggt ccgtcaggct 120 ccaggaaagg ggctggagtg ggctcgagtc atggattata atgggtccac atactacgctg 180 agctggcgaa aaggccgatt caccatctcc agagacaataa ccaagaccac ggtgttatctt 240 caaataaaca gctctggagtc tgaggacact gctgtgtatt tctgtgtctatc agggggacatc 300 tggggccaag ggaccctcgat caccgtctcg agcgccctcca ccaaggccc atcggttttc 360 ccccctggcac cctcctccaa gagcacctct gggggcacaag cggccctggg ctgcctggtc 420 aaggactact tcccccaacc ggtgacgggtc tcgttggaaact caggcgccct gaccagccgc 480 gtgcacaccc tccccggctgt cctacagtcc tcaggactat actccctcag cagcgtggtg 540 accgtgcctt ccagcagctt gggccacccag acctacatcc gcaacgtgaa tcacaaggccc 600 agoaacaacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660 ccaccgtgcc cagcacctga actcttgggg ggaccgttag tcttcctt ccccccaaaa 720 cccaaggaca ccctcatgat ctccggacc cctgagggtca catgcgttgt ggtggacgtg 780 agccacacca agccgtggat caagttaac tggtacgtgg acggcgtggaa ggtgtataat 840 gccaagacaa agccgcggga ggacgactac gccagcactg accgtgttgt cagcgtctc 900 accgtctgc accaggactg gctgaatggc aaggagttaca agtgcaaggt ctccaacaaa 960 gccctcccaag ccccccatacgaa aaaaaccatc tccaaagccaa aaggccggccc ccgagaacca 1020 cagggttaca ccctggccccc atccggggag gagatgacca agaaccaggta cagcgtgacc 1080 tgcctggtca aaggcttcta tcccagcgcac atcgccgtgg agtggggagag caatgggcag 1140 ccggagaacaa actacaagac cacgcctccc gtgtggact ccgcacggctc cttttcttc 1200	

US 12,384,837 B2

107

108

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tacagcaaggc tcaccgtgga caagaggcagg tggcagcagg ggaacgtctt ctcatgcctc 1260
 tgatgcgtg aggctctgca caaccactac acgcagaaga gcctccctt gtctccgggt 1320
 aatga 1326

SEQ ID NO: 172 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 172
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcttgtcag tctctggaaat cgacctcagt ggctactaca tgaactgggt ccgtcaggt 120
 ccaggaaagg ggctggagtg ggtcgagtc atggattata atggtgcac atactacg 180
 agctggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
 caaatgaaca gcttgagacg tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
 tggggccaag ggaccctcg caccgtctcg agc 333

SEQ ID NO: 173 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 173
 gaggtgcagc ttgtggagtc tgggggaggo ttggtccagc ctggggggtc cctgagactc 60
 tcttgtcag tctctggaaat cgacctcagt 90

SEQ ID NO: 174 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 174
 ggctactaca tgaac 15

SEQ ID NO: 175 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 175
 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 176 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 176
 gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 177 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 177
 cgattcacca tctccagaga caattccaag accacgggt atcttcaaattt gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 178 moltype = length =
 SEQUENCE: 178
 000

SEQ ID NO: 179 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence

US 12,384,837 B2

109

110

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source          1..33
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 179
tggggccaag ggaccctcg taccgtctcg agc                               33

SEQ ID NO: 180      moltype = DNA  length = 993
FEATURE          Location/Qualifiers
misc_feature     1..993
note = Engineered antibody sequence
source           1..993
               mol_type = other DNA
               organism = synthetic construct
SEQUENCE: 180
gcctccacca aggccccatc ggtttcccc ctggcaccc cctccaagag cacctctggg  60
ggcacagccg ccctgggtg cctgtcaag gactacttc cccaaacggt gacggtgtcg 120
tggaaactcg ggcgcctgac cagcggcggt cacaccccttc cggctgtctt acagtcccta 180
ggactctact ccctcagcag cgtggtggacc gtgccttcga ctagcttggg caccaggacc 240
tacatctgca acgttaatca caaaggccac aacaccaagg tggacaagg agttgagccc 300
aaatcttgcg acaaatactca cacatgccca cccgtccca caccgttaact cctgggggga 360
ccgtcgtct tccttcccccc cccaaaaccc aaggacacc cccatgtatc cccggaccct 420
gagggttgcgt gctgtgggtt ggacgtgago cacaaaggcc cttgggttcaa gttcaactgg 480
tacgtggacg gctgtggatgtt gcataatggc aacaccaagg cccggggggg gcaatgtggcc 540
agoacgtacc gtgtggtgcg cgttccatc gtcctgcacc aggactggct gaatggcaag 600
gagttacaatgtt gcaaggcttc caaaggccccc cccatcgagaa aaccatctcc 660
aaaggccaaag ggcagcccccc agaaccaccc gttgtacacc cccggggggg 720
atgaccaaga accaggctcg cctgttccatc gttgttcaaa gtttcatatcc cccgggggg 780
gcctgtggatgtt gggagagccaa tggcggccg gagaacaact acaagaccac gcctccctgt 840
ctggactccg acggcttccctt ctccatc agcaatgttca cccgtggacaa gagcgggtgg 900
cagcaggggg acgttccatc atgttccatc atgttccatc ctctgcacaa ccactacacg 960
cagaagagcc tctccctgtc tccgggtaaa tga                               993

SEQ ID NO: 181      moltype = AA  length = 219
FEATURE          Location/Qualifiers
REGION           1..219
note = Engineered antibody sequence
source           1..219
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 181
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCN LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGECA                               219

SEQ ID NO: 182      moltype = AA  length = 113
FEATURE          Location/Qualifiers
REGION           1..113
note = Engineered antibody sequence
source           1..113
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 182
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKR           113

SEQ ID NO: 183      moltype = AA  length = 22
FEATURE          Location/Qualifiers
REGION           1..22
note = Engineered antibody sequence
source           1..22
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 183
QVLTQSPSSL SASVGDRVTI NC                               22

SEQ ID NO: 184      moltype = AA  length = 13
FEATURE          Location/Qualifiers
REGION           1..13
note = Engineered antibody sequence
source           1..13
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 184
QASQSVYHNT YLA                                         13

SEQ ID NO: 185      moltype = AA  length = 15
FEATURE          Location/Qualifiers
REGION           1..15

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source	note = Engineered antibody sequence 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 185 WYQQKPGKVP KQLIY		15
SEQ ID NO: 186 FEATURE REGION	moltype = AA length = 7 Location/Qualifiers 1..7 note = Engineered antibody sequence	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 186 DASTLAS		7
SEQ ID NO: 187 FEATURE REGION	moltype = AA length = 32 Location/Qualifiers 1..32 note = Engineered antibody sequence	
source	1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 187 GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC		32
SEQ ID NO: 188 FEATURE REGION	moltype = AA length = 13 Location/Qualifiers 1..13 note = Engineered antibody sequence	
source	1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 188 LGSYDCTNGD CFV		13
SEQ ID NO: 189 FEATURE REGION	moltype = AA length = 11 Location/Qualifiers 1..11 note = Engineered antibody sequence	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 189 FGGGTKVEIK R		11
SEQ ID NO: 190 FEATURE REGION	moltype = AA length = 106 Location/Qualifiers 1..106 note = Engineered antibody sequence	
source	1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 190 TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		106
SEQ ID NO: 191 FEATURE misc_feature	moltype = DNA length = 660 Location/Qualifiers 1..660 note = Engineered antibody sequence	
source	1..660 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 191 caagtgtctg cccagttctcc atccccctg tctgcatctg taggagacag agtcaccatc aattggcagg ccagtcatcg tgtttatcat aacaccttacc tggcctggta tcagcagaaaa ccaggaaag ttccataagca actgatctat gatgcattca ctctggcatc tgggttccca tctcgttca gtggcagtgg atctggaca gatttcactc tcaccatcag cagcctgcag cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgatgt tttgtttcg gggaggaaac caagggtggaa atcaaactgta cggtggtgc accatctgtc ttcatcttcc cgccatctga tgagcagtgg aaatctggaa ctgcctctgt tgggtgcctg ctgaataact tctatccca agaggccaaa gtacagtggaa aggtggataa cgcctccaa tgggttaact cccaggagag tgcacagag caggacacca aggacagcac ctacagcctc agcagcacc c tgacgctgag caaaggcagac tacgagaaac acaaagtcta cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttag	60 120 180 240 300 360 420 480 540 600 660	
SEQ ID NO: 192	moltype = DNA length = 339	

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FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 192
 caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgcagg ccagtccatcg tgtttatcat aacaccttca tggcctggta tcagcagaaa 120
 ccaggaaag ttccataagca actgtatcca gatgcacatc ctctggatc tgggtccca 180
 ttcgttca gtggcactgg atctggaca gatttcactc tcacccatcag cagctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggtagttatg attgtactaa tggtgatgt 300
 ttgtttcg gcccggaaac caagggtggaa atcaaacacgt 339

SEQ ID NO: 193 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 193
 caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 194 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 194
 caggccatc agagtgttta tcataaacacc tacctggcc 39

SEQ ID NO: 195 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 195
 tggtatcagc agaaaccagg gaaagttctt aagcaactga tctat 45

SEQ ID NO: 196 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 196
 gatgcaccca ctctggatc t 21

SEQ ID NO: 197 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 197
 ggggtccccat ctcgtttcag tggcgttggaa tctggggacat atttcactctt caccatcagc 60
 agccctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 198 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 198
 ctggggcaggat atgattgtac taatgggtat tgttttgtt 39

SEQ ID NO: 199 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33

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source          note = Engineered antibody sequence
1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 199
ttcggcgagg gAACCAAGGT ggAAATCAAa cgt                         33

SEQ ID NO: 200      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
note = Engineered antibody sequence
source           1..321
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 200
acgggtggctg caccatctgt ctcatcttc ccgcattctg atgagcagg taaatcttga 60
actgcctctg ttgtgtccg gctaaataac ttctatccca gagaggccaa agtacatgg 120
aagggtggata acggcctcca atcggtaac tccaggaga gtgtcacaga gcaggacgc 180
aaggacacga cttacacgct cagcagcacc ctgacgtca gcaaaacgaca ctacgagaaa 240
cacaaggct acgcctgcga agtcacccat cagggcctga gtcgcgggtt cacaaggagc 300
ttcaacacgg gagggttta g                                         321

SEQ ID NO: 201      moltype = AA length = 441
FEATURE          Location/Qualifiers
REGION           1..441
note = Engineered antibody sequence
source           1..441
mol_type = protein
organism = synthetic construct
SEQUENCE: 201
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
PLAPSSKSTS CGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAPLQS SGLYSLSSVV 180
TVPSSSLGQ TYICNVNHPK SNTKVDARVE TPCPAPELLG GPSVFLPPK 240
PKDTLMISR PPEVTCVVVDV SHDEPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K                                         441

SEQ ID NO: 202      moltype = AA length = 111
FEATURE          Location/Qualifiers
REGION           1..111
note = Engineered antibody sequence
source           1..111
mol_type = protein
organism = synthetic construct
SEQUENCE: 202
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV IGINGATYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S                                         111

SEQ ID NO: 203      moltype = AA length = 30
FEATURE          Location/Qualifiers
REGION           1..30
note = Engineered antibody sequence
source           1..30
mol_type = protein
organism = synthetic construct
SEQUENCE: 203
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS                                         30

SEQ ID NO: 204      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
note = Engineered antibody sequence
source           1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 204
GYMMN                                         5

SEQ ID NO: 205      moltype = AA length = 14
FEATURE          Location/Qualifiers
REGION           1..14
note = Engineered antibody sequence
source           1..14
mol_type = protein
organism = synthetic construct
SEQUENCE: 205
WVRQAPGKGL EWVG                                         14

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SEQ ID NO: 206      moltype = AA length = 16
FEATURE          Location/Qualifiers
REGION           1..16
source            note = Engineered antibody sequence
                  1..16
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 206
VIGINGATYY ASWAKG                                         16

SEQ ID NO: 207      moltype = AA length = 32
FEATURE          Location/Qualifiers
REGION           1..32
source            note = Engineered antibody sequence
                  1..32
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 207
RFTISRDNSK TTVYQLQMSL RAEDTAVYFC AR                         32

SEQ ID NO: 208      moltype = length =
SEQUENCE: 208
000

SEQ ID NO: 209      moltype = AA length = 11
FEATURE          Location/Qualifiers
REGION           1..11
source            note = Engineered antibody sequence
                  1..11
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 209
WGQGTLVTVS S                                              11

SEQ ID NO: 210      moltype = AA length = 330
FEATURE          Location/Qualifiers
REGION           1..330
source            note = Engineered antibody sequence
                  1..330
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 210
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  60
GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDARVEP KSCDKTHTCP PCPAPELGG 120
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFWN YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT LPHQDWLNKG EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFPYPSDI AVEWESENQGP ENNYKTTPPV LSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                           330

SEQ ID NO: 211      moltype = DNA length = 1326
FEATURE          Location/Qualifiers
misc_feature     1..1326
source            note = Engineered antibody sequence
                  1..1326
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 211
gaggtgcagc ttgtggagtc tggggggaggc ttggtccagc ctggggggtc cctgagactc  60
tccctgtcag tctctggaat cgacctca ggcgtactaca tgaactgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggc attggtattt atggtgcac atactacgcg 180
agctggggaa aaggccgatt caccatctca agagacaat ccaagacccac ggttatctt 240
caaataatgca caacttgcgac tgaggactt gctgtgtattt tctgtgttagt aggggacatc 300
tggggccaag ggacctctgt caccgtctcg agccgcctca ccaaggcccc atcggtcttc 360
cccccgtggc ac cctctccaa gageacctct gggggccacag cggccctggg ctgcctggc 420
aaggactact tccccgaacc ggtgacgggtg tcgtggaaact caggccgcctt gaccagccgc 480
gtgcacaccc tccccggccctt cctacttgcgactt actccctca gaggcgtggc 540
accgtgcgcctt ccacgtttt gggccacccatg accttacatcc gcaacgtgaa tcacaaggcc 600
agaacacacca aggtggacgc gagaatggat cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgc ac cggcacctga actctgggg ggaccgtca gtttccctttt ccccccaaaa 720
cccaaggaca ccctcatgtat cttccggacc cctgagggtca catgcgttgtt ggtggacgtg 780
agccacacca accctggatgta caagtcaac tggtaacgtgg acggcgtgg ggtgcataat 840
gccaagacaa agccgcggga ggagcgtac gccagcacgtt accgtgttgtt cagcgtcctc 900
accgtccctgc accaggactg gctaatggc aagggttaca agtgcgttgtt ctccaaacaaa 960
gcgcctcccg ccccccattca gaaaaccatc tccaaagccca aaggccgcctt ccggagaacca 1020
cagggtgtaca ccctggccccc atccggggag gagatgacca agaaccaggc tggcgtgacc 1080
tgcctggta aaggcttcta tcccagcgc ac tggccgtgg agtggggagag caatggcag 1140
ccggagaaca actacaagac cacgcctccc gtgtggactt ccgcacggcctt cttttctc 1200
tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtt ctcatgtcc 1260

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gtgatgcata aggctctgca caaccactac acgcagaaga gcctccct gtccgggt 1320
aatga 1326

SEQ ID NO: 212 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 212
gagggtgcagc ttgtggagtc tgggggaggo ttgtccagc ctggggggc cctgagactc 60
tctctgtgcag tctctggaat cgacctcagt ggctactaca tgaactcggt ccgtcaggct 120
ccaggaaagg ggtcgagtg ggtcgagtg attggcacc atactacgg 180
agctggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaataatgaaca gcctgagagc tgaggacact gctgtgtatt tctgtgttag aggggacatc 300
tggggccaag ggaccctcgta caccgtctcg agc 333

SEQ ID NO: 213 moltype = DNA length = 90
FEATURE Location/Qualifiers
misc_feature 1..90
note = Engineered antibody sequence
source 1..90
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 213
gagggtgcagc ttgtggagtc tgggggaggo ttgtccagc ctggggggc cctgagactc 60
tctctgtgcag tctctggaat cgacctcagt 90

SEQ ID NO: 214 moltype = DNA length = 15
FEATURE Location/Qualifiers
misc_feature 1..15
note = Engineered antibody sequence
source 1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 214
ggctactaca tgaac 15

SEQ ID NO: 215 moltype = DNA length = 42
FEATURE Location/Qualifiers
misc_feature 1..42
note = Engineered antibody sequence
source 1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 215
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 216 moltype = DNA length = 48
FEATURE Location/Qualifiers
misc_feature 1..48
note = Engineered antibody sequence
source 1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 216
gtcattggta ttaatggtgc cacatactac gcgagctggg cgaaaggc 48

SEQ ID NO: 217 moltype = DNA length = 96
FEATURE Location/Qualifiers
misc_feature 1..96
note = Engineered antibody sequence
source 1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 217
cgattccacca tctccagaga caattccaaag accacgggtg atcttcaa at gaacagcctg 60
agagctgagg acactgctgt gtatttctgt gctaga 96

SEQ ID NO: 218 moltype = length =
SEQUENCE: 218
000

SEQ ID NO: 219 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
note = Engineered antibody sequence
source 1..33

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 219
tggggccaag ggaccctcg taccgtctcg agc 33

SEQ ID NO: 220      moltype = DNA length = 993
FEATURE          Location/Qualifiers
misc_feature    1..993
note = Engineered antibody sequence
source          1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 220
gcctccacca agggcccatc ggtttcccc ctggcaccc cctccaagag cacctctggg 60
ggcacagccg ccctggctg cctgtcaag gactacttc cccgaacccgt gacgggtcg 120
tggaaactcg gcgcctgac cagcggctg cacaccttc cggctgtctt acatgcctca 180
ggactctact ccctcagcg cgtgttgacc gtggccctca gcagcttggg caccaggacc 240
tacatctgc aacgtgaatc caagcccgc aacaccaagg tggacgcgg agttgaggccc 300
aaatcttgtc aaaaaactca cacaatggccca cccgtggcccg cacccttaact cctgggggga 360
ccgtcagtct tccttctccc cccaaaaccc aaggacacc tcattgtatcc ccggaccct 420
gagggtcacat cgggtgggtt ggacgtgago cccggacacc ctggggctaa gttcaactgg 480
tacgtggacg cgtgtgggggt gcataatgcc aagacaaagg cccggggagg gacgtacgcc 540
agcacgtacc gtgtggctcg cgtcttcacc gtcctgcacc aggactggt gaatggcaag 600
gagttacaagg gcaaggcttc caacaaagcc cttcccgacc cccatcgagaa aaccatctcc 660
aaaggccaaag ggcaggcccg agaaccacag gtgtacaccc tgcccccattt ccggggaggag 720
atgaccaaga accagggtcg cctggacccgt ctggtcaaaag gtttctatcc cccggacatc 780
gccgtggagt gggagagcaa tggggcagccg gagaacaaact acaagaccac gcctccctgt 840
ctggactccg acggctctt ctteatctac agcaagctca cccgtggacaa gaggcagggtgg 900
cagcagggggaa acgtttctc atgtccgtg atgtcatggg ctctgcacaa ccactacacg 960
cagaagggcc tttccctgtc tccgggtaaa tga 993

SEQ ID NO: 221      moltype = AA length = 219
FEATURE          Location/Qualifiers
REGION          1..219
note = Engineered antibody sequence
source          1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 221
QLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 222      moltype = AA length = 113
FEATURE          Location/Qualifiers
REGION          1..113
note = Engineered antibody sequence
source          1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 222
QLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY DASTLASGVP 60
SRFSGSGGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC FVFGGGTKVE IKR 113

SEQ ID NO: 223      moltype = AA length = 22
FEATURE          Location/Qualifiers
REGION          1..22
note = Engineered antibody sequence
source          1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 223
QLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 224      moltype = AA length = 13
FEATURE          Location/Qualifiers
REGION          1..13
note = Engineered antibody sequence
source          1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 224
QASQSVYHNT YLA 13

SEQ ID NO: 225      moltype = AA length = 15
FEATURE          Location/Qualifiers
REGION          1..15
note = Engineered antibody sequence

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source	1..15	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 225		
WYQQKPGKVP KQLIY		15
SEQ ID NO: 226	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
	note = Engineered antibody sequence	
source	1..7	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 226		
DASTLAS		7
SEQ ID NO: 227	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
	note = Engineered antibody sequence	
source	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 227		
GVPSRFSGSG SGTDFLTIS SLQPEDVATY YC		32
SEQ ID NO: 228	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
	note = Engineered antibody sequence	
source	1..13	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 228		
LGSYDCTNGD CFV		13
SEQ ID NO: 229	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
	note = Engineered antibody sequence	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 229		
FGGGTKVEIK R		11
SEQ ID NO: 230	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
	note = Engineered antibody sequence	
source	1..106	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 230		
TVAAAPSVFIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60	
KDSTYSLSST LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC	106	
SEQ ID NO: 231	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
	note = Engineered antibody sequence	
source	1..660	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 231		
caagtgtga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc	60	
aattgcagg ccagtcagag tgttatcat aacacctacc tggcctggta tcagcagaaa	120	
ccaggaaag ttccctaagca actgtatctt gatgcattcca ctctggcatc tgggtccca	180	
tcccgtttca gtggcagtgg atctggaca gatttcactt tcaccatcag cagctgcag	240	
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt	300	
tttggtttccg goggaggaaac caagggtggaa atcaaacgtt cgggtggctgc accatctgtc	360	
ttcatcttcc cccatctgtg tgagcagtgg aaatctggaa ctgcctctgt tggtgctgt	420	
ctgaataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa	480	
tcgggttaact cccaggagag tgcacagag cagcacagcac ctacagcctc	540	
agcagcaccc tgacgttgag caaaggcagac tacgagaaac acaaagtcta cgcctgcgaa	600	
gtcacccatc agggccttagt ctcggccgtc acaaaggttca acaacagggg agagtgttag	660	
SEQ ID NO: 232	moltype = DNA length = 339	
FEATURE	Location/Qualifiers	

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misc_feature	1..339	
source	note = Engineered antibody sequence	
	1..339	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 232		
caagtgtcg cccagtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	60	
aattgcagg ccagtccatg tgtttatcat aacacctacc tggctggta tcacgaaaaa	12	
ccaggaaag ttccaaacca actgatctat gatgcaccca ctctggatcc tggggccca	18	
tctcgtttca gtggcgttgg atctgggaca gatttcactc tcaccatcg cagctgcag	24	
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtactaa tggtgattgt	30	
tttttttcg gcgaggaaac caagggtggaa atcaaacgt	33	
SEQ ID NO: 233	moltype = DNA length = 66	
FEATURE	Location/Qualifiers	
misc_feature	1..66	
source	note = Engineered antibody sequence	
	1..66	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 233		
caagtgtcg cccagtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	60	
aattgc	66	
SEQ ID NO: 234	moltype = DNA length = 39	
FEATURE	Location/Qualifiers	
misc_feature	1..39	
source	note = Engineered antibody sequence	
	1..39	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 234		
caggccagtc agagtgttta tcataaacacc tacctggcc	39	
SEQ ID NO: 235	moltype = DNA length = 45	
FEATURE	Location/Qualifiers	
misc_feature	1..45	
source	note = Engineered antibody sequence	
	1..45	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 235		
tggtatcagc agaaaccagg gaaagttctt aagcaactga tcttat	45	
SEQ ID NO: 236	moltype = DNA length = 21	
FEATURE	Location/Qualifiers	
misc_feature	1..21	
source	note = Engineered antibody sequence	
	1..21	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 236		
gatgcaccca ctctggatct t	21	
SEQ ID NO: 237	moltype = DNA length = 96	
FEATURE	Location/Qualifiers	
misc_feature	1..96	
source	note = Engineered antibody sequence	
	1..96	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 237		
ggggtccccat ctcgtttcag tggcagtggaa tctgggacag atttcaactct caccatcaggc	60	
agcctgcagc ctgaagatgt tgcaacttat tactgt	96	
SEQ ID NO: 238	moltype = DNA length = 39	
FEATURE	Location/Qualifiers	
misc_feature	1..39	
source	note = Engineered antibody sequence	
	1..39	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 238		
ctgggcaggat atgattgtac taatgggtat tggtttgg	39	
SEQ ID NO: 239	moltype = DNA length = 33	
FEATURE	Location/Qualifiers	
misc_feature	1..33	
	note = Engineered antibody sequence	

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source 1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 239
ttcggcgagg gAACCAAGGT ggAAATCAAA CGT 33

SEQ ID NO: 240 moltype = DNA length = 321
FEATURE Location/Qualifiers
misc_feature 1..321
note = Engineered antibody sequence
source 1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 240
acgggtggctt caccatctgt ctccatcttc ccgcgcattctg atgagcaggta gaaatctgg 60
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcggttaac tccccaggaga gtgtcacaga gcaggacagc 180
aaggacagaca cctacagcc tccgcgcacc ctgcacgtga gcaaagcaga ctacgaaaa 240
cacaaggatctt acggctgcga agtaccccat cagggtcgta gtcgcggctg cacaagagc 300
ttcaacagggg gagagtgtta g 321

SEQ ID NO: 241 moltype = AA length = 440
FEATURE Location/Qualifiers
REGION 1..440
note = Engineered antibody sequence
source 1..440
mol_type = protein
organism = synthetic construct

SEQUENCE: 241
QEQLKESGGR LVTPGTSLTL TCTVSGIDLS NHYMQWVRQA PGKGLEWIGV VGINGRTYYA 60
SWAKGRFTIS RTSSTTVDLK MTRLTTEDTA TYPCARGDIW GPGTLVTVSS ASTKGPSVFP 120
LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT 180
VPSSSLGTQT YICNVNWKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG PSVFLFPKPK 240
KDITLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNKA KTKPREEQYA STYRVVSVLT 300
VLHQDWLNGK EYKCKVSNKA LPAPIEKTTIS KAKGQPREGQ VYTLPPSREE MTKNQVSLTC 360
LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LBSDGSFFLY SKLTVDKSRW QQGNVFSCSV 420
MHEALHNHYT QKSLSLSPKG 440

SEQ ID NO: 242 moltype = AA length = 110
FEATURE Location/Qualifiers
REGION 1..110
note = Engineered antibody sequence
source 1..110
mol_type = protein
organism = synthetic construct

SEQUENCE: 242
QEQLKESGGR LVTPGTSLTL TCTVSGIDLS NHYMQWVRQA PGKGLEWIGV VGINGRTYYA 60
SWAKGRFTIS RTSSTTVDLK MTRLTTEDTA TYPCARGDIW GPGTLVTVSS 110

SEQ ID NO: 243 moltype = AA length = 30
FEATURE Location/Qualifiers
REGION 1..30
note = Engineered antibody sequence
source 1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 243
QEQLKESGGR LVTPGTSLTL TCTVSGIDLS 30

SEQ ID NO: 244 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 244
NHYMQ 5

SEQ ID NO: 245 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 245
WVRQAPGKGL EWIG 14

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SEQ ID NO: 246 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 246
 VVGINGRTYY ASWAKG 16

SEQ ID NO: 247 moltype = AA length = 31
 FEATURE Location/Qualifiers
 REGION 1..31
 note = Engineered antibody sequence
 source 1..31
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 247 RFTISRTSST TVDLKMTRLT TEDTATYFCA R 31

SEQ ID NO: 248 moltype = length =
 SEQUENCE: 248 000

SEQ ID NO: 249 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 249 WGPGLTIVTS S 11

SEQ ID NO: 250 moltype = AA length = 330
 FEATURE Location/Qualifiers
 REGION 1..330
 note = Engineered antibody sequence
 source 1..330
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 250 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
 GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
 PSVFLFPVKP KDTLMISRTP EVTCVVVDVS HEDPEVKENW YVDGEVHNKA KTKPREEQYA 180
 STYRVSLSVT VLHQDWLNKG EYCKKVSNKA LPAPIEKTN KAKGQPPREQV VTLYPLPSREE 240
 MTKNQVSLTC LVKGFYPSDI AVEWEWSNGQP ENNYKTPPPV LDSDGSFFLY SKLTVDKSRW 300
 QQGNVFSCSM MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 251 moltype = DNA length = 1323
 FEATURE Location/Qualifiers
 misc_feature 1..1323
 note = Engineered antibody sequence
 source 1..1323
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 251 caggagcgc tgaaggagtc cgggggtcgc ctggtaacgc ctgggacata cctgacactc 60
 acctgcacccg tctctggat ccacccctcgat aaccactaca tgcaatgggt ccgcggcggt 120
 ccaggaaagg ggctggagtg gatcgagtc gttggattata atggtcgcac atactacgcg 180
 agctggcgca aaggccgat caccatctcc agaacccctgt cgaccacggg ggatctgaaa 240
 atggacccgcg tgacaacccg ggacacggcc acctatcttc gtgcggacgg ggacatctgg 300
 ggccgcggca cccctggatc cgttcgcggc gcctccacca agggccatcc ggttctcccc 360
 ctggcacccc cttccaagag cacctctggg ggcacacggg ccctggctgt cctggtaag 420
 gactactcc cggaaacgggt gacgggttcg tggaaacttcg ggcgcctgcg cagccggctg 480
 cacaccccttc cggctgttcc acatgttcga ggactctact ccctcagcag cgtgtgtgacc 540
 gtgccttcga cggatctggg caccggacc tacatctgc acgtgaatca caagcccgac 600
 aacacaaagg tggacaaggat agtgtggccaaatcttgc aacaaactca catatggcca 660
 ccgtgccccac cacctgaact cctgggggaa ccgtcaagtcc tcctcttccc cccaaaaaccc 720
 aaggacaccc tcatgtatcc cggacccctt gaggtacatcg gcgtgggtt ggacgtgagc 780
 cacgaagacc ctggggatccaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc 840
 aagacaaaggc cggccggggaa gcaatgcgc agcaacttccgttgcgtgttccgcgtccatcc 900
 gtctgcaccc aggtatggccat gatgtggccatc gatgtggccatc gcaatgttcccaacaaaggc 960
 ctcccaaggcc ccatcgagaa aaccatctcc aaaggccaaagg ggcaggcccc agaaccacag 1020
 gtgtacaccctt cggccggggatc atgaccaaga accaggatcg cctgacccctgc 1080
 ctggatccaaatc cggccggggatc atgaccaaga accaggatcg cctgacccctgc 1140
 gagaacaaaggc acaagaccac gctccctcgat ctggactccgc acggcccttccatcc 1200
 agcaacgttcc cccgtggccatc gaggatggccatc gaggccggatc acgttccatcc 1260
 atccatqaqq ctctqacaaa ccaactacacc caqaaqaqcc tctccctqtc tccggqtaaa 1320

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tga	1323
SEQ ID NO: 252	moltype = DNA length = 330
FEATURE	Location/Qualifiers
misc_feature	1..330
	note = Engineered antibody sequence
source	1..330
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 252	
caggagcgc tgaaggagtc cgggggtcgc ctggtaacgc ctgggacatc cctgacactc	60
acctgcaccg tctctggaat cgacctcagt aaccactaca tgcaatgggt ccggcaggct	120
cgaggaaagg ggctggagggt gatcgaggatc gtggattata atggcgac atactacgg	180
agctggggcatt caccatccg agaacctcgat cgaccacgggt ggatctgaaa	240
atgaccaggc tgacaaccga ggacacggcc acctatttct gtcccgagg ggacatctgg	300
ggccaggca ccctggtcac cgtctcgagc	330
SEQ ID NO: 253	moltype = DNA length = 90
FEATURE	Location/Qualifiers
misc_feature	1..90
	note = Engineered antibody sequence
source	1..90
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 253	
caggagcgc tgaaggagtc cgggggtcgc ctggtaacgc ctgggacatc cctgacactc	60
acctgcaccg tctctggaat cgacctcagt	90
SEQ ID NO: 254	moltype = DNA length = 15
FEATURE	Location/Qualifiers
misc_feature	1..15
	note = Engineered antibody sequence
source	1..15
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 254	
aaccactaca tgcaa	15
SEQ ID NO: 255	moltype = DNA length = 42
FEATURE	Location/Qualifiers
misc_feature	1..42
	note = Engineered antibody sequence
source	1..42
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 255	
tggtccgcc aggctccagg gaaggggctg gagtggatcg ga	42
SEQ ID NO: 256	moltype = DNA length = 48
FEATURE	Location/Qualifiers
misc_feature	1..48
	note = Engineered antibody sequence
source	1..48
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 256	
gtcggtggta ttatggtcg cacatactac gcgagctggg cgaaaggc	48
SEQ ID NO: 257	moltype = DNA length = 93
FEATURE	Location/Qualifiers
misc_feature	1..93
	note = Engineered antibody sequence
source	1..93
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 257	
cgattcacca tctccagaac ctgcgtcacc acgggtggatc tgaaaatgac caggctgaca	60
acccaggaca cggccaccta tttctgtgcc aga	93
SEQ ID NO: 258	moltype = length =
SEQUENCE: 258	
000	
SEQ ID NO: 259	moltype = DNA length = 33
FEATURE	Location/Qualifiers
misc_feature	1..33
	note = Engineered antibody sequence
source	1..33
	mol_type = other DNA

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organism = synthetic construct

SEQUENCE: 259
tggggcccaag gcaccctggc caccgtctcg agc 33

SEQ ID NO: 260 moltype = DNA length = 993
FEATURE Location/Qualifiers
misc_feature 1..993
note = Engineered antibody sequence
source 1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 260
gcctccacca aggccccatc ggctttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagccg ccctgggtc cctgtcaag gactacttc cccgaaccgg gacgggtgtg 120
tggaaacttag cgcgcctgac cagcgccgtg cacaccttc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtgttgacc gtgccttcga gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caagcccgaa aacccaaagg tggacaaggag agttggggcc 300
aaatatctgtc aaaaaactca cacatggccca cccgtggccaa cccatgtactt cctgggggaa 360
ccctcgtctt cccttcggcc aaggacaccctt ccatgtatcc cccggaccct 420
gagggtcacat ggctgggtgtt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
tacgtggacg ggggtggatg gcataatggc aagacaaaagg ccgcggggaga gcagtgacgcc 540
agcacgtacc gtgtgggtc cgttccatcc gtcctgcacc aggactgggt gaatggcaag 600
gagttacaatg gcaagggtctc caaaaaaggcc cttcccgccccc ccattggaaa aaccatctcc 660
aaaggccaaag ggcagccccgg agaaccacag gtgtacacc ttggcccccacc ccggggaggag 720
atgaccaaga accagggtcag cctgtacccg ctggtaaaagg gtttctatcc cagcgacatc 780
gcccgtggatg gggagggacaa tggggagccg gagaacaact acaaggaccac gcctccctgt 840
ctggactccg acggcttcctt ctteccatca agcaaggtca cccgtggacaa gagcgggtgg 900
cagcaggggaa acgttccatcc atgtccgtg atgtcatggg ctctgcacaa ccactacacg 960
cagaagggcc ttcctccgtc tccgggtaaa tga 993

SEQ ID NO: 261 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 261
QVLTQTASPV SAAVGSTVTI NCQASQSVYN YNYLAWYQQK PGQPPKQLIY STSTLASGV 60
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKKHVKYACE VTHQGLSSPV TKSFNLRGEC 219

SEQ ID NO: 262 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 262
QVLTQTASPV SAAVGSTVTI NCQASQSVYN YNYLAWYQQK PGQPPKQLIY STSTLASGV 60
SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSTGDC FVFGGGTEVV VKR 113

SEQ ID NO: 263 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 263
QVLTQTASPV SAAVGSTVTI NC 22

SEQ ID NO: 264 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 264 QASQSVYNYN YLA 13

SEQ ID NO: 265 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15

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mol_type = protein
organism = synthetic construct

SEQUENCE: 265
WYQQKPGQPP KQLIY                                         15

SEQ ID NO: 266      moltype = AA length = 7
FEATURE
REGION           Location/Qualifiers
1..7             note = Engineered antibody sequence
source            1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 266
STSTLAS                                         7

SEQ ID NO: 267      moltype = AA length = 32
FEATURE
REGION           Location/Qualifiers
1..32            note = Engineered antibody sequence
source            1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 267
GVSSRFKGSG SGTQFTLTIS DVQCDDAATY YC                                         32

SEQ ID NO: 268      moltype = AA length = 13
FEATURE
REGION           Location/Qualifiers
1..13            note = Engineered antibody sequence
source            1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 268
LGSYDCSTGD CFV                                         13

SEQ ID NO: 269      moltype = AA length = 11
FEATURE
REGION           Location/Qualifiers
1..11            note = Engineered antibody sequence
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 269
FGGGTEVVVK R                                         11

SEQ ID NO: 270      moltype = AA length = 106
FEATURE
REGION          Location/Qualifiers
1..106           note = Engineered antibody sequence
source            1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 270
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC                                         106

SEQ ID NO: 271      moltype = DNA length = 660
FEATURE
misc_feature     Location/Qualifiers
1..660           note = Engineered antibody sequence
source            1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 271
caagtgtcga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattggcagg ccagtcagag tgtttataat tacaactacc ttgcctggta tcagcagaaa 120
ccaggggcagg ctcccaaga actgatctat tctacatcca ctctggcatc tggggtctca 180
tcgcgatcca aaggcagttg atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
tgtgacgatg ctgccactta ctactgtcta ggcagttatg actgtatgtc tggtgattgt 300
tttggtttcg gcgaggggac cgagggttg gtcaaacgtg cggggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tggtgctgt 420
ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagag tgcacagag caggacagca aggacagcac ctacagcctc 540
agcagcaccc tgacgtctag caaagcagac tacggagaa acaaagtcta cgcctcgaa 600
gtcaccatccatc agggccttag ctcgcccgtc acaaagagct tcaacagggg agagtgttag 660

SEQ ID NO: 272      moltype = DNA length = 339
FEATURE
misc_feature     Location/Qualifiers
1..339

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source          note = Engineered antibody sequence
1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 272
caagtgcgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgcagg ccagtcagag tgtttataat tacaactacc ttgcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgatctat tctacatcca ctctggcatc tgggtctca 180
tcgcgattca aaggcagtg  atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
tggacgtatcg ctgcactta ctactgtcta ggcagttatc actgttagtac tggtgatgt 300
tttgtttcg ggggggac cgagggtgttgcgtaaacatc 339

SEQ ID NO: 273      moltype = DNA length = 66
FEATURE           Location/Qualifiers
misc_feature      1..66
note = Engineered antibody sequence
source            1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 273
caagtgcgtga cccagactgc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgc                                     66

SEQ ID NO: 274      moltype = DNA length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 274
caggccagtc agagtgttta taattacaac taccttgcc                                39

SEQ ID NO: 275      moltype = DNA length = 45
FEATURE           Location/Qualifiers
misc_feature      1..45
note = Engineered antibody sequence
source            1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 275
tggtatcagg agaaaccagg gcagcctccc aagcaactga tctat                                45

SEQ ID NO: 276      moltype = DNA length = 21
FEATURE           Location/Qualifiers
misc_feature      1..21
note = Engineered antibody sequence
source            1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 276
tctacatcca ctctggcatc t                                         21

SEQ ID NO: 277      moltype = DNA length = 96
FEATURE           Location/Qualifiers
misc_feature      1..96
note = Engineered antibody sequence
source            1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 277
gggttctcat cgcgattcaa aggcaactgga tctgggacac agttcaactt caccatcagc 60
gacgtgcagt gtgacgtgc tgccacttac tactgt                                96

SEQ ID NO: 278      moltype = DNA length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 278
ctaggcagtt atgactgttag tactggtgat tgttttgtt                                39

SEQ ID NO: 279      moltype = DNA length = 33
FEATURE           Location/Qualifiers
misc_feature      1..33
note = Engineered antibody sequence
source            1..33

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 279
ttcggcgag ggaccgaggt ggtggtcaaa cgt                                33

SEQ ID NO: 280      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
note = Engineered antibody sequence
source           1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 280
acggtgtgtg caccatctgt cttagatcttc ccgcacatctg atgaggcaggta gaaatcttgg 60
actgccttc ttgtgtgcct gctaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgcctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacagc 180
aaggacacgca cctacagcct cagcagcacc ctgacgctga gcaaagcaga ctacgagaaa 240
cacaaggatct acgcctgcga agtccccat caggcctga gtcgcggcgt cacaaggagc 300
ttaaacaggg gagagtgtt a g                                         321

SEQ ID NO: 281      moltype = AA length = 441
FEATURE          Location/Qualifiers
REGION           1..441
note = Engineered antibody sequence
source           1..441
mol_type = protein
organism = synthetic construct

SEQUENCE: 281
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS NHYMQWVRQA PGKGLEWVG VGINGRTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTIVTVS SASTKGPSVF 120
PLAPSSKSTS CGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAPLQS SGLYSLSSVV 180
TVPVSSSLGTQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLPPK 240
PKDTLMISRT PEVTCVVVD SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG LEVKCKVSNK ALPAPIEKT SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNQG PENNYKTPPP VLSDGSPF YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG K                                         441

SEQ ID NO: 282      moltype = AA length = 111
FEATURE          Location/Qualifiers
REGION           1..111
note = Engineered antibody sequence
source           1..111
mol_type = protein
organism = synthetic construct

SEQUENCE: 282
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS NHYMQWVRQA PGKGLEWVG VGINGRTYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTIVTVS S             111

SEQ ID NO: 283      moltype = AA length = 30
FEATURE          Location/Qualifiers
REGION           1..30
note = Engineered antibody sequence
source           1..30
mol_type = protein
organism = synthetic construct

SEQUENCE: 283
EVOLVESGGG LVQPGGSLRL SCAVSGIDLS                                         30

SEQ ID NO: 284      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
note = Engineered antibody sequence
source           1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 284
NHYMQ                                                       5

SEQ ID NO: 285      moltype = AA length = 14
FEATURE          Location/Qualifiers
REGION           1..14
note = Engineered antibody sequence
source           1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 285
WVRQAPGKGL EWVG                                              14

SEQ ID NO: 286      moltype = AA length = 16

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FEATURE REGION	Location/Qualifiers 1..16 note = Engineered antibody sequence
source	1..16 mol_type = protein organism = synthetic construct
SEQUENCE: 286 VVGINGRTYY ASWAKG	
	16
SEQ ID NO: 287	moltype = AA length = 32
FEATURE REGION	Location/Qualifiers 1..32 note = Engineered antibody sequence
source	1..32 mol_type = protein organism = synthetic construct
SEQUENCE: 287 RFTISRDNSK TTVYIQLQNSL RAEDTAVYFC AR	
	32
SEQ ID NO: 288	moltype = length =
SEQUENCE: 288 000	
SEQ ID NO: 289	moltype = AA length = 11
FEATURE REGION	Location/Qualifiers 1..11 note = Engineered antibody sequence
source	1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 289 WGQGTLTVTS S	
	11
SEQ ID NO: 290	moltype = AA length = 330
FEATURE REGION	Location/Qualifiers 1..330 note = Engineered antibody sequence
source	1..330 mol_type = protein organism = synthetic construct
SEQUENCE: 290 ASTKGPSVK LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60 GLYSLSSVFT VPSSSLGTQT YICNVNHPKS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120 PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330	
SEQ ID NO: 291	moltype = DNA length = 1326
FEATURE misc_feature	Location/Qualifiers 1..1326 note = Engineered antibody sequence
source	1..1326 mol_type = other DNA organism = synthetic construct
SEQUENCE: 291 gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60 tccctgtcgac ttctctggat cgacctcaagt aaccactacta tgcaatgggt ccgtcaggct 120 ccagggagg ggtctggatg ggtcgaggatc gtgggtatca atggtcgcac atatacgcg 180 agctggcgca aaggccgattt caccatctcc agagacaat ccaagaccac ggtgtatctt 240 caaataatgaaca gccttgagac tgaggacact gctgtgtatt tctgtgttag agggggacatc 300 tggggccaag ggacctctcg cacccgtctcg agccgcctcca ccaaggccc atccgtcttc 360 ccccctggcac cctccctccaa gagecacctt gggggcacag cggccctggg ctgcctggc 420 aaggactact tcccccgaacc ggtgcgttg tctgtggactt cagggccctt gaccagccgc 480 gtgcacaccc tcccccgtgt cttacagtcc tcaggactctt actccctcaag cagcgtgggt 540 accgtgcacctt ccagcagcgtt gggcaccccaag acctacatctt gcaacgtgaa tcacaagccc 600 agaacaacacca aggtggacacca gagagttag cccaaatctt gtgacaaaac tcacacatgc 660 ccaccgtgcc cagcacatgtca actccctgggg ggacccgtcactt cttccctttt ccccccaaaaa 720 cccaaggaca cccctcatgtat cttccggacc cctggaggatca catcgctgtt ggtggacgtg 780 agccacacgaag accctggatgtt caagttaaac tggtaacgtgg acggcggtt ggtgcataat 840 gccaaagacaa agccgcggga ggagcagttt gccagcactt accgtgttgtt cagcgtcttc 900 accgtcttcg accaggactt gctaatggc aaggagttaca agtgcacggc ttccaaacaaa 960 gccctcccag ccccccatacgaa gaaaaccatc tccaaagccca aaggggcagcc ccgagaacca 1020 cagggttaca ccctggccccc atccccggag gagatggccca agaaccaggat cagcgttgcacc 1080 tgccctggtca aaggcttcta tcccgacgcac atccggctgg agtggggagag caatgggcag 1140 ccggagaaca actacaagac cacgcctccc gtgtggactt ccgacggctc cttcttc 1200 tacagcaagc tcaccgtggc caagagcagg tggcagcagg ggaacgttcc ctcatgtcc 1260 gtgtatgcatg aggctctgca caaccactac acgcagaaga gctctccctt gtctccgggt 1320 aaatga 1326	

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SEQ ID NO: 292      moltype = DNA length = 333
FEATURE           Location/Qualifiers
misc_feature      1..333
source            note = Engineered antibody sequence
                  1..333
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 292
gaggtgcagc ttgtggagtc tgggggggaggc ttgggtccagc ctgggggggtc cctgagactc 60
tccctgtcgac tctctggaat cgacctcagt aaccactaca tgcaatgggt ccgtcagggt 120
ccagggaaagg ggctggagtg ggtcgaggc ttgggtatca atggtcgac atactacgcg 180
agctgggcga aaggccgatt caccatctcc agagacaattt ccaagaccac ggtgtatctt 240
caaatgtaca gcctgagacg tgaggacaactt gctgtgtatcc ttgtgttagt agggggacatc 300
tggggccaaag ggaccctcgta caccgtctcg agc                                333

SEQ ID NO: 293      moltype = DNA length = 90
FEATURE           Location/Qualifiers
misc_feature      1..90
source            note = Engineered antibody sequence
                  1..90
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 293
gaggtgcagc ttgtggagtc tgggggggaggc ttgggtccagc ctgggggggtc cctgagactc 60
tccctgtcgac tctctggaat cgacctcagt                                90

SEQ ID NO: 294      moltype = DNA length = 15
FEATURE           Location/Qualifiers
misc_feature      1..15
source            note = Engineered antibody sequence
                  1..15
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 294
aaccactaca tgcaa                                         15

SEQ ID NO: 295      moltype = DNA length = 42
FEATURE           Location/Qualifiers
misc_feature      1..42
source            note = Engineered antibody sequence
                  1..42
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 295
tgggtccgtc aggctccagg gaaggggtcg gagtgggtcg ga                                42

SEQ ID NO: 296      moltype = DNA length = 48
FEATURE           Location/Qualifiers
misc_feature      1..48
source            note = Engineered antibody sequence
                  1..48
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 296
gtcggttggta tcaatggtcg cacatactac gcqagctggc cgaaaggc                                48

SEQ ID NO: 297      moltype = DNA length = 96
FEATURE           Location/Qualifiers
misc_feature      1..96
source            note = Engineered antibody sequence
                  1..96
mol_type          other DNA
organism          synthetic construct
SEQUENCE: 297
cgatttccacca tctccagaga caatttccaag accacgggtt atcttcaaat gaacagctgt 60
agagctgagg acactgttgt gtatttctgt gctaga                                96

SEQ ID NO: 298      moltype = length =
SEQUENCE: 298
000

SEQ ID NO: 299      moltype = DNA length = 33
FEATURE           Location/Qualifiers
misc_feature      1..33
source            note = Engineered antibody sequence
                  1..33
mol_type          other DNA
organism          synthetic construct

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SEQUENCE: 299
tggggccaag ggaccctcgtaaccgtctcg agc 33

SEQ ID NO: 300 moltype = DNA length = 993
FEATURE Location/Qualifiers
misc_feature 1..993
note = Engineered antibody sequence
source 1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 300
gcctccacca agggccccatc ggtttcccc ctggcacccct cctccaagag cacctctggg 60
ggcacagccg ccctgggtcg cctgtcaag gactacttc cccgaaccgggt gacgggtgtcg 120
tggaaactcgag cggccgtac cacaccccttc cggctgtct acagtcctca 180
ggactctact ccctcagcag cgtggtgacc gtggccctca gcagcttggg caccaggacc 240
tacactctgtca acgtgaatca caagcccagc aacaccaagg tggacaagag agttgagccc 300
aaatcttgtg aaaaaactctc cacaatccca cccgtggccag caccctactt cctggggggga 360
ccgtcagtcttcccttccccc aaaaacccc aaggacaccc teatgtatctc ccggaccct 420
gagggtcacat ggggtgggtgg gggatgtggc cacaaggacc ctggaggccaa qttcaactgg 480
tacgtggacg ggggtggaggt gcataatggc aagacaaagg cggggggagga gcaagtacgcc 540
agcacgtacc tggtgggtcg cgtgtccacc gtcctgcacc aggactggt gaatggcaag 600
gagttacaatg gcaagggtctc caacaatccca ctcccaagccccc ccatecgagaa aaccatctcc 660
aaaggccaaag gggcagccccc agaaccacag ggtgtacaccctt ccggggggag 720
atgaccaaga accagggttag cctgacccctc ctggtcaaaag gtttctatcc cagcgacatc 780
gcgggtggaggt gggagagcaa tggggcagccg gagaacaaactt acaagaccac gcctccctgg 840
ctggactccg acgggtcttcccttccctc agcaagcttac ccgtggacaa gggcagggtgg 900
cagcaggggaa acgttccctc atgtccctgtg atgcatgagg ctctgcacaa ccactacacg 960
cagaagggcc ttccctgtc tccgggtaaa tga 993

SEQ ID NO: 301 moltype = AA length = 219
FEATURE Location/Qualifiers
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 301
QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SREFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWVVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEHKHVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 302 moltype = AA length = 113
FEATURE Location/Qualifiers
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 302
QVLTQSPSSL SASVGDRVTI NCQASQSVYN YNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SREFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSTGDC FVFGGGTKVE IKR 113

SEQ ID NO: 303 moltype = AA length = 22
FEATURE Location/Qualifiers
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 303
QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 304 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 304
QASQSVYNN YLA 13

SEQ ID NO: 305 moltype = AA length = 15
FEATURE Location/Qualifiers
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein

-continued

organism = synthetic construct

SEQUENCE: 305
WYQQKPGKVP KQLIY 15

SEQ ID NO: 306 moltype = AA length = 7
FEATURE Location/Qualifiers
REGION 1..7
source note = Engineered antibody sequence
1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 306
STSTLAS 7

SEQ ID NO: 307 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
source note = Engineered antibody sequence
1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 307
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 308 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
source note = Engineered antibody sequence
1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 308
LGSYDCSTGD CFV 13

SEQ ID NO: 309 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
source note = Engineered antibody sequence
1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 309
FGGGTKVEIK R 11

SEQ ID NO: 310 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
source note = Engineered antibody sequence
1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 310
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC 106

SEQ ID NO: 311 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
source note = Engineered antibody sequence
1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 311
caagtgtctga cccaggtctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattggcagg ccagtctcgat tgtttacaat tacaactacc ttgcctggta tcagcagaaaa 120
ccaggaaagat ttcctaagca actgtatctat tctacatcca ctctggcatc tgggtcccc 180
tctcggttca gtggcagttg atctgggaca gatttcactcg tcaccatcg cagccgtcag 240
cctcagaatgt ttgcacttgat ggcagttatcg attgttagtc tggtgtatgt 300
tttgttttcg gcccggaaac caagggtggaa atcaaacgtt cgggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgagoagttg aaatctggaa ctgcctctgt tgggtgcctg 420
ctgaataact tctatccctc agaggccaaa gtacagtggaa aggtggataa cggccctccaa 480
tcgggtaaact cccaggagat tgtcacatcg caggacacac ctacagctc 540
agcagcaccc tgacgctgat caaaggccac tacggaaaac acaaagtcta cgcctgcgaa 600
gtcacccatc aggggctgat ctcggccgtc acaaaggagct tcaacagggg agagtgttag 660

SEQ ID NO: 312 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence

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source          1..339
               mol_type = other DNA
               organism = synthetic construct

SEQUENCE: 312
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtccagg tgtttacaat tacaactacc ttgcctggta tcagcagaaa 120
ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tgggtccta 180
tctcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgttagtac tggtgatgt 300
tttggggcggc gcccggggaa acagggtggaa atcaaacgtg 339

SEQ ID NO: 313      moltype = DNA  length = 66
FEATURE           Location/Qualifiers
misc_feature      1..66
note = Engineered antibody sequence
source            1..66
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 313
caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc             66

SEQ ID NO: 314      moltype = DNA  length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 314
caggccagtc agagtgttta caattacaac taccttgcc 39

SEQ ID NO: 315      moltype = DNA  length = 45
FEATURE           Location/Qualifiers
misc_feature      1..45
note = Engineered antibody sequence
source            1..45
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 315
tggtatcagc agaaaccagg gaaagttctt aagcaactga tctat 45

SEQ ID NO: 316      moltype = DNA  length = 21
FEATURE           Location/Qualifiers
misc_feature      1..21
note = Engineered antibody sequence
source            1..21
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 316
tctacatcca ctctggcatc t 21

SEQ ID NO: 317      moltype = DNA  length = 96
FEATURE           Location/Qualifiers
misc_feature      1..96
note = Engineered antibody sequence
source            1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 317
gggggtcccat ctcgtttcag tggcagttgg a tctgggacag atttcactt caccatcagc 60
agcctgcagc ctgaagatgt tgcaacttat tactgtg 96

SEQ ID NO: 318      moltype = DNA  length = 39
FEATURE           Location/Qualifiers
misc_feature      1..39
note = Engineered antibody sequence
source            1..39
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 318
ctgggcagtt atgattttag tacttgtat tgttttgtt 39

SEQ ID NO: 319      moltype = DNA  length = 33
FEATURE           Location/Qualifiers
misc_feature      1..33
note = Engineered antibody sequence
source            1..33
mol_type = other DNA

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organism = synthetic construct

SEQUENCE: 319
ttcggccggag gaaccaagggt ggaaatcaaaa cgt 33

SEQ ID NO: 320 moltype = DNA length = 321
FEATURE Location/Qualifiers
misc_feature 1..321
note = Engineered antibody sequence
source 1..321
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 320
acggtggctg caccatctgt ctcatcttc ccgcattctg atgaggcaggtaaaatcttggaa 60
actgcctctg ttgtgtgcgt gctgaataac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acgccttcca atcggttaac tcccaggaga gtgtcacaga gcaggacgc 180
aaggacacga cctacagcct cagcagcacc ctgacgctga gcaaaggcaga ctacgagaaa 240
cacaaggatctt accgcctgcga agtcacccat cagggcctga gtcgcggcgtt cacaaggagc 300
ttcaacacagggg gagagtgtta g 321

SEQ ID NO: 321 moltype = AA length = 439
FEATURE Location/Qualifiers
REGION 1..439
note = Engineered antibody sequence
source 1..439
mol_type = protein
organism = synthetic construct

SEQUENCE: 321
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS YYMQWVRQSP GRGLEWIGVI GSDGKTYYAT 60
WAKGRFTISK TSSTTVDLRM ASLTTEDTAT YFCTRGIWG PGTLVTVSSA STKGPSVFPL 120
APSSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSVSVTV 180
PSSSLGTQTY ICNVNHPKSN TKVDRKVEPK SCDKTHTCPPK CPAPELLGGP SVFLPPPKPK 240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VGVEVHNKA TKPREEQYAS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
VKGFYPSDIA VEWESNGQPE NNYKTPPPVLDSDGSFFFLYS KLTVDKSRWQ QGNVFSCSVM 420
HEALHNHYTQ KSLSLSPGK 439

SEQ ID NO: 322 moltype = AA length = 109
FEATURE Location/Qualifiers
REGION 1..109
note = Engineered antibody sequence
source 1..109
mol_type = protein
organism = synthetic construct

SEQUENCE: 322
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS YYMQWVRQSP GRGLEWIGVI GSDGKTYYAT 60
WAKGRFTISK TSSTTVDLRM ASLTTEDTAT YFCTRGIWG PGTLVTVSS 109

SEQ ID NO: 323 moltype = AA length = 29
FEATURE Location/Qualifiers
REGION 1..29
note = Engineered antibody sequence
source 1..29
mol_type = protein
organism = synthetic construct

SEQUENCE: 323
QSLEESGGRL VTPGTPLTLT CTVSGIGLSS 29

SEQ ID NO: 324 moltype = AA length = 5
FEATURE Location/Qualifiers
REGION 1..5
note = Engineered antibody sequence
source 1..5
mol_type = protein
organism = synthetic construct

SEQUENCE: 324 SYYMQ 5

SEQ ID NO: 325 moltype = AA length = 14
FEATURE Location/Qualifiers
REGION 1..14
note = Engineered antibody sequence
source 1..14
mol_type = protein
organism = synthetic construct

SEQUENCE: 325 WVRQSPGRGL EWIG 14

SEQ ID NO: 326 moltype = AA length = 16
FEATURE Location/Qualifiers

-continued

REGION	1..16
source	note = Engineered antibody sequence
	1..16
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 326	
VIGSDGKTYY ATWAKG	16
SEQ_ID_NO: 327	moltype = AA length = 31
FEATURE	Location/Qualifiers
REGION	1..31
source	note = Engineered antibody sequence
	1..31
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 327	
RFTISKTSST TVDLRMASLT TEDTATYFCT R	31
SEQ_ID_NO: 328	moltype = length =
SEQUENCE: 328	
000	
SEQ_ID_NO: 329	moltype = AA length = 11
FEATURE	Location/Qualifiers
REGION	1..11
source	note = Engineered antibody sequence
	1..11
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 329	
WGPGLTLVTVS S	11
SEQ_ID_NO: 330	moltype = AA length = 330
FEATURE	Location/Qualifiers
REGION	1..330
source	note = Engineered antibody sequence
	1..330
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 330	
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60	
GLYSLSVSVT VPSSSLGTQT YICVNHHPKS NTKVDKRVEP KSCDKTHTCP PCPAPELGG 120	
PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFWN VYDGVEVHNA KTKPREEQYA 180	
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240	
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300	
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK	330
SEQ_ID_NO: 331	moltype = DNA length = 1320
FEATURE	Location/Qualifiers
misc_feature	1..1320
source	note = Engineered antibody sequence
	1..1320
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 331	
catctcgctgg aggagtccgg gggtcgcctg qtcacgcctg ggacaccctt gacactcacc 60	
tgcacagtct ctggaaatcgg cctcaagtgc tactacatgc agtgggtccg ccagtctcca 120	
gggagggggc tggaaatggat cggagtattt ggttagtgcata gtaagacata ctacgcgacc 180	
tgggcgaaag gccgattcac catctcgatgc acctcgatgc ccacgggttgc tctgagaatg 240	
gccagtcgta caacccgaggc cacggccacc tattttctgtt ccagaggggc catctgggc 300	
ccggggaccc tcgtcaccgt ctgcgatgc tccaccaagg gcccattcggt ttccccctg 360	
gcaccctctt ccaaggagcc ctctggggcc acaggcccccc tgggctgcgtt ggtcaaggac 420	
tacttccccc aaccgggtgac ggttgcgttg aactcaggccg ccgttgcacccg cggcgtgcac 480	
accttccccc ctgttcatac gtcttcaggat ctctactcc tcagcagctt ggttgcgttg 540	
ccctcccgac gtttgggcac ccagacccatc atctgcacac tgaatcacaa gcccaccaac 600	
accaagggtgg acaagagagt tgagccaaa tcttgtgaca aaactcaccat atgcccaccc 660	
tgcccacac ctgaactctt cggggggccgg tcgttcttc tcttcccccc aaaacccaaag 720	
gacaccctca tgatctcccg gacccttcgat gtcacatgcg tgggtggta cgttgcaccc 780	
gaagaccctg aggtcaagtt caacttgcgtt gttggacggcc tggagggttca taatgcac 840	
acaaaggccgc gggaggaggca gtacgcccgg acgttccggg tgggtcagctt ccttccggc 900	
ctgcaccagg actggctgaa tggcaaggag tacaagtgcgat aggtctccaa caaaggccctc 960	
ccagcccccac tggagaaaaac catctccaaa gccaaaggcc accccccggaga accacagggt 1020	
tacaccctgc ccccatcccg ggaggagat accaagaacc aggtcagctt gacccgcctg 1080	
gtcaaaggctt tctatcccg cgatcatgcg tggagttgg agagcaatgg gcagccggag 1140	
aacaactaca agaccacggc tccctgtgtt gactccggac gtccttctt ccttctacac 1200	
aagctcaccg tggacaagag caggtggccg cagggggacg tcttctcatg ctccctgtatg 1260	
catgaggctc tgcacaacca ctacacgcgac aagacgcctt ccctgtctt gggtaatga 1320	
SEQ_ID_NO: 332	moltype = DNA length = 327

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FEATURE Location/Qualifiers
 misc_feature 1..327
 note = Engineered antibody sequence
 source 1..327
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 332
 cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccccct gacactcacc 60
 tgcacagtct ctggaatcgg cctcagtagt tactacatgc agtgggtccg ccagtctcca 120
 gggagggggc tggaaatggat cggagtcatt ggttagtgcata gtaagacata ctacgcgacc 180
 tggcgcaaaag gocgattcac catctccaag acctcgctcgaa ccacgggtgaa tctgagaatg 240
 gccagtgta caaccgagga cacggccacc tatttctgtt ccagagggga catctggggc 300
 cccggggacc tcgtcaccgt ctgcgac 327

SEQ ID NO: 333 moltype = DNA length = 87
 FEATURE Location/Qualifiers
 misc_feature 1..87
 note = Engineered antibody sequence
 source 1..87
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 333
 cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg ggacaccccct gacactcacc 60
 tgcacagtct ctggaatcgg cctcagtagt 87

SEQ ID NO: 334 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 334
 agtactaca tgcag 15

SEQ ID NO: 335 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 335
 tgggtccccc agtctccagg gagggggctg gaatggatcg ga 42

SEQ ID NO: 336 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 336
 gtcattggta gtgatggtaa gacatactac gcgacacctggg cgaaaaggc 48

SEQ ID NO: 337 moltype = DNA length = 93
 FEATURE Location/Qualifiers
 misc_feature 1..93
 note = Engineered antibody sequence
 source 1..93
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 337
 cgattcacca tctccaagac ctcgtcgacc acgggtggatc tgagaatggc cagtctgaca 60
 accggaggaca cggccaccta tttctgtacc aga 93

SEQ ID NO: 338 moltype = length =
 SEQUENCE: 338
 000

SEQ ID NO: 339 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 339
 tggggccccgg ggaccctcgat caccgtctcg agc 33

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SEQ ID NO: 340      moltype = DNA length = 993
FEATURE           Location/Qualifiers
misc_feature      1..993
source            note = Engineered antibody sequence
                  1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 340
gcctccacca agggcccatc ggtttcccc ctggcaccc cctcaagag cacctctggg 60
ggcacagcgg ccctggctg cctgtcaag gactacttc cgcgaaccgt gacgggtcg 120
tggaaactcg gcgcctgac cagcgggtg cacacccctc cggctgtct acagtcc 180
ggactctact ccctcagcg cgtgtgtacc gtgccctcca gcagcttggg caccaggacc 240
tacatctgc aacgtgaatca caagcccagg aadaccaagg tggacaagag agttggacc 300
aaatcttgtc aaaaaactca cacaatggccca ccgtgtcccg caccctgactt cctgggggg 360
ccgtcagtct tcctttccc cccaaaaccc aaggacacc tcataatgttc ccggggccct 420
gaggtcacat ggtgtgtgtt ggacgtgago cacaagagg ctgggttcaa gttaactgg 480
tacgtggacg cgtgtggagggt gcataatgc aagacaaggc cggggggaga gcagtacgcc 540
agcacgtacc gtgtgtttag cgtcttccac gtctgttggc accgtgttggc gaatggcaag 600
gagtacaagt gcaagggttcc caacaaaggcc ctcccaaggccc ccatacgagaa aaccatctcc 660
aaagccaaag ggcagccccc agaaccaccc ggttacaccc tgcccccattc ccggggaggag 720
atgaccaaga accaggatcg cctgttccatc ctgggttcaaagg gtttctatcc cagcgacatc 780
gccgtggagt gggagagcaa tggcagccg gagaacaact acaagaccac gcctccctgt 840
ctggactccg acggcttctt ctgcgttccatc agcaaggtca cctgtggacaa gaggcagggtt 900
cagcaggggaa acgttttctc atgttccatc atgttccatc ctgttccatc ccactacacg 960
cagaagggcc ttccttgc tccgggtaaa tga 993

SEQ ID NO: 341      moltype = AA length = 219
FEATURE           Location/Qualifiers
REGION            1..219
source            note = Engineered antibody sequence
                  1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 341
QVLQTQTPSPV SAAVGSTVTI NCQASQNLYNNYLAWSQQK PGQPPKQLIY STSTLASGVS 60
SRFRGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSRGDC FVFGGGTEVV VKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 342      moltype = AA length = 113
FEATURE           Location/Qualifiers
REGION            1..113
source            note = Engineered antibody sequence
                  1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 342
QVLQTQTPSPV SAAVGSTVTI NCQASQNLYNNYLAWSQQK PGQPPKQLIY STSTLASGVS 60
SRFRGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSRGDC FVFGGGTEVV VKR 113

SEQ ID NO: 343      moltype = AA length = 22
FEATURE           Location/Qualifiers
REGION            1..22
source            note = Engineered antibody sequence
                  1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 343
QVLQTQTPSPV SAAVGSTVTI NC 22

SEQ ID NO: 344      moltype = AA length = 13
FEATURE           Location/Qualifiers
REGION            1..13
source            note = Engineered antibody sequence
                  1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 344
QASQNLYNNN YLA 13

SEQ ID NO: 345      moltype = AA length = 15
FEATURE           Location/Qualifiers
REGION            1..15
source            note = Engineered antibody sequence
                  1..15
mol_type = protein
organism = synthetic construct

SEQUENCE: 345

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US 12,384,837 B2

159

160

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WYQQKPGQPP KQLIY

15

SEQ ID NO: 346 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 346
STSTLAS

7

SEQ ID NO: 347 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 347
GVSSRFRGSG SGTQFTLTIS DVQCDDAATY YC

32

SEQ ID NO: 348 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 348
LGSYDCSRGD CFV

13

SEQ ID NO: 349 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 349
FGGGTEVVVK R

11

SEQ ID NO: 350 moltype = AA length = 106
 FEATURE Location/Qualifiers
 REGION 1..106
 note = Engineered antibody sequence
 source 1..106
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 350
TVAAPSVIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSSLT LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 351 moltype = DNA length = 660
 FEATURE Location/Qualifiers
 misc_feature 1..660
 note = Engineered antibody sequence
 source 1..660
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 351
caagtgtga cccagactcc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
aattgccagg ccagtccagg tgtttataat aacaacttacc tagcttggta tcagcagaaaa 120
ccaggggcagc ctcccaagca actgtatctat tctacgttca ctctggcatc tggggctctca 180
tcgcgattca gaggcagtgg atctggaca cagttcactc tcaccatcag cgacgtgcag 240
tgtgacgatg ctggccactta ctactgtcta ggcagttatg attgttagtcg tggtgattgt 300
tttgttttcg gggggggcagg cgagggtggtg gtcaaaacgta cgggtggctgc accatctgtc 360
ttcatcttcc cgccatctga tgacgatgtt aaatctggta ctgcctctgt tggtgctcg 420
ctgaataact ttatcccag agggccaaa gtacagtggta aggtggataa cgcctccaa 480
tcgggtaact cccaggagag tgcacagag caggacagca aggacagcac ctacagctc 540
agcagcacc c tgcgcgtgag caaaggcagac tacgagaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggcctgag ctcgccccgtc acaaagagct tcaacaggaggg agagtgttag 660

SEQ ID NO: 352 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA

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organism = synthetic construct

SEQUENCE: 352
 caagtgtga cccagactcc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgccagg ccagtcaagaa tgtttataat aacaactacc tagcctggta tcagcagaaa 120
 ccaggcagc ctcccaagaac actgtatcat tctacgtcca ctctggatc tgggtctca 180
 tcgcgattca gaggcagtgg atctgggaca cagttcactc taccatcag cgacgtgcag 240
 tggtagcatg ctgcactta ctactgtcta ggcaatggat attgtatcg tggtgatgt 300
 ttgttttcg cgccggggac cgagggtggtg gtcaaacgt 339

SEQ ID NO: 353 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 353
 caagtgtga cccagactcc atccccgtg tctgcagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 354 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 354
 caggccagtc agaatgttta taataacaac tacctagcc 39

SEQ ID NO: 355 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 355
 tggtatcagc agaaaccagg gcagcctccc aagcaactga tctat 45

SEQ ID NO: 356 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 356
 tctacgtcca ctctggatc t 21

SEQ ID NO: 357 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 357
 ggggtctcat cgcgatttcag aggcaatggaa tctgggacac agttcaatct caccatcagc 60
 gacgtgcagt gtgacgtgc tgccacttac tactgt 96

SEQ ID NO: 358 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 358
 ctaggcaggat atgattgttag tcgtggatgat tgttttgtt 39

SEQ ID NO: 359 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 359

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ttcggcggag ggaccgaggt ggtggtcaaa cgt	33
SEQ ID NO: 360	moltype = DNA length = 321
FEATURE	Location/Qualifiers
misc_feature	1..321
	note = Engineered antibody sequence
source	1..321
	mol_type = other DNA
	organism = synthetic construct
SEQUENCE: 360	
acgtggcgtt caccatctgt ctcatcttc ccgcgcattgt atgagcaggtaa gaaatcttggaa 60	
actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120	
aagggtggata acggccctcca atcggttac tcccaggaga gtgtcacaga gcaggacacg 180	
aaggacagaca octacagccct cagcgcaccctt ctgacgcgtt gcaaagcaga ctacgagaaa 240	
cacaaggatctt acgcctgcgtt agtcacccat caggccgtt gctcgccgtt cacaaggagc 300	
ttcaacagggg gagagtgttta g 321	
SEQ ID NO: 361	moltype = AA length = 441
FEATURE	Location/Qualifiers
REGION	1..441
	note = Engineered antibody sequence
source	1..441
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 361	
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGIV IGSDGKTYA 60	
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRIDI WQQGTLVTVS SASTKGPSVF 120	
PLAPSSKSTS GGTAAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSVV 180	
TVPSSSLGQ TYICNVNHPK SNTKVDKRV PKSCDKTHTC PPCPAPELLG GPSVFLFPK 240	
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSVL 300	
TWLVHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360	
CLVKGFYPSD IAVEWESNGQ PENNYKTPPP VLSDGSPFL YSKLTVDKSR WQQGNVFSCS 420	
VMHEALHNHY TQKSLSLSPG K 441	
SEQ ID NO: 362	moltype = AA length = 111
FEATURE	Location/Qualifiers
REGION	1..111
	note = Engineered antibody sequence
source	1..111
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 362	
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS SYYMQWVRQA PGKGLEWVGIV IGSDGKTYA 60	
TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRIDI WQQGTLVTVS S 111	
SEQ ID NO: 363	moltype = AA length = 30
FEATURE	Location/Qualifiers
REGION	1..30
	note = Engineered antibody sequence
source	1..30
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 363	
EVQLVESGGG LVQPGGSLRL SCAVSGIGLS 30	
SEQ ID NO: 364	moltype = AA length = 5
FEATURE	Location/Qualifiers
REGION	1..5
	note = Engineered antibody sequence
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 364	
SYYMQ 5	
SEQ ID NO: 365	moltype = AA length = 14
FEATURE	Location/Qualifiers
REGION	1..14
	note = Engineered antibody sequence
source	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 365	
WVRQAPGKGL EWVG 14	
SEQ ID NO: 366	moltype = AA length = 16
FEATURE	Location/Qualifiers
REGION	1..16
	note = Engineered antibody sequence

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source	1..16	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 366		
VIGSDGKTYY ATWAKG		16
SEQ ID NO: 367	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
	note = Engineered antibody sequence	
source	1..32	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 367		
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC TR		32
SEQ ID NO: 368	moltype = length =	
SEQUENCE: 368		
000		
SEQ ID NO: 369	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
	note = Engineered antibody sequence	
source	1..11	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 369		
WGQGTLVTVS S		11
SEQ ID NO: 370	moltype = AA length = 330	
FEATURE	Location/Qualifiers	
REGION	1..330	
	note = Engineered antibody sequence	
source	1..330	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 370		
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS	60	
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG	120	
PSVFLFPKP KDLMISRTP EVTCVVVDWS HEDPEVKFWN YVDGVEVHNA KTKPREEQYA	180	
STYRVVSVLT VLHQDWLNGK EYKCKVSNAK LPAPIEKTS KAKGQPREPQ VYTLPSSREE	240	
MTKNQVSLTC LVKGFYPSDI AWEVESNQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	300	
QQGNVVFSCSV MHEALHNHYT QKSLSLSPGK	330	
SEQ ID NO: 371	moltype = DNA length = 1326	
FEATURE	Location/Qualifiers	
misc_feature	1..1326	
	note = Engineered antibody sequence	
source	1..1326	
	mol_type = other DNA	
	organism = synthetic construct	
SEQUENCE: 371		
gaggtgcagc ttgtggagtc tgggggaggc ttgggtccagc ctggggggtc cctgagactc	60	
tccctgtcag tctctggaat cggcctcagt agtactaca tgcaatgggt ccgtcaggt	120	
ccaggaaagg ggctggagtg ggtcgagtc atggtaqgt atggtaaacat atactacgct	180	
acctggcgca aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt	240	
caaataaaca gctgtggagc tgaggactact gctgtatgt tctgttaccag aggggacatc	300	
tggggccaag ggacccctgt caccgtctcg agetcctcca ccaaggccc atcggcttcc	360	
cacctggcac cttctcccaa gagacctctt gggggcacaag cggccctggg ctgctgtc	420	
aaggactact tccccgaacc ggtgacgggt tcgtggaaact caggcgcctt gaccaggcgc	480	
gtgcacacact tcccggtctgt cctcagaatcc tcaggactct actccctcag cagcgtgt	540	
accgtgcctc ccaggcggctt gggccacccag acctacatcg gcaacgtgaa tcacaaggccc	600	
agcaacaccaa aggtggacaa gagatgttag cccaaatctt gtgacaaaac tcacacatgc	660	
ccaccgtgcc cagcacctga actctgggg ggaccgtcaat tcttcctt ccccccaaaa	720	
cccaaggaca ccctcatgtat ctcgggacc cctgaggatca catcgcttgt ggtggacgt	780	
agccacaaag accctggatgt caatcgatgttggatcgatggcgttgc ggtgcataat	840	
gcaagacaa agcccgccggaa ggacgttac gccacgttgc accgtgttgtt cagcgtctc	900	
accgtcttcg accaggactg gctaatggc aagggttaca agtgcgttgtt ctccaaacaaa	960	
gcccctcccg ccccccattca gaaaaccatc tccaaagccca aaggccggcc ccgagaacca	1020	
cagggtgtaca ccctggggcc atccgggag gagatgtacca agaaccatgtt cagcgttgc	1080	
tgcctggatca aaggcttcta tccccggcgttgc atccggcgttgc aatggggcgttgc	1140	
ccggagaaca actacaagac cacgttcccg tggatcgatgttgc accgttgttcc	1200	
taacgttgcgttcaacccgttgcgaaatggatgttgc tccatgttgc	1260	
gtgtatgttgc aaggcttgc caaccactac acgcagaaga gatgttgcgttgc	1320	
aaatgttgc	1326	
SEQ ID NO: 372	moltype = DNA length = 333	
FEATURE	Location/Qualifiers	

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misc_feature      1..333
                  note = Engineered antibody sequence
source           1..333
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 372
gaggtgcagc ttgtggagtc tggggggaggo ttgggtccagc ctgggggggtc cctgagactc 60
tcctgtgcag tctctggaat cggcctcagt agctactaca tgcaatgggt ccgtcaggct 120
ccaggaaagg ggctggagtg ggctggagtg atggtagtg atggtaaagac atactacgct 180
acctggcgatt caccatctcc agagacaattt ccaagaccac ggtgttatctt 240
caaataacaac gctgtggagtc tgaggacact gctgttatctt tggttaccac aggggacatc 300
tggggccaag ggaccctcgat caccgtctcg agc 333

SEQ ID NO: 373      moltype = DNA length = 90
FEATURE
misc_feature      1..90
                  note = Engineered antibody sequence
source           1..90
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 373
gaggtgcagc ttgtggagtc tggggggaggo ttgggtccagc ctgggggggtc cctgagactc 60
tcctgtgcag tctctggaat cggcctcagt 90

SEQ ID NO: 374      moltype = DNA length = 15
FEATURE
misc_feature      1..15
                  note = Engineered antibody sequence
source           1..15
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 374
agctactaca tgcaa 15

SEQ ID NO: 375      moltype = DNA length = 42
FEATURE
misc_feature      1..42
                  note = Engineered antibody sequence
source           1..42
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 375
tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 376      moltype = DNA length = 48
FEATURE
misc_feature      1..48
                  note = Engineered antibody sequence
source           1..48
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 376
gtcattggta gtgatggtaa gacataactac gcgacacctggc cgaaaggc 48

SEQ ID NO: 377      moltype = DNA length = 96
FEATURE
misc_feature      1..96
                  note = Engineered antibody sequence
source           1..96
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 377
cgatttcacca tctccagaga caattccaaag accacgggtgt atcttcaaat gaacagcctg 60
agagctgagg acactgctgt gtatttctgt accaga 96

SEQ ID NO: 378      moltype = length =
SEQUENCE: 378
000

SEQ ID NO: 379      moltype = DNA length = 33
FEATURE
misc_feature      1..33
                  note = Engineered antibody sequence
source           1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 379
tggggccaag ggaccctcgat caccgtctcg agc 33

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SEQ ID NO: 380 moltype = DNA length = 993
 FEATURE Location/Qualifiers
 misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 380
 gcctccacca agggccatc ggttccccc ctggcaccc cttccaaagg cacctctggg 60
 ggcacagccg ccctggctg cctggtaag gactacttc cggaaagggt gacgggtgtcg 120
 tggaaacttag cggccctgac cagggcgctg cacaccccttc cggctgtct acagtcccta 180
 ggactctact ccctcagcag cgtgtgacc gtgccttcca gcagcttggg caccaggacc 240
 tacatctgca accgtaaatca caagccca gaccaaggaa tggacaaggag agttgagccc 300
 aaatcttgtt aaaaaatca cacatggcca cctgtggccaa cacttgaact cctgggggga 360
 ccgtcagtct tccttctccc cccaaaaccc aaggacaccc tcatgtatctc ccggaccct 420
 gaggtcataat gctgtgggtt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
 tacgtggacg gctgtggatg gcataatgcc aagacaaaagg cgcgggaggaa gcagtgaccc 540
 agcacgtacc gtgtggtagc cgttccatcc gtcctgcacc aggactgggt gaatggcaag 600
 gagaatcataatg gcaagggtctc caaaaaaggcc cttccagcccc ccategagaa aaccatctcc 660
 aaaggccaaag ggcagccccg agaaccacag gtgtacacc tgccccatc ccgggaggag 720
 atgaccaaga accagggttag cctgacccgtc ctggtaaaag gtttctatcc cagegacatc 780
 gccgtggagt gggagagcaa tgggcagccg gagaacaact acaagaccac gcctccctg 840
 ctggactccg acggctcttcc tcctcttac agcaagtcac cctgtggacaa gagcaggatgg 900
 cagcaggggaa acgttcttc atgtccgtg atgcattggg ctctgcacaa ccactacacg 960
 cagaagagcc ttccctgtc tccgggtaaa tga 993

SEQ ID NO: 381 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 381
 QVLTQSPSSL SASVGDRVTI NCQASQNVYN NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
 FIPPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRRGEC 219

SEQ ID NO: 382 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 382
 QVLTQSPSSL SASVGDRVTI NCQASQNVYN NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR 113

SEQ ID NO: 383 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 383
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 384 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 384
 QASQNVYNNN YLA 13

SEQ ID NO: 385 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 385
 WYQQKPGKVP KQLIY 15

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SEQ ID NO: 386 moltype = AA length = 7
 FEATURE Location/Qualifiers
 REGION 1..7
 note = Engineered antibody sequence
 source 1..7
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 386
 STSTLAS 7

SEQ ID NO: 387 moltype = AA length = 32
 FEATURE Location/Qualifiers
 REGION 1..32
 note = Engineered antibody sequence
 source 1..32
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 387
 GPSPSRFSGSG SGTDFTLTIS SLQPEDVATY YC 32

SEQ ID NO: 388 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 388
 LGSYDCSRGD CFV 13

SEQ ID NO: 389 moltype = AA length = 11
 FEATURE Location/Qualifiers
 REGION 1..11
 note = Engineered antibody sequence
 source 1..11
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 389
 FGGGTTKVEIK R 11

SEQ ID NO: 390 moltype = AA length = 106
 FEATURE Location/Qualifiers
 REGION 1..106
 note = Engineered antibody sequence
 source 1..106
 mol_type = protein
 organism = synthetic construct
 SEQUENCE: 390
 TVAAPSVIF PPSDEQLKG TASVVCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
 KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 391 moltype = DNA length = 660
 FEATURE Location/Qualifiers
 misc_feature 1..660
 note = Engineered antibody sequence
 source 1..660
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 391
 caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattggcagg ccagtcacatcg ttttgcacatcg aacaactacc tagcctggta tcagcggaaa 120
 ccaggaaag ttccataagca actgtatcatcg ttttgcacatcg ctctggcata tggggtcaca 180
 ttccgttcca gtggcagttgg atctgggaca gatttcactc tcacccatcg cagccgtcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg attttagtgc tggtgtatgt 300
 ttgttttcg gcccggggaaac caagggtggaa atcaaacgtt cgggtggctgc accatctgtc 360
 ttcatctcc cggccatctca tgaggatgg aaatctggaa ctgcctctgt tggtgtgcgt 420
 ctgaataact tttatcccg agaggccaaa gtacaggatggaa aggtggataa cgccctccaa 480
 tcgggttaact cccaggagag tgtcacatcg cggacacatcg aggacacac ctacagctc 540
 agcagcaccc tgacgttgatgg caaaggatgg tacgagaaac acaaagtcta cggctcgaa 600
 gtcacccatc agggccttgatgg ctcggccgttca acaaaggatgg agagtgttag 660

SEQ ID NO: 392 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

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SEQUENCE: 392
caagtgcgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa 120
ccagggaaag ttccctaagca actgatctat tctacatcca ctctggcatc tggggtccta 180
tctcgttca gtggcagttgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
cctgaagatg ttgcaactta ttactgtctg ggcagttatg attgtatcg tggtgtatgt 300
tttgttttcg goggaggaac caaggtggaa atcaaaccgt 339

SEQ ID NO: 393 moltype = DNA length = 66
FEATURE Location/Qualifiers
misc_feature 1..66
 note = Engineered antibody sequence
source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 393
caagtgcgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
aattgc 66

SEQ ID NO: 394 moltype = DNA length = 39
FEATURE Location/Qualifiers
misc_feature 1..39
 note = Engineered antibody sequence
source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 394
caggccagtc agaatgttta caataacaac taccttagcc 39

SEQ ID NO: 395 moltype = DNA length = 45
FEATURE Location/Qualifiers
misc_feature 1..45
 note = Engineered antibody sequence
source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 395
tggtatcagc agaaaccagg gaaagttcct aagcaactga tctat 45

SEQ ID NO: 396 moltype = DNA length = 21
FEATURE Location/Qualifiers
misc_feature 1..21
 note = Engineered antibody sequence
source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 396
tctacatcca ctctggcatc t 21

SEQ ID NO: 397 moltype = DNA length = 96
FEATURE Location/Qualifiers
misc_feature 1..96
 note = Engineered antibody sequence
source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 397
ggggtcccat ctgcgttcag tggcagtgg a tctgggacag atttcactct caccatcagc 60
agectgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 398 moltype = DNA length = 39
FEATURE Location/Qualifiers
misc_feature 1..39
 note = Engineered antibody sequence
source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 398
ctgggcagtt atgattgttag tcgtggat tgttttgtt 39

SEQ ID NO: 399 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
 note = Engineered antibody sequence
source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 399
ttcggcggag gaaccaaggt ggaaatcaaa cg 33

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SEQ ID NO: 400      moltype = DNA length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
note = Engineered antibody sequence
source           1..321
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 400
acggtgtggctg caccatctgt ctcatcttc ccgcgcattcg atgaggcgtt gaaatcttga 60
actgcctctg ttgtgtgcct gctaataac ttttatccca gagaggccaa agtacagtgg 120
aagggtggata acggccctcca atcgggttaac tcccaggaga gtgtcacaaga gcaggacagc 180
aaggacacgca cttacagcct cagcagcacc ctgacgctga gcaaagcaga ctacqgaaa 240
cacaaggatc acggctgcga agtccacccat cagggcgtga gtcgcggcgt cacaaggagc 300
ttcaaacaggg gagagtgtta g 321

SEQ ID NO: 401      moltype = AA length = 439
FEATURE          Location/Qualifiers
REGION           1..439
note = Engineered antibody sequence
source           1..439
mol_type = protein
organism = synthetic construct
SEQUENCE: 401
QSLEESGGRL VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS 60
WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSSA STKGPSVFPPL 120
APSSSKSTSGG TAALGLVLKD YFPEPVTVSW NSGALTSGVH TPPAVLQSSG LYSLSSVVTV 180
PSSSLGTQTY ICNVINHKPSN TKVDKRVEPK SCDKTHTCPV CPAPPELLGGP SVFLFPPKPK 240
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAAK TKPREEQYAS TYRVVSVLTV 300
LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSREEM TKNQVSLTCL 360
VKGFYPSDIA VEWESENQPE NNYKTTPPPVL DSDGSFFFLYS KLTVDKSRWQ QGNVFSCVM 420
HEALHNYHTQ KSLSLSPGK 439

SEQ ID NO: 402      moltype = AA length = 109
FEATURE          Location/Qualifiers
REGION           1..109
note = Engineered antibody sequence
source           1..109
mol_type = protein
organism = synthetic construct
SEQUENCE: 402
QSLEESGGRL VTPGGSLTLT CTVSGIDVTN YYMQWVRQAP GKGLEWIGVI GVNGKRYYAS 60
WAKGRFTISK TSSTTVDLKM TSLTTEDTAT YFCARGDIWG PGTLVTVSS 109

SEQ ID NO: 403      moltype = AA length = 29
FEATURE          Location/Qualifiers
REGION           1..29
note = Engineered antibody sequence
source           1..29
mol_type = protein
organism = synthetic construct
SEQUENCE: 403
QSLEESGGRL VTPGGSLTLT CTVSGIDVTN 29

SEQ ID NO: 404      moltype = AA length = 5
FEATURE          Location/Qualifiers
REGION           1..5
note = Engineered antibody sequence
source           1..5
mol_type = protein
organism = synthetic construct
SEQUENCE: 404
NYYMQ 5

SEQ ID NO: 405      moltype = AA length = 14
FEATURE          Location/Qualifiers
REGION           1..14
note = Engineered antibody sequence
source           1..14
mol_type = protein
organism = synthetic construct
SEQUENCE: 405
WVRQAPGKGL EWIG 14

SEQ ID NO: 406      moltype = AA length = 16
FEATURE          Location/Qualifiers
REGION           1..16
note = Engineered antibody sequence
source           1..16

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mol_type = protein
organism = synthetic construct

SEQUENCE: 406
VIGVNGKRYY ASWAKG                                         16

SEQ ID NO: 407      moltype = AA length = 31
FEATURE
REGION           Location/Qualifiers
1..31
note = Engineered antibody sequence
source            1..31
mol_type = protein
organism = synthetic construct

SEQUENCE: 407
RFTISKTSST TVDLKMTSLT TEDTATYFCA R                         31

SEQ ID NO: 408      moltype = length =
SEQUENCE: 408
000

SEQ ID NO: 409      moltype = AA length = 11
FEATURE
REGION           Location/Qualifiers
1..11
note = Engineered antibody sequence
source            1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 409
WGPGTIVTVS S                                              11

SEQ ID NO: 410      moltype = AA length = 330
FEATURE
REGION           Location/Qualifiers
1..330
note = Engineered antibody sequence
source            1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 410
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICNVNHPKS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTI KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESENQGP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                           330

SEQ ID NO: 411      moltype = DNA length = 1320
FEATURE
misc_feature       Location/Qualifiers
1..1320
note = Engineered antibody sequence
source             1..1320
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 411
cagtcgtgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
tgcacagtct ctggaaatcgca cgtcaactaac tactatatcg aatgggtccg ccaggctcca 120
gggaaggggc tggaaatggat cggatctt ggtgtaaatg gtaagagata ctacgcgagc 180
tggcgaaag gcccattcac catctccaaa acctcgtcgca ccacggtgaa tctgaaaatg 240
accatgtcgaa caaccgagga cacggccacc tatttctgtt ccacggggca catctggggc 300
ccggggaccctt ctgtcaccgtt ctggacgc accccatcggt ctteccccctg 360
gcacccttcc ctcaagagac ctctggggcc acagcggccg tgggtcgctt ggtcaaggac 420
tacttccccc aaccgggtac ggtgtcggtt aactcggccg ccctgaccag cggcggtcac 480
accttccccc ctgtccatca gtcctcggaa ctctactccc teacgcgggtt ggtgaccgtt 540
ccctccacca gtttggggcac ccacgttaccat atctgcacatc tgaatcacaac gcccac 600
accaaagggtgg acaaaaggatg tgagccccaa tcttgcacaa aactcacaat atgcccacccg 660
tgcccgacat ctgaactctt cttttggggaccg tcagttttcc tttttcccccc aaaaccccaag 720
gacaccctca tgatctcccg gaccccttag gtcacatcgcc tgggtgggtt cgtgacccac 780
gaagaccctg aggtcaagtt caactgggtac gtggacccggc tggaggatgca taatgccaag 840
acaaaggccgc gggaggagca gtacggccac acgttacccgtt tgggtcgctt ccttacccgtt 900
ctgcacccagg actgggtggaa tggcaaggag tacaaggatcgca aggtctccaa caaaggccctc 960
ccagccccca ttggaaaaac catctccaaa gccaaggccg acccccgaga accacagggtt 1020
tacaccctgc ccccatcccg ggaggagatg accaagaacc aggtcagctt gacccgtctg 1080
gtcaaaggctt tctatcccg cgacatcgcc gtggaggatgg agagcaatgg gcagccggag 1140
aacaactaca agaccacggcc tccctgtgtt gactccgacg gtccttctt ccttacaccg 1200
aagctcaccg tggacaagag cagggtggcag caggggaaacg tcttctcatg ctccgtgtatg 1260
cataggctc tgcacaacca ctacacgcgaa aagacccctt ccctgtctt gggtaaatga 1320

SEQ ID NO: 412      moltype = DNA length = 327
FEATURE
misc_feature       Location/Qualifiers
1..327
note = Engineered antibody sequence

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source 1..327
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 412
cagtcgtctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
tgcacagtct ctggaatcga cgtcaactac tactatatgc aatgggtccg ccaggctcca 120
ggaaaggggc tggaaatggat cgaggatcatt ggtgtgaatg gtaagagata ctacgcgac 180
tgggcgaaag gccgattcac catctccaaa acctcgtcga ccacgggtgga tctgaaaatg 240
accagtctga caacccgagga cacggccaco tatttctgtg ccagaggcga catctgggc 300
ccggggacc ctcgtaccgt ctcgagc 327

SEQ ID NO: 413 moltype = DNA length = 87
FEATURE Location/Qualifiers
misc_feature 1..87
note = Engineered antibody sequence
source 1..87
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 413
cagtcgtctgg aggagtccgg gggtcgcctg gtcacgcctg gaggatccct gacactcacc 60
tgcacagtct ctggaatcga cgtcaact 87

SEQ ID NO: 414 moltype = DNA length = 15
FEATURE Location/Qualifiers
misc_feature 1..15
note = Engineered antibody sequence
source 1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 414
aactactata tgcaa 15

SEQ ID NO: 415 moltype = DNA length = 42
FEATURE Location/Qualifiers
misc_feature 1..42
note = Engineered antibody sequence
source 1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 415
tgggtccccc aggctccagg gaaggggctg gaatggatcg ga 42

SEQ ID NO: 416 moltype = DNA length = 48
FEATURE Location/Qualifiers
misc_feature 1..48
note = Engineered antibody sequence
source 1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 416
gtcattggtg tgaatggtaa gagataactac gcgagctggg cgaaaggc 48

SEQ ID NO: 417 moltype = DNA length = 93
FEATURE Location/Qualifiers
misc_feature 1..93
note = Engineered antibody sequence
source 1..93
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 417
cgattcacca tctccaaaac ctcgtcgacc acgggtggatc tgaaaaatgac cagtctgaca 60
accgaggaca cggccaccta tttctgtgcc aga 93

SEQ ID NO: 418 moltype = length =
SEQUENCE: 418
000

SEQ ID NO: 419 moltype = DNA length = 33
FEATURE Location/Qualifiers
misc_feature 1..33
note = Engineered antibody sequence
source 1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 419
tggggccccgg ggacctctcg caccgtctcg agc 33

SEQ ID NO: 420 moltype = DNA length = 993
FEATURE Location/Qualifiers

-continued

misc_feature 1..993
 note = Engineered antibody sequence
 source 1..993
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 420
 gcctccacca agggcccatc ggtttcccc ctggcaccc cctccaagag cacctctggg 60
 ggcacagcgg ccctgggctg cctggtaag gactacttc cgcgaccgtt gacgggttcg 120
 tggaaacttag ggcgcctgac cagggcgctg cacacccctt cggctgtctt acagtccctca 180
 ggactctact ccctcagcag cgttgcgtacc gtgccttcga gcaagcttggg caccaggacc 240
 tacatctgca acgttaaatca caagccca aacccaagg tggacaagg agttgaggccc 300
 aaatcttg acaaactca cacatgcca cctggccca cctgttggg caccgttactt cctgggggg 360
 cctgttggat ttcttcccccc cccaaaaccc aaggacaccc tcattatctt cccggaccct 420
 gaggttccat cgcgttgggtt ggacgttggacat cagaagaccc ctgggttcaat gttcaactgg 480
 tacgttggacg ggcgttggat gtcataatgcc aagacaaacg cgcggggaggga gcaagtacgcc 540
 agcacgtacc gtgttgcgtt cgttccatcc gtccttcacc aggactggct gaatggcaag 600
 gatgtacaatg gcaagggtctc caaacaaggcc ctcccaaggcc ccatecgagaa aaccatctcc 660
 aaagccaaag ggcaggcccg agaaccacag gtgtacacc tggccatcc cccggggaggag 720
 atgaccaaga accaggatccat cctgttggat ttcttccatcc cccgggggggg 780
 gccgttggat gggagagaa tggcagccg gagaacaact acaagaccac gcttccctgt 840
 ctggactccg acggcttccctt cttcttctac agcaagctca cctggacaa gaggagggtt 900
 cagcaggggg acgttccatcc atgtccgtt atgcatggg ctgttccatcc ccaactacacg 960
 cagaagagcc ttccctgttccatcc tccgggtaaa tga 993

SEQ ID NO: 421 moltype = AA length = 219
 FEATURE Location/Qualifiers
 REGION 1..219
 note = Engineered antibody sequence
 source 1..219
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 421
 QVLQTQASPV SPAVGSTVTI NCRASQSVYY NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
 SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSNGDC FVFGGGTEVV VKRTVAAPSV 120
 FIPPPSDEQL KSGTASVVCN LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC 219

SEQ ID NO: 422 moltype = AA length = 113
 FEATURE Location/Qualifiers
 REGION 1..113
 note = Engineered antibody sequence
 source 1..113
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 422
 QVLQTQASPV SPAVGSTVTI NCRASQSVYY NNYLAWYQQK PGQPPKQLIY STSTLASGVS 60
 SRFKGSGSGT QFTLTISDVQ CDDAATYYCL GSYDCSNGDC FVFGGGTEVV VKR 113

SEQ ID NO: 423 moltype = AA length = 22
 FEATURE Location/Qualifiers
 REGION 1..22
 note = Engineered antibody sequence
 source 1..22
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 423
 QVLQTQASPV SPAVGSTVTI NC 22

SEQ ID NO: 424 moltype = AA length = 13
 FEATURE Location/Qualifiers
 REGION 1..13
 note = Engineered antibody sequence
 source 1..13
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 424
 RASQSVYYNN YLA 13

SEQ ID NO: 425 moltype = AA length = 15
 FEATURE Location/Qualifiers
 REGION 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 425
 WYQQKPGQPP KQLIY 15

SEQ ID NO: 426 moltype = AA length = 7

-continued

FEATURE Location/Qualifiers
REGION 1..7
note = Engineered antibody sequence
source 1..7
mol_type = protein
organism = synthetic construct

SEQUENCE: 426
STSTLAS 7

SEQ ID NO: 427 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 427
GVSSRFKGSG SGTQFTLTIS DVQCDDAATY YC 32

SEQ ID NO: 428 moltype = AA length = 13
FEATURE Location/Qualifiers
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 428
LGSYDCSNGD CFV 13

SEQ ID NO: 429 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 429
FGGGTEVVVK R 11

SEQ ID NO: 430 moltype = AA length = 106
FEATURE Location/Qualifiers
REGION 1..106
note = Engineered antibody sequence
source 1..106
mol_type = protein
organism = synthetic construct

SEQUENCE: 430
TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS 60
KDSTYSLSS LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 431 moltype = DNA length = 660
FEATURE Location/Qualifiers
misc_feature 1..660
note = Engineered antibody sequence
source 1..660
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 431
caggtgctga cccagactgc atcccccggt tctccagctg tgggaagcac agtcaccatc 60
aattgcgggg ccagtcaagat tgtttattat aacaactacc tagcctggta tcagcagaaa 120
ccagggcagc ctcccaagca actgtatctat tctacatcca ctctggcatc tgggtctca 180
tcgcgggtca aaggcagttg atctggggaca cagttcaactc tcaccatcag cgacgtgcag 240
tgtgacgtatg ctggccatca ctactgtcta ggcagttatg attgttagaa tggtgatgt 300
tttggtttcg gggggggac cgagggttgc gtcaaacgtt cgggtgcgc accatctgtc 360
ttcatcttcc cgccatctga tgagoagttt aaatctggaa ctgcctctgt tggtgctgt 420
ctgaataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa 480
tcgggttaact cccaggagag tgtcacagag caggacacgac ctacagcctc 540
agcagcaccc tgacgctgag caaagcagac tagggaaaac acaaagtcta cgcctgcgaa 600
gtcacccatc agggccttagt ctgcggcgtc acaaagggc agagtgttag 660

SEQ ID NO: 432 moltype = DNA length = 339
FEATURE Location/Qualifiers
misc_feature 1..339
note = Engineered antibody sequence
source 1..339
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 432
caggtgctga cccagactgc atcccccggt tctccagctg tgggaagcac agtcaccatc 60

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aattgccggg ccagtccagag tggtttattat aacaactacc tagcctggta tcagcagaaa 120
 ccaggccggc ctcccaagca actgtatcat tctacatcca ctctggcatc tggggctca 180
 tcgcgggtca aaggcagtgaa atctgggaca cagttcactc tcaccatcag cgacgtgcag 240
 tgtgacgtg ctgccactt caactgtcta ggcagttatg attgttagtaa tggtgattgt 300
 ttgttttcg gggggggac cgagggtggtg gtcaaacgt 339

SEQ ID NO: 433 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 433
 caggtgtcga cccagactgc atccccgtg tctccagctg tgggaagcac agtcaccatc 60
 aattgc 66

SEQ ID NO: 434 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 434
 cggggccagtc agagtgttta ttataacaac tacctagcc 39

SEQ ID NO: 435 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 435
 tggtatcagc agaaaaccagg gcagcctccc aagcaactga tctat 45

SEQ ID NO: 436 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 436
 tctacatcca ctctggcatc t 21

SEQ ID NO: 437 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 437
 ggggtctcat cgccgggtcaa aggcaagtggaa tctgggacac agttcactct caccatcagc 60
 gacgtgcagt gtgacgtgc tgccacttac tactgt 96

SEQ ID NO: 438 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 438
 cttaggcagtt atgattgttag taatggtgat tgttttgtt 39

SEQ ID NO: 439 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct
 SEQUENCE: 439
 ttccggcgag ggaccggaggt ggtggtcaaa cgt 33

SEQ ID NO: 440 moltype = DNA length = 321

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FEATURE Location/Qualifiers
 misc_feature 1..321
 note = Engineered antibody sequence
 source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 440
 acgggtggctg caccatctgt ctcatcttc ccgcacatctg atgagcaggaaatcttga 60
 actgcctctg ttgtgtccct gctgataaac tttatccca gagaggccaa agtacatgg 120
 aagggtggata acggcctcca acggatataac tcccaggaga gtgtcacaga gcaggacagc 180
 aaggacacca cttacacgctt cttacacgctt gcaaaacgaca ctacqagaaa 240
 cacaaggatct acgcctgcga agtcacccat cttacacgctt gtcgcggcgat cacaaggagc 300
 ttcaacaggagactt 321

SEQ ID NO: 441 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence
 source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 441
 EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMHQWVRQA PGKGLEWVGIVGVNGKRYVA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS CGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAPVLQS SGLYSLSSVV 180
 TVPSSSLGQ TYICCNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 240
 PKDTLMISRT PEVTCVVVDV SHEDPEVKPN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSPFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 442 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 442
 EVQLVESGGG LVQPGGSLRL SCAVSGIDVT NYYMHQWVRQA PGKGLEWVGIVGVNGKRYVA 60
 SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WGQGTLVTVS S 111

SEQ ID NO: 443 moltype = AA length = 30
 FEATURE Location/Qualifiers
 REGION 1..30
 note = Engineered antibody sequence
 source 1..30
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 443
 EVQLVESGGG LVQPGGSLRL SCAVSGIDVT 30

SEQ ID NO: 444 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 444
 NYYMQ 5

SEQ ID NO: 445 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 445
 WVRQAPGKGL EWVG 14

SEQ ID NO: 446 moltype = AA length = 16
 FEATURE Location/Qualifiers
 REGION 1..16
 note = Engineered antibody sequence
 source 1..16
 mol_type = protein
 organism = synthetic construct

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SEQUENCE: 446
VIGVNGKRYY ASWAKG 16

SEQ ID NO: 447 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 447 RFTISRDNSK TTVYLQMNSL RAEDTAVYFC AR 32

SEQ ID NO: 448 moltype = length =

SEQUENCE: 448 000

SEQ ID NO: 449 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 449 WQQGTLVTVS S 11

SEQ ID NO: 450 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 450 ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGEVHNA KTKPREEQYA 180
STYRVRVSVLT VLHQDWLNKG EYKCKVSNSKA LPAPIEKTSI KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFPYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 451 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 451 gagggtcagc ttgtggagtc tggggggggc ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcag tctctggaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgagtc attgggtgta atggtaagag atactacgcg 180
agctggcaga aaggccgatt caccatctcc agagacaat ccaagaccac ggtgtatctt 240
caaataatgaa cccctggatc tgaggacact gctgtgtatt tctgtgcacg aggggacatc 300
tggggccaag ggacccctcg tcccgatccg acggccctca ccaaggcccc atccgtcttc 360
cccctggcac cctcctccaa gagcacctct gggggccacac cggccctggg ctgcctggtc 420
aaggactact tcccgaaacc ggtgacgggtg tcgttggaaact cagggccctt gaccagccgc 480
gtgcacacact ccccggtgtg cctacagtcc tcaggactact aetccttcag cagcgtggtg 540
accgtgcctt ccagcagctt gggccacccatc acctacatctt gcaacgtgaa tcacaagccc 600
agcaacacca aagggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagccatctt actcttgggg ggaccgtcaag tcttcctt ccccccaaaa 720
cccaaggaca ccctcatgtat ctcggggatc cctggggatc catcgctgtt ggtggacgtg 780
agccacaaag accctggatc caatgttccaa tggttacgttg acggccgtt ggtgcataat 840
gccaagacaa agccggggga ggagcgtac gccagcacgtt accgtgtgtt cagcgtcttc 900
accgtccctc accaggactt gctgaatggc aaggaggatc aagtgcacgtt ctccaaacaaa 960
gcgcctcccg ccccatcgaa gaaaaccatc tccaaagccaa aaggccggcc cccgaaacca 1020
cagggtgtaca ccctggggcc atccggggatc gagatgtacca agaaccaggat cagcgttgcacc 1080
tgccctgttca aaggcttcttca tcccgatgtt atccgggttgg agtggggatc caatggccag 1140
ccggagaaca actacaagac cacgttccca gtgtgttgc acggccgtt cttttcttc 1200
tacagcaagc tcaccgttgcgaa caagagcagg tggcagcagg ggaacgtt ctcatgttcc 1260
gtgtatgtatc aggtcttgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
aatatga 1326

SEQ ID NO: 452 moltype = DNA length = 333
FEATURE Location/Qualifiers
misc_feature 1..333
note = Engineered antibody sequence
source 1..333

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mol_type = other DNA
organism = synthetic construct

SEQUENCE: 452
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcgag tctctggaat cgacgtcaact aactactaca tgcaatgggt ccgtcaggct 120
ccagggaaagg ggctggagtg ggtcgaggatc attgggtgtga atggtaagag atatacgcg 180
agctgggcga aaggccgatt caccatctcc agagacaatt ccaagaccac ggtgtatctt 240
caaataatgaaca ggctgagagc tgaggacact gctgtgtatt tctgtggccag aggggacatc 300
tggggccaag ggaccctcgat caccgtctcg agc 333

SEQ ID NO: 453      moltype = DNA length = 90
FEATURE             Location/Qualifiers
misc_feature        1..90
note = Engineered antibody sequence
source              1..90
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 453
gagggtgcagc ttgtggagtc tgggggaggo ttgggtccagc ctggggggtc cctgagactc 60
tccctgtcgag tctctggaat cgacgtcaact 90

SEQ ID NO: 454      moltype = DNA length = 15
FEATURE             Location/Qualifiers
misc_feature        1..15
note = Engineered antibody sequence
source              1..15
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 454
aactactaca tgcaa 15

SEQ ID NO: 455      moltype = DNA length = 42
FEATURE             Location/Qualifiers
misc_feature        1..42
note = Engineered antibody sequence
source              1..42
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 455
tgggtccgtc aggctccagg gaaggggctg gagttgggtc ga 42

SEQ ID NO: 456      moltype = DNA length = 48
FEATURE             Location/Qualifiers
misc_feature        1..48
note = Engineered antibody sequence
source              1..48
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 456
gtcatttgtt tgaatggtaa gagataactac gcgagctggg cgaaaaggc 48

SEQ ID NO: 457      moltype = DNA length = 96
FEATURE             Location/Qualifiers
misc_feature        1..96
note = Engineered antibody sequence
source              1..96
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 457
cgatttacca tctccagaga caattccaag accacgggtt atcttcaaattt gaacagcctg 60
agagctgagg acactgtgt gtatttctgt gccaga 96

SEQ ID NO: 458      moltype = length =
SEQUENCE: 458
000

SEQ ID NO: 459      moltype = DNA length = 33
FEATURE             Location/Qualifiers
misc_feature        1..33
note = Engineered antibody sequence
source              1..33
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 459
tggggccaag ggaccctcgat caccgtctcg agc 33

SEQ ID NO: 460      moltype = DNA length = 993
FEATURE             Location/Qualifiers
misc_feature        1..993

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-continued

source note = Engineered antibody sequence
 1..993
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 460
 gcctccacca agggccccatc ggttttccc ctggcacccct cctccaagag cacctctggg 60
 ggacacaggg ccctgggctg cctgttcaag gactacttc cccgaaccgggt gacgggttcg 120
 tggaaactcg ggcgcctgac cagcggcggtg cacacccctcc cggctgtctt acagtccctca 180
 ggactctact ccctcagcag cgtgttgaccc gtggccctccca gcagcttggg caccaggacc 240
 tacatctgtca acgttgaatca caagccca aacaccaagg tggacaagag agttggcc 300
 aaatcttgtc acaaaaactca ccatggccca cccgtgccccag caccctttaactt ccttgggggaa 360
 ccgtcgttct tccttttccc cccaaaaccc aaggacaccc tcatgtatcc ccggaccct 420
 gaggttgcacat ggcgtgggttgg ggcgttgaccc cccgttggccaa gttaacttgg 480
 tacgttggaccc ggcgtgggggttgg gtcataatgc aagacaaaggcc cccgtgggggaa gcgttacggcc 540
 agcacgttacc ttgttgggttccatc gtccttccacc gtccttgcacc aggactgttggt gaatggcaag 600
 gagtacaagt gcaagggttcc caacaaaggcc ctcccaaggcc ccatcgagaa aaccatctcc 660
 aaaggccaaagg ggcagcccccc agaaccacccatc tgcccccattt ccggggaggag 720
 atgaccaagaaccagggttccatc cctgttgcacc ttgttgcaccatc cccgtgggggaa 780
 gccgttggagt gggagagcaatggccagc gagaacaactt acaagaccac qccctccctg 840
 ctggactccg acgggttccctt cttcttctac agcaaggttccatc ccgtggaccaaa gaggcagggtgg 900
 cagcaggggaa acgttccatc atggttgcaccatc atgcatgagg ctctgcaccaa ccactacacg 960
 cagaagggccatc ttccttgcaccaatggccatc tccgggtaaa tga 993

SEQ ID NO: 461 **moltype** = AA **length** = 219
FEATURE **Location/Qualifiers**
REGION 1..219
note = Engineered antibody sequence
source 1..219
mol_type = protein
organism = synthetic construct

SEQUENCE: 461
 QVLTQSPSSL SASVGDRVTI NCRASQSVYY NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSNGDC FVFGGGTKVE IKRTVAAPSV 120
 FIFPPSDEQL KSGTASVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL 180
 STSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGECC 219

SEQ ID NO: 462 **moltype** = AA **length** = 113
FEATURE **Location/Qualifiers**
REGION 1..113
note = Engineered antibody sequence
source 1..113
mol_type = protein
organism = synthetic construct

SEQUENCE: 462
 QVLTQSPSSL SASVGDRVTI NCRASQSVYY NNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
 SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCSNGDC FVFGGGTKVE IKR 113

SEQ ID NO: 463 **moltype** = AA **length** = 22
FEATURE **Location/Qualifiers**
REGION 1..22
note = Engineered antibody sequence
source 1..22
mol_type = protein
organism = synthetic construct

SEQUENCE: 463
 QVLTQSPSSL SASVGDRVTI NC 22

SEQ ID NO: 464 **moltype** = AA **length** = 13
FEATURE **Location/Qualifiers**
REGION 1..13
note = Engineered antibody sequence
source 1..13
mol_type = protein
organism = synthetic construct

SEQUENCE: 464
 RASQSVYYNN YLA 13

SEQ ID NO: 465 **moltype** = AA **length** = 15
FEATURE **Location/Qualifiers**
REGION 1..15
note = Engineered antibody sequence
source 1..15
mol_type = protein
organism = synthetic construct

SEQUENCE: 465
 WYQQKPGKVP KQLIY 15

SEQ ID NO: 466 **moltype** = AA **length** = 7
FEATURE **Location/Qualifiers**

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REGION	1..7 note = Engineered antibody sequence	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 466		7
STSTLAS		
SEQ ID NO: 467	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence 1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 467		
GVPSRFSGSG SGTDFLTIS SLQPEDVATY YC		32
SEQ ID NO: 468	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 468		
LGSYDCSNGD CFV		13
SEQ ID NO: 469	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = Engineered antibody sequence 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 469		
FGGGTTKVEIK R		11
SEQ ID NO: 470	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
source	note = Engineered antibody sequence 1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 470		
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS	60	
KDSTYSLSST LTLSKADYEK HKVYACEVTN QGLSSPVTKS FNRGEC	106	
SEQ ID NO: 471	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
source	note = Engineered antibody sequence 1..660 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 471		
caagtgtga cccagtcctcc atcctccctg tctgcatactg taggagacag agtcaccatc	60	
aattggccgg cgagtca gagatgtttactat aacaactacc tagcctggta tcagcagaaaa	120	
ccaggaaag ttccataagca actgatctat tctacatcca ctctggcatc tggggtccca	180	
tctcgttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag	240	
cctgaaatgttgcgatgttca ttactgtctg ggcagttatg attgtatgttggatgtgt	300	
tttggggatcg gggggggaaac caagggtggaa atcaaaacgtt cggggctgc accatctgtc	360	
ttcatcttcc ccggcatctga tgacgttgtt aatatgtggaa ctgcctctgt tggatgtgt	420	
ctgaataact tctatcccag agaggccaaa gtacagtggaa aggtggataa cggccctccaa	480	
tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc	540	
tgacgtgttcc caaaacgttca tggggatcg acaaaatgttca cggccctccaa	600	
gttcacccatc agggccttagt ctcggccgtc acaaaggttca tcaacagggg agagtgttag	660	
SEQ ID NO: 472	moltype = DNA length = 339	
FEATURE	Location/Qualifiers	
misc_feature	1..339	
source	note = Engineered antibody sequence 1..339 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 472		
caagtgtga cccagtcctcc atcctccctg tctgcatactg taggagacag agtcaccatc	60	
aattggccgg cgagtca gagatgtttactat aacaactacc tagcctggta tcagcagaaaa	120	

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ccagggaaag ttcctaagca actgatctat tctacatcca ctctggcatc tggggtccca 180
 ttcgttca gtggcagtgg atctggaca gattcactc tcaccatcg cagcctgcag 240
 cctgaagatg ttgcaactta ttactgtctg ggcagttatg atttgtatgaa tggtgattgt 300
 tttgtttcg gcggaggaaac caaggtggaa atcaaacgt 339

SEQ ID NO: 473 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 473
 caagtgtga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 474 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 474
 cgggccagtc agagtgttta ctataacaac tacctagcc 39

SEQ ID NO: 475 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 475
 tggtatcagc agaaaccagg gaaagttctt aagcaactga tctat 45

SEQ ID NO: 476 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 476
 tctacatcca ctctggcatc t 21

SEQ ID NO: 477 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 477
 ggggtcccat ctcgtttcag tggcagtgg a tttcactct caccatcagc 60
 agcctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 478 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 478
 ctgggcagtt atgattgttag taatggtgat tgttttgtt 39

SEQ ID NO: 479 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 479
 ttcggcgagg gAACCAAGGT ggAAATCAAA CGT 33

SEQ ID NO: 480 moltype = DNA length = 321
 FEATURE Location/Qualifiers

-continued

misc_feature 1..321
 note = Engineered antibody sequence

source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 480
 acgggtggctt caccatctgt ctccatcttc ccgcacatctg atgagcaggaaatctggaa 60
 actgcctctg ttgtgtgcct gctgaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acggccatcca atcggttaatcccccaggaga gtgtcacaga gcaggacacg 180
 aaggacagaca cttacagccct cagcgcacccttgcacgc gcaaagcaca ctacgagaaa 240
 cacaaggatctt acggctgcga agtaccccat caggccctgatgtcgccgt cacaaggagc 300
 ttcaacacggggagatgtta g 321

SEQ ID NO: 481 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence
 source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 481
 QSVVEESGGGL VQPEGSLTLT CTASGFDSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
 SWVNNGRFSIS KTSSTTVTLQ LNSLTVAADTA TYYCARDLWL WGPGLTVTS SASTKGPVSF 120
 PLAPSSKSTS GGTAAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV 180
 TVPSSSLGTO TYICCNVNHKP SNTKVDKRV PKSCDKTHTC PPCPAPELLG GPSVLFPPK 240
 PKDTLMSRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVSLSL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNGQ PENNYKTTTPP VLSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 482 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 482
 QSVVEESGGGL VQPEGSLTLT CTASGFDSS NAMWWVRQAP GKGLEWIGCI YNGDGSTYYA 60
 SWVNNGRFSIS KTSSTTVTLQ LNSLTVAADTA TYYCARDLWL WGPGLTVTS S 111

SEQ ID NO: 483 moltype = AA length = 29
 FEATURE Location/Qualifiers
 REGION 1..29
 note = Engineered antibody sequence
 source 1..29
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 483
 QSVVEESGGGL VQPEGSLTLT CTASGFDSS 29

SEQ ID NO: 484 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 484
 SNAMW 5

SEQ ID NO: 485 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 485
 WVRQAPGKGL EWIG 14

SEQ ID NO: 486 moltype = AA length = 17
 FEATURE Location/Qualifiers
 REGION 1..17
 note = Engineered antibody sequence
 source 1..17
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 486

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CIYNGDGSTY YASWVNG	17
SEQ ID NO: 487	moltype = AA length = 31
FEATURE	Location/Qualifiers
REGION	1..31
source	note = Engineered antibody sequence 1..31 mol_type = protein organism = synthetic construct
SEQUENCE: 487	RFSISKTSST TVTLQLNSLT VADTATYYCA R
	31
SEQ ID NO: 488	moltype = AA length = 4
FEATURE	Location/Qualifiers
REGION	1..4
source	note = Engineered antibody sequence 1..4 mol_type = protein organism = synthetic construct
SEQUENCE: 488	DLLL
	4
SEQ ID NO: 489	moltype = AA length = 11
FEATURE	Location/Qualifiers
REGION	1..11
source	note = Engineered antibody sequence 1..11 mol_type = protein organism = synthetic construct
SEQUENCE: 489	WGPGLTVTVS S
	11
SEQ ID NO: 490	moltype = AA length = 330
FEATURE	Location/Qualifiers
REGION	1..330
source	note = Engineered antibody sequence 1..330 mol_type = protein organism = synthetic construct
SEQUENCE: 490	ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS 60 GLYSLSVSVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELGG 120 PSVFLFPPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFWV YVDGVEVHNA KTKPREEQYA 180 STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTS KAKGQPREPQ VYTLPPSREE 240 MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW 300 QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330
SEQ ID NO: 491	moltype = DNA length = 1326
FEATURE	Location/Qualifiers
misc_feature	1..1326
source	note = Engineered antibody sequence 1..1326 mol_type = other DNA organism = synthetic construct
SEQUENCE: 491	cagtccgtgg aggagtccgg gggaggcctg qtccagcctg agggatccct gacactcacc 60 tgcacagcct ctggattcga cttcaagtgc aatgcaatgt ggtgggtccg ccaggctcca 120 ggaaaggggc tggagttggat cggatgcatt tacaatggtg atggcagcac atactacgcg 180 agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgcaa 240 ctgaatagtc tgacagtcgc ggacacggcc acgttattat tcgtcgagaga tcttgacttg 300 tggggccccc gcacccctcgat caccgtctcg agcgcttcca ccaaggccc atcggttcc 360 ccccctggcac cctccatccaa gagcacctt gggggcacag cggccctggg ctgcctggc 420 aaggactact tcccccaacc ggtgagctgt tcgtggaaact caggcgcctt gaccaggcgc 480 gtgcacactt tcccggtctgt cctacatgc tcgactactt actccctcag cagcgtgtg 540 accgtgcctt ccagcagctt gggcacccag acctacatctt gcaacgtgaa tcacaagccc 600 agcaacacca aggtggacaa gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660 ccaccgtggc cagcaccttga actccctgggg ggaccgtcaq tcttcctt ccccccaaaa 720 cccaaggaca cctctatgtat ctcccgacc cctgagggtca catgcgttgt ggtggacgtg 780 agccacaaag accctggaggt caagttcaac ttgtacgttg acggcgtgaa ggtgcataat 840 gccaagacaa agccggggga ggagoagttt gcccacgtt accgtgttgtt cagcgtctc 900 accgtccgc accaggactt gctgaatggc aaggagttaca agtgcacggt ctccaaacaaa 960 gccctcccaag ccccatcgaa gaaaaccatc tccaaagccaa aaggcagccc ccgagaacca 1020 cagggttaca ccctggccccc atcccgggag gagatgttaca agaaccaggat cagcgtgacc 1080 tgccctggtca aaggcttctat tcccgacatc atcccggtt agtggagag caatggcag 1140 ccggagaaca actacaagac cacgcctccg gtgtctggact ccgacggctc cttttctcc 1200 tacagcaagc tcaccgtggc caagagcagg tggcagcagg ggaacgtt ctcgtctcc 1260 gtgtatgcata aggctctgca caaccactac acgcagaaga gctctccctt gtctccgggt 1320 aatga 1326

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SEQ ID NO: 492 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 492
 cagtccgtgg aggagtcgg gggaggcctg gtccagcctg agggatccct gacactcacc 60
 tgcacagcct ctggattcga ctteagtagt aatgcaatgt ggtgggtccg ccaggctcca 120
 gggaaaggggc tggagtgatgat cggatgcatt tacaatgttg atggcagcac atatacagcg 180
 agctgggtga atggccgatt ctccatctcc aaaacctcgat cgaccacggt gactctgcaa 240
 ctgaatagtc tgacagtcgc ggacacggcc acgtattatt gtgcgagaga tcttgacttg 300
 tggggccccgg gcaccctcgat caccgtctcg agc 333

SEQ ID NO: 493 moltype = DNA length = 87
 FEATURE Location/Qualifiers
 misc_feature 1..87
 note = Engineered antibody sequence
 source 1..87
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 493
 cagtccgtgg aggagtcgg gggaggcctg gtccagcctg agggatccct gacactcacc 60
 tgcacagcct ctggattcga ctteagtagt 87

SEQ ID NO: 494 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 494
 agcaatgaa tgtgg 15

SEQ ID NO: 495 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 495
 tgggtccggc aggctccagg gaaggggctg gatggatcg ga 42

SEQ ID NO: 496 moltype = DNA length = 51
 FEATURE Location/Qualifiers
 misc_feature 1..51
 note = Engineered antibody sequence
 source 1..51
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 496
 tgcatttaca atgggtatgg cagcacatac tacgcgagct gggtaatgg c 51

SEQ ID NO: 497 moltype = DNA length = 93
 FEATURE Location/Qualifiers
 misc_feature 1..93
 note = Engineered antibody sequence
 source 1..93
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 497
 cgattctcca tctccaaaac ctcgtcgacc acgggtgactc tgcaactgaa tagtctgaca 60
 gtgcgcccggaca cggccacgtat ttattgtgcg aga 93

SEQ ID NO: 498 moltype = DNA length = 12
 FEATURE Location/Qualifiers
 misc_feature 1..12
 note = Engineered antibody sequence
 source 1..12
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 498
 gatcttgact tg 12

SEQ ID NO: 499 moltype = DNA length = 33
 FEATURE Location/Qualifiers

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misc_feature      1..33
                  note = Engineered antibody sequence
source           1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 499
tggggccccc gcaccctcggt caccgtctcg agc                         33

SEQ ID NO: 500          moltype = DNA  length = 993
FEATURE             Location/Qualifiers
misc_feature        1..993
                  note = Engineered antibody sequence
source            1..993
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 500
gcctccacca agggccccatc ggttttcccc ctggcacccct cctccaagag cacctctggg  60
ggcacacggg ccctggcgctg cctgtcaag gactatttc cccaaagggt gacgggtcg 120
tggaaacttag cgcgcctgac cagcgcgtg cacacccctt cggctgtctt acagtcccta 180
ggactctact ccctcagcag cgtggtgacc gtgccttcca gcagcttggg caccaggacc 240
tacatctgca acgtgaatca caaggcccg aacaccaagg tggacaagg agttgaggcc 300
aaatcttggt cccaaaatca cacatggcca cccgtccca actgtcaact cctgggggga 360
ccgtcgtctt ttctttccc cccaaaatcc aaggacaccc tcatgtatcc cccggccct 420
gagggtcacat gctgtgtgggt ggacgtgago cacgaagacc ctgagggtcaa gttcaactgg 480
taacgtggacg ggggtggagggt gcataatgcc aagacaaagg cgccggaggaa gcagtgacgcc 540
agoacacgtacc ttgtgggtcg cgtcttcacc gtccctgcacc aggactggct gaatggcaag 600
gagttacaatgt gcaagggtctc caacaaaggcc ctcccaagccccc ccatacgagaa aaccatctcc 660
aaaggccaaag ggcagcccccg agaaccacag gtgtacacc tgccccatcc ccggggaggag 720
atgaccaaga accagggtcag cctgacccctt ctgtcaaaag gtttctatcc cagggacatc 780
gcggcgtggagg ggggagagcaa tggggaggcc gagaacaaact acaagacac ccctccctg 840
ctggactcccg acgggtctt ccctcttac agcaaggtca ccgtggacaa gagcagggtgg 900
cagcaggggaa acgttcttc atgtccgtg atgtcatgagg ctctgcacaa ccactacacg 960
cagaagagcc ttccctgtc tccgggtaaa tga                         993

SEQ ID NO: 501          moltype = AA  length = 219
FEATURE             Location/Qualifiers
REGION             1..219
                  note = Engineered antibody sequence
source            1..219
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 501
AIVMTQTPSS KSVPVGDTVT INCQASESLY NNNNALAWPQQ KPGQPPKRLLI YDASKLASGV 60
PSRFSGGGSG TQFTLTISGV QCDDAATYYC GGYRSDSVVG VAFAGGTEVV VKRTVAAPSV 120
FIPPPSDEQL KSGTASVVCL LNNFVYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTLTLASKD YEKHKVYACE VTHQGLSSPV TKSFNRGEC                         219

SEQ ID NO: 502          moltype = AA  length = 113
FEATURE             Location/Qualifiers
REGION             1..113
                  note = Engineered antibody sequence
source            1..113
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 502
AIVMTQTPSS KSVPVGDTVT INCQASESLY NNNNALAWPQQ KPGQPPKRLLI YDASKLASGV 60
PSRFSGGGSG TQFTLTISGV QCDDAATYYC GGYRSDSVVG VAFAGGTEVV VKR                         113

SEQ ID NO: 503          moltype = AA  length = 23
FEATURE             Location/Qualifiers
REGION             1..23
                  note = Engineered antibody sequence
source            1..23
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 503
AIVMTQTPSS KSVPVGDTVT INC                                         23

SEQ ID NO: 504          moltype = AA  length = 13
FEATURE             Location/Qualifiers
REGION             1..13
                  note = Engineered antibody sequence
source            1..13
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 504
QASESLYNNN ALA                                              13

SEQ ID NO: 505          moltype = AA  length = 15

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FEATURE REGION	Location/Qualifiers 1..15 note = Engineered antibody sequence	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 505 WFQQKPGQPP KRLIY		15
SEQ ID NO: 506	moltype = AA length = 7	
FEATURE REGION	Location/Qualifiers 1..7 note = Engineered antibody sequence	
source	1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 506 DASKLAS		7
SEQ ID NO: 507	moltype = AA length = 32	
FEATURE REGION	Location/Qualifiers 1..32 note = Engineered antibody sequence	
source	1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 507 GVPSRFSGGG SGTQFTLTIS GVQCDDAATY YC		32
SEQ ID NO: 508 GGYRSDSVDG VA	moltype = AA length = 12	12
FEATURE REGION	Location/Qualifiers 1..12 note = Engineered antibody sequence	
source	1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 508 GGYRSDSVDG VA		12
SEQ ID NO: 509 FAGGTEVVVK R	moltype = AA length = 11	11
FEATURE REGION	Location/Qualifiers 1..11 note = Engineered antibody sequence	
source	1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 509 FAGGTEVVVK R		11
SEQ ID NO: 510 FEATURE REGION	moltype = AA length = 106	
source	Location/Qualifiers 1..106 note = Engineered antibody sequence 1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 510 TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		60 106
SEQ ID NO: 511 FEATURE misc_feature	moltype = DNA length = 660	
source	Location/Qualifiers 1..660 note = Engineered antibody sequence 1..660 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 511 ggccatcgta tgaccaggac tccatcttcc aagtctgtc ctgtgggaga cacagtca atcaattgcc aggccagtga gagttttat aataacaacg ccttggctcg gtttcagc aaaccagggc agcctccaa gcgcctgatc tatgtatgc tatcaactggc atctgggtc ccatcgccgt tcagtgccgg tgggtctggg acacagttca ctctcacat cagtgccgt cagtggtacg atgctgccat ttactactgt ggaggctaca gaagtatgtatgtatgt gttgcttcgg cgggaggac cgagggttgt gtcaaacatgc cgggttgtgc accatctgtc ttcatcttcc cgccatctga tgagoagttt aaatctggaa ctgcctctgt tttgtgc ctgatataact tctatccccag agaggccaaa gtacagtggaa aggtggataa cgcctccaa tcgggttaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagctc agcagcaccc tgacgcttag caaaggcagac tacgagaaac acaaagtcta cgcctgc gtcaccatc agggccttag ctgcggcgtc acaaagagct tcaacagggg agagtgttag	60 120 180 240 300 360 420 480 540 600 660	

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SEQ ID NO: 512      moltype = DNA  length = 339
FEATURE
misc_feature
1..339
note = Engineered antibody sequence
1..339
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 512
ggcatcgta tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtacc 60
atcaattgcc aggccagtga gagttttat aataacaacg ccttggctg gtttcagcag 120
aaaccagggc agcccccac ggcctgtatc tatgtatcat ccaaactggc atctgggtc 180
ccatcgccgt tcagtggcg  tgggtctgg acacagtcc ctctcaccat cagtggcg 240
cagtgtgacg atgtggcac ttactactg ggaggctaca gaagtgtatag tggatgtt 300
gttgcttcg cggaggac cgagggtgt 339
gtcaaacgt

SEQ ID NO: 513      moltype = DNA  length = 69
FEATURE
misc_feature
1..69
note = Engineered antibody sequence
1..69
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 513
ggcatcgta tgacccagac tccatcttcc aagtctgtcc ctgtgggaga cacagtacc 60
atcaattgc 69

SEQ ID NO: 514      moltype = DNA  length = 39
FEATURE
misc_feature
1..39
note = Engineered antibody sequence
1..39
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 514
caggccagtg agagtcttta taataacaac gccttggcc 39

SEQ ID NO: 515      moltype = DNA  length = 45
FEATURE
misc_feature
1..45
note = Engineered antibody sequence
1..45
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 515
tggtttacg agaaaaccagg gcagcctccc aagcgcctga tctat 45

SEQ ID NO: 516      moltype = DNA  length = 21
FEATURE
misc_feature
1..21
note = Engineered antibody sequence
1..21
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 516
gatgcattca aactggcatc t 21

SEQ ID NO: 517      moltype = DNA  length = 96
FEATURE
misc_feature
1..96
note = Engineered antibody sequence
1..96
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 517
gggttcccat cgcggttcag tggcggtgg tctgggacac agttcaactt caccatagt 60
ggcggtcact gtgacgtgc tgccacttac tactgt 96

SEQ ID NO: 518      moltype = DNA  length = 36
FEATURE
misc_feature
1..36
note = Engineered antibody sequence
1..36
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 518
ggaggctaca gaagtgtatag tggatgtt 36
gttgct

SEQ ID NO: 519      moltype = DNA  length = 33

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FEATURE Location/Qualifiers
 misc_feature 1..33
 note = Engineered antibody sequence
 source 1..33
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 519
 ttcgcggag ggaccgaggt ggtggtcaaa cgt 33

SEQ ID NO: 520 moltype = DNA length = 321
 FEATURE Location/Qualifiers
 misc_feature 1..321
 note = Engineered antibody sequence
 source 1..321
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 520
 acggtgttgcg cccatctgt ctcatcttc ccgcattctg atgaggcgtt gaaatcttga 60
 actgcctctg ttgtgtgcct gctaataac ttctatccca gagaggccaa agtacagtgg 120
 aagggtggata acgcctcca atcgggttaac tcccaggaga gtgtcacaga gcaggacgc 180
 aaggacacga ctttacagctt cagcagcacc ctgacgcgtt gcaaaaggaga ctacgagaaa 240
 cacaaggatctt acgcctgcgtt agtccccat caggccgtt gtcggccgtt cacaaggagc 300
 ttcaacagggg gagatgttta g 321

SEQ ID NO: 521 moltype = AA length = 441
 FEATURE Location/Qualifiers
 REGION 1..441
 note = Engineered antibody sequence
 source 1..441
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 521
 EVOLVESGGG LVQPGGSLRL SCAVSGIGLSSYYMQWVRQA PGKGLEWVGVI GSDGKTYA 60
 TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS SASTKGPSVF 120
 PLAPSSKSTS GGTAALGCLV KDYPPEPVTV SWNSGALTSG VHTFPAPLQS SGLYLSLSSVV 180
 TVPSSSLGTO TYICCNVNHPK SNKVDARVE PKSCDKTHTC PPCPAPELLG GPSVPLFFPK 240
 PDKTLMISRT PEVTCVVVDV SHEDPEVKFN WYDGVVEVHN AKTKPREEQY ASTYRVVSVL 300
 TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
 CLVKGFYPSD IAVEWESNGQ PENNYKTTPPP VLDSDGSSFL YSKLTVDKSR WQQGNVFSCS 420
 VMHEALHNHY TQKSLSLSPG K 441

SEQ ID NO: 522 moltype = AA length = 111
 FEATURE Location/Qualifiers
 REGION 1..111
 note = Engineered antibody sequence
 source 1..111
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 522
 EVOLVESGGG LVQPGGSLRL SCAVSGIGLSSYYMQWVRQA PGKGLEWVGVI GSDGKTYA 60
 TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS S 111

SEQ ID NO: 523 moltype = AA length = 30
 FEATURE Location/Qualifiers
 REGION 1..30
 note = Engineered antibody sequence
 source 1..30
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 523
 EVQLVESGGG LVQPGGSLRL SCAVSGIGLSSYYMQWVRQA PGKGLEWVGVI GSDGKTYA 60
 TWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCTRGRDI WGQGTLVTVS S 111

SEQ ID NO: 524 moltype = AA length = 5
 FEATURE Location/Qualifiers
 REGION 1..5
 note = Engineered antibody sequence
 source 1..5
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 524 SYYMQW 5

SEQ ID NO: 525 moltype = AA length = 14
 FEATURE Location/Qualifiers
 REGION 1..14
 note = Engineered antibody sequence
 source 1..14
 mol_type = protein
 organism = synthetic construct

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SEQUENCE: 525
WVRQAPGKGL EWVG

SEQ ID NO: 526 moltype = AA length = 16
FEATURE Location/Qualifiers
REGION 1..16
note = Engineered antibody sequence
source 1..16
mol_type = protein
organism = synthetic construct

SEQUENCE: 526
VIGSDGKTYY ATWAKG

SEQ ID NO: 527 moltype = AA length = 32
FEATURE Location/Qualifiers
REGION 1..32
note = Engineered antibody sequence
source 1..32
mol_type = protein
organism = synthetic construct

SEQUENCE: 527
RFTISRDNSK TTVYLQMNSL RAEDTAVYFC TR

SEQ ID NO: 528 moltype = length =
SEQUENCE: 528
000

SEQ ID NO: 529 moltype = AA length = 11
FEATURE Location/Qualifiers
REGION 1..11
note = Engineered antibody sequence
source 1..11
mol_type = protein
organism = synthetic construct

SEQUENCE: 529
WGQQTIVTVS S

SEQ ID NO: 530 moltype = AA length = 330
FEATURE Location/Qualifiers
REGION 1..330
note = Engineered antibody sequence
source 1..330
mol_type = protein
organism = synthetic construct

SEQUENCE: 530
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS 60
GLYSLSVSVT VPSSSLGTQT YICNVNHPKS NTKVDARVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKPK KDTLMISRTP EVTCVVVDVS HEDPEVKFNV YVDGVENVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTTPV LDSDGSFFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 330

SEQ ID NO: 531 moltype = DNA length = 1326
FEATURE Location/Qualifiers
misc_feature 1..1326
note = Engineered antibody sequence
source 1..1326
mol_type = other DNA
organism = synthetic construct

SEQUENCE: 531
gagggtgcagc ttgtggagtc tgggggaggc ttgggccagc ctggggggtc cctgagactc 60
tctctgtcgac tctctggat cggccctca agtactactaca tgcaactgggt ccgtcaggct 120
ccaggggagg ggtctggatg ggtctggatg attggtagtg atggtaagac atactacgcg 180
acctggggca aaggccgatt caccatctcc agagacaata ccaagaccac ggttatctt 240
caaataatgaca gccttgagagc tgaggacact gctgtgtatt tctgttaccag agggggacatc 300
tgggggccaag ggaccttcgt caccgtctcg agccgcctcca ccaaggccc atcggtcttc 360
ccccctggac cctccatccaa gagcacctctt gggggccacag cggccctggg ctgcctggc 420
aaggactact tcccccaacc ggttgccatgg tcgttggaaact caggccgcctt gaccaggccg 480
gtgcacacact tcccggtctgt cttacagtcc tcaggactctt actccctcaag cagcgtgttg 540
accgtgcctt ccagcagctt gggccacccag acctacatctt gcaacgtgaa tcacaagccc 600
agcaacacca aggtggacgc gagagtttag cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcc cagcacctca actccctgggg ggaccgtcaag tcttcctt ccccccaaaa 720
cccaaggaca cctctcatgt ctccggacc cttggatgtca catgcgttgtt ggtggacgtt 780
agccacaaag accctggatg caaagtcaac tggtagctgg acggccgtt ggtgcataat 840
gccaagacaa agccggggga ggagccgtac gccagcacgtt accgtgttgtt cagcgtctc 900
accgtccctc accaggactg gctgaatggc aaggagttaca agtgcacatgtt ctccaaacaaa 960
gccctccatcga gaaaaccatc tccaaagccaa aaggccagcc ccgagaacca 1020
cagggttaca ccctggcccc atccggggag gagatgacca agaaccaggat cagcgttgc 1080
tgcctggatca aaggcttcta tcccaagccgac atcggccgtt ggtggagatccatggcc 1140

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ccggagaaca actacaagac cacgcctccc gtgctggact ccgacggcgc cttcttcctc 1200
 tacagcaagc tcaccgtgga caagagcagg tggcagcagg ggaacgtt ctcatgtcc 1260
 gtgatgcata aggctctgca caaccactac acgcagaaga gcctctccct gtctccgggt 1320
 aaatga 1326

SEQ ID NO: 532 moltype = DNA length = 333
 FEATURE Location/Qualifiers
 misc_feature 1..333
 note = Engineered antibody sequence
 source 1..333
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 532
 gaggtgcaga ttgtggagtc tggggggaggc ttggtccagc ctggggggc cctgagactc 60
 tcctgtcag tctctgaaat cgccctcaagt agctactaca tgcaatgggt ccgtcaggct 120
 ccagggaaagg ggctggagtg ggtcgagtc attggtagt atggtaagac atactacgcg 180
 acctggcgaa aaggccgatt caccatctcc agagacaat ccaagaccac ggtgtatctt 240
 caaatgaaca gcctgagac tgaggacact gctgtgtatt tctgttaccag aggggacatc 300
 tggggccaag ggacctctgt caccgtctcg agc 333

SEQ ID NO: 533 moltype = DNA length = 90
 FEATURE Location/Qualifiers
 misc_feature 1..90
 note = Engineered antibody sequence
 source 1..90
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 533
 gaggtgcaga ttgtggagtc tggggggaggc ttggtccagc ctggggggc cctgagactc 60
 tcctgtcag tctctgaaat cgccctcaagt 90

SEQ ID NO: 534 moltype = DNA length = 15
 FEATURE Location/Qualifiers
 misc_feature 1..15
 note = Engineered antibody sequence
 source 1..15
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 534
 agctactaca tgcaa 15

SEQ ID NO: 535 moltype = DNA length = 42
 FEATURE Location/Qualifiers
 misc_feature 1..42
 note = Engineered antibody sequence
 source 1..42
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 535
 tgggtccgtc aggctccagg gaaggggctg gagtgggtcg ga 42

SEQ ID NO: 536 moltype = DNA length = 48
 FEATURE Location/Qualifiers
 misc_feature 1..48
 note = Engineered antibody sequence
 source 1..48
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 536
 gtcattggta gtgatggtaa gacatactac gcgacctggg cgaaaggc 48

SEQ ID NO: 537 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 537
 cgattcacca tctccagaga caattccaag accacggtgt atcttcaaattt gaacagcctg 60
 agagctgagg acactgctgt gtatttctgt accaga 96

SEQ ID NO: 538 moltype = length =

SEQUENCE: 538
 000

SEQ ID NO: 539 moltype = DNA length = 33
 FEATURE Location/Qualifiers
 misc_feature 1..33

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source          note = Engineered antibody sequence
1..33
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 539
tggggccaag ggaccctcg caccgtctcg agc                         33

SEQ ID NO: 540      moltype = DNA length = 993
FEATURE
misc_feature       Location/Qualifiers
1..993
note = Engineered antibody sequence
source             1..993
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 540
gcctccacca agggcccatc ggtttcccc ctggcaccc cctccaagag caccctctgg  60
ggcacagccg ccctgggctg cctgttcaag gactacttcc cccgaaccgg gacgggttcg 120
tggaaactcg cgcccttgac cagccgtg acacacttcc cggctgtctt acagtccca 180
ggactctact ccctcagcag cgtgttgcac gtgccctca cgcacgttgg caccaggacc 240
tacatctgca acgtgaatca caagcccgac aacaccaagg tggacgccc agtttggccc 300
aaatcttgtc aaaaaactca cacatggccca cccgtgcccag caccctaactt ccttgggggga 360
ccgtcagtct tcctttccc cccaaaaccc aaggacacccttccatgtatcc ccggaccct 420
gaggtcacat gctgttgggtt ggacgttgcac cacaagacc ctggaggtaaa gttcaacttgg 480
tacgtggacg cgctggagggt gcataatggc aagacaaaggc cgcggggagg gcaagtacggc 540
agcacgttacc gtgttggtcag cgttccatcc gtcctgcacc aggactggtt gaatggcaag 600
gagtacaatgttcc caacaaggcc ccccccaccc ccatcgagaa aaccatctcc 660
aaaggccaaag ggcaggccccc agaaccacac gtttacacccttccatgggggggg 720
atgaccaaga accagggttag cctgttccatcc ctggtcaaa gtttctatcc cagcgacatc 780
gcctgttgggtt gggagggccaa tgggcagccg gagaacaaactt acaagaccac gcctccctgg 840
ctggacttccg acgggttccctt ctccatcttccatggcaacttccatggcagggtgg 900
caggcaggccaa acgttccatcc atgttccatggt atgttccatggt ctgttccatggcagg 960
cagaagggcc ttccatgttccatggcagggtgg 993

SEQ ID NO: 541      moltype = AA length = 219
FEATURE
REGION            Location/Qualifiers
1..219
note = Engineered antibody sequence
source             1..219
mol_type = protein
organism = synthetic construct
SEQUENCE: 541
QVLTQSPSSL SASVGDRVVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKRTVAAPSV 120
FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWVKVDNALQ SGNSQESVTE QDSKDSTYSL 180
STSTTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC                         219

SEQ ID NO: 542      moltype = AA length = 113
FEATURE
REGION            Location/Qualifiers
1..113
note = Engineered antibody sequence
source             1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 542
QVLTQSPSSL SASVGDRVVTI NCQASQNLYNNYLAWYQQK PGKVPKQLIY STSTLASGVP 60
SRFSGSGSGT DFTLTISLQ PEDVATYYCL GSYDCSRGDC FVFGGGTKVE IKR                         113

SEQ ID NO: 543      moltype = AA length = 22
FEATURE
REGION            Location/Qualifiers
1..22
note = Engineered antibody sequence
source             1..22
mol_type = protein
organism = synthetic construct
SEQUENCE: 543
QVLTQSPSSL SASVGDRVVTI NC                                         22

SEQ ID NO: 544      moltype = AA length = 13
FEATURE
REGION            Location/Qualifiers
1..13
note = Engineered antibody sequence
source             1..13
mol_type = protein
organism = synthetic construct
SEQUENCE: 544
QASQNLYNNN YLA                                                 13

SEQ ID NO: 545      moltype = AA length = 15
FEATURE

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REGION	1..15 note = Engineered antibody sequence	
source	1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 545		
WYQQKPGKVP KQLIY		15
SEQ ID NO: 546	moltype = AA length = 7	
FEATURE	Location/Qualifiers	
REGION	1..7	
source	note = Engineered antibody sequence 1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 546		
STSTLAS		7
SEQ ID NO: 547	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
REGION	1..32	
source	note = Engineered antibody sequence 1..32 mol_type = protein organism = synthetic construct	
SEQUENCE: 547		
GVPSRFSGSG SGTDFTLTIS SLQPEDVATY YC		32
SEQ ID NO: 548	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
REGION	1..13	
source	note = Engineered antibody sequence 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 548		
LGSYDCSRGD CFV		13
SEQ ID NO: 549	moltype = AA length = 11	
FEATURE	Location/Qualifiers	
REGION	1..11	
source	note = Engineered antibody sequence 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 549		
FGGGTKVEIK R		11
SEQ ID NO: 550	moltype = AA length = 106	
FEATURE	Location/Qualifiers	
REGION	1..106	
source	note = Engineered antibody sequence 1..106 mol_type = protein organism = synthetic construct	
SEQUENCE: 550		
TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS KDSTYSLSS		60
LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC		106
SEQ ID NO: 551	moltype = DNA length = 660	
FEATURE	Location/Qualifiers	
misc_feature	1..660	
source	note = Engineered antibody sequence 1..660 mol_type = other DNA organism = synthetic construct	
SEQUENCE: 551		
caagtgtctga cccagtcctcc atcctccctg tctgcacatcg taggagacag agtcaccatc	60	
aattgccagg ccagtcagaa tgtttacaat aacaactacc tagcctggta tcagcagaaa	120	
ccaggaaag ttccctaagca actgatctat tctacatcca ctctggatc tgggttccca	180	
tctcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcg cagcctgcag	240	
cctgaagatg ttgcaactta ttactgtctg ggcaagttatg attgttagtcg tggtgatgt	300	
tttggtttgc gcccggaaac caaggtggaa atcaaacgtc cggtggctgc accatctgtc	360	
ttcatcttcc cggccatctga tgacgatgtt aaatctggaa ctgcctctgt tggatgtc	420	
ctgaataact ttatccccag agaggccaaa gtacagtggaa aggtggataa cggccctccaa	480	
tcgggttaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc	540	
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa	600	
gtcaccatc agggcctgag ctcgcctgca acaaagact tcaacagggg agagtgttag	660	

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SEQ ID NO: 552 moltype = DNA length = 339
 FEATURE Location/Qualifiers
 misc_feature 1..339
 note = Engineered antibody sequence
 source 1..339
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 552
 caagtgtga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
 aattgccagg ccagtcatggaa tggttacaat aacaactacc tagectggta tcagcagaaaa 120
 ccaggaaag ttccataagca actgtatctat tctacatcca ctctggatc tggggtccca 180
 ttcgtttca gtggcagtgg atctgggaca gatttcactc tcaccatcag cagcctgcag 240
 cctgaagatg ttgcactta ttactgtctg ggcaagtatg attgttagtgc tggtgatgt 300
 ttgtttcg gggaggaaac caagggtggaa atcaaacgt 339

SEQ ID NO: 553 moltype = DNA length = 66
 FEATURE Location/Qualifiers
 misc_feature 1..66
 note = Engineered antibody sequence
 source 1..66
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 553
 caagtgtga cccagtcctcc atcctccctg tctgcatctg taggagacag agtcaccatc 60
 aattgc 66

SEQ ID NO: 554 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 554
 caggccagtc agaatgttta caataacaac tacctagcc 39

SEQ ID NO: 555 moltype = DNA length = 45
 FEATURE Location/Qualifiers
 misc_feature 1..45
 note = Engineered antibody sequence
 source 1..45
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 555
 tggtatcagc agaaaccagg gaaagttctt aagcaactga tctat 45

SEQ ID NO: 556 moltype = DNA length = 21
 FEATURE Location/Qualifiers
 misc_feature 1..21
 note = Engineered antibody sequence
 source 1..21
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 556
 tctacatcca ctctggatc t 21

SEQ ID NO: 557 moltype = DNA length = 96
 FEATURE Location/Qualifiers
 misc_feature 1..96
 note = Engineered antibody sequence
 source 1..96
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 557
 ggggtcccat ctcgtttcag tggcagtggaa tctgggacag atttcactct caccatcagc 60
 agcctgcagc ctgaagatgt tgcaacttat tactgt 96

SEQ ID NO: 558 moltype = DNA length = 39
 FEATURE Location/Qualifiers
 misc_feature 1..39
 note = Engineered antibody sequence
 source 1..39
 mol_type = other DNA
 organism = synthetic construct

SEQUENCE: 558
 ctgggcagtt atgattgttag tcgtggatgat tggtttgtt 39

SEQ ID NO: 559 moltype = DNA length = 33
 FEATURE Location/Qualifiers

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misc_feature      1..33
                  note = Engineered antibody sequence
source           1..33
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 559
ttcggcgagg gAACCAAGGT ggAAATCAAA CGT                               33

SEQ ID NO: 560      moltype = DNA  length = 321
FEATURE          Location/Qualifiers
misc_feature     1..321
                  note = Engineered antibody sequence
source           1..321
                  mol_type = other DNA
                  organism = synthetic construct
SEQUENCE: 560
acgggtggctg caccatctgt cttcatcttc ccgcctatctg atgagcagggt gaaatctgga  60
actgcctctg ttgtgtgcct gcttaaac ttctatccca gagaggccaa agtacagtgg 120
aagggtggata acggcctcca atcggttaac tcccaggaga gtgtcacaga gcaggacacg 180
aaggacacgca cctacagcct cagcagcacc ctgacgctga gcaaaggaga ctacgagaaa 240
cacaaggctc acggcctgcga agtcacccat cagggcctga gctcgccgt cacaaggagc 300
ttcaacacagg gagagtgtta g                                         321

SEQ ID NO: 561      moltype = AA   length = 37
FEATURE          Location/Qualifiers
VARIANT          37
source            1..37
                  mol_type = protein
                  organism = Homo sapiens
SEQUENCE: 561
ACDTATCVTH RLAGLLSRSG GVVKNNFVPT NVGSKAF                               37

SEQ ID NO: 562      moltype = AA   length = 37
FEATURE          Location/Qualifiers
VARIANT          37
source            1..37
                  mol_type = protein
                  organism = Homo sapiens
SEQUENCE: 562
ACNTATCVTH RLAGLLSRSG GMVKSNFVPT NVGSKAF                               37

SEQ ID NO: 563      moltype = AA   length = 106
FEATURE          Location/Qualifiers
source           1..106
                  mol_type = protein
                  organism = Homo sapiens
SEQUENCE: 563
TVAAPSVIF PPSDEQLKSG TASVVCCLNN FYPREAKVQW KVDNALQSGN SQESVTEQDS  60
KDSTYSLSSLT LTLSKADYEK HKVYACEVTH QGLSSPVTKS FNRGEC 106

SEQ ID NO: 564      moltype = AA   length = 330
FEATURE          Location/Qualifiers
REGION           1..330
                  note = Engineered antibody sequence
source            1..330
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 564
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSSFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPGK                                         330

SEQ ID NO: 565      moltype = AA   length = 329
FEATURE          Location/Qualifiers
REGION           1..329
                  note = Engineered antibody sequence
source            1..329
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 565
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS  60
GLYSLSSVVT VPSSSLGTQT YICCNVNHKPS NTKVDKRVEP KSCDKTHTCP PCPAPELLGG 120
PSVFLFPKP KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYA 180
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIIS KAKGQPREPQ VYTLPPSREE 240
MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSSFLY SKLTVDKSRW 300
QQGNVFSCSV MHEALHNHYT QKSLSLSPG                                         329

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SEQ ID NO: 566          moltype = AA length = 440
FEATURE
REGION
1..440
note = Engineered antibody sequence
1..440
mol_type = protein
organism = synthetic construct
SEQUENCE: 566
EVQLVESGGGVVQGLVSGVSLRL SCAVGIDLS GYYMNWVRQAGPKGLEWVGVI GINGATYYA 60
SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI WQGQTLVTVS SASTKGPSVF 120
PLAPSSKSTS GGTAALGCLV KDYFPEPVTV SWNSGALTSG VHTFPVALQS SGLYSLSSVV 180
TVPSSSLGQT TYICNVNHPK SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVPLFFPK 240
PKDTLMISR PPEVTCVVVDV SHEDPVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE EMTKNQVSLT 360
CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLSDGSFFL YSKLTVDKSR WQQGNVFSCS 420
VMHEALHNHY TQKSLSLSPG 440

SEQ ID NO: 567          moltype = DNA length = 1323
FEATURE
misc_feature
1..1323
note = Engineered antibody sequence
1..1323
mol_type = other DNA
organism = synthetic construct
SEQUENCE: 567
gagggtgcagc ttgtggagtc tggggggagcc ttgttccagc ctggggggtc cctggactc 60
tcttgtgcag tctctggaaat cgacccctagt ggctactaca tgaactgggt ccgtcaggct 120
ccagggtaaagg ggctggaggc ggtggggatc atgggttata atgggtccac atactacggc 180
agotggggcaga aaggccgatt caccatctcc agagacaaat ccaagacccac ggtgtatctt 240
caaataatggaca tgaggagact cgtgtgttatt tctgtgtctag agggggacatc 300
tggggccaaag ggaccctcggt caccgtctcg agggccctcca ccaagggccc atccgttcc 360
ccccctggcac cttccctccaa gggcacctct gggggccaaag cggggccctggg ctggctgtc 420
aaggactact tcccccggaaac ggtggggatc tctggggact caggccgccc gaccaggcc 480
gtgcacacact tcccggtgt ctacatggcc tcaggactct actcccttag cagcgtgggt 540
accgtgcctt ccaggcagctt gggcacccag acctacatctt gcaacgtgaa tcacaaggcc 600
agcaacacca aggtggacgc gagaggttgg cccaaatctt gtgacaaaac tcacacatgc 660
ccaccgtgcg caccactctgaa actccctgggg ggaccgttcgat tcttccctt ccccccacaaa 720
cccaaggaca ccctcatgtat ctccggacc cctggggatc catggctgtt ggtggacgtg 780
agccacaaag accctggggatc caagttcaac tggtaacgtgg acggcggtt ggtgcataat 840
gccaagacaa agccgcggga ggagcagttt gcaagcactt accgtgttgtt cagcgtctc 900
accgtgcgtcc accaggactgt gtcataatgg aaggagtttca agtgtcaatgtt ctccaaacaaa 960
ggccctcccgcc ccccccattgtat cccaaatggcc aaggggccggcc cccggaaacca 1020
caagtttacaatccctggggatc atccggggatc gggatgttttcccaacccatcc 1080
tgccgtgtca aagggttctat tcccaagcgtat atccgggtt ggtggggatc caatggggatc 1140
ccggagaaca actacaagac caccgttccgat gtcgtggactt ccggacggctc ctccatgttcc 1200
tacagcaagc tcaccgttgcgat caagggcggcc tggcggggatc gggatgttttcc 1260
gtgtatgtatc aggtgttgcgat caaccactac acggcggccatc ggtttccctt gttccgggt 1320
tgaatccatcc 1323

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What is claimed is:

1. A method of individual therapy in a patient suffering from migraine, comprising:
 (a) identifying a most bothersome symptom (MBS) of the patient, wherein the MBS is a symptom which is associated with the migraine of the patient and is most bothersome to the patient;
 (b) intravenously administering to the patient an effective amount of an anti-calcitonin gene related peptide (CGRP) antibody;
 (c) assessing changes in the MBS after the administration of (a); and
 (d) if the MBS is improved in the assessment of (c), further intravenously administering to the patient an effective amount of the anti-CGRP antibody,
 wherein the anti-CGRP antibody comprises:
 (A) a heavy chain variable domain (VH) comprising heavy chain complementarity-determining region (CDR) 1, 2, and 3 polypeptide sequences of SEQ ID NOS: 204, 206, and 208, respectively; and
 (B) a light chain variable domain (VL) comprising light chain CDR 1, 2, and 3 polypeptide sequences of SEQ ID NO: 224, 226, and 228, respectively.
2. The method of claim 1, wherein the assessing in (c) is performed at 1-12 hours, within 1 month, within 3 months, or within 6 months from the administering in (a).
3. The method of claim 1, wherein:
 (A) the amino acid sequence of the VH comprises SEQ ID NO: 202; and/or
 (B) the amino acid sequence of the VL comprises SEQ ID NO: 222.
4. The method of claim 1, wherein the anti-CGRP comprises:
 (A) a heavy chain polypeptide comprising SEQ ID NO: 201 or SEQ ID NO: 566; and/or
 (B) a light chain polypeptide comprising SEQ ID NO: 221.
5. The method of claim 1, wherein the MBS identified in (a) is not headache and not pain.
6. The method of claim 1, wherein the MBS identified in (a) is selected from the group consisting of: sensitivity to light (photophobia); nausea and/or vomiting; sensitivity to sound (phonophobia); aura; throbbing and/or pulsation; cognitive disruption; fatigue; mood changes; sensitivity to smell (osmophobia or olfactophobia); visual impact; pressure and/or tightness; dizziness; inactivity; sensory disturbance; sleep disturbance; and speech difficulty.

227

7. The method of claim 1, wherein the MBS identified in (a) is selected from the group consisting of: vomiting; throbbing and/or pulsation; cognitive disruption; fatigue; mood changes; sensitivity to smell (osmophobia or olfactophobia); visual impact; pressure and/or tightness; dizziness; inactivity; sensory disturbance; sleep disturbance; and speech difficulty. 5

8. The method of claim 1, wherein the effective amount in (b) and/or (d) is between about 100 mg and about 300 mg, optionally about 100 mg, about 125 mg, about 150 mg, 10 about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, or about 300 mg.

9. The method of claim 1, wherein the administering in (d) is performed about 10-14 weeks, optionally 11-13 weeks, further optionally about 12 weeks or about 3 months, after 15 the administering in (b).

10. The method of claim 1, wherein the administering in (d) is performed every 10-14 weeks, optionally every 11-13 weeks, further optionally every 12 weeks.

11. The method of claim 1, wherein the patient has 20 chronic migraine when the administering in (b) is performed.

12. The method of claim 1, wherein the patient has episodic migraine when the administering in (b) is performed. 25

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228