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(54) **ANTI-CD3 ANTIBODIES AND USES THEREOF**

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(57) **ABSTRACT**

The present disclosure relates generally to immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof) that can bind to the CD3 protein. The antibodies of the present technology are useful in methods for detecting and treating cancer or a CD3 -associated pathology in a subject in need thereof.

Specification includes a Sequence Listing.

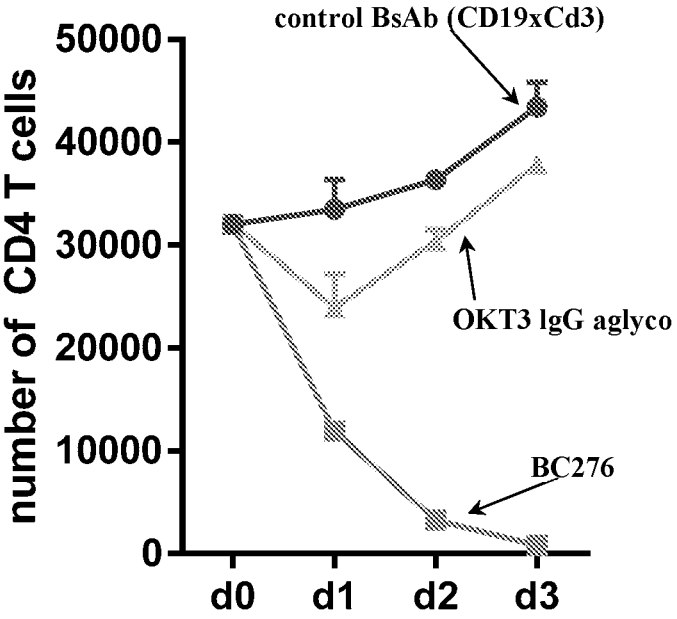


Figure 1A

Modular IgG-scFv

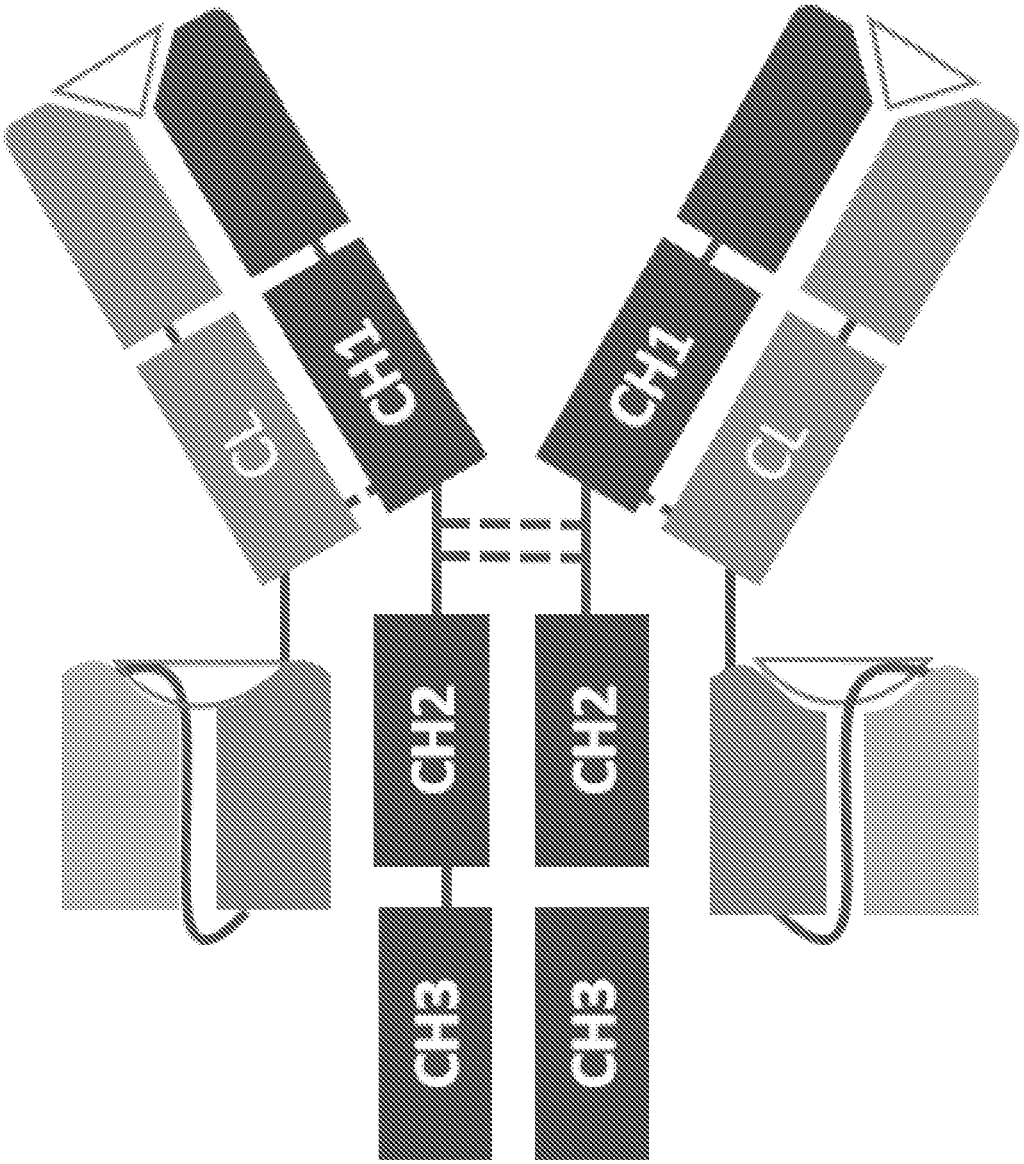
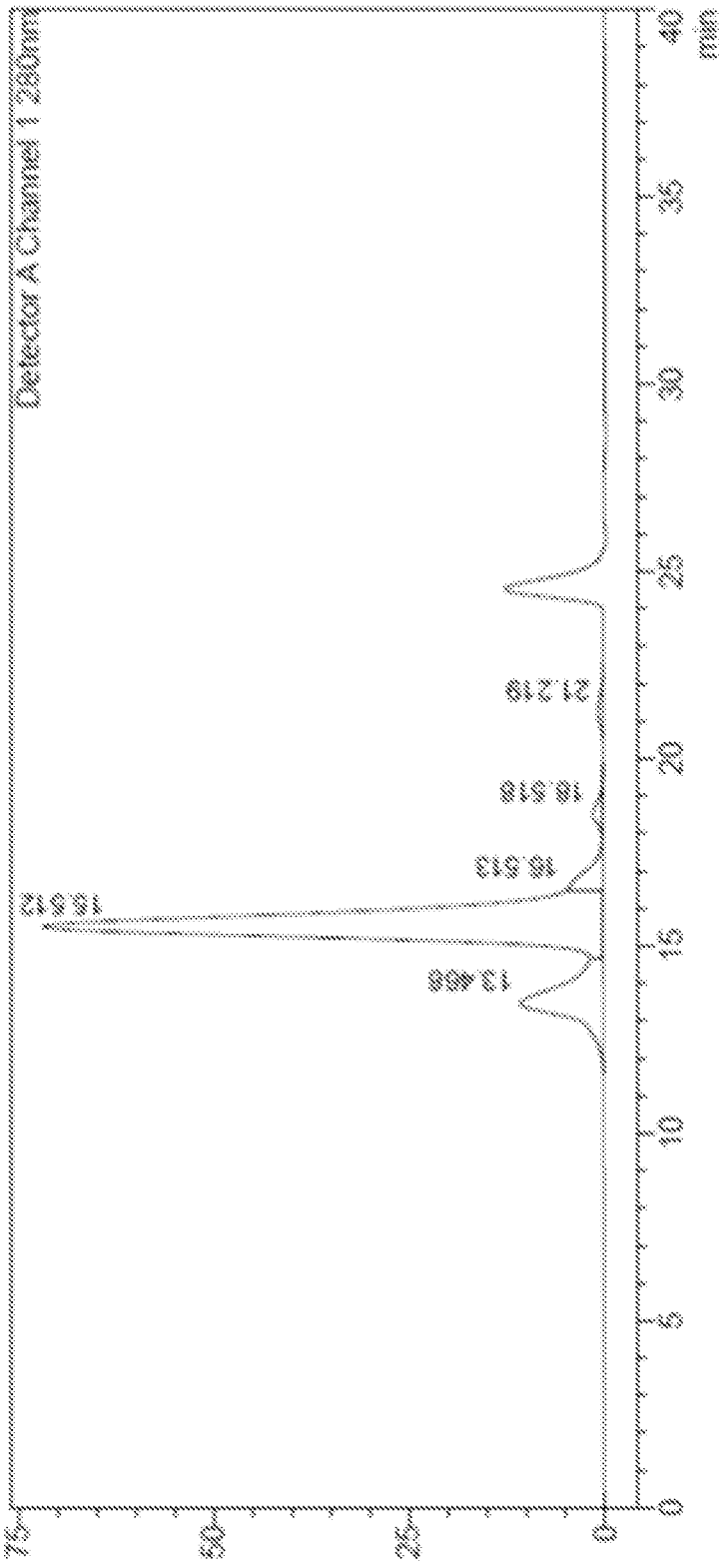


Figure 1B



Peak#	Ret. Time	Area	Height	Mark	Area%
1	13.468	649474	10046		16.092
2	15.512	3150675	71726	V M	78.066
3	16.513	155873	4577	SV M	3.862
4	18.518	47965	1108	T	1.188
5	21.219	31939	657		0.791
Total		4035926	88805		100.000

Figure 2

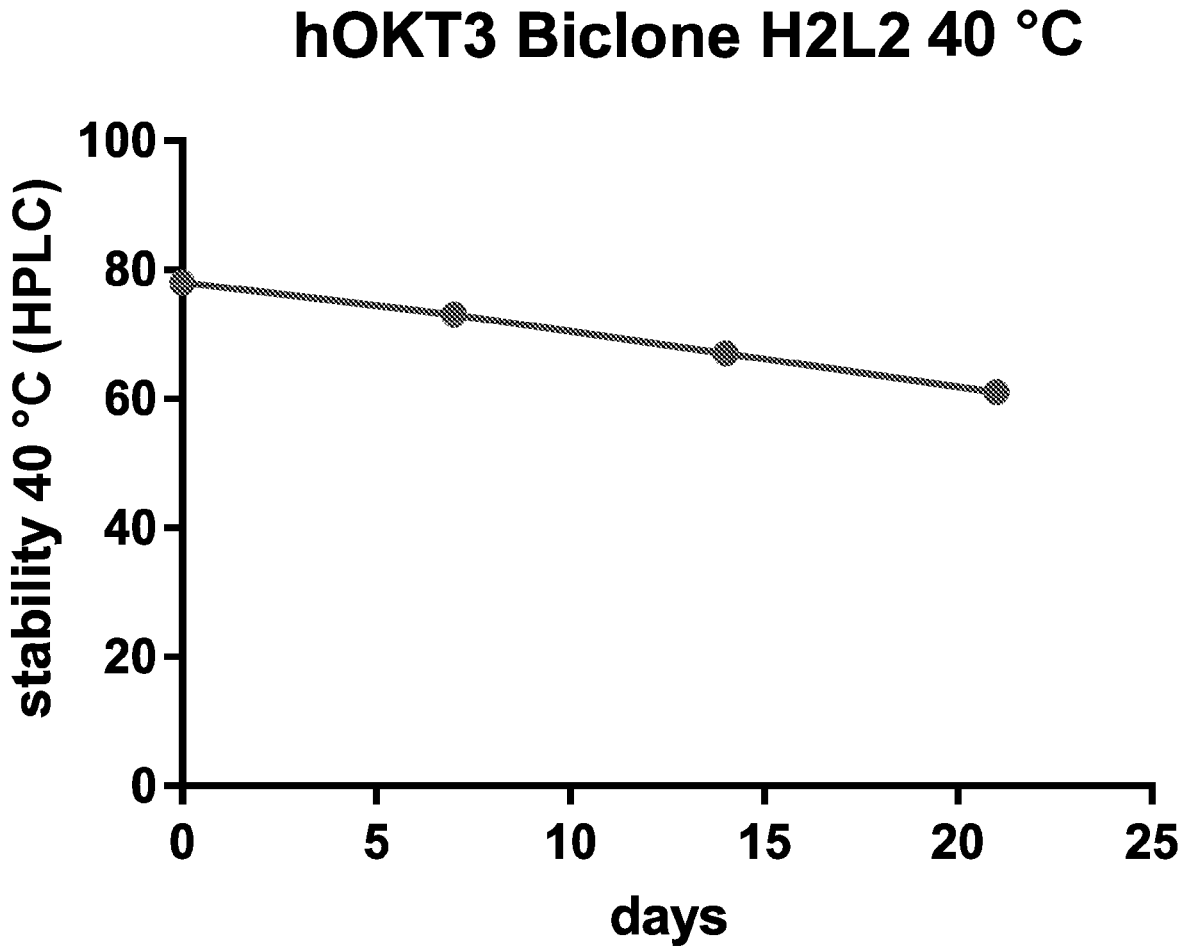

hOKT3 Biclone H2L2 40 °C
stability 40 °C (HPLC)
100
80
60
40
20
0
0
5
10
15
20
25
days

Figure 3A

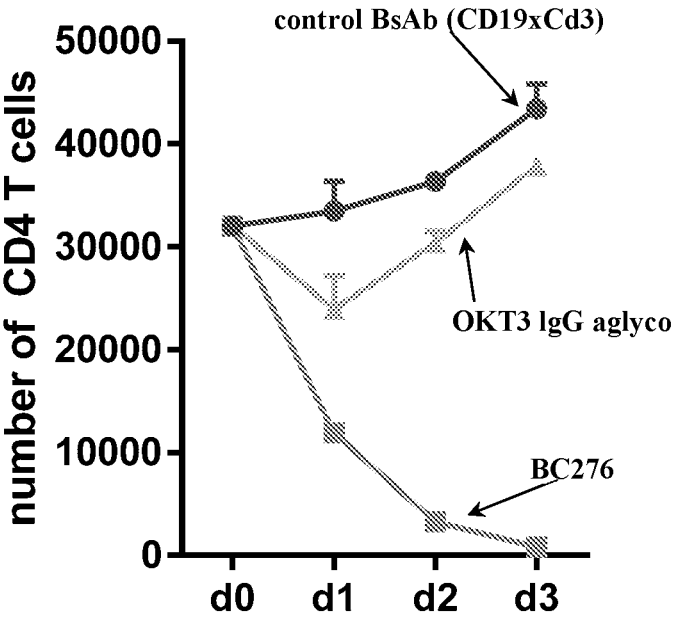


Figure 3B

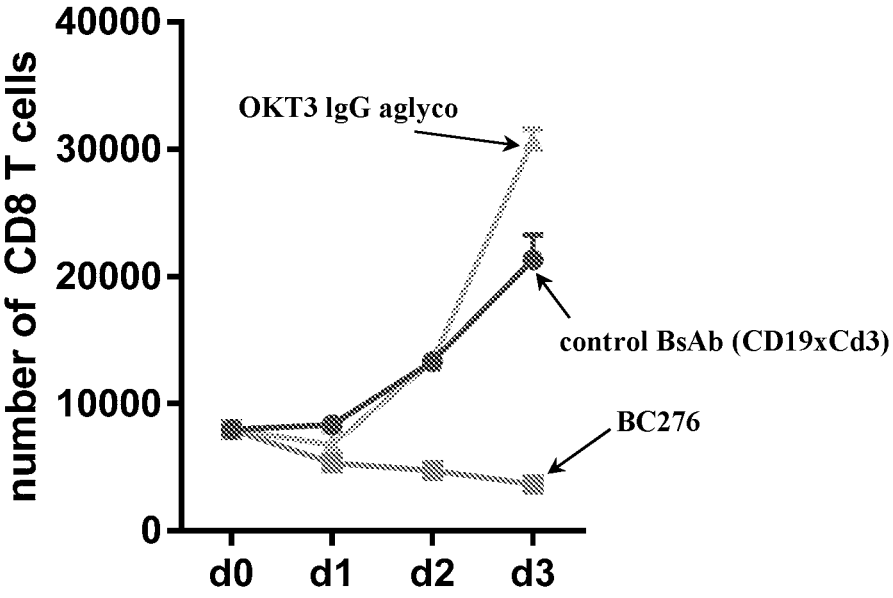


Figure 4A

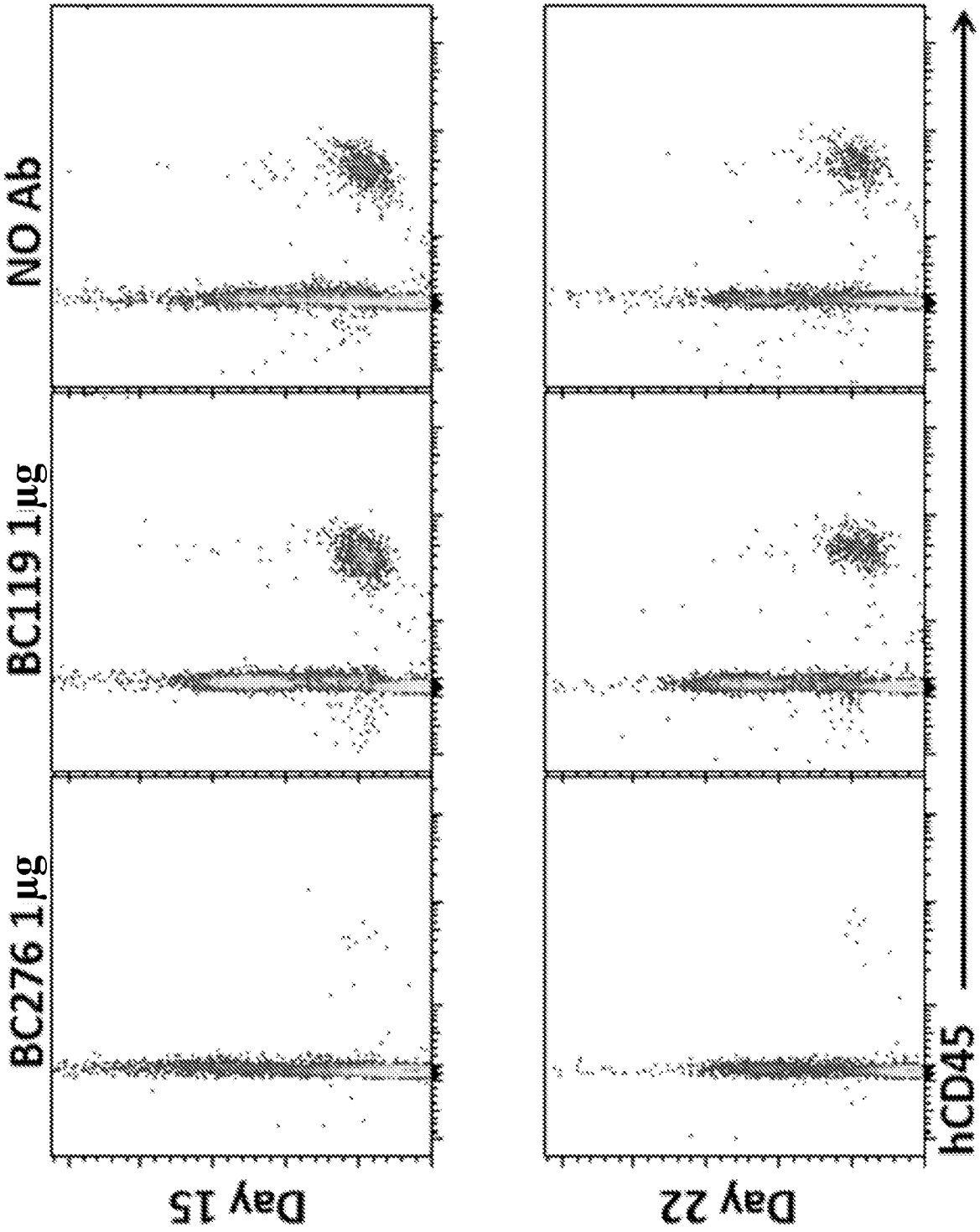


Figure 4B

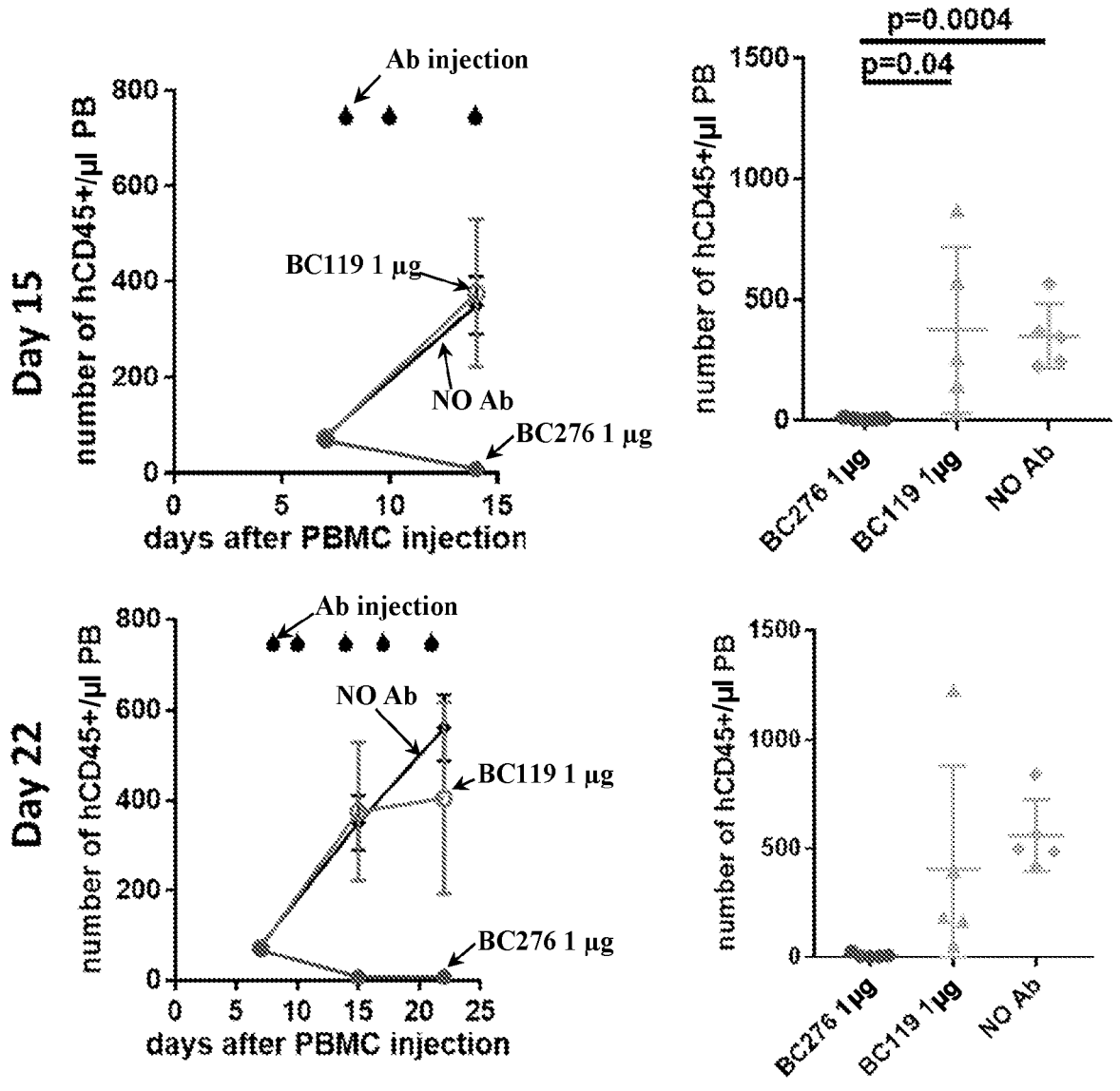

Day 15
Ab injection
number of hCD45+/µl PB
800
600
400
200
0
BC119 1 µg
NO Ab
BC276 1 µg
0
5
10
15
days after PBMC injection
p=0.0004
p=0.04
1500
1000
500
0
number of hCD45+/µl PB
BC276 1µg
BC119 1µg
NO Ab
Day 22
Ab injection
NO Ab
BC119 1 µg
BC276 1 µg
0
5
10
15
20
25
days after PBMC injection
1500
1000
500
0
BC276 1µg
BC119 1µg
NO Ab

Figure 5A

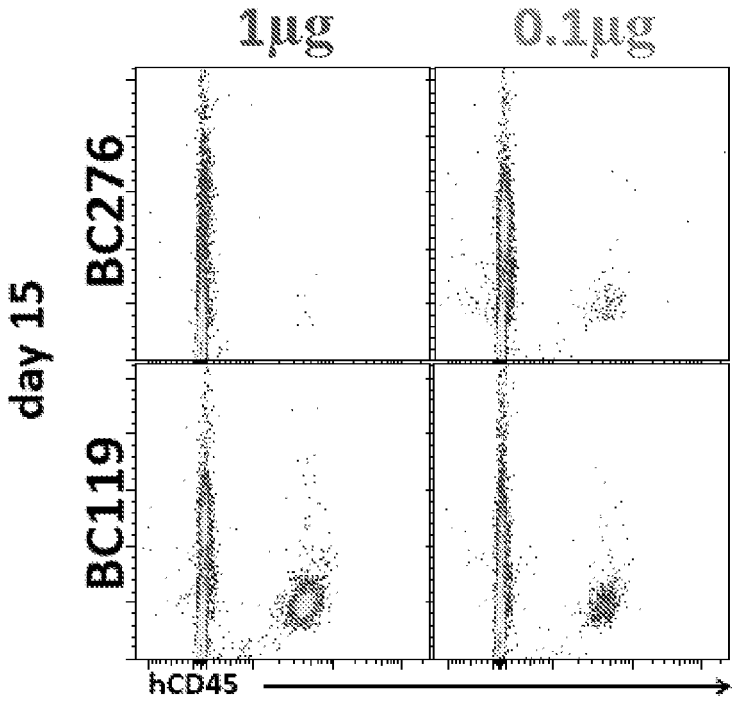


Figure 5B

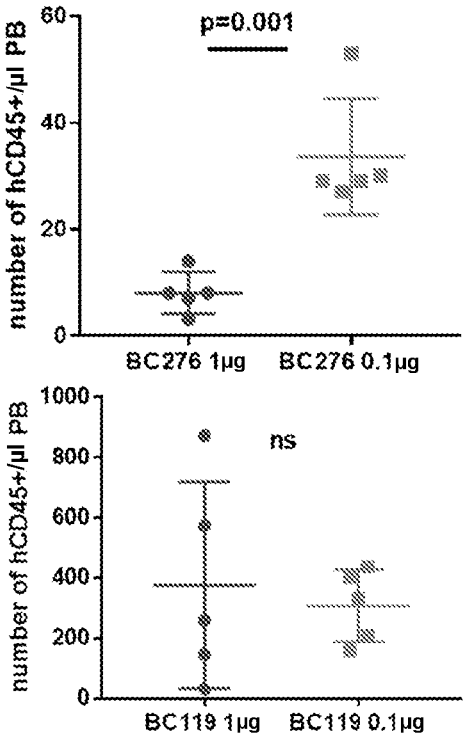


Figure 6A

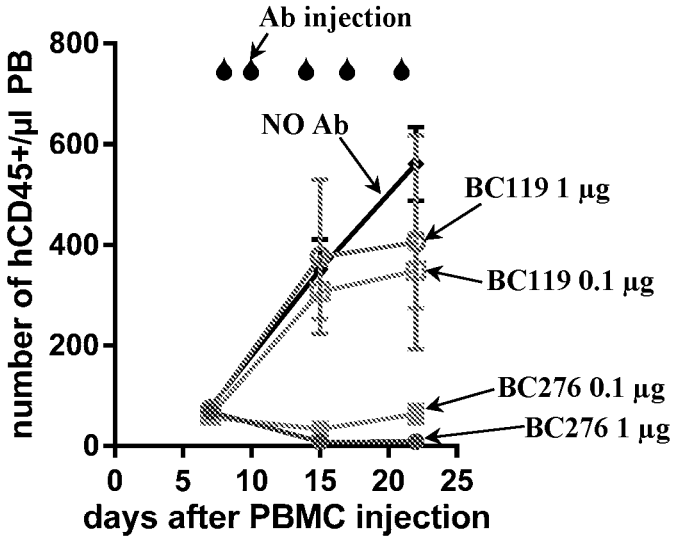


Figure 6B

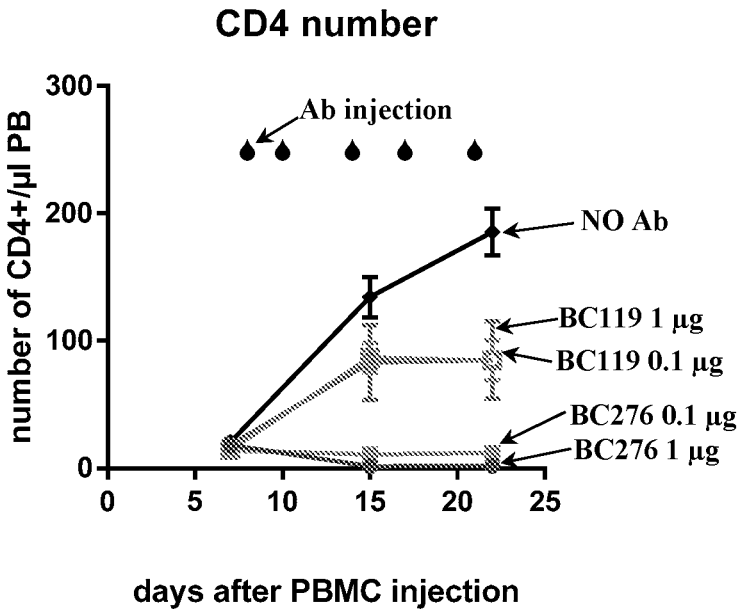


Figure 6C

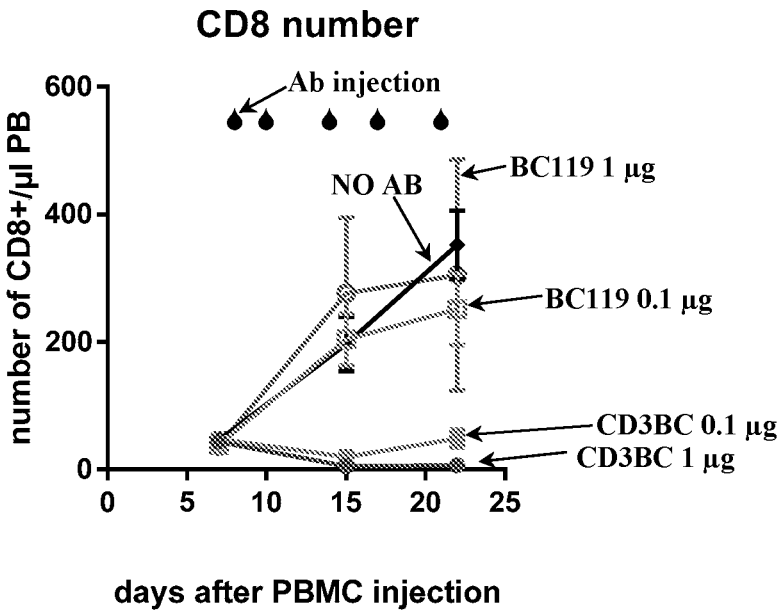

CD8 number
Ab injection
NO AB
BC119 1 μg
BC119 0.1 μg
CD3BC 0.1 μg
CD3BC 1 μg
number of CD8+/μl PB
600
400
200
0
0
5
10
15
20
25
days after PBMC injection

Figure 7

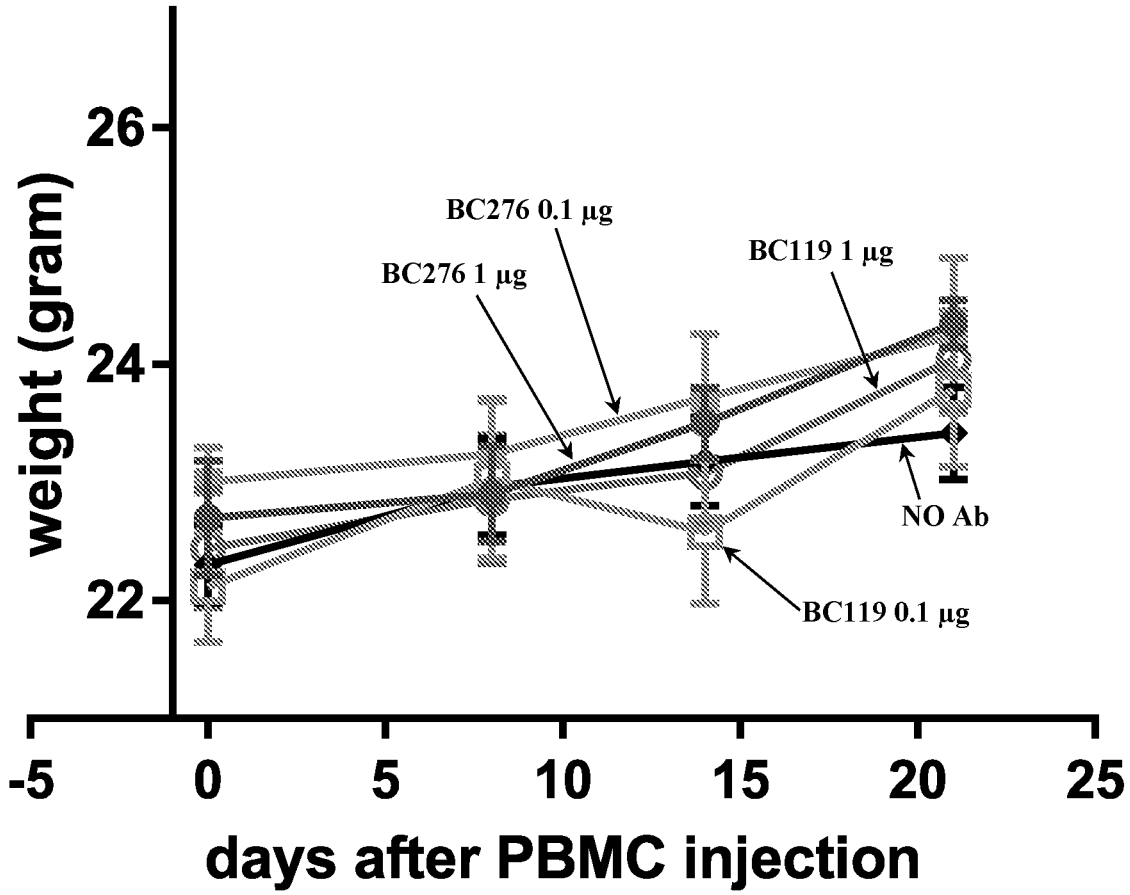

26
24
22
weight (gram)
BC276 0.1 µg
BC276 1 µg
BC119 1 µg
NO Ab
BC119 0.1 µg
-5
0
5
10
15
20
25
days after PBMC injection

Figure 8A

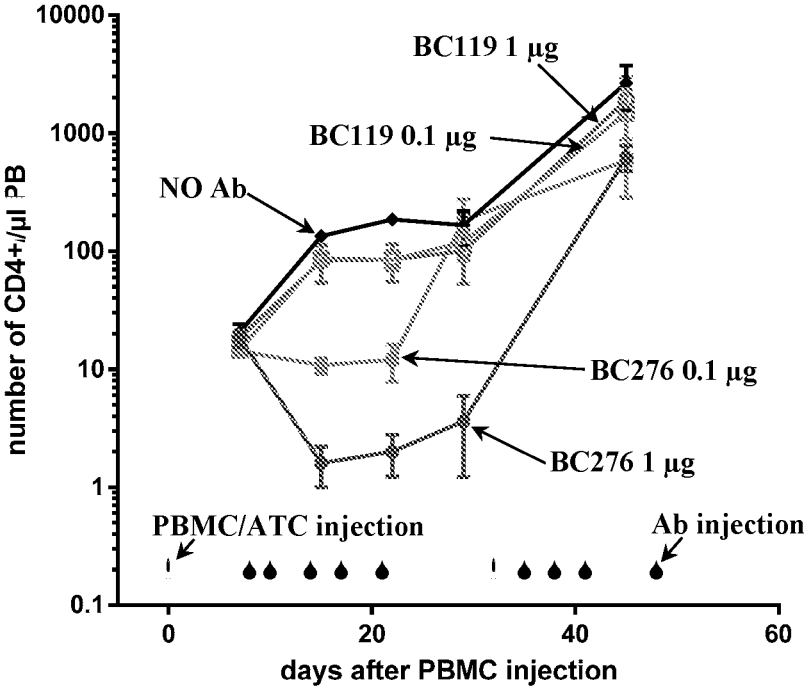


Figure 8B

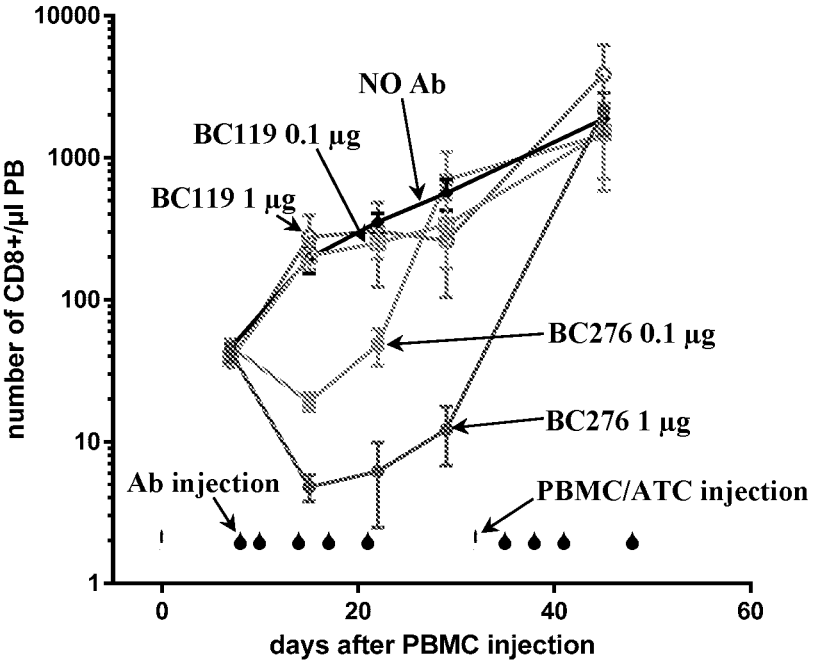


Figure 9

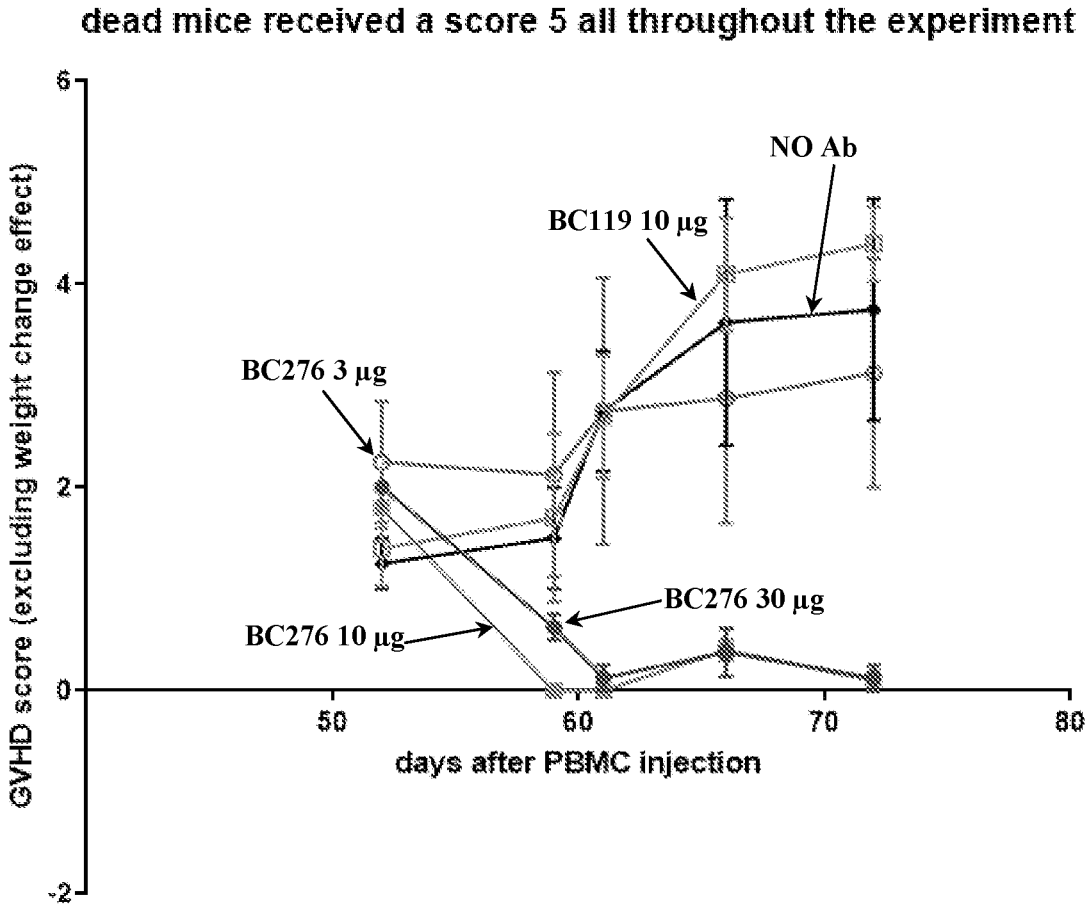

dead mice received a score 5 all throughout the experiment
GVHD score (excluding weight change effect)
6
4
2
0
-2
50
60
70
80
days after PBMC injection
NO Ab
BC119 10 µg
BC276 3 µg
BC276 30 µg
BC276 10 µg

Figure 10

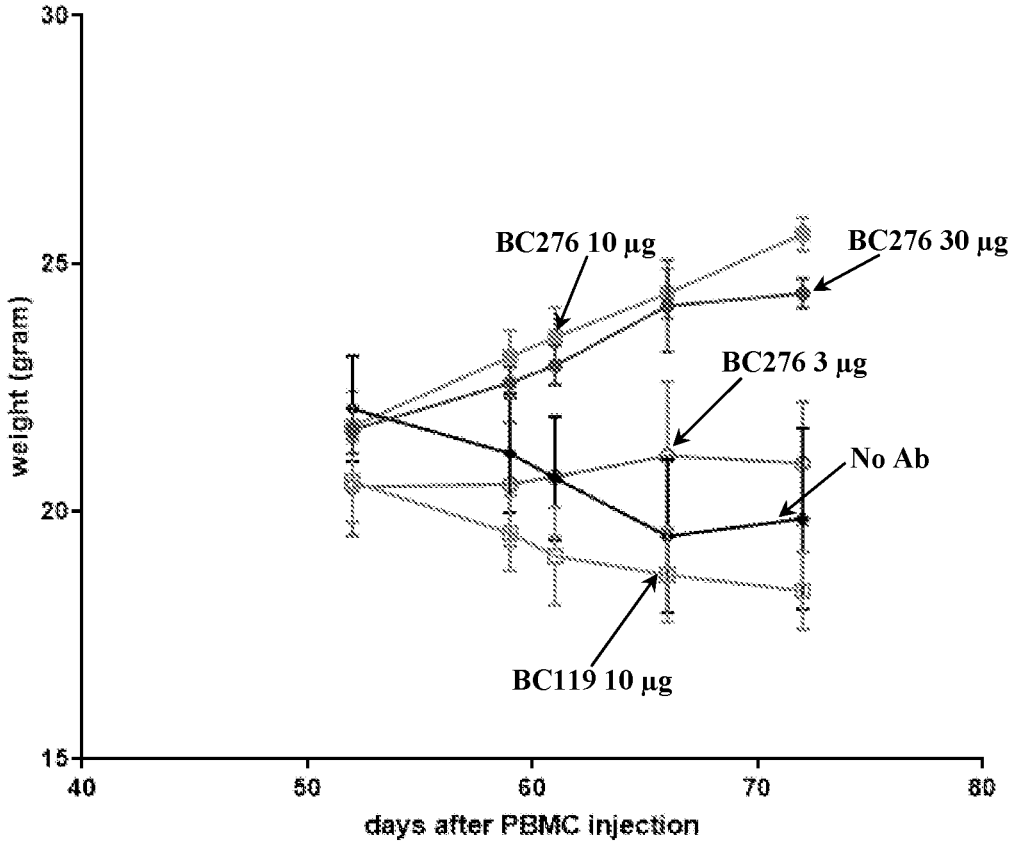

30
25
20
15
weight (gram)
40
50
60
70
80
days after PBMC injection
BC276 10 µg
BC276 30 µg
BC276 3 µg
No Ab
BC119 10 µg

Figure 11

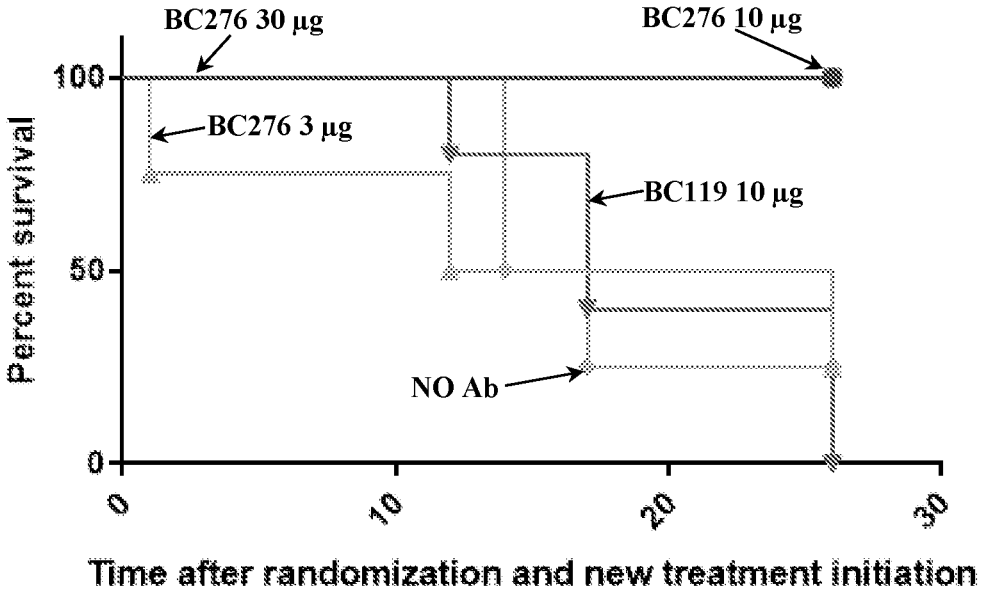

BC276 30 µg
BC276 10 µg
BC276 3 µg
BC119 10 µg
NO Ab
Percent survival
100
50
0
0
10
20
30
Time after randomization and new treatment initiation

Figure 12A

OKT3_VH (murine, humanness 72.4%) (SEQ ID NO: 1)

QVQLQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSR
GYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWG
QGTTLTVSS

VH-1 (humanness 85.7%) (SEQ ID NO: 7)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL
DYWGQGTTLTVSS

VH-2 (humanness 85.7%) (SEQ ID NO: 8)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG
YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYS
LDYWGQGTTLTVSS

VH-3 (humanness 85.7%) (SEQ ID NO: 9)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL
DYWGQGTTLTVSS

VH-4 (humanness 85.7%) (SEQ ID NO: 10)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHYSLD
YWGQGTTLTVSS

Figure 12A (contd.)

VH-1 H105 (humanness 85.7%) (SEQ ID NO: 5)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL DYWGCGTTLTVSS

VH-2 H105 (humanness 85.7%) (SEQ ID NO: 43)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYS LDYWGCGTTLTVSS

VH-3 H105 (humanness 85.7%) (SEQ ID NO: 44)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL DYWGCGTTLTVSS

VH-4 H105 (humanness 85.7%) (SEQ ID NO: 45)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHYSLD YWGCGTTLTVSS

Figure 12A (contd.)

VH-1 H44 (humanness 85.7%) (SEQ ID NO: 46)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQCLEWIGY INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL DYWGQGTTLTVSS

VH-2 H44 (humanness 85.7%) (SEQ ID NO: 47)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQCLEWMG YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYS LDYWGQGTTLTVSS

VH-3 H44 (humanness 85.7%) (SEQ ID NO: 48)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQCLEWIGY INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL DYWGQGTTLTVSS

VH-4 H44 (humanness 85.7%) (SEQ ID NO: 49)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQCLEWIGY INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHYSLD YWGQGTTLTVSS

Figure 12A (contd.)

VH-1 H100B (humanness 85.7%) (SEQ ID NO: 50)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSC
DYWGQGTTLTVSS

VH-2 H100B (humanness 85.7%) (SEQ ID NO: 51)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG
YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYS
CDYWGQGTTLTVSS

VH-3 H100B (humanness 85.7%) (SEQ ID NO: 52)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSC
DYWGQGTTLTVSS

VH-4 H100B (humanness 85.7%) (SEQ ID NO: 53)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY
INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHYSC
DYWGQGTTLTVSS

Figure 12A (contd.)

VH-1 H100 (humanness 85.7%) (SEQ ID NO: 54)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHCSL DYWGQGTTLTVSS

VH-2 H100 (humanness 85.7%) (SEQ ID NO: 55)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHCS LDYWGQGTTLTVSS

VH-3 H100 (humanness 85.7%) (SEQ ID NO: 56)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHCSL DYWGQGTTLTVSS

VH-4 H100 (humanness 85.7%) (SEQ ID NO: 57)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHCSLD YWGQGTTLTVSS

Figure 12A (contd.)

VH-1 H101 (humanness 85.7%) (SEQ ID NO: 58)

QVQLQQSGAEVAKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYAQKFQGRATLTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL CYWGQGTTLTVSS

VH-2 H101 (humanness 85.7%) (SEQ ID NO: 59)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYS LCYWGQGTTLTVSS

VH-3 H101 (humanness 85.7%) (SEQ ID NO: 60)

QVQLVQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRATMTTDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL CYWGQGTTLTVSS

VH-4 H101 (humanness 85.7%) (SEQ ID NO: 61)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGY INPSRGYTNYNQKFKDRVTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHYSLC YWGQGTTLTVSS

Figure 12B

OKT3_VL (murine, humanness 61.1%) (SEQ ID NO: 11)

QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTSKLASGV

PAHFRGSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEINR

VL-1 (humanness 85.2%) (SEQ ID NO: 15)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRLIYDTSK

LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-2 (humanness 85.2%) (SEQ ID NO: 16)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSK

LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-3 (humanness 85.2%) (SEQ ID NO: 17)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYDTSKL

ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-4 (humanness 85.2%) (SEQ ID NO: 18)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYDTSKL

ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-5 (humanness 85.2%) (SEQ ID NO: 19)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSK

LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-6 (humanness 85.2%) (SEQ ID NO: 20)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLWIYDTSK

LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 12B (contd.)

VL-1 L100 (humanness 85.2%) (SEQ ID NO: 62)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGCGTKLEINR

VL-2 L100 (humanness 85.2%) (SEQ ID NO: 63)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGCGTKLEINR

VL-3 L100 (humanness 85.2%) (SEQ ID NO: 64)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYDTSKL
ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGCGTKLEINR

VL-4 L100 (humanness 85.2%) (SEQ ID NO: 65)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYDTSKL
ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGCGTKLEINR

VL-5 L100 (humanness 85.2%) (SEQ ID NO: 66)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGCGTKLEINR

VL-6 L100 (humanness 85.2%) (SEQ ID NO: 67)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLWIYDTSK
LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGCGTKLEINR

Figure 12B (contd.)

VL-1 L43 (humanness 85.2%) (SEQ ID NO: 68)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKCPKRLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-2 L43 (humanness 85.2%) (SEQ ID NO: 69)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKCPKLLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-3 L43 (humanness 85.2%) (SEQ ID NO: 70)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKCPKLLIYDTSKL
ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-4 L43 (humanness 85.2%) (SEQ ID NO: 71)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKCPKLLIYDTSKL
ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-5 L43 (humanness 85.2%) (SEQ ID NO: 72)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKCPKRWIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-6 L43 (humanness 85.2%) (SEQ ID NO: 73)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKCPKLWIYDTSK
LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 12B (contd.)

VL-1 L49 (humanness 85.2%) (SEQ ID NO: 74)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRLICDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-2 L49 (humanness 85.2%) (SEQ ID NO: 75)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLICDTSK
LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-3 L49 (humanness 85.2%) (SEQ ID NO: 76)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLICDTSKL
ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-4 L49 (humanness 85.2%) (SEQ ID NO: 77)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLICDTSKL
ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-5 L49 (humanness 85.2%) (SEQ ID NO: 78)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWICDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-6 L49 (humanness 85.2%) (SEQ ID NO: 79)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLWICDTSK
LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 12B (contd.)

VL-1 L50 (humanness 85.2%) (SEQ ID NO: 80)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRLIYCTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-2 L50 (humanness 85.2%) (SEQ ID NO: 81)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYCTSK
LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-3 L50 (humanness 85.2%) (SEQ ID NO: 82)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYCTSKL
ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-4 L50 (humanness 85.2%) (SEQ ID NO: 83)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLLIYCTSKL
ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-5 L50 (humanness 85.2%) (SEQ ID NO: 84)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYCTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-6 L50 (humanness 85.2%) (SEQ ID NO: 85)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKLWIYCTSK
LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 12B (contd.)

VL-1 L46 (humanness 85.2%) (SEQ ID NO: 86)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKCLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-2 L46 (humanness 85.2%) (SEQ ID NO: 87)

DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKCLIYDTSK
LASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-3 L46 (humanness 85.2%) (SEQ ID NO: 88)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKCLIYDTSKL
ASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-4 L46 (humanness 85.2%) (SEQ ID NO: 89)

DIQLTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKCLIYDTSKL
ASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-5 L46 (humanness 85.2%) (SEQ ID NO: 90)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKCWIYDTSK
LASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

VL-6 L46 (humanness 85.2%) (SEQ ID NO: 91)

DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKCWIYDTSK
LASGVPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 13A

BC276 (hOKT3 H2L2DS) Light chain full amino acid sequence (N to C terminal) [signal peptide-hOKT3 L2-CL-linker-hOKT3 VH2 H44-linker-hOKT3 VL2 L100] (SEQ ID NO: 21)

MGWSCIILFLVATATGVHS*DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTK LEINR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS***G GGGSGGGGSGGGGS****QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQ CLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHY SLDYWGQGTTLTVSS****GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS****DIQMTQSPSSLSA SVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTIS SMQPEDFATYYCQQWSSNPFTFGCGTKLEINR*

BC276 (hOKT3 H2L2DS) Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 22)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGTGCACT
CCGACATCCAGATGACCCAGTCTCCTAGCTCCCTGAGCGCCTCCGTGGGCGATAG
GGTGACCATGACATGCTCTGCCTCTAGCTCCGTGAGCTACATGAACTGGTATCAG
CAGAAGCCCGGCAAGGCCCCTAAGCTGCTGATCTACGACACATCTAAGCTGGCC
AGCGGCGTGCCCTCCAGATTCTCTGGCAGCGGCTCCGGCACCGACTTTACCCTGA
CAATCTCTAGCATGCAGCCAGAGGATTTCGCCACATACTATTGTCAGCAGTGGTC
CTCTAACCCCTTCACCTTTGGCTCCGGCACAAAGCTGGAGATCAATCGGACCGTG
GCCGCCCCCTCCGTGTTCATCTTCCCCCCCTCCGACGAGCAGCTGAAGTCCGGCA
CCGCCTCCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCA
GTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAGTCCGTGACCGA
GCAGGACTCCAAGGACTCCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAG
GCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTG
TCCTCCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGC
GGCTCTGGAGGAGGAGGCAGCGGCGGAGGAGGCTCCCAGGTGCAGCTGCAGCA
GTCCGGCGCCGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAGGC
CTCTGGCTACACCTTCACACGGTATACCATGCACTGGGTGAGACAGGCCCCAGGC
CAGTGTCTGGAGTGGATGGGCTACATCAACCCCAGCCGGGGCTACACAAACTAT
AATCAGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGCACC
GCCTATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATTGC
GCCCGGTACTATGACGATCACTACTCCCTGGACTATTGGGGCCAGGGCACCACAC
TGACCGTGAGCTCCGGAGGAGGAGGCTCTGGCGGCGGCGGCAGCGGCGGCGGA
GGCTCCGGAGGCGGCGGCTCTGGGGGAGGCGGCAGCGGCGGCGGCGGCTCCGA
CATCCAGATGACACAGAGCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGGTG
ACCATGACATGTTCTGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCAGA
AGCCCGGCAAGGCCCCTAAGCTGCTGATCTACGATACCTCTAAGCTGGCCAGCG
GAGTGCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACAAT
CTCCTCTATGCAGCCTGAGGATTTCGCCACATACTATTGCCAGCAGTGGAGCTCC
AACCCATTCACCTTTGGCTGTGGCACAAAGCTGGAGATCAATAGA

Figure 13B

BC276 or BC276.1 (hOKT3 H2) Heavy chain full amino acid sequence (N to C terminal)

[signal peptide-hOKT3 VH2-CH1-3] (SEQ ID NO: 23)

MGWSCIILFLVATATGVHS*QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQ APGQGLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYY DDHYSLDYWGQGTTLTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

BC276.1 (hOKT3 H2) Heavy chain full nucleotide sequence (SEQ ID NO: 24)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGTGCACA GCCAGGTGCAGCTGCAGCAGTCCGGAGCAGAGGTGGCAAAGCCAGGAGCCTCCG TGAAGGTGTCTTGCAAGGCCAGCGGCTACACCTTCACACGGTATACCATGCACTG GGTGAGACAGGCACCAGGACAGGGCCTGGAGTGGATGGGCTACATCAACCCTTC TAGGGGCTACACAAACTATAATCAGAAGTTTAAGGACAGGGCCACCCTGACACG CGATAAGTCTATCAGCACCGCCTATATGGAGCTGTCCCGGCTGAGATCTGACGAT ACAGCCGTGTACTATTGTGCCAGATACTATGACGATCACTACAGCCTGGACTATT GGGGCCAGGGCACCACACTGACCGTGAGCTCCGCCTCCACCAAGGGCCCCTCTG TGTTTCCTCTGGCCCCCTCCAGCAAGTCCACCTCTGGTGGAACAGCCGCCCTGGG CTGCCTCGTGAAGGACTACTTTCCCGAGCCCGTGACCGTGTCCTGGAACTCTGGC GCTCTGACCTCTGGCGTGCACACCTTCCCTGCTGTGCTGCAGTCTAGCGGCCTGT ACTCCCTGTCCTCCGTCGTGACAGTGCCCTCCAGCTCTCTGGGCACCCAGACCTA CATCTGCAACGTGAACCACAAGCCCTCCAATACCAAGGTGGACAAGCGGGTGGA ACCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTG CTGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGA TCTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCC TGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGAC CAAGCCTAGAGAGGAACAGTACGCCTCCACCTACCGGGTGGTGTCCGTGCTGAC AGTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAA CAAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCC CCGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAA CCAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTG GAATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTG CTGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCC GGTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACA ACCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAA

Figure 13C

BC276.1 (hOKT3 H2L2) Light chain full amino acid sequence (N to C terminal) [signal peptide-hOKT3 L2-CL-linker-hOKT3 VH2-linker-hOKT3 VL2] (SEQ ID NO: 92)

MGWSCIILFLVATATGVHS*DIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTK LEINR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS***G GGGSGGGGSGGGGS****QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQ GLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHY SLDYWGQGTTLTVSS****GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS****DIQMTQSPSSLSA SVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTIS SMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

BC276.1 (hOKT3 H2L2) Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 93)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGTGCACT
CCGACATCCAGATGACCCAGTCTCCTAGCTCCCTGAGCGCCTCCGTGGGCGATAG
GGTGACCATGACATGCTCTGCCTCTAGCTCCGTGAGCTACATGAACTGGTATCAG
CAGAAGCCCGGCAAGGCCCCTAAGCTGCTGATCTACGACACATCTAAGCTGGCC
AGCGGCGTGCCCTCCAGATTCTCTGGCAGCGGCTCCGGCACCGACTTTACCCTGA
CAATCTCTAGCATGCAGCCAGAGGATTTCGCCACATACTATTGTCAGCAGTGGTC
CTCTAACCCCTTCACCTTTGGCTCCGGCACAAAGCTGGAGATCAATCGGACCGTG
GCCGCCCCCTCCGTGTTCATCTTCCCCCCCTCCGACGAGCAGCTGAAGTCCGGCA
CCGCCTCCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCA
GTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAGTCCGTGACCGA
GCAGGACTCCAAGGACTCCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAG
GCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTG
TCCTCCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGA
GGATCTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTGCAGCA
GTCCGGAGCAGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAGG
CCTCTGGCTACACCTTCACACGGTATACCATGCACTGGGTGAGACAGGCACCAG
GACAGGGCCTGGAGTGGATGGGCTACATCAACCCCTCTCGGGGCTACACAAACT
ATAATCAGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGCA
CCGCCTATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATTG
TGCCCGGTACTATGACGATCACTACAGCCTGGACTATTGGGGCCAGGGCACCAC
ACTGACCGTGAGCTCTGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCGGAG
GAGGCTCCGGAGGAGGCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGCTCC
GACATCCAGATGACACAGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGG
TGACCATGACATGCTCTGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCA
GAAGCCCGGCAAGGCCCCTAAGCTGCTGATCTACGATACCTCTAAGCTGGCCAG
CGGAGTGCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACA
ATCTCCTCTATGCAGCCTGAGGATTTCGCCACATACTATTGTCAGCAGTGGAGCT
CCAACCCATTCACCTTTGGCAGCGGCACAAAGCTGGAGATCAATAGA

Figure 14A

h3F8 x hOKT3 L2H2 Light chain full amino acid sequence (N to C terminal) [signal peptide-h3F8-CL-linker-hOKT3 VH2-linker-hOKT3 VL2] (SEQ ID NO: 94)

MGWSCIILFLVATATG*EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAP RLLIYSASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKR*TV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGGGSGG GGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMG YINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDYWG QGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS****DIQMTQSPSSLSASVGD RVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQP EDFATYYCQQWSSNPFTFGSGTKLEINR*

h3F8 x hOKT3 L2H2 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 95)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGATCG
TGATGACACAGACCCCTGCCACCCTGTCCGTGTCTGCTGGCGAGAGAGTGACCAT
TACCTGCAAGGCCTCCCAGTCCGTGTCCAACGACGTGACCTGGTATCAGCAGAA
GCCCGGCCAGGCCCCCAGACTGCTGATCTACTCCGCCTCCAACCGGTACTCTGGC
GTGCCCGCTAGATTCTCCGGCTCTGGCTACGGCACCGAGTTTACCTTCACCATCT
CCTCCGTGCAGTCCGAGGACTTCGCCGTGTACTTCTGTCAGCAAGACTACTCCAG
CTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGT
GTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTG
TGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAG
GACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGA
AGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGA
CCAAGTCTTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGAGGATCTGGCGGAG
GTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTGCAGCAGTCCGGAGCAGAG
GTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACC
TTCACACGGTATACCATGCACTGGGTGAGACAGGCACCAGGACAGGGCCTGGAG
TGGATGGGCTACATCAACCCCTCTCGGGGCTACACAAACTATAATCAGAAGTTTA
AGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGCACCGCCTATATGGAGC
TGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATTGTGCCCGGTACTATGA
CGATCACTACAGCCTGGACTATTGGGGCCAGGGCACCACACTGACCGTGAGCTC
TGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCGGAGGAGGCTCCGGAGGAG
GCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGCTCCGACATCCAGATGACAC
AGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGGTGACCATGACATGCTC
TGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCAGAAGCCCGGCAAGGC
CCCTAAGCTGCTGATCTACGATACCTCTAAGCTGGCCAGCGGAGTGCCTTCCCGC
TTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACAATCTCCTCTATGCAGC
CTGAGGATTTCGCCACATACTATTGTCAGCAGTGGAGCTCCAACCCATTCACCTT
TGGCAGCGGCACAAAGCTGGAGATCAATAGA

Figure 14B

h3F8 Heavy chain full amino acid sequence (N to C terminal) **[signal peptide-h3F8-CH1-3] (SEQ ID NO: 96)**

MGWSCIILFLVATATGVHS*QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQP PGKGLEWLGVIWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG HYGYALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

h3F8 Heavy chain full nucleotide sequence **(SEQ ID NO: 97)**

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTGCACA GCCAGGTGCAGCTGGTGGAGTCCGGCCCCGGCGTGGTGCAGCCCGGCCGGTCCC TGCGGATCTCCTGCGCCGTGTCCGGCTTCTCCGTGACCAACTACGGCGTGCACTG GGTGCGACAGCCTCCAGGCAAGGGCCTGGAGTGGCTGGGCGTGATCTGGGCCGG CGGCATCACCAACTACAACTCCGCCTTCATGTCCCGGCTGACCATCTCCAAGGAC AACTCCAAGAACACCGTGTACCTGCAGATGAACTCCCTGCGGGCCGAGGACACC GCCATGTACTACTGCGCCTCCCGGGGCGGCCACTACGGCTACGCCCTGGACTACT GGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCCTCCACCAAGGGCCCCTCTGT GTTTCCTCTGGCCCCCTCCAGCAAGTCCACCTCTGGTGGAACAGCCGCCCTGGGC TGCCTCGTGAAGGACTACTTTCCCGAGCCCGTGACCGTGTCCTGGAACTCTGGCG CTCTGACCTCTGGCGTGCACACCTTCCCTGCTGTGCTGCAGTCTAGCGGCCTGTA CTCCCTGTCCTCCGTCGTGACAGTGCCCTCCAGCTCTCTGGGCACCCAGACCTAC ATCTGCAACGTGAACCACAAGCCCTCCAATACCAAGGTGGACAAGCGGGTGGAA CCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGC TGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGAT CTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCT GAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACC AAGCCTAGAGAGGAACAGTACGCCTCCACCTACCGGGTGGTGTCCGTGCTGACA GTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAAC AAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCC CGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGG AATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGC TGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCG GTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAA

Figure 15A

hM195 x hOKT3 L2H2 Light chain full amino acid sequence (N to C terminal) **[signal peptide-hM195-CL-linker-hOKT3 VH2-linker-hOKT3 VL2] (SEQ ID NO: 98)**

MGWSCIILFLVATATG*EIVLTQSPATLSVSLGERATISCRASESVDNYGISFMNWFQQKPG QPPRLLIYAASNQGSGVPARFSGSGPGTDFTLTISSMEPEDFAMYFCQQSKEVPWTFGGG TKLEIKR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS **GGGGSGGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAP GQGLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYD DHYSLDYWGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS**DIQMTQS PSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTD FTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hM195 x hOKT3 L2H2 Light chain full nucleotide sequence. Signal sequence underlined **(SEQ ID NO: 99)**

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGATCG
TGCTGACTCAGTCTCCTGCCACCCTGTCCGTGTCCCTGGGCGAGAGAGCCACCAT
CTCTTGCAGAGCCTCCGAGTCCGTGGACAACTACGGCATCTCCTTCATGAACTGG
TTCCAGCAGAAGCCCGGCCAGCCTCCTCGGCTGCTGATCTACGCCGCTTCCAATC
AGGGCTCTGGCGTGCCCGCTAGATTCTCCGGATCTGGCCCTGGCACCGACTTTAC
CCTGACCATCTCCTCCATGGAACCCGAGGACTTCGCCATGTACTTTTGCCAGCAG
TCCAAAGAGGTGCCCTGGACCTTTGGCGGAGGCACCAAGCTGGAAATCAAGCGG
ACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGT
CCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAA
GGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGT
GACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTGACCCTG
AGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACCCACCAG
GGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGCACTAGTGGCG
GCGGAGGATCTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTG
CAGCAGTCCGGAGCAGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGC
AAGGCCTCTGGCTACACCTTCACACGGTATACCATGCACTGGGTGAGACAGGCA
CCAGGACAGGGCCTGGAGTGGATGGGCTACATCAACCCCTCTCGGGGCTACACA
AACTATAATCAGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAGTCTATC
AGCACCGCCTATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCCGTGTAC
TATTGTGCCCGGTACTATGACGATCACTACAGCCTGGACTATTGGGGCCAGGGCA
CCACACTGACCGTGAGCTCTGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCG
GAGGAGGCTCCGGAGGAGGCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGC
TCCGACATCCAGATGACACAGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATA
GGGTGACCATGACATGCTCTGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCA
GCAGAAGCCCGGCAAGGCCCCTAAGCTGCTGATCTACGATACCTCTAAGCTGGC
CAGCGGAGTGCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTG
ACAATCTCCTCTATGCAGCCTGAGGATTTCGCCACATACTATTGTCAGCAGTGGA
GCTCCAACCCATTCACCTTTGGCAGCGGCACAAAGCTGGAGATCAATAGA

Figure 15B

hM195 Heavy chain full amino acid sequence (N to C terminal) **[signal peptide-M195-CH1-3] (SEQ ID NO: 100)**

MGWSCIILFLVATATG*EVQLVQSGPEVVKPGASVKISCKASGYTFTDYNMHWVRQAHGQ SLEWIGYIYPYNGGTGYNQKFKSRATLTVDNSASTAYMEVSSLRSEDTAVYYCARGRPAMD YWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

hM195 Heavy chain full nucleotide sequence (SEQ ID NO: 101)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGGTGC
AGCTGGTGCAGTCTGGACCCGAGGTCGTGAAGCCTGGCGCCTCCGTGAAGATCT
CCTGCAAGGCCTCCGGCTACACCTTCACCGACTACAACATGCACTGGGTGCGACA
GGCCCACGGCCAGTCCCTGGAATGGATCGGCTACATCTACCCCTACAACGGCGG
CACCGGCTACAACCAGAAGTTCAAGTCTCGGGCCACCCTGACCGTGGACAACTC
TGCCTCTACCGCCTACATGGAAGTGTCCTCCCTGAGATCCGAGGACACCGCCGTG
TACTACTGCGCCAGAGGCAGACCCGCCATGGACTATTGGGGCCAGGGCACCCTC
GTGACCGTGTCTAGCGCTTCTACCAAGGGCCCCTCTGTGTTTCCTCTGGCCCCCTC
CAGCAAGTCCACCTCTGGTGGAACAGCCGCCCTGGGCTGCCTCGTGAAGGACTA
CTTTCCCGAGCCCGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCTCTGGCGTG
CACACCTTCCCTGCTGTGCTGCAGTCTAGCGGCCTGTACTCCCTGTCCTCCGTCGT
GACAGTGCCCTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAACCAC
AAGCCCTCCAATACCAAGGTGGACAAGCGGGTGGAACCCAAGTCCTGCGACAAG
ACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCGTGTT
CCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGAAGTG
ACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAATTGGT
ACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACAG
TACGCCTCCACCTACCGGGTGGTGTCCGTGCTGACAGTGCTGCACCAGGACTGGC
TGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAACAAGGCCCTGCCTGCCCCCA
TCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTGTACA
CACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACCTGTC
TCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACGGCCA
GCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCTCATTC
TTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAGGGCAACGTG
TTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGTCCC
TGTCCCTGAGCCCCGGCAAA

Figure 16A

hGPC3 x hOKT3 H2L5 Light chain full amino acid sequence (N to C terminal) [signal peptide-hGPC3-CL-linker-hOKT3 VH2-linker-hOKT3 VL5] (SEQ ID NO: 102)

MGWSCIILFLVATATG*DIVMTQSPSSLVVSIGERVTMNCKSSQSLLYSSNQKNYLAWYQQ KPGQSPKLLIYWASSRESGVPDRFSGSGSGTDFTLTISSVKAEDVAVYYCQQYYNYPLTFGA GTKLELKR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC TS**GGGGSGGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQA PGQGLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYD DHYSLDYWGQGTTLTVSS**GGGGSGGGGSGGGGSGGGGSGGGGS***DIQMTQS PSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLASGVPSRFSGSGSGTD FTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hGPC3 x hOKT3 H2L5 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 103)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGACATCG
TGATGACCCAGTCCCCCTCCTCCCTGGTGGTGTCCATTGGCGAGCGCGTGACCAT
GAACTGCAAGTCCTCCCAGTCCCTGCTGTACTCCTCCAACCAGAAGAACTACCTG
GCCTGGTATCAGCAGAAGCCCGGCCAGTCCCCTAAGCTGCTGATCTACTGGGCCT
CCAGCCGCGAGTCTGGCGTGCCCGATAGATTCTCCGGCTCTGGCTCTGGCACCGA
CTTTACCCTGACCATCTCCTCCGTGAAGGCCGAGGACGTGGCCGTGTACTACTGC
CAGCAGTACTACAACTACCCCCTGACCTTCGGCGCTGGCACCAAGCTGGAACTG
AAGAGAACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCTTCCGACGAGCAGC
TGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACTTCTACCCCCGCGA
GGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGA
ATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCCTGTCCTCCACCCTG
ACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAAGTGACC
CACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCGAGTGCACTA
GTGGCGGCGGAGGATCTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAGGTG
CAGCTGCAGCAGTCCGGAGCAGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGT
GTCCTGCAAGGCCTCTGGCTACACCTTCACACGGTATACCATGCACTGGGTGAGA
CAGGCACCAGGACAGGGCCTGGAGTGGATGGGCTACATCAACCCCTCTCGGGGC
TACACAAACTATAATCAGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAG
TCTATCAGCACCGCCTATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCC
GTGTACTATTGTGCCAGATACTATGACGATCACTACAGCCTGGACTATTGGGGCC
AGGGCACCACACTGACCGTGAGCTCTGGCGGCGGCGGCTCTGGAGGAGGAGGCA
GCGGCGGAGGAGGCTCCGGAGGAGGCGGCTCTGGCGGCGGCGGCAGCGGCGGC
GGCGGCTCCGACATCCAGATGACACAGTCCCCATCTAGCCTGTCCGCCTCTGTGG
GCGATAGGGTGACCATCACATGCTCTGCCTCCTCTAGCGTGAGCTACATGAATTG
GTATCAGCAGAAGCCCGGCAAGGCCCCTAAGAGGTGGATCTACGATACCTCTAA
GCTGGCCAGCGGAGTGCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTT
ACCCTGACAATCTCCTCTCTGCAGCCTGAGGATTTCGCCACATACTATTGTCAGC
AGTGGAGCTCCAACCCATTCACCTTTGGCAGCGGCACAAAGCTGGAGATCAATC
GG

Figure 16B

hGPC3 Heavy chain full amino acid sequence (N to C terminal) [signal peptide-hGPC3-CH1-3] (SEQ ID NO: 104)

MGWSCIILFLVATATG*EVQLVESGGGLVQPEGSLKLSCAASGFTFNKNAMNWVRQAPG KGLEWVARIRNKTNNYATYYADSVKARFTISRDDSQSMLYLQMNSLKIEDTAMYYCVAGNS FAYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

hGPC3 Heavy chain full nucleotide sequence (SEQ ID NO: 105)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGGTGC
AGCTGGTGGAATCTGGCGGAGGACTGGTGCAGCCTGAGGGCTCCCTGAAGCTGT
CTTGTGCCGCCTCCGGCTTCACCTTCAACAAGAACGCCATGAACTGGGTGCGACA
GGCCCCTGGCAAGGGCCTGGAATGGGTGGCCCGGATCAGAAACAAGACCAACA
ACTACGCCACCTACTACGCCGACTCCGTGAAGGCCCGGTTCACCATCTCTCGGGA
CGACTCCCAGTCCATGCTGTACCTGCAGATGAACAGCCTGAAGATCGAGGACAC
CGCCATGTACTACTGCGTGGCCGGCAACTCCTTCGCCTATTGGGGCCAGGGCACC
CTCGTGACCGTGTCCTCTGCTTCTACCAAGGGCCCCTCTGTGTTTCCTCTGGCCCC
CTCCAGCAAGTCCACCTCTGGTGGAACAGCCGCCCTGGGCTGCCTCGTGAAGGA
CTACTTTCCCGAGCCCGTGACCGTGTCCTGGAACTCTGGCGCTCTGACCTCTGGC
GTGCACACCTTCCCTGCTGTGCTGCAGTCTAGCGGCCTGTACTCCCTGTCCTCCGT
CGTGACAGTGCCCTCCAGCTCTCTGGGCACCCAGACCTACATCTGCAACGTGAAC
CACAAGCCCTCCAATACCAAGGTGGACAAGCGGGTGGAACCCAAGTCCTGCGAC
AAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGCTGGGCGGACCTTCCG
TGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGATCTCCCGGACCCCCGA
AGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCTGAAGTGAAGTTCAA
TTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGA
ACAGTACGCCTCCACCTACCGGGTGGTGTCCGTGCTGACAGTGCTGCACCAGGAC
TGGCTGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAACAAGGCCCTGCCTGCC
CCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGGGAACCCCAGGTG
TACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAGGTGTCCCTGACC
TGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAACG
GCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGGACTCCGACGGCT
CATTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTGGCAGCAGGGCA
ACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAA
GTCCCTGTCCCTGAGCCCCGGCAAA

Figure 17A

hFMC63 x hOKT3 H2L5 Light chain full amino acid sequence (N to C terminal) [signal peptide-hFMC63-CL-linker-hOKT3 VH2-linker-hOKT3 VL5] (SEQ ID NO: 106)

MGWSCIILFLVATATG*DIQMTQSPSSLSASVGDRVTITCQASQDISKYLNWYQQKPGKAV KLLIYHTSRLHSGVPSRFSGSGSGTDYTLTISSLQPEDIATYFCQQGNTLPYTFGGGTKLEIT R*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGGGS GGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEW MGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDY WGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS****DIQMTQSPSSLSAS VGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDFTLTISS LQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hFMC63 x hOKT3 H2L5 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 107)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGACATCC
AGATGACCCAGTCTCCAAGCTCCCTGTCCGCCTCTGTGGGCGACAGGGTGACCAT
CACATGCCAGGCCAGCCAGGATATCTCCAAGTACCTGAACTGGTATCAGCAGAA
GCCAGGCAAGGCCGTGAAGCTGCTGATCTACCACACATCTCGGCTGCACAGCGG
AGTGCCATCCAGATTCAGCGGCTCCGGCTCTGGCACCGACTATACCCTGACAATC
TCTAGCCTGCAGCCCGAGGATATCGCCACATACTTCTGTCAGCAGGGCAATACCC
TGCCTTATACATTTGGCGGCGGCACCAAGCTGGAGATCACACGGACCGTGGCCG
CCCCCTCCGTGTTCATCTTCCCCCCCTCCGACGAGCAGCTGAAGTCCGGCACCGC
CTCCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGG
AAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAGTCCGTGACCGAGCAG
GACTCCAAGGACTCCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCG
ACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCTGTCCT
CCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGAGGAT
CTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTGCAGCAGTCCG
GAGCAGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAGGCCTCTG
GCTACACCTTCACACGGTATACCATGCACTGGGTGAGACAGGCACCAGGACAGG
GCCTGGAGTGGATGGGCTACATCAACCCCTCTCGGGGCTACACAAACTATAATC
AGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGCACCGCCT
ATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATTGTGCCA
GATACTATGACGATCACTACAGCCTGGACTATTGGGGCCAGGGCACCACACTGA
CCGTGAGCTCTGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCGGAGGAGGC
TCCGGAGGAGGCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGCTCCGACATC
CAGATGACACAGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGGTGACCA
TCACATGCTCTGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCAGAAGCC
CGGCAAGGCCCCTAAGAGGTGGATCTACGATACCTCTAAGCTGGCCAGCGGAGT
GCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACAATCTCC
TCTCTGCAGCCTGAGGATTTCGCCACATACTATTGTCAGCAGTGGAGCTCCAACC
CATTCACCTTTGGCAGCGGCACAAAGCTGGAGATCAATCGG

Figure 17B

hFMC63 Heavy chain full amino acid sequence (N to C terminal) [signal peptide-hFMC63-CH1-3] (SEQ ID NO: 108)

MGWSCIILFLVATATG*QVQLQESGPGLVKPSETLSVTCTVSGVSLPDYGVSWIRQPPGKG LEWIGVIWGSETTYYNPSLKSRVTISVDTSKNQVSLKLSSVTAADTAVYYCAKHYYYGGSYA MDYWGQGTSVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPI EKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK

hFMC63 Heavy chain full nucleotide sequence (SEQ ID NO: 109)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCCAGGTGC AGCTGCAGGAGTCCGGCCCAGGCCTGGTGAAGCCATCTGAGACCCTGAGCGTGA CCTGCACAGTGTCCGGCGTGTCTCTGCCTGACTATGGCGTGTCTTGGATCAGACA GCCACCTGGCAAGGGCCTGGAGTGGATCGGCGTGATCTGGGGCAGCGAGACCAC ATACTATAACCCCAGCCTGAAGTCCAGAGTGACCATCTCCGTGGACACATCTAAG AATCAGGTGTCTCTGAAGCTGAGCTCCGTGACCGCCGCCGATACAGCCGTGTACT ATTGTGCCAAGCACTACTATTACGGCGGCAGCTATGCTATGGACTACTGGGGCCA GGGCACCTCCGTGACAGTGTCTAGCGCCTCCACCAAGGGCCCATCGGTCTTCCCC CTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTG GTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTG ACCAGCGGCGTGCACACCTTCCCGGCCGTCCTACAGTCCTCAGGACTCTACTCCC TCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTACATCTG CAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCA AATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTCCTGGG GGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC CGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAG GTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAACGCCAAGACCAAG CCTAGAGAGGAACAGTACGCCTCCACCTACCGGGTGGTGTCCGTGCTGACAGTG CTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAACAAG GCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCCCGG GAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAACCAG GTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGGAAT GGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGCTGG ACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCGGTG GCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAACCA CTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAA

Figure 18A

hSTEAP1 x hOKT3 H2L5 Light chain full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-CL-linker-hOKT3 VH2-linker-hOKT3 VL5] (SEQ ID NO: 110)

MGWSCIILFLVATATGVHS*DIVMTQSPDSLAVSVGERVTMNCKSSQSLLYRSNQKNYLAW YQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYNYPR TFGGGTKVEIKR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGECTS**GGGGSGGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMH WVRQAPGQGLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYY CARYYDDHYSLDYWGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS** *DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLASGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hSTEAP1 x hOKT3 H2L5 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 111)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCATA
GCGACATCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCGTGGGGGAAA
GAGTGACAATGAACTGTAAGAGCAGCCAGTCCCTGCTGTACCGGTCTAACCAGA
AGAATTACCTGGCCTGGTATCAGCAGAAGCCAGGCCAGCCCCCTAAGCTGCTGA
TCTATTGGGCCTCTACCAGGGAGAGCGGAGTGCCAGACAGATTCTCTGGCAGCG
GCTCCGGCACAGACTTCACCCTGACAATCAGCTCCGTGCAGGCAGAGGACGTGG
CCGTGTACTATTGTCAGCAGTATTACAACTACCCCAGAACTTTTGGAGGCGGCAC
TAAGGTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCT
TCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACT
TCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG
GCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCC
TGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACG
CCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCG
GGGCGAGTGCACTAGTGGCGGCGGAGGATCTGGCGGAGGTGGAAGTGGGGGAG
GCGGATCTCAGGTGCAGCTGCAGCAGTCCGGAGCAGAGGTGGCAAAGCCAGGA
GCCAGCGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACCTTCACACGGTATACCA
TGCACTGGGTGAGACAGGCACCAGGACAGGGCCTGGAGTGGATGGGCTACATCA
ACCCCTCTCGGGGCTACACAAACTATAATCAGAAGTTTAAGGACAGGGCCACCC
TGACACGCGATAAGTCTATCAGCACCGCCTATATGGAGCTGAGCCGGCTGAGAT
CCGACGATACAGCCGTGTACTATTGTGCCAGATACTATGACGATCACTACAGCCT
GGACTATTGGGGCCAGGGCACCACACTGACCGTGAGCTCTGGCGGCGGCGGCTC
TGGAGGAGGAGGCAGCGGCGGAGGAGGCTCCGGAGGAGGCGGCTCTGGCGGCG
GCGGCAGCGGCGGCGGCGGCTCCGACATCCAGATGACACAGTCCCCATCTAGCC
TGTCCGCCTCTGTGGGCGATAGGGTGACCATCACATGCTCTGCCTCCTCTAGCGT
GAGCTACATGAATTGGTATCAGCAGAAGCCCGGCAAGGCCCCTAAGAGGTGGAT
CTACGATACCTCTAAGCTGGCCAGCGGAGTGCCTTCCCGCTTCAGCGGCTCCGGC
TCTGGAACCGACTTTACCCTGACAATCTCCTCTCTGCAGCCTGAGGATTTCGCCA
CATACTATTGTCAGCAGTGGAGCTCCAACCCATTCACCTTTGGCAGCGGCACAAA
GCTGGAGATCAATCGG

Figure 18B

hSTEAP1 Heavy chain full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-CH1-3] (SEQ ID NO: 112)

MGWSCIILFLVATATGVHS*DVQVQESGPGLVKPSQTLSLTCTVTGYSITSDYAWNWIRQP PGKGLEWMGYISNSGSTSYNPSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARERNYDY DDYYYAMDYWGQGTTLTVSA*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK

hSTEAP1 Heavy chain full nucleotide sequence (SEQ ID NO: 113)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCACT CCGATGTGCAGGTGCAGGAAAGCGGCCCAGGACTGGTGAAGCCCTCCCAGACTC TGTCTCTGACTTGTACCGTGACCGGCTACAGCATCACCTCCGACTATGCCTGGAA CTGGATCAGACAGCCACCTGGCAAGGGCCTGGAGTGGATGGGCTACATCTCTAA CAGCGGCTCCACATCTTATAATCCCTCTCTGAAGAGCAGGATCACCATCTCCCGC GATACATCTAAGAACCAGTTCAGCCTGAAGCTGAGCTCCGTGACCGCAGCAGAC ACAGCCGTGTACTATTGCGCCCGGGAGAGAAATTACGATTATGATGACTACTATT ATGCTATGGATTACTGGGGACAGGGGACTACTCTGACCGTCTCCGCCgcctccaccaaG GGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAG CGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTG GAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTACAGTCC TCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCA CCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACA AGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAG CACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGA CACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGC CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTC AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCC AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCG ACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC ACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCG TGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Figure 19A

hHIM34 x hOKT3 H2L5 Light chain full amino acid sequence (N to C terminal) [signal peptide-hHIM34-CL-linker-hOKT3 VH2-linker-hOKT3 VL5] (SEQ ID NO: 114)

MGWSCIILFLVATATGVHS*DIQMTQSPSSLSASVGDRVTITCKASQDINKYIAWYQHKPG KAPKLLIYYASNLQPGVPSRFSGSGSGRDFTFTISSLQPEDIATYYCLQYDNLLTFGAGTKLE LKR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGG GSGGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGL EWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSL DYWGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS****DIQMTQSPSSLS ASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLASGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hHIM34 x hOKT3 H2L5 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 115)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGTGCACA
GCGACATCCAGATGACCCAGTCCCCTAGCTCCCTGTCCGCCTCTGTGGGCGACAG
GGTGACCATCACATGCAAGGCCTCCCAGGATATCAACAAGTACATCGCCTGGTA
TCAGCACAAGCCAGGCAAGGCCCCCAAGCTGCTGATCTACTATGCCTCTAATCTG
CAGCCAGGAGTGCCTAGCCGGTTCAGCGGCTCCGGCTCTGGAAGAGATTTCACCT
TTACAATCTCTAGCCTGCAGCCCGAGGACATCGCCACATACTATTGTCTGCAGTA
CGATAACCTGCTGACCTTTGGCGCCGGCACAAAGCTGGAGCTGAAGCGGACCGT
GGCCGCCCCCTCCGTGTTCATCTTCCCCCCCTCCGACGAGCAGCTGAAGTCCGGC
ACCGCCTCCGTGGTGTGCCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGC
AGTGGAAGGTGGACAACGCCCTGCAGTCCGGCAACTCCCAGGAGTCCGTGACCG
AGCAGGACTCCAAGGACTCCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAA
GGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT
GTCCTCCCCCGTGACCAAGTCCTTCAACCGGGGCGAGTGCACTAGTGGCGGCGG
AGGATCTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTGCAGC
AGTCCGGAGCAGAGGTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAG
GCCTCTGGCTACACCTTCACACGGTATACCATGCACTGGGTGAGACAGGCACCA
GGACAGGGCCTGGAGTGGATGGGCTACATCAACCCCTCTCGGGGCTACACAAAC
TATAATCAGAAGTTTAAGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGC
ACCGCCTATATGGAGCTGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATT
GTGCCAGATACTATGACGATCACTACAGCCTGGACTATTGGGGCCAGGGCACCA
CACTGACCGTGAGCTCTGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCGGAG
GAGGCTCCGGAGGAGGCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGCTCC
GACATCCAGATGACACAGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGG
TGACCATCACATGCTCTGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCA
GAAGCCCGGCAAGGCCCCTAAGAGGTGGATCTACGATACCTCTAAGCTGGCCAG
CGGAGTGCCTTCCCGCTTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACA
ATCTCCTCTCTGCAGCCTGAGGATTTCGCCACATACTATTGTCAGCAGTGGAGCT
CCAACCCATTCACCTTTGGCAGCGGCACAAAGCTGGAGATCAATCGG

Figure 19B

hHIM34 Heavy chain full amino acid sequence (N to C terminal) [signal peptide-hHIM34-CH1-3] (SEQ ID NO: 116)

MGWSCIILFLVATATGVHS*QVQLQQSGAEVVKPGASVKVSCKASGYSFTDYNMYWVRQ APGQGLEWMGYIDPYKGGTIYNQKFQGRATLTRDTSISTAYMELSRLRSDDTAVYYCARE MITAYYFDYWGQGSSVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSN KALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK

hHIM34 Heavy chain full nucleotide sequence (SEQ ID NO: 117)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCGCCACCGGCGTGCACA GCCAGGTGCAGCTGCAGCAGTCCGGAGCAGAGGTGGTGAAGCCAGGAGCCTCTG TGAAGGTGAGCTGCAAGGCCAGCGGCTACTCCTTCACCGACTACAACATGTATTG GGTGCGGCAGGCACCAGGACAGGGCCTGGAGTGGATGGGCTACATCGACCCTTA TAAGGGCGGCACAATCTACAATCAGAAGTTTCAGGGAAGGGCCACCCTGACAAG GGACACCTCCATCTCTACAGCCTATATGGAGCTGTCCCGGCTGAGATCTGACGAT ACCGCCGTGTACTATTGTGCCAGGGAGATGATCACAGCCTACTATTTCGATTATT GGGGCCAGGGCAGCTCCGTGACCGTGTCTAGCGCCTCCACCAAGGGCCCCTCTGT GTTTCCTCTGGCCCCCTCCAGCAAGTCCACCTCTGGTGGAACAGCCGCCCTGGGC TGCCTCGTGAAGGACTACTTTCCCGAGCCCGTGACCGTGTCCTGGAACTCTGGCG CTCTGACCTCTGGCGTGCACACCTTCCCTGCTGTGCTGCAGTCTAGCGGCCTGTA CTCCCTGTCCTCCGTCGTGACAGTGCCCTCCAGCTCTCTGGGCACCCAGACCTAC ATCTGCAACGTGAACCACAAGCCCTCCAATACCAAGGTGGACAAGCGGGTGGAA CCCAAGTCCTGCGACAAGACCCACACCTGTCCCCCTTGTCCTGCCCCTGAACTGC TGGGCGGACCTTCCGTGTTCCTGTTCCCCCCAAAGCCCAAGGACACCCTGATGAT CTCCCGGACCCCCGAAGTGACCTGCGTGGTGGTGGATGTGTCCCACGAGGACCCT GAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACC AAGCCTAGAGAGGAACAGTACGCCTCCACCTACCGGGTGGTGTCCGTGCTGACA GTGCTGCACCAGGACTGGCTGAACGGCAAAGAGTACAAGTGCGCCGTGTCCAAC AAGGCCCTGCCTGCCCCCATCGAAAAGACCATCTCCAAGGCCAAGGGCCAGCCC CGGGAACCCCAGGTGTACACACTGCCCCCTAGCAGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAAGGCTTCTACCCCTCCGATATCGCCGTGG AATGGGAGTCCAACGGCCAGCCTGAGAACAACTACAAGACCACCCCCCCTGTGC TGGACTCCGACGGCTCATTCTTCCTGTACAGCAAGCTGACCGTGGACAAGTCCCG GTGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA CCACTACACCCAGAAGTCCCTGTCCCTGAGCCCCGGCAAA

Figure 20A

h3F8DS x hOKT3 H2L2 TP53 SADA full amino acid sequence (N to C terminal) [signal peptide-h3F8-linker-VL-linker-VH-linker-hOKT3-linker-VH2-linker-VL2-TP53-spacer] (SEQ ID NO: 118)

MGWSCIILFLVATATG*EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAP RLLIYSASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGCGTKLEIKR***G GGGSGGGGSGGGGSGGGGSGGGGSGGGGS***QVQLVESGPGVVQPGRSLRISCAVSG FSVTNYGVHWVRQPPGKCLEWLGVIWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLR AEDTAMYYCASRGGHYGYALDYWGQGTLVTVSS**GGGGSGGGGSGGGGSGGGGS***QVQ LQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMGYINPSRGYTNYNQ KFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDYWGQGTTLTVSS**GGG GSGGGGSGGGGSGGGGSGGGGSGGGGS***DIQMTQSPSSLSASVGDRVTMTCSASSSVS YMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQW SSNPFTFGSGTKLEINR***TPLGDTTHT***SG*KPLDGEYFTLQIRGRERFEMFRELNEALELKD AQAGKEP*GGSGGAP**HHHHHH**

Figure 20B

hSTEAP1 x hOKT3 H2L2 TP53 SADA full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-linker-VL-linker-VH-linker-hOKT3-linker-VH2-linker-VL2-TP53-spacer] (SEQ ID NO: 119)

MGWSCIILFLVATATGVHS*DIVMTQSPDSLAVSVGERVTMNCKSSQSLLYRSNQKNYLAW YQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYNYPR TFGGGTKVEIK**GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS***DVQVQESGPGLVK PSQTLSLTCTVTGYSITSDYAWNWIRQPPGKGLEWMGYISNSGSTSYNPSLKSRITISRDTSK NQFSLKLSSVTAADTAVYYCARERNYDYDDYYYAMDYWGQGTTLTVSA**GGGGSGGGGS GGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEW MGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDY WGQGTTLTVSS**GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS***DIQMTQSPSSLSAS VGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISS MQPEDFATYYCQQWSSNPFTFGSGTKLEINR***TPLGDTTHT***SG*KPLDGEYFTLQIRGRER FEMFRELNEALELKDAQAGKEP*GGSGGAP**HHHHHH**

Figure 20C

hHER2 x hOKT3 H2L2 TP53 SADA full amino acid sequence (N to C terminal) [signal peptide-HER2-linker-VL-linker-VH-linker-hOKT3-linker-VH2-linker-VL2-TP53-spacer] (SEQ ID NO: 120)

MGWSCIILFLVATATG*DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAP*
KLLIYSASFLYSGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
*R***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS***EVQLVESGGGLVQPGGSLRLSCAA*
SGFNIKDTYIHWVRQAPGKGLEWVARIYPTNGYTRYADSVKGRFTISADTSKNTAYLQMNS
*LRAEDTAVYYCSRWGGDGFYAMDYWGQGTLVTVSS***GGGGSGGGGSGGGGSGGGGS**
QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMGYINPSRGYTN
*YNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDYWGQGTTLTVSS***G**
GGGSGGGGSGGGGSGGGGSGGGGSGGGGS*DIQMTQSPSSLSASVGDRVTMTCSASS*
SVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQ
*QWSSNPFTFGSGTKLEINR***TPLGDTTHT**SG*KPLDGEYFTLQIRGRERFEMFRELNEALEL*
*KDAQAGKEP*GGSGGAP**HHHHHH**

Figure 20D

hFMC63 x hOKT3 H2L2 TP53 SADA full amino acid sequence (N to C terminal) [signal peptide-FMC63-linker-VL-linker-VH-linker-hOKT3-linker-VH2-linker-VL2-TP53-spacer] (SEQ ID NO: 121)

MGWSCIILFLVATATGVHS*DIQMTQSPSSLSASVGDRVTITCQASQDISKYLNWYQQKPG*
KAVKLLIYHTSRLHSGVPSRFSGSGSGTDYTLTISSLQPEDIATYFCQQGNTLPYTFGGGTK
*LEITR***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS***QVQLQESGPGLVKPSETLSVT*
CTVSGVSLPDYGVSWIRQPPGKGLEWIGVIWGSETTYYNPSLKSRVTISVDTSKNQVSLKLS
*SVTAADTAVYYCAKHYYYGGSYAMDYWGQGTSVTVSS***GGGGSGGGGSGGGGSGGGGS**
QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMGYINPSRGYTN
*YNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDYWGQGTTLTVSS***G**
GGGSGGGGSGGGGSGGGGSGGGGSGGGGS*DIQMTQSPSSLSASVGDRVTMTCSASS*
SVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQ
*QWSSNPFTFGSGTKLEINR***TPLGDTTHT**SG*KPLDGEYFTLQIRGRERFEMFRELNEALEL*
*KDAQAGKEP*GGSGGAP**HHHHHH**

Figure 21A

h3F8 x hC825 Light chain 1 full amino acid sequence (N to C terminal) [signal peptide-h3F8-CL-linker-hC825 VH-linker-hC825 VL] (SEQ ID NO: 122)

MGWSCIILFLVATATG*EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQAP RLLIYSASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIKR*TV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGGGSGG GGSGGGGS***HVQLVESGGGLVQPGGSLRLSCAASGFSLTDYGVHWVRQAPGKGLEWLG VIWSGGGTAYNTALISRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRGSYPYNYFDAWG CGTLVTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS**QAVVTQEPSLTVSPGG TVTLTCGSSTGAVTASNYANWVQQKPGQCPRGLIGGHNNRPPGVPARFSGSLLGGKAALT LLGAQPEDEAEYYCALWYSDHWVIGGGTKLTVLG*

h3F8 x hC825 Light chain 1 full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 123)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGATCG
TGATGACACAGACCCCTGCCACCCTGTCCGTGTCTGCTGGCGAGAGAGTGACCAT
TACCTGCAAGGCCTCCCAGTCCGTGTCCAACGACGTGACCTGGTATCAGCAGAA
GCCCGGCCAGGCCCCCAGACTGCTGATCTACTCCGCCTCCAACCGGTACTCTGGC
GTGCCCGCTAGATTCTCCGGCTCTGGCTACGGCACCGAGTTTACCTTCACCATCT
CCTCCGTGCAGTCCGAGGACTTCGCCGTGTACTTCTGTCAGCAAGACTACTCCAG
CTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGT
GTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTG
TGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAG
GACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGA
AGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGA
CCAAGTCTTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGAGGATCTGGCGGAG
GTGGAAGTGGGGGAGGCGGATCTCATGTGCAGCTGGTGGAAAGCGGAGGCGGC
CTGGTGCAGCCTGGGGGATCTCTGAGACTGTCTTGTGCCGCCAGCGGCTTCTCCC
TGACCGATTATGGCGTGCACTGGGTGCGACAGGCCCCTGGCAAAGGACTGGAAT
GGCTGGGAGTGATTTGGAGTGGCGGAGGCACCGCCTACAACACCGCCCTGATCT
CCCGGTTCACCATCAGCCGGGACAACTCCAAGAACACCCTGTACCTGCAGATGA
ACTCCCTGCGGGCCGAGGACACCGCTGTGTACTACTGCGCCAGACGGGGCTCCT
ACCCCTACAACTACTTCGACGCTTGGGGCTGCGGCACCCTCGTGACAGTGTCTAG
CGGAGGGGGAGGTTCTGGGGGCGGAGGTTCAGGTGGTGGTGGTTCCGGGGGTGG
TGGCTCTGGTGGCGGTGGTTCTGGCGGTGGCGGATCTCAGGCTGTCGTGACCCAG
GAACCCAGCCTGACTGTGTCTCCTGGCGGAACCGTGACCCTGACCTGCGGATCTT
CTACCGGCGCTGTGACCGCCAGCAACTACGCCAATTGGGTGCAGCAGAAACCTG
GACAGTGCCCTAGAGGCCTGATCGGCGGCCACAACAACAGACCTCCAGGCGTGC
CAGCCCGGTTCTCTGGATCTCTGCTGGGCGGAAAGGCCGCTCTGACACTGCTGGG
TGCTCAGCCTGAGGACGAGGCCGAGTACTACTGTGCCCTGTGGTACTCCGACCAC
TGGGTCATCGGAGGCGGGACCAAGCTGACCGTGCTGGGA

Figure 21B

h3F8 x hOKT3 H2L2 Light chain 2 full amino acid sequence (N to C terminal) [signal peptide-h3F8-CL-linker-hOKT3 VH2-linker-hOKT3 VL2] (SEQ ID NO: 124)

MGWSCIILFLVATATGVHS*EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPG QAPRLLIYSASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYFCQQDYSSFGQGTKLEIK R*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGGGS GGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEW MGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHYSLDY WGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS**DIQMTQSPSSLSAS VGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLASGVPSRFSGSGSGTDFTLTISS MQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

h3F8 x hOKT3 H2L2 Light chain 2 full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 125)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGAGATCG
TGATGACACAGACCCCTGCCACCCTGTCCGTGTCTGCTGGCGAGAGAGTGACCAT
TACCTGCAAGGCCTCCCAGTCCGTGTCCAACGACGTGACCTGGTATCAGCAGAA
GCCCGGCCAGGCCCCCAGACTGCTGATCTACTCCGCCTCCAACCGGTACTCTGGC
GTGCCCGCTAGATTCTCCGGCTCTGGCTACGGCACCGAGTTTACCTTCACCATCT
CCTCCGTGCAGTCCGAGGACTTCGCCGTGTACTTCTGTCAGCAAGACTACTCCAG
CTTCGGCCAGGGCACCAAGCTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGT
GTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTG
TGCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGAC
AACGCCCTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAG
GACAGCACCTACTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGA
AGCACAAGGTGTACGCCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGA
CCAAGTCTTTCAACCGGGGCGAGTGCACTAGTGGCGGCGGAGGATCTGGCGGAG
GTGGAAGTGGGGGAGGCGGATCTCAGGTGCAGCTGCAGCAGTCCGGAGCAGAG
GTGGCAAAGCCAGGAGCCAGCGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACC
TTCACACGGTATACCATGCACTGGGTGAGACAGGCACCAGGACAGGGCCTGGAG
TGGATGGGCTACATCAACCCCTCTCGGGGCTACACAAACTATAATCAGAAGTTTA
AGGACAGGGCCACCCTGACACGCGATAAGTCTATCAGCACCGCCTATATGGAGC
TGAGCCGGCTGAGATCCGACGATACAGCCGTGTACTATTGTGCCCGGTACTATGA
CGATCACTACAGCCTGGACTATTGGGGCCAGGGCACCACACTGACCGTGAGCTC
TGGCGGCGGCGGCTCTGGAGGAGGAGGCAGCGGCGGAGGAGGCTCCGGAGGAG
GCGGCTCTGGCGGCGGCGGCAGCGGCGGCGGCGGCTCCGACATCCAGATGACAC
AGTCCCCATCTAGCCTGTCCGCCTCTGTGGGCGATAGGGTGACCATGACATGCTC
TGCCTCCTCTAGCGTGAGCTACATGAATTGGTATCAGCAGAAGCCCGGCAAGGC
CCCTAAGCTGCTGATCTACGATACCTCTAAGCTGGCCAGCGGAGTGCCTTCCCGC
TTCAGCGGCTCCGGCTCTGGAACCGACTTTACCCTGACAATCTCCTCTATGCAGC
CTGAGGATTTCGCCACATACTATTGTCAGCAGTGGAGCTCCAACCCATTCACCTT
TGGCAGCGGCACAAAGCTGGAGATCAATAGA

Figure 21C

h3F8 Heavy chain K full amino acid sequence (N to C terminal) [signal peptide-h3F8-CH1-3] (SEQ ID NO: 126)

MGWSCIILFLVATATGVHS*QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQP*
PGKGLEWLGVIWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG
*HYGYALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS
WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNK
ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN
GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS
LSLSPGK

h3F8 Heavy chain K full nucleotide sequence (SEQ ID NO: 127)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCACCACCGGCGTGCACA
GCCAGGTGCAGCTGGTGGAGTCCGGCCCCGGCGTGGTGCAGCCCGGCCGGTCCC
TGCGGATCTCCTGCGCCGTGTCCGGCTTCTCCGTGACCAACTACGGCGTGCACTG
GGTGCGACAGCCTCCAGGCAAGGGCCTGGAGTGGCTGGGCGTGATCTGGGCCGG
CGGCATCACCAACTACAACTCCGCCTTCATGTCCCGGCTGACCATCTCCAAGGAC
AACTCCAAGAACACCGTGTACCTGCAGATGAACTCCCTGCGGGCCGAGGACACC
GCCATGTACTACTGCGCCTCCCGGGGCGGCCACTACGGCTACGCCCTGGACTACT
GGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCCTCCACCAAGGGCCCATCGG
TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGA
GCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTC
CTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCA
ACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
CCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG
TGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Figure 21D

h3F8 Heavy chain F full amino acid sequence (N to C terminal) [signal peptide-h3F8-CH1-3] (SEQ ID NO: 137)

MGWSCIILFLVATTTGVHS*QVQLVESGPGVVQPGRSLRISCAVSGFSVTNYGVHWVRQP PGKGLEWLGVIWAGGITNYNSAFMSRLTISKDNSKNTVYLQMNSLRAEDTAMYYCASRGG HYGYALDYWGQGTLVTVSS*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKR VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK

h3F8 Heavy chain F full nucleotide sequence (SEQ ID NO: 138)

ATGGGCTGGTCCTGCATCATCCTGTTCCTGGTGGCCACCACCACCGGCGTGCACA
GCCAGGTGCAGCTGGTGGAGTCCGGCCCCGGCGTGGTGCAGCCCGGCCGGTCCC
TGCGGATCTCCTGCGCCGTGTCCGGCTTCTCCGTGACCAACTACGGCGTGCACTG
GGTGCGACAGCCTCCAGGCAAGGGCCTGGAGTGGCTGGGCGTGATCTGGGCCGG
CGGCATCACCAACTACAACTCCGCCTTCATGTCCCGGCTGACCATCTCCAAGGAC
AACTCCAAGAACACCGTGTACCTGCAGATGAACTCCCTGCGGGCCGAGGACACC
GCCATGTACTACTGCGCCTCCCGGGGCGGCCACTACGGCTACGCCCTGGACTACT
GGGGCCAGGGCACCCTGGTGACCGTGTCCTCCGCCTCCACCAAGGGCCCATCGG
TCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGG
CTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGC
GCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTACAGTCCTCAGGACTCT
ACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTTGGGCACCCAGACCTA
CATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGA
GCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAACTC
CTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGA
TCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACC
CTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGA
CAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGTGTGGTCAGCGTCCTCA
CCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCGCGGTCTCCA
ACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGC
CCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGA
ACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGT
GGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCG
TGCTGGACTCCGACGGCTCCTTCCTCCTCTACAGCAAGCTCACCGTGGACAAGAG
CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCAC
AACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA

Figure 22A

hSTEAP1 x hC825 Light chain 1 full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-CL-linker-hC825 VH-linker-hC825 VL] (SEQ ID NO: 128)

MGWSCIILFLVATATGVHS*DIVMTQSPDSLAVSVGERVTMNCKSSQSLLYRSNQKNYLAWYQQKP GQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYNYPRTFGGGTKVEIK R*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECTS**GGGGSGGGGSGGGG S***HVQLVESGGGLVQPGGSLRLSCAASGFSLTDYGVHWVRQAPGKGLEWLGVIWSGGGTAYNTALI SRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRGSYPYNYFDAWGCGTLVTVSS**GGGGSGGGGS GGGGSGGGGSGGGGSGGGGS***QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTASNYANWVQQKP GQCPRGLIGGHNNRPPGVPARFSGSLLGGKAALTLLGAQPEDEAEYYCALWYSDHWVIGGGTKLT VLG*

hSTEAP1 x hC825 Light chain 1 full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 129)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCATAGCGAC
ATCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCGTGGGGGAAAGAGTGACAAT
GAACTGTAAGAGCAGCCAGTCCCTGCTGTACCGGTCTAACCAGAAGAATTACCTGGCCT
GGTATCAGCAGAAGCCAGGCCAGCCCCCTAAGCTGCTGATCTATTGGGCCTCTACCAGG
GAGAGCGGAGTGCCAGACAGATTCTCTGGCAGCGGCTCCGGCACAGACTTCACCCTGAC
AATCAGCTCCGTGCAGGCAGAGGACGTGGCCGTGTACTATTGTCAGCAGTATTACAACTA
CCCCAGAACTTTTGGAGGCGGCACTAAGGTGGAAATCAAGCGGACCGTGGCCGCTCCCT
CCGTGTTCATCTTCCCACCTTCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGT
GCCTGCTGAACAACTTCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCC
CTGCAGTCCGGCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTA
CTCCCTGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACGC
CTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCGGGGCG
AGTGCACTAGTGGCGGCGGAGGATCTGGCGGAGGTGGAAGTGGGGGAGGCGGATCTCAT
GTGCAGCTGGTGGAAAGCGGAGGCGGCCTGGTGCAGCCTGGGGGATCTCTGAGACTGTC
TTGTGCCGCCAGCGGCTTCTCCCTGACCGATTATGGCGTGCACTGGGTGCGACAGGCCCC
TGGCAAAGGACTGGAATGGCTGGGAGTGATTTGGAGTGGCGGAGGCACCGCCTACAACA
CCGCCCTGATCTCCCGGTTCACCATCAGCCGGGACAACTCCAAGAACACCCTGTACCTGC
AGATGAACTCCCTGCGGGCCGAGGACACCGCTGTGTACTACTGCGCCAGACGGGGCTCC
TACCCCTACAACTACTTCGACGCTTGGGGCTGCGGCACCCTCGTGACAGTGTCTAGCGGA
GGGGGAGGTTCTGGGGGCGGAGGTTCAGGTGGTGGTGGTTCCGGGGGTGGTGGCTCTGG
TGGCGGTGGTTCTGGCGGTGGCGGATCTCAGGCTGTCGTGACCCAGGAACCCAGCCTGA
CTGTGTCTCCTGGCGGAACCGTGACCCTGACCTGCGGATCTTCTACCGGCGCTGTGACCG
CCAGCAACTACGCCAATTGGGTGCAGCAGAAACCTGGACAGTGCCCTAGAGGCCTGATC
GGCGGCCACAACAACAGACCTCCAGGCGTGCCAGCCCGGTTCTCTGGATCTCTGCTGGGC
GGAAAGGCCGCTCTGACACTGCTGGGTGCTCAGCCTGAGGACGAGGCCGAGTACTACTG
TGCCCTGTGGTACTCCGACCACTGGGTCATCGGAGGCGGGACCAAGCTGACCGTGCTGG
GA

Figure 22B

hSTEAP1 x hOKT3 H2L5 Light chain full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-CL-linker-hOKT3 VH2-linker-hOKT3 VL5] (SEQ ID NO: 130)

MGWSCIILFLVATATGVHS*DIVMTQSPDSLAVSVGERVTMNCKSSQSLLYRSNQKNYLAW YQQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYNYPR TFGGGTKVEIKR*TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGECTS**GGGGSGGGGSGGGGS***QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMH WVRQAPGQGLEWMGYINPSRGYTNYNQKFKDRATLTRDKSISTAYMELSRLRSDDTAVYY CARYYDDHYSLDYWGQGTTLTVSS***GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS** *DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLASGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR*

hSTEAP1 x hOKT3 H2L5 Light chain full nucleotide sequence. Signal sequence underlined (SEQ ID NO: 131)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCATA
GCGACATCGTGATGACCCAGAGCCCTGATAGCCTGGCCGTGAGCGTGGGGGAAA
GAGTGACAATGAACTGTAAGAGCAGCCAGTCCCTGCTGTACCGGTCTAACCAGA
AGAATTACCTGGCCTGGTATCAGCAGAAGCCAGGCCAGCCCCCTAAGCTGCTGA
TCTATTGGGCCTCTACCAGGGAGAGCGGAGTGCCAGACAGATTCTCTGGCAGCG
GCTCCGGCACAGACTTCACCCTGACAATCAGCTCCGTGCAGGCAGAGGACGTGG
CCGTGTACTATTGTCAGCAGTATTACAACTACCCCAGAACTTTTGGAGGCGGCAC
TAAGGTGGAAATCAAGCGGACCGTGGCCGCTCCCTCCGTGTTCATCTTCCCACCT
TCCGACGAGCAGCTGAAGTCCGGCACCGCTTCTGTCGTGTGCCTGCTGAACAACT
TCTACCCCCGCGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGTCCG
GCAACTCCCAGGAATCCGTGACCGAGCAGGACTCCAAGGACAGCACCTACTCCC
TGTCCTCCACCCTGACCCTGTCCAAGGCCGACTACGAGAAGCACAAGGTGTACG
CCTGCGAAGTGACCCACCAGGGCCTGTCTAGCCCCGTGACCAAGTCTTTCAACCG
GGGCGAGTGCACTAGTGGCGGCGGAGGATCTGGCGGAGGTGGAAGTGGGGGAG
GCGGATCTCAGGTGCAGCTGCAGCAGTCCGGAGCAGAGGTGGCAAAGCCAGGA
GCCAGCGTGAAGGTGTCCTGCAAGGCCTCTGGCTACACCTTCACACGGTATACCA
TGCACTGGGTGAGACAGGCACCAGGACAGGGCCTGGAGTGGATGGGCTACATCA
ACCCCTCTCGGGGCTACACAAACTATAATCAGAAGTTTAAGGACAGGGCCACCC
TGACACGCGATAAGTCTATCAGCACCGCCTATATGGAGCTGAGCCGGCTGAGAT
CCGACGATACAGCCGTGTACTATTGTGCCAGATACTATGACGATCACTACAGCCT
GGACTATTGGGGCCAGGGCACCACACTGACCGTGAGCTCTGGCGGCGGCGGCTC
TGGAGGAGGAGGCAGCGGCGGAGGAGGCTCCGGAGGAGGCGGCTCTGGCGGCG
GCGGCAGCGGCGGCGGCGGCTCCGACATCCAGATGACACAGTCCCCATCTAGCC
TGTCCGCCTCTGTGGGCGATAGGGTGACCATCACATGCTCTGCCTCCTCTAGCGT
GAGCTACATGAATTGGTATCAGCAGAAGCCCGGCAAGGCCCCTAAGAGGTGGAT
CTACGATACCTCTAAGCTGGCCAGCGGAGTGCCTTCCCGCTTCAGCGGCTCCGGC
TCTGGAACCGACTTTACCCTGACAATCTCCTCTCTGCAGCCTGAGGATTTCGCCA
CATACTATTGTCAGCAGTGGAGCTCCAACCCATTCACCTTTGGCAGCGGCACAAA
GCTGGAGATCAATCGG

Figure 22C

hSTEAP1 Heavy chain K full amino acid sequence (N to C terminal) [signal peptide-hSTEAP1-CH1-3] (SEQ ID NO: 132)

MGWSCIILFLVATATGVHS*DVQVQESGPGLVKPSQTLSLTCTVTGYSITSDYAWNWIRQP PGKGLEWMGYISNSGSTSYNPSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARERNYDY DDYYYAMDYWGQGTTLTVSA*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK

hSTEAP1 Heavy chain K full nucleotide sequence (SEQ ID NO: 133)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCACT
CCGATGTGCAGGTGCAGGAAAGCGGCCCAGGACTGGTGAAGCCCTCCCAGACTC
TGTCTCTGACTTGTACCGTGACCGGCTACAGCATCACCTCCGACTATGCCTGGAA
CTGGATCAGACAGCCACCTGGCAAGGGCCTGGAGTGGATGGGCTACATCTCTAA
CAGCGGCTCCACATCTTATAATCCCTCTCTGAAGAGCAGGATCACCATCTCCCGC
GATACATCTAAGAACCAGTTCAGCCTGAAGCTGAGCTCCGTGACCGCAGCAGAC
ACAGCCGTGTACTATTGCGCCCGGGAGAGAAATTACGATTATGATGACTACTATT
ATGCTATGGATTACTGGGGACAGGGGACTACTCTGACCGTCTCCGCCGCCTCCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC
ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGT
GGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTG
CCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCC
AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGAC
GTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG
GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGT
GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC
AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG
GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTAT
CCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTA
CAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAGG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA

Figure 22D

hSTEAP1 Heavy chain F full amino acid sequence (N to C terminal) [signal peptide-h3F8-CH1-3] (SEQ ID NO: 139)

MGWSCIILFLVATATGVHS*DVQVQESGPGLVKPSQTLSLTCTVTGYSITSDYAWNWIRQP PGKGLEWMGYISNSGSTSYNPSLKSRITISRDTSKNQFSLKLSSVTAADTAVYYCARERNYDY DDYYYAMDYWGQGTTLTVSA*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCAVS NKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFLLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK

hSTEAP Heavy chain F full nucleotide sequence (SEQ ID NO: 140)

ATGGGCTGGTCCTGCATCATCCTGTTTCTGGTGGCTACCGCCACCGGCGTCCACT
CCGATGTGCAGGTGCAGGAAAGCGGCCCAGGACTGGTGAAGCCCTCCCAGACTC
TGTCTCTGACTTGTACCGTGACCGGCTACAGCATCACCTCCGACTATGCCTGGAA
CTGGATCAGACAGCCACCTGGCAAGGGCCTGGAGTGGATGGGCTACATCTCTAA
CAGCGGCTCCACATCTTATAATCCCTCTCTGAAGAGCAGGATCACCATCTCCCGC
GATACATCTAAGAACCAGTTCAGCCTGAAGCTGAGCTCCGTGACCGCAGCAGAC
ACAGCCGTGTACTATTGCGCCCGGGAGAGAAATTACGATTATGATGACTACTATT
ATGCTATGGATTACTGGGGACAGGGGACTACTCTGACCGTCTCCGCCGCCTCCAC
CAAGGGCCCATCGGTCTTCCCCCTGGCACCCTCCTCCAAGAGCACCTCTGGGGGC
ACAGCGGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTG
TCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCCGTCCTAC
AGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAGCTT
GGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGT
GGACAAGAGAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTG
CCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCC
AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGAC
GTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAG
GTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACGCCAGCACGTACCGT
GTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTAC
AAGTGCGCGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCC
AAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG
GATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTAT
CCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTA
CAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCCTCCTCTACAGCAAG
CTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG
ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGG
GTAAA

Figure 23A

GD2 cytotoxicity

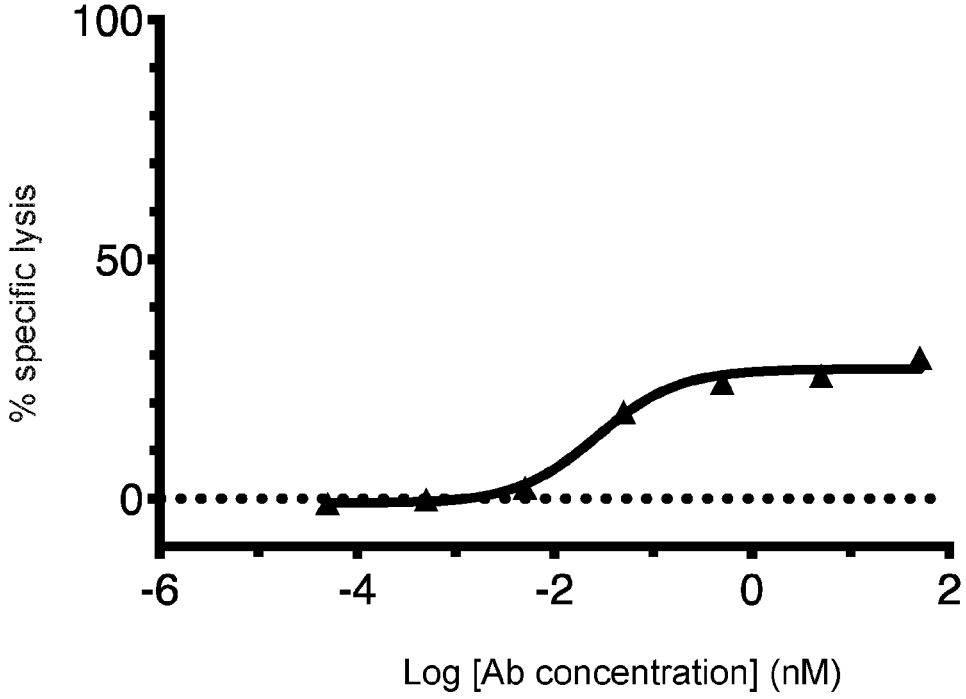


Figure 23B

GPC3 cytotoxicity

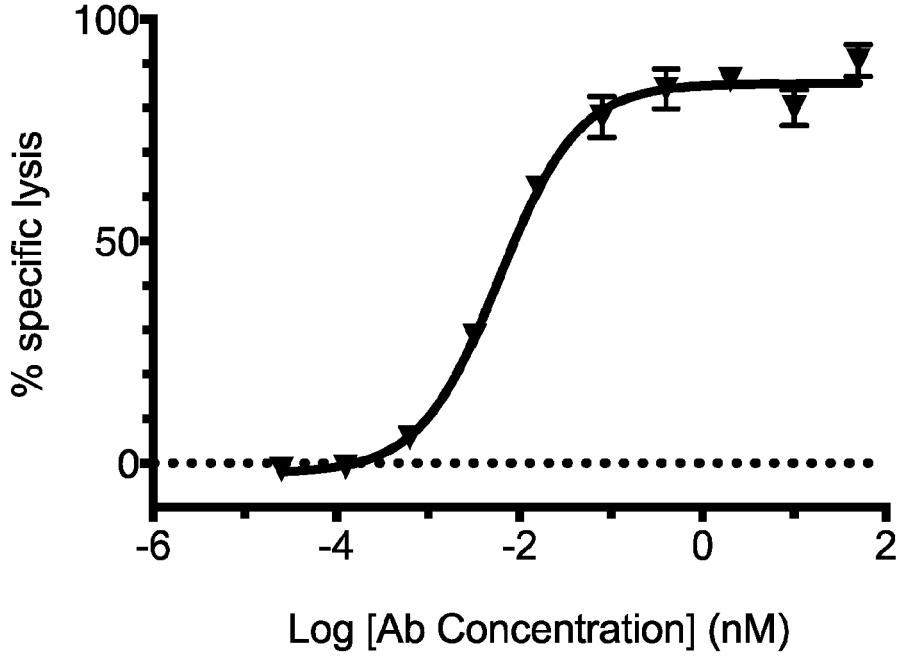


Figure 24A

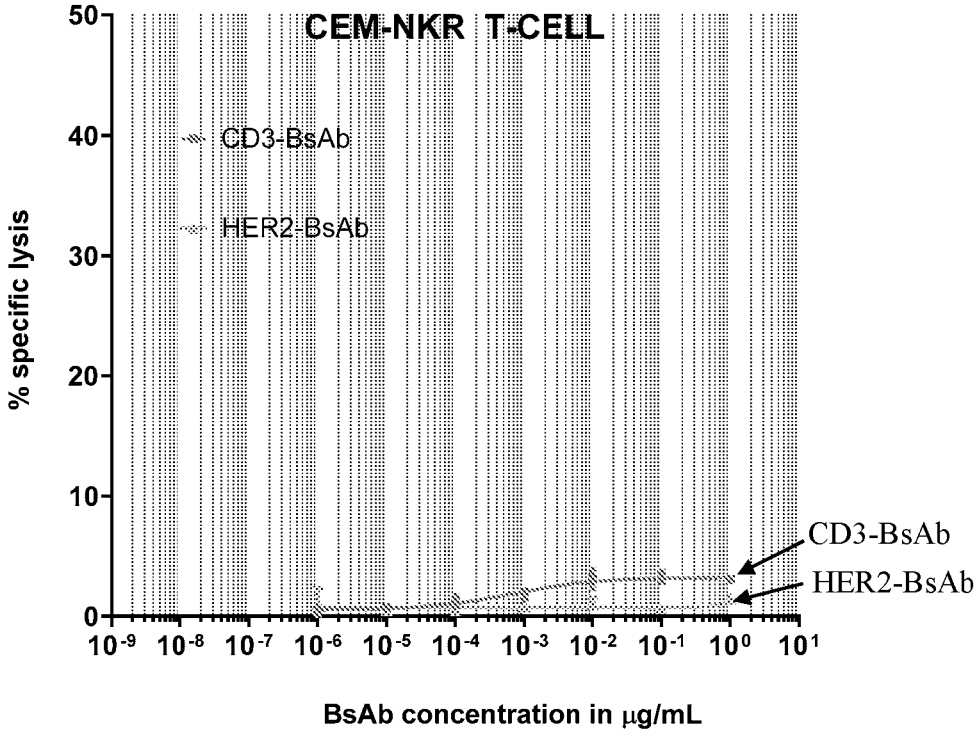


Figure 24B

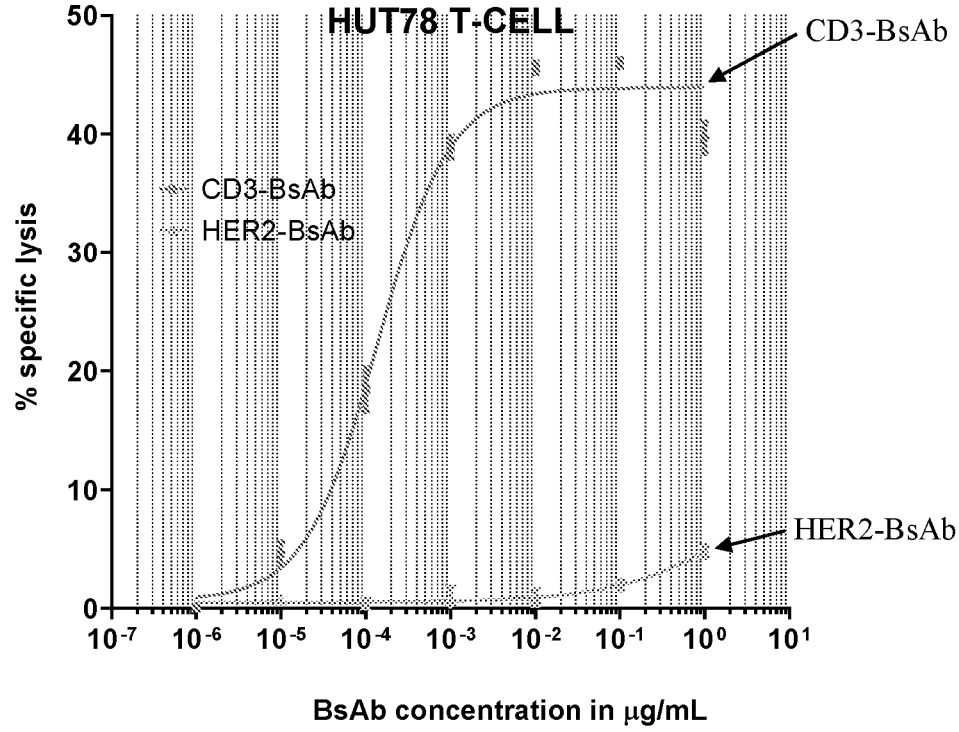


Figure 24C

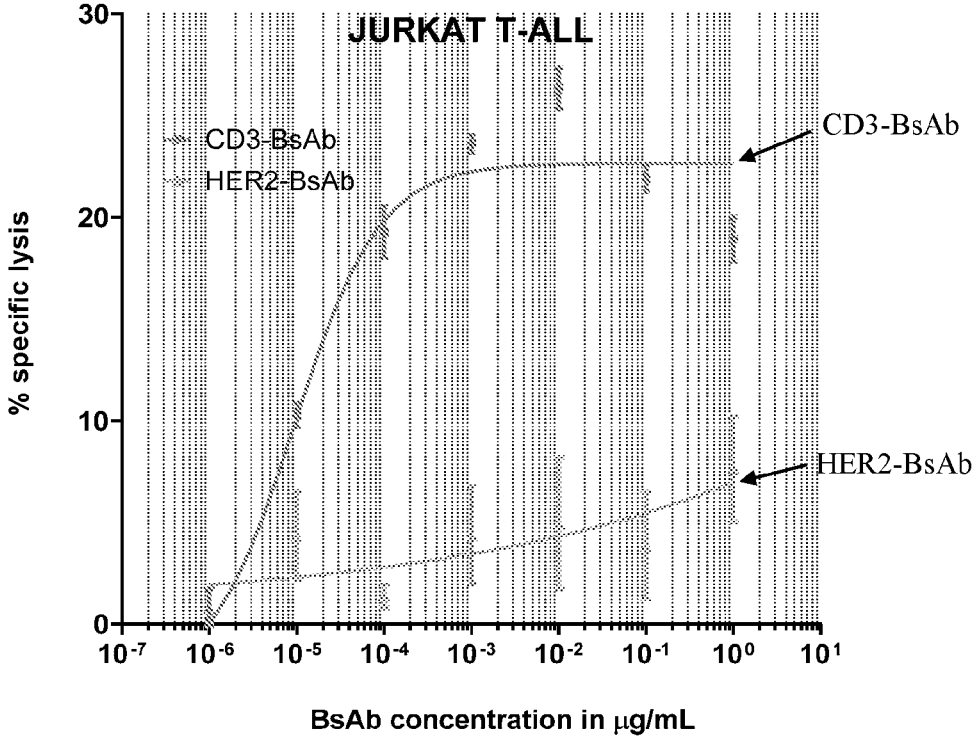


Figure 24D

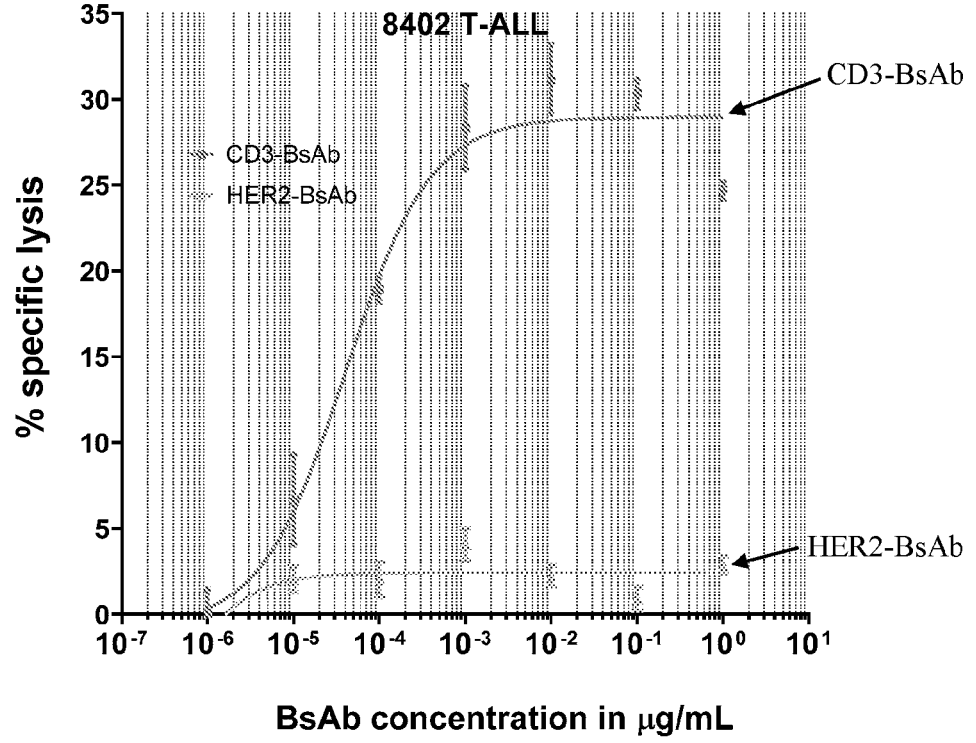


Figure 24E

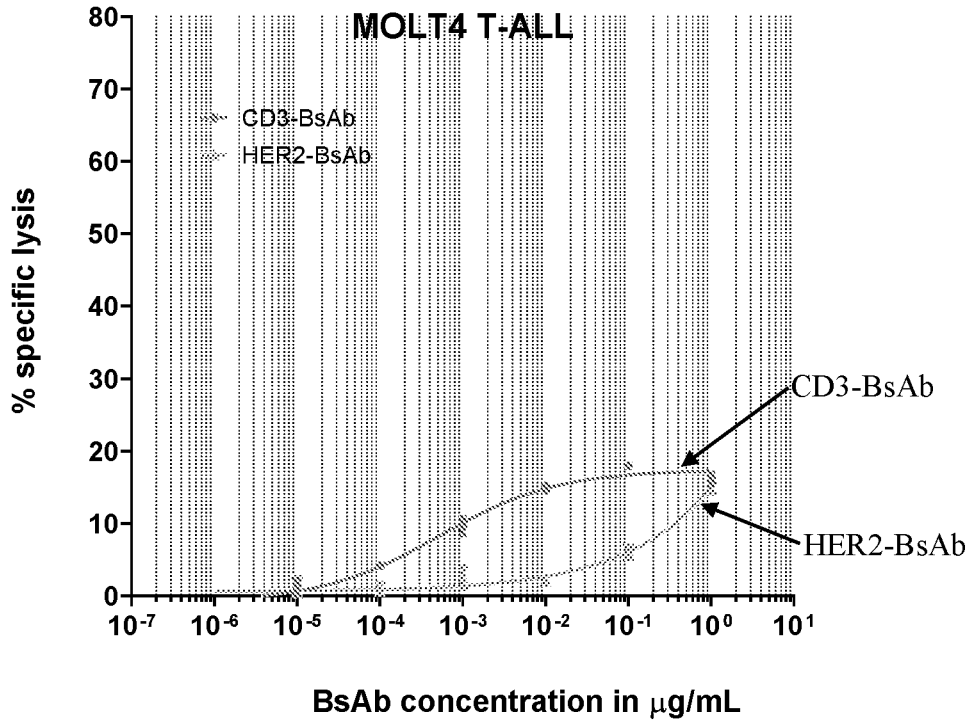

MOLT4 T-ALL
CD3-BsAb
HER2-BsAb
% specific lysis
80
70
60
50
40
30
20
10
0
10^{-7}
10^{-6}
10^{-5}
10^{-4}
10^{-3}
10^{-2}
10^{-1}
10^{0}
10^{1}
BsAb concentration in μg/mL

Figure 25

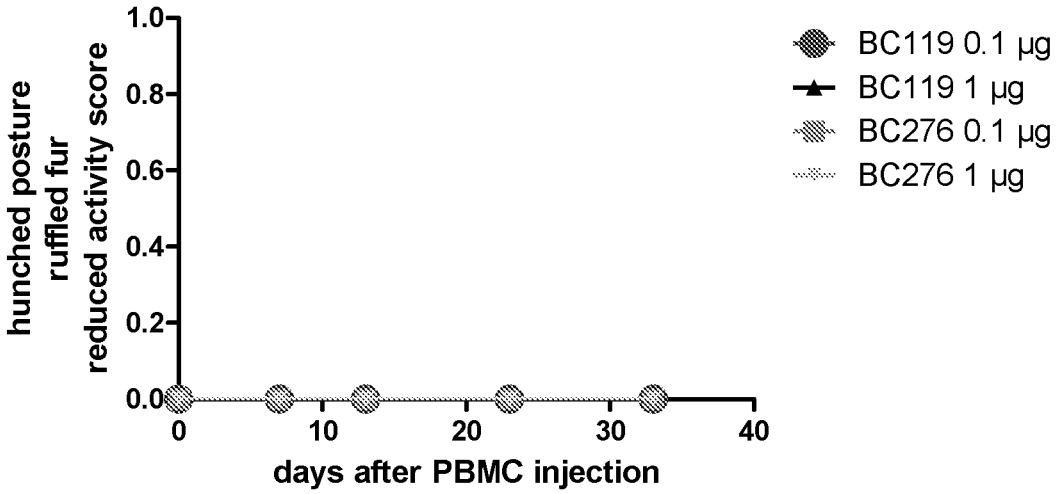

hunched posture
ruffled fur
reduced activity score
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
days after PBMC injection
BC119 0.1 µg
BC119 1 µg
BC276 0.1 µg
BC276 1 µg

Figure 26

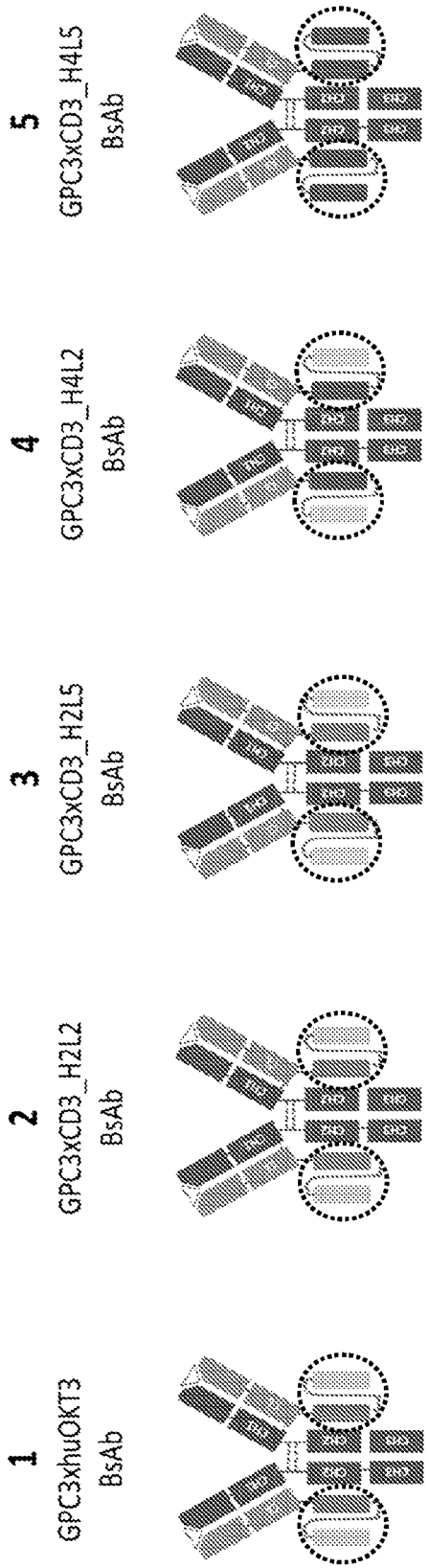

1
GPC3xhuOKT3
BsAb
2
GPC3xCD3_H2L2
BsAb
3
GPC3xCD3_H2L5
BsAb
4
GPC3xCD3_H4L2
BsAb
5
GPC3xCD3_H4L5
BsAb

Figure 27

1. huOKT3 scfv [OKT3 ds] (SEQ ID NO: 141)

QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGK***C***LEWIGYINPSRGYTNYNQKFKDRF
TISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYSLDYWGQGTPVTVSS**GGGGSGGGGSGGGGSG**
GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLA
SGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFG***C***GTKLQITR

2. OT3-H2L2 scfv [OT3-C100JS VH2-(30)-VL2] (SEQ ID NO: 142)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMGYINPSRGYTNYNQKFKD
RATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHY***S***LDYWGQGTTLTVSS**GGGGSGGGGSGGGGSG**
GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLA
SGVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

3. OT3-H2L5 scfv [OT3-C100JS VH2-(30)-VL5] (SEQ ID NO: 143)

QVQLQQSGAEVAKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWMGYINPSRGYTNYNQKFKD
RATLTRDKSISTAYMELSRLRSDDTAVYYCARYYDDHY***S***LDYWGQGTTLTVSS**GGGGSGGGGSGGGGSG**
GGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLA
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

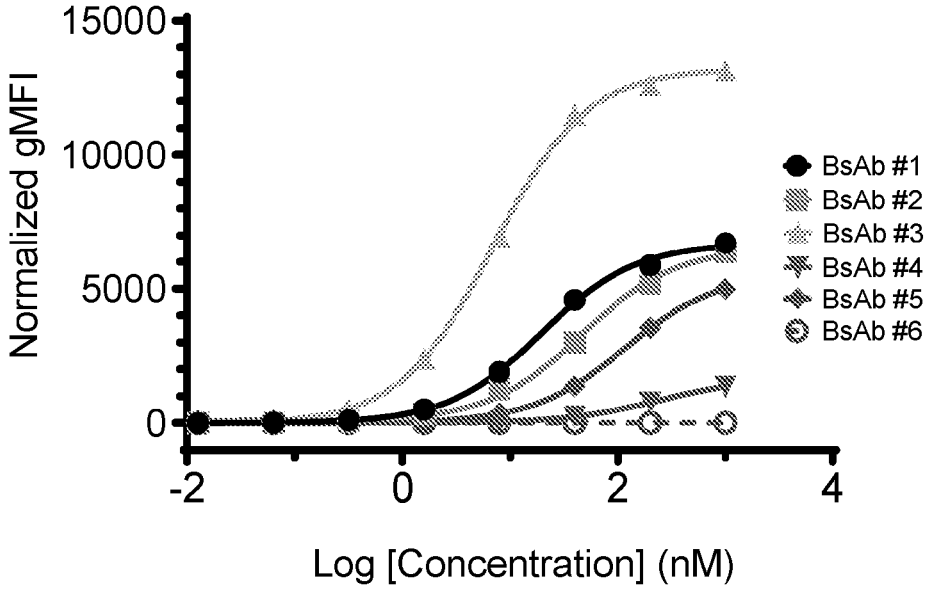
4. OT3-H4L2 scfv [OT3-C100JS VH4-(30)-VL2] (SEQ ID NO: 144)

QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYNQKFKDR
VTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHY***S***LDYWGQGTTLTVSS**GGGGSGGGGSGGGGSGG**
GGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKLLIYDTSKLAS
GVPSRFSGSGSGTDFTLTISSMQPEDFATYYCQQWSSNPFTFGSGTKLEINR

5. OT3-H4L5 scfv [OT3-C100JS VH4-(30)-VL5] (SEQ ID NO: 145)

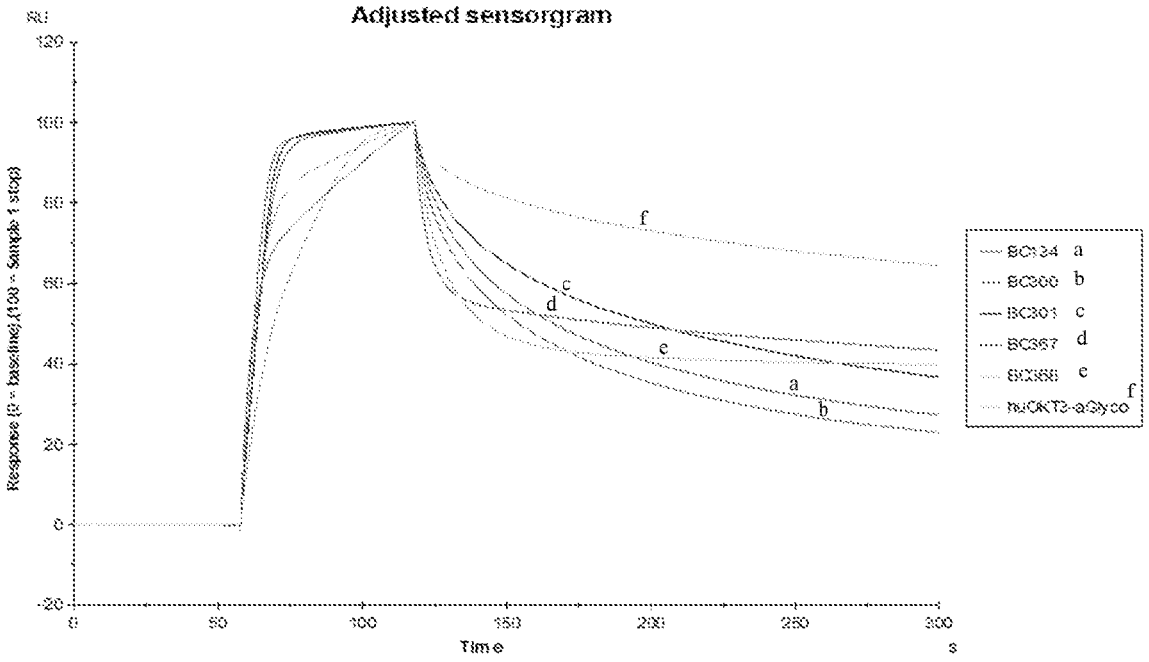
QVQLQQSGAEVKKPGASVKMSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYNQKFKDR
VTLTTDTSISTAYMELSRLRSDDTAVYYCARYYDDHY***S***LDYWGQGTTLTVSS**GGGGSGGGGSGGGGSGG**
GGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRWIYDTSKLAS
GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPFTFGSGTKLEINR

Figure 28



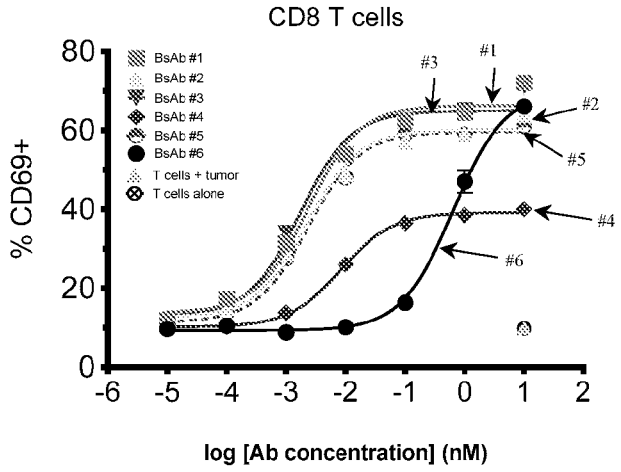
ID	Fab target	scfv target, clone	IC50 (nM)	Highest binding, Geometric MFI
#1 : GPC3 x CD3	GPC3	CD3, huOKT3 (SEQ ID NO: 141)	19.52	6,692
#2 : GPC3 x CD3	GPC3	CD3, H2L2 (SEQ ID NO: 142)	46.71	6,541
#3 : GPC3 x CD3	GPC3	CD3, H2L5 (SEQ ID NO: 143)	6.98	13,222
#4 : GPC3 x CD3	GPC3	CD3, H4L2 (SEQ ID NO: 144)	238	1,679
#5 : GPC3 x CD3	GCP3	CD3, H4L5 (SEQ ID NO: 145)	118.1	5,602
#6 : GD2 x DOTA	GD2	DOTA, C825	-	3.311

Figure 29



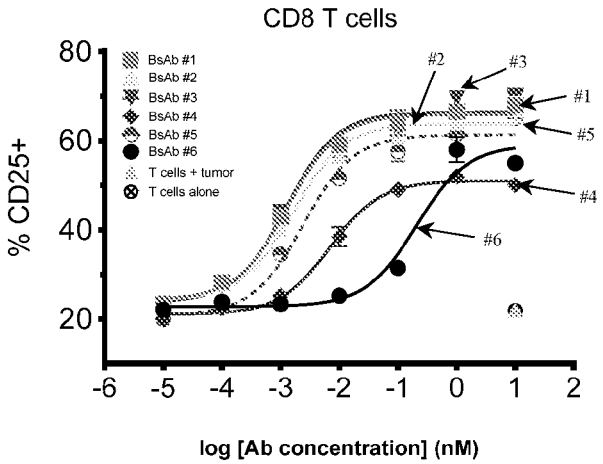
ID	Fab target	scfv target, clone	ka1 (1/Ms)	kd1 (1/s)	ka2 (1/s)	kd2 (1/s)	KD (M)
#1 : GPC3 x CD3	GPC3	CD3, huOKT3	6.51E+06	7.18E-02	5.20E-03	5.37E-03	5.60E-09
#2 : GPC3 x CD3	GPC3	CD3, H2L2	1.70E+07	1.55E-01	3.91E-03	5.25E-03	5.23E-09
#3 : GPC3 x CD3	GPC3	CD3, H2L5	1.27E+07	8.62E-02	6.96E-03	5.72E-03	3.06E-09
#4 : GPC3 x CD3	GPC3	CD3, H4L2	1.88E+06	3.23E-01	1.52E-02	1.47E-03	1.52E-08
#5 : GPC3 x CD3	GCP3	CD3, H4L5	3.98E+06	1.91E-01	7.69E-03	5.79E-04	3.36E-09
#6 : CD3	huOKT3	NA	3.90E+06	2.76E-01	5.88E-02	2.93E-03	3.36E-09

Figure 30



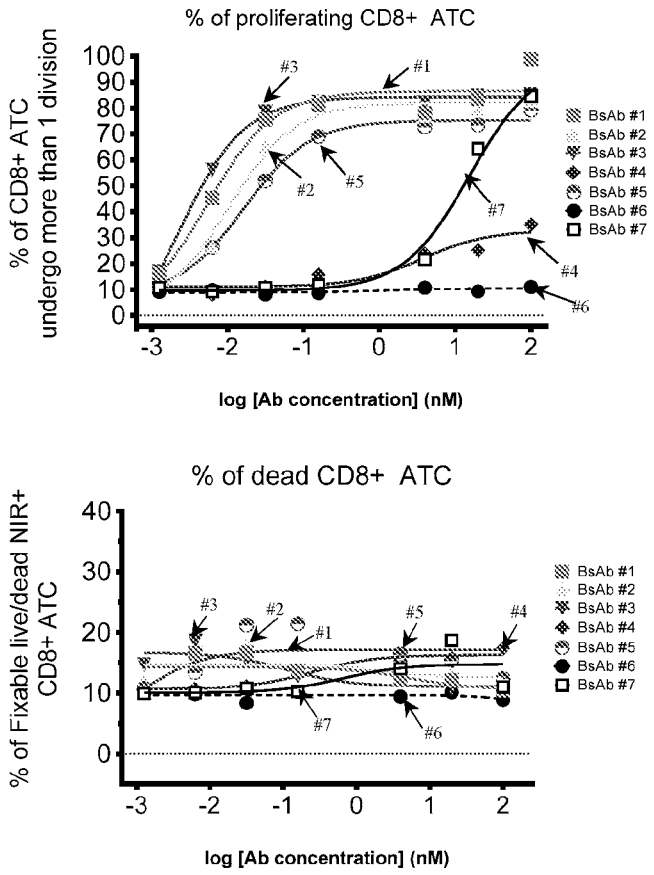
ID	Fab target	scfv target, clone	IC50 (pM)	Highest binding, % CD69+ T cells
#1 : GPC3 x CD3	GPC3	CD3, huOKT3	2.32	66.34
#2 : GPC3 x CD3	GPC3	CD3, H2L2	2.27	60.13
#3 : GPC3 x CD3	GPC3	CD3, H2L5	1.69	64.95
#4 : GPC3 x CD3	GPC3	CD3, H4L2	8.33	39.19
#5 : GPC3 x CD3	GCP3	CD3, H4L5	2.34	59.58
#6 : GD2 x CD3	GD2	CD3, huOKT3	637	69.89

Figure 31



ID	Fab target	scfv target, clone	IC50 (pM)	Highest binding, % CD25+ T cells
#1 : GPC3 x CD3	GPC3	CD3, huOKT3	1.30	65.88
#2 : GPC3 x CD3	GPC3	CD3, H2L2	1.64	63.83
#3 : GPC3 x CD3	GPC3	CD3, H2L5	1.25	66.46
#4 : GPC3 x CD3	GPC3	CD3, H4L2	6.93	51.03
#5 : GPC3 x CD3	GCP3	CD3, H4L5	2.41	61.35
#6 : GD2 x CD3	GD2	CD3, huOKT3	207	59.07

Figure 32A



ID	Fab target	scfv target, clone	IC50 (pM)	Highest % of dividing CD8 T cells
#1 : GPC3 x CD3	GPC3	CD3, huOKT3	5.50	86.42
#2 : GPC3 x CD3	GPC3	CD3, H2L2	10.41	82.09
#3 : GPC3 x CD3	GPC3	CD3, H2L5	2.25	84.20
#4 : GPC3 x CD3	GPC3	CD3, H4L2	3,786	32.92
#5 : GPC3 x CD3	GCP3	CD3, H4L5	16.46	75.23
#6 : GPC3 x DOTA	GPC3	DOTA, C825	-	10.43
#7 : CD33 x CD3	CD33	CD3, huOKT3	-	98.00

Figure 32B

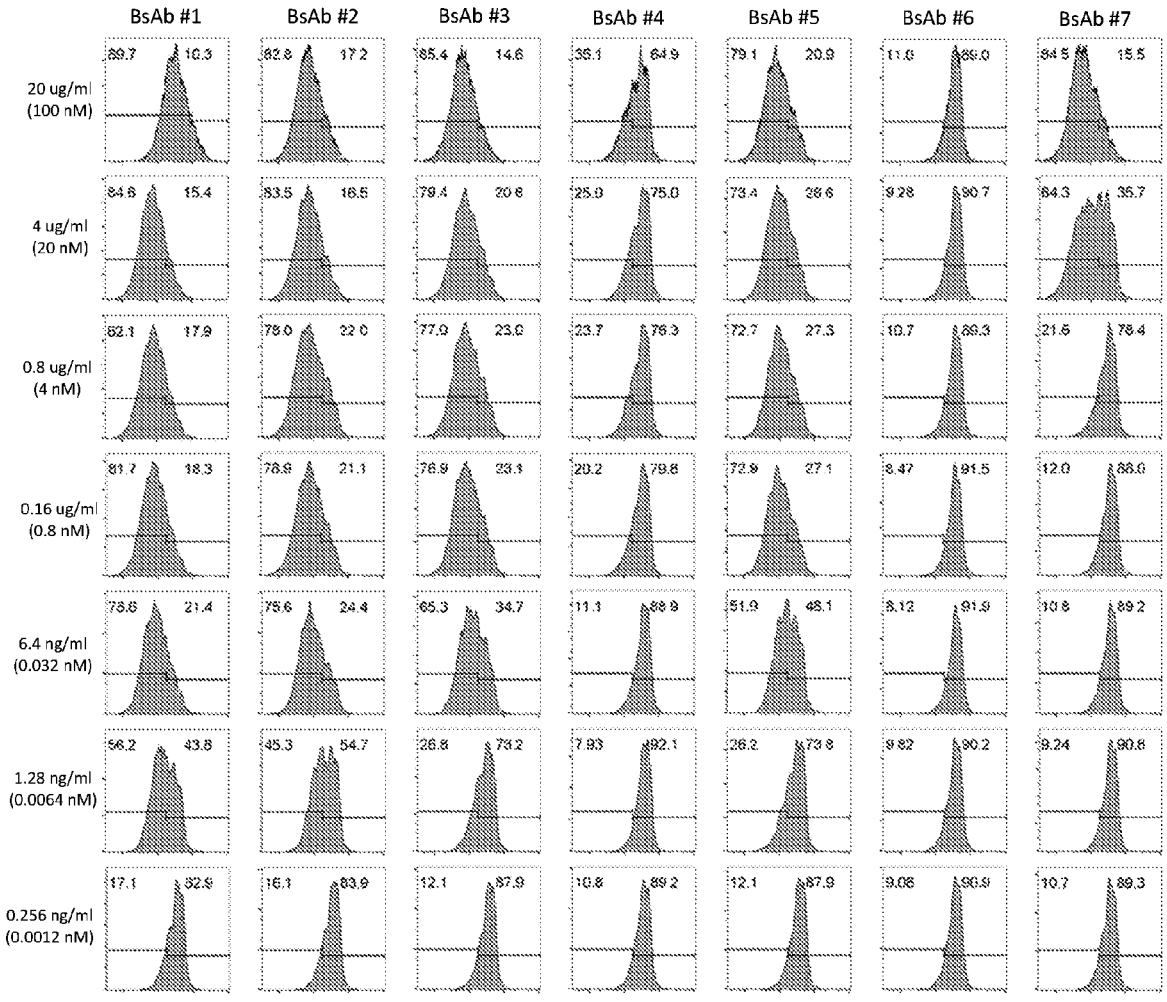
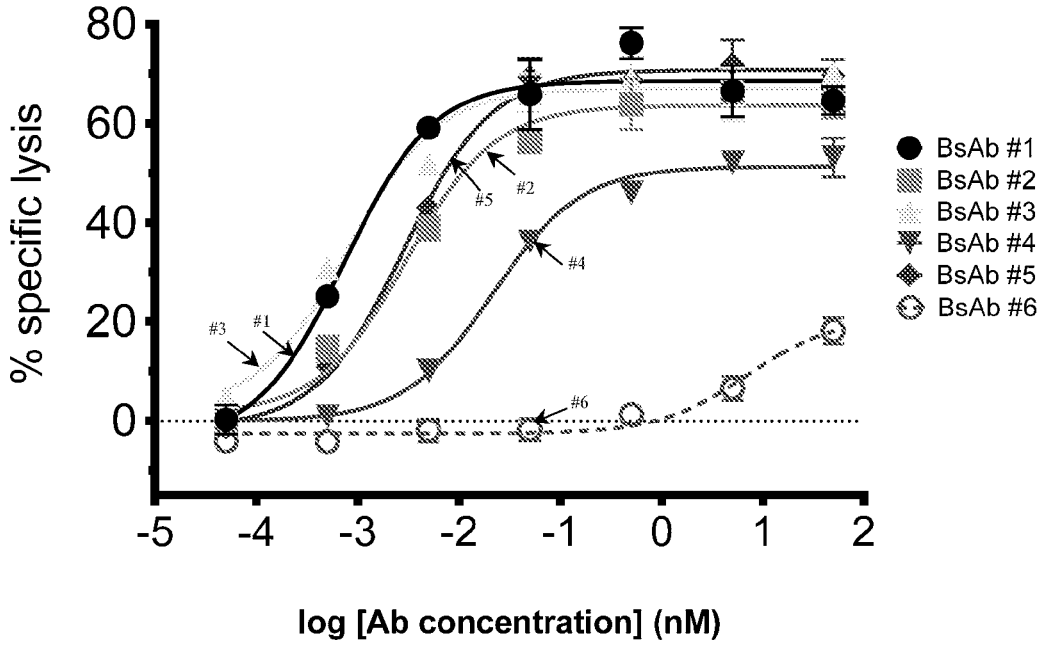

BsAb #1
BsAb #2
BsAb #3
BsAb #4
BsAb #5
BsAb #6
BsAb #7
20 ug/ml (100 nM)
4 ug/ml (20 nM)
0.8 ug/ml (4 nM)
0.16 ug/ml (0.8 nM)
6.4 ng/ml (0.032 nM)
1.28 ng/ml (0.0064 nM)
0.256 ng/ml (0.0012 nM)

Figure 33



ID	Fab target	scfv target, clone	EC50 (pM)	Highest % specific lysis
#1 : GPC3 x CD3	GPC3	CD3, huOKT3	0.75	68.55
#2 : GPC3 x CD3	GPC3	CD3, H2L2	3.04	63.59
#3 : GPC3 x CD3	GPC3	CD3, H2L5	0.81	66.96
#4 : GPC3 x CD3	GPC3	CD3, H4L2	21.5	51.30
#5 : GPC3 x CD3	GCP3	CD3, H4L5	2.88	70.72
#6 : CD33 x CD3	CD33	CD3, huOKT3	6880	20.86

Figure 34A

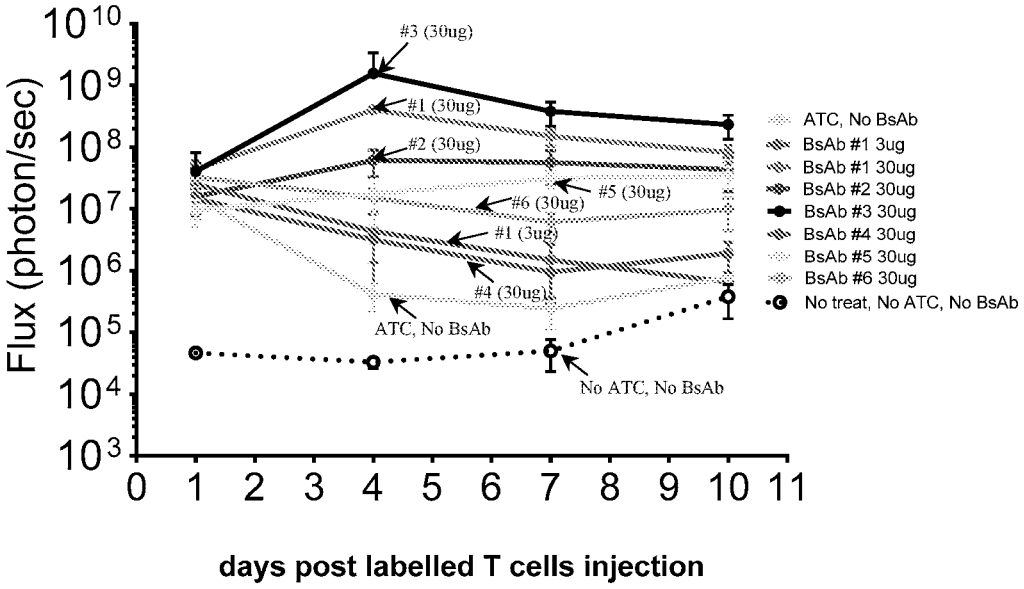
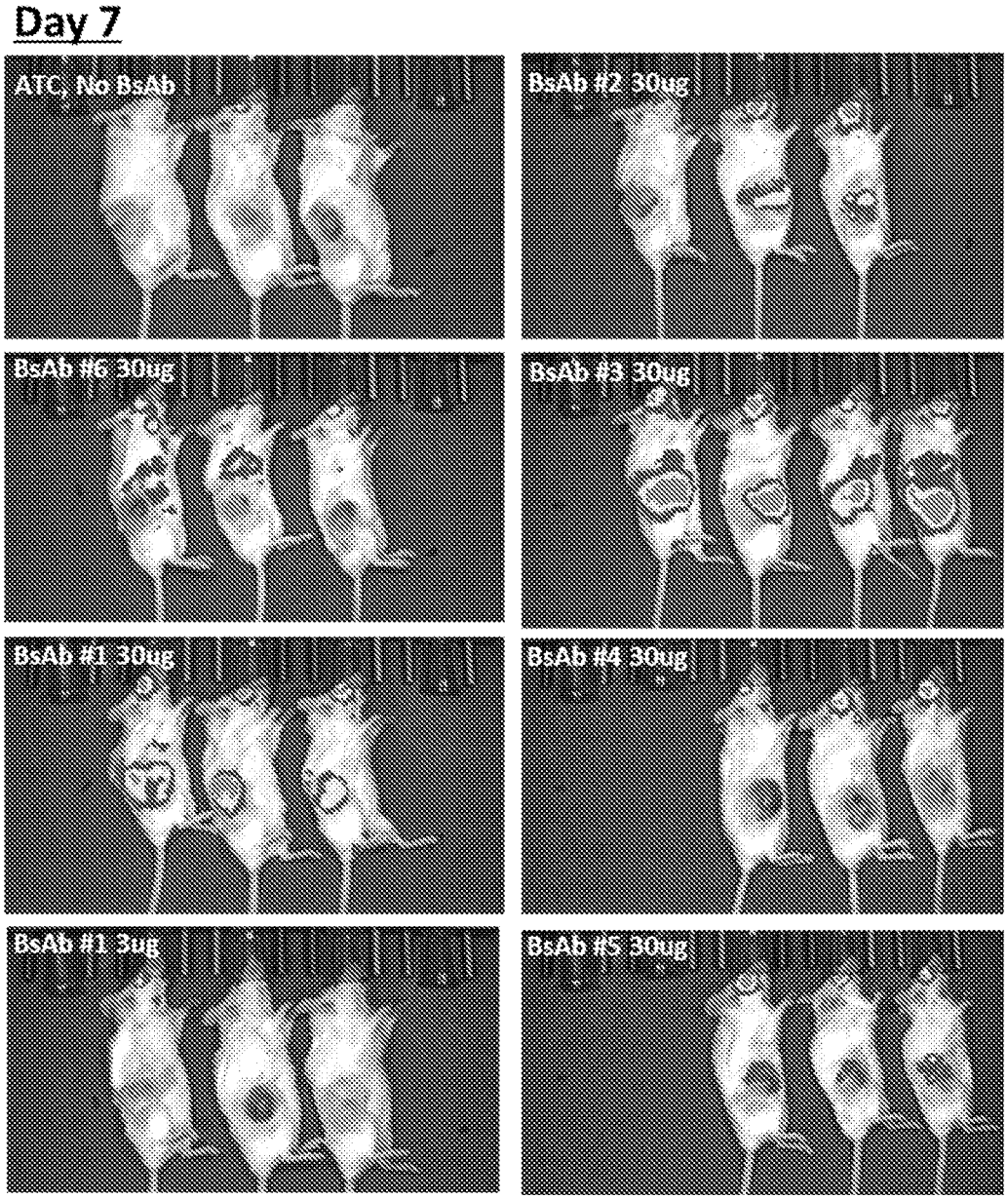

Flux (photon/sec)
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
10^{4}
10^{3}
0 1 2 3 4 5 6 7 8 9 10 11
days post labelled T cells injection
#3 (30ug)
#1 (30ug)
#2 (30ug)
#5 (30ug)
#6 (30ug)
#1 (3ug)
#4 (30ug)
ATC, No BsAb
No ATC, No BsAb
ATC, No BsAb
BsAb #1 3ug
BsAb #1 30ug
BsAb #2 30ug
BsAb #3 30ug
BsAb #4 30ug
BsAb #5 30ug
BsAb #6 30ug
No treat, No ATC, No BsAb

Figure 34B


Day 7
ATC, No BsAb
BsAb #2 30ug
BsAb #6 30ug
BsAb #3 30ug
BsAb #1 30ug
BsAb #4 30ug
BsAb #1 3ug
BsAb #5 30ug

ANTI-CD3 ANTIBODIES AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a U.S. National Stage Application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2021/028798, filed on Apr. 23, 2021, which claims the benefit of and priority to U.S. Provisional Pat. Application No. 63/015,149, filed Apr. 24, 2020, the entire contents of each of which are incorporated herein by reference.

SEQUENCE LISTING

[0002] [0001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jun. 3, 2021, is named 115872-2199_SL.txt and is 294,362 bytes in size.

TECHNICAL FIELD

[0003] The present technology relates generally to the preparation of immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof) that specifically bind CD3 protein and uses of the same. In particular, the present technology relates to the preparation of CD3 binding antibodies and their use in detecting and treating cancer or CD3-associated pathologies.

BACKGROUND

[0004] The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

[0005] Autoimmunity arises when the immune system of the patient reacts against its own normal tissues. In humans, the autoimmune diseases commonly involve both B cells and T cells. Although T cells play important roles in various autoimmune diseases including those mediated primarily via autoimmune antibodies or immune complexes, there are diseases that are primarily T cell mediated including sympathetic ophthalmia, multiple sclerosis, and type-1 diabetes mellitus. The treatment of autoimmune diseases is mainly based on immunosuppression with either corticosteroids or T cell activation pathway antagonists. Arevalo et al., *Middle East Afr J Ophthalmol* 19(1): 13-21 (2012): Galea et al., BMJ350: h1765 (2015).

[0006] Allergenic hematopoietic cell transplantation (AHCT) is a powerful treatment for several types of diseases including leukemia, immune deficiency, metabolic defects, and hemoglobinopathies. Hatzimichael and Tuthill *Stem Cells Cloning* 3: 105-117 (2010). One major complication of AHCT is graft versus host disease that occurs in 35-50% of patients. Jacobsohn and Vogelsang *Orphanet J Rare Dis* 2: 35 (2007). Most treatment options are based on immunosuppression and corticosteroids are the mainstay treatment modality for treatment of grade II and higher acute GVHD. Nevertheless, corticosteroids have several adverse metabolic systemic effects, such as dampening the whole immune system including the innate and adaptive immunity and increasing the risk of opportunistic infections (Jacobsohn and Vogelsang, *supra* (2007), Hatzimichael and Tuthill, *supra* (2010)). In addition, some patients are resistant to corticosteroid treatment. Unfortunately, the survival rate of patients with grade IV GVHD is only 5%, thus necessitating the development of more effective and safer treatment options for these patients (Cahn et al., *Blood* 106(4): 1495-1500 (2005)).

SUMMARY OF THE PRESENT TECHNOLOGY

[0007] In one aspect, the present disclosure provides an antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein (a) the V_H comprises a V_H-CDR1 sequence of

GYTFTRYT

(SEQ ID NO: 2), a V_H-CDR2 sequence of

INPSRGYT

(SEQ ID NO: 3), and a V_H-CDR3 sequence of

ARYYDDHYSLDY

(SEQ ID NO: 6),

ARYYDDHYSCDY

(SEQ ID NO: 134),

ARYYDDHCSLDY

(SEQ ID NO: 135), or

ARYYDDHYSLCY

(SEQ ID NO: 136); and/or; (b) the V_L comprises a V_L-CDR1 sequence of SSVSY (SEQ ID NO: 12), a V_L-CDR2 sequence of DT (SEQ ID NO: 13), and a V_L—CDR3 sequence of

QQWSSNPFT

(SEQ ID NO: 14).

[0008] In one aspect, the present disclosure provides an antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein: (a) the V_H comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61; and/or (b) the V_L comprises an amino acid sequence selected from any one of SEQ ID NOs: 15-20 or 62–91.

[0009] In any of the above embodiments, the antibody may further comprise an Fc domain of an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE. In some embodiments, the antibody comprises an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments, the antibody comprises an IgG4 constant region comprising a S228P mutation. In certain embodiments, the antigen binding fragment is selected from the group consisting of Fab, $F(ab')_2$, Fab', scF_v, and F_v. In some embodiments, the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or a multi-specific antibody. In certain embodiments, the antibody or antigen binding fragment binds to the extracellular domain of a CD3 polypeptide. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop).

[0010] In another aspect, the present disclosure provides an antibody comprising a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 23, SEQ ID NO: 96, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 112, SEQ ID NO: 116, SEQ ID NO: 126, SEQ ID NO: 132, SEQ ID NO: 137, SEQ ID NO: 139, or a variant thereof having one or more conservative amino acid substitutions, and/or a light chain (LC) amino acid sequence comprising SEQ ID NO: 21, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 98, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 114, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 128, SEQ ID NO: 130, or a variant thereof having one or more conservative amino acid substitutions. In some embodiments, the antibody comprises a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of: SEQ ID NO: 23 and SEQ ID NO: 21, SEQ ID NO: 23 and SEQ ID NO: 92, SEQ ID NO: 96 and SEQ ID NO: 94, SEQ ID NO: 100 and SEQ ID NO: 98, SEQ ID NO: 104 and SEQ ID NO: 102, SEQ ID NO: 108 and SEQ ID NO: 106, SEQ ID NO: 112 and SEQ ID NO: 110, and SEQ ID NO: 116 and SEQ ID NO: 114, respectively. Additionally or alternatively, in some embodiments, the antibody comprises a first LC amino acid sequence, a second LC amino acid sequence, a first HC amino acid sequence, and a second HC amino acid sequence selected from the group consisting of SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, and SEQ ID NO: 137; and SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 139, respectively.

[0011] In one aspect, the present disclosure provides an antibody comprising (a) a light chain immunoglobulin variable domain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the light chain immunoglobulin variable domain sequence of any one of SEQ ID NOs: 15-20 or 62-91; and/or (b) a heavy chain immunoglobulin variable domain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the heavy chain immunoglobulin variable domain sequence of any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61.

[0012] In another aspect, the present disclosure provides an antibody comprising (a) a LC sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the LC sequence present in SEQ ID NO: 21, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 98, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 114, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 128, or SEQ ID NO: 130; and/or (b) a HC sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the HC sequence present in SEQ ID NO: 23, SEQ ID NO: 96, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 112, SEQ ID NO: 116, SEQ ID NO: 126, SEQ ID NO: 132, SEQ ID NO: 137, or SEQ ID NO: 139.

[0013] In any of the above embodiments, the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or a multi-specific antibody. Additionally or alternatively, in some embodiments, the antibody comprises an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. In certain embodiments, the antibody of the present technology comprises an IgG4 constant region comprising a S228P mutation. In any of the above embodiments, the antibody binds to the extracellular domain of a CD3 polypeptide. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop).

[0014] Additionally or alternatively, in some embodiments, the antibody of the present technology lacks α-1,6-fucose modifications.

[0015] In one aspect, the present disclosure provides a multi-specific antigen binding fragment comprising a first polypeptide chain, wherein: the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (iii) a light chain variable domain of the first immunoglobulin; (iv) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_4$ (SEQ ID NO: 149); (v) a heavy chain variable domain of a second immunoglobulin that is capable of specifically binding to a second epitope; (vi) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (vii) a light chain variable domain of the second immunoglobulin; (viii) a flexible peptide linker sequence comprising the amino acid sequence TPLGDTTHT (SEQ ID NO: 150); and (ix) a self-assembly disassembly (SADA) polypeptide, wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0016] In another aspect, the present disclosure provides a multi-specific antigen binding fragment comprising a first polypeptide chain, wherein: the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a flexible

peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (iii) a heavy chain variable domain of the first immunoglobulin; (iv) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_4$ (SEQ ID NO: 149); (v) a heavy chain variable domain of a second immunoglobulin that is capable of specifically binding to a second epitope; (vi) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (vii) a light chain variable domain of the second immunoglobulin; (viii) a flexible peptide linker sequence comprising the amino acid sequence TPLGDTTHT (SEQ ID NO: 150); and (ix) a self-assembly disassembly (SADA) polypeptide, wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0017] In certain embodiments of the multi-specific antigen binding fragments disclosed herein, the SADA polypeptide comprises a tetramerization, pentamerization, or hexamerization domain. In some embodiments, the SADA polypeptide comprises a tetramerization domain of any one of p53, p63, p73, hnRNPC, SNA-23, Stefin B, KCNQ4, and CBFA2T1.

[0018] In one aspect, the present disclosure provides a multi-specific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain are covalently bonded to one another, and wherein: (a) each of the first polypeptide chain and the fourth polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin; (iii) a flexible peptide linker comprising the amino acid sequence (

GGGGS

$)_3$ (SEQ ID NO: 151); and (iv) a light chain variable domain of a second immunoglobulin that is linked to a complementary heavy chain variable domain of the second immunoglobulin, or a heavy chain variable domain of a second immunoglobulin that is linked to a complementary light chain variable domain of the second immunoglobulin, wherein the light chain and heavy chain variable domains of the second immunoglobulin are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence (

GGGGS

$)_6$ (SEQ ID NO: 148) to form a single-chain variable fragment; and (b) each of the second polypeptide chain and the third polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin that is capable of specifically binding to the first epitope; and (ii) a heavy chain constant domain of the first immunoglobulin; and wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0019] In one aspect, the present disclosure provides a recombinant nucleic acid sequence encoding any of the antibodies or antigen binding fragments described herein. In some embodiments, the recombinant nucleic acid sequence is selected from the group consisting of: SEQ ID NOs: 22, 24, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 138, and 140.

[0020] In another aspect, the present disclosure provides a host cell or vector comprising any of the recombinant nucleic acid sequences disclosed herein.

[0021] In one aspect, the present disclosure provides a composition comprising an antibody or antigen binding fragment of the present technology and a pharmaceutically-acceptable carrier, wherein the antibody or antigen binding fragment is optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

[0022] Additionally or alternatively, in some embodiments, the multi-specific antibody or antigen binding fragment of the present technology binds to T cells, B-cells, myeloid cells, plasma cells, or mast-cells. Additionally or alternatively, in some embodiments, the multi-specific antibody or antigen binding fragment binds to CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N- acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PIGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Le^y) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pme117, LMP2, or WT1), or a small molecule DOTA hapten. The small molecule DOTA hapten may be selected from the group consisting of DOTA,

DOTA-Bn, DOTA-desferrioxamine, DOTA-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-NH_2, Ac-Lys(HSG)D-Tyr-Lys(HSG)-Lys(Tscg-Cys)-NH_2, DOTA-D-Asp-D-Lys(HSG)-D-Asp-D-Lys(HSG)-NH_2; DOTA-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2, DOTA-D-Tyr-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2, DOTA-D-Ala-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2, DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH_2, Ac-D-Phe-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-NH_2, Ac-D-Phe-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2, Ac-D-Phe-D-Lys(Bz-DTPA)-D-Tyr-D-Lys(Bz-DTPA)-NH_2, Ac-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2, DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2, (Tscg-Cys)-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(DOTA)-NH_2, Tscg-D-Cys-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2, (Tscg-Cys)-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2, Ac-D-Cys-D-Lys(DOTA)-D-Tyr-D-Ala-D-Lys(DOTA)-D-Cys-NH_2, Ac-D-Cys-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2, Ac-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-D-Lys(Tscg-Cys)-NH_2, and Ac-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-D-Lys(Tscg-Cys)-NH_2.

[0023] In another aspect, the present disclosure provides a method for treating a CD3-associated autoimmune disease in a subject in need thereof, comprising administering to the subject an effective amount of an antibody comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of SEQ ID NO: 23 and SEQ ID NO: 21, SEQ ID NO: 23 and SEQ ID NO: 92, SEQ ID NO: 96 and SEQ ID NO: 94, SEQ ID NO: 100 and SEQ ID NO: 98, SEQ ID NO: 104 and SEQ ID NO: 102, SEQ ID NO: 108 and SEQ ID NO: 106, SEQ ID NO: 112 and SEQ ID NO: 110, and SEQ ID NO: 116 and SEQ ID NO: 114, respectively, wherein the antibody specifically binds to CD3. Examples of CD3-associated autoimmune disease include, but are not limited to, multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus, Celiac disease, Sympathetic ophthalmia, Type 1 diabetes, and graft-versus-host disease.

[0024] In yet another aspect, the present disclosure provides a method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of an antibody comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of SEQ ID NO: 23 and SEQ ID NO: 21, SEQ ID NO: 23 and SEQ ID NO: 92, SEQ ID NO: 96 and SEQ ID NO: 94, SEQ ID NO: 100 and SEQ ID NO: 98, SEQ ID NO: 104 and SEQ ID NO: 102, SEQ ID NO: 108 and SEQ ID NO: 106, SEQ ID NO: 112 and SEQ ID NO: 110, and SEQ ID NO: 116 and SEQ ID NO: 114, respectively, wherein the antibody specifically binds to CD3. Examples of cancer include, but are not limited to, precursor T acute lymphoblastic leukemia/lymphoma, anaplastic large-cell lymphoma, lymphomatoid papulosis type A, Mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, Sezary disease, adult T-cell leukemia/lymphoma, cutaneous large T cell lymphoma, pleomorphic T-cell lymphoma, lymphomatoid papulosis type B, secondary cutaneous CD30+ large-cell lymphoma, hepatosplenic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, subcutaneous T-cell lymphoma, large granular lymphocytic leukemia, and acute biphenotypic leukemia. Other examples of cancer include, but are not limited to, adrenal cancers, bladder cancers, blood cancers, bone cancers, brain cancers, breast cancers, carcinoma, cervical cancers, colon cancers, colorectal cancers, corpus uterine cancers, ear, nose and throat (ENT) cancers, endometrial cancers, esophageal cancers, gastrointestinal cancers, head and neck cancers, Hodgkin's disease, intestinal cancers, kidney cancers, larynx cancers, acute and chronic leukemias, liver cancers, lymph node cancers, lymphomas, lung cancers, melanomas, mesothelioma, myelomas, nasopharynx cancers, neuroblastomas, non-Hodgkin's lymphoma, oral cancers, ovarian cancers, pancreatic cancers, penile cancers, pharynx cancers, prostate cancers, rectal cancers, sarcoma, seminomas, skin cancers, stomach cancers, teratomas, testicular cancers, thyroid cancers, uterine cancers, vaginal cancers, vascular tumors, and metastases thereof.

[0025] Additionally or alternatively, in some embodiments of the method, the antibody or antigen binding fragment is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent. Examples of additional therapeutic agents include one or more of alkylating agents, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, bisphosphonate therapy agents. Other examples of additional therapeutic agents include non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, glucocorticoids, and conventional disease-modifying anti-rheumatic drugs (cDMARDs).

[0026] In one aspect, the present disclosure provides a method for detecting tumors in a subject in need thereof comprising (a) administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that binds to the radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex; and (b) detecting the presence of tumors in the subject by detecting radioactive levels emitted by the complex that are higher than a reference value. In some embodiments, the subject is human.

[0027] In another aspect, the present disclosure provides a method for detecting cancer in a subject in vivo comprising (a) administering to the subject an effective amount of an antibody or antigen binding fragment of the present technology, wherein the antibody or antigen binding fragment is configured to localize to a cancer cell expressing CD3, and is labeled with a radioisotope; and (b) detecting the presence of a tumor in the subject by detecting radioactive levels emitted by the antibody or antigen binding fragment that are higher than a reference value. In some embodiments, the subject is diagnosed with or is suspected of having cancer. Radioactive levels emitted by the antibody or antigen binding fragment may be detected using positron emission tomography or single photon emission computed tomography.

[0028] Additionally or alternatively, in some embodiments, the method further comprises administering to the subject an effective amount of an immunoconjugate comprising an antibody or antigen binding fragment of the pre-

sent technology conjugated to a radionuclide. In some embodiments, the radionuclide is an alpha particle-emitting isotope, a beta particle-emitting isotope, an Auger-emitter, or any combination thereof. Examples of beta particle-emitting isotopes include ^{86}Y, ^{90}Y, ^{89}Sr, ^{165}Dy, ^{186}Re, ^{188}Re, ^{177}Lu, and ^{67}Cu. In some embodiments of the method, non-specific FcR-dependent binding in normal tissues is eliminated or reduced (e.g., via N297A mutation in Fc region, which results in aglycosylation).

[0029] Also disclosed herein are kits for the detection and/or treatment of CD3-associated pathologies, comprising at least one immunoglobulin-related composition of the present technology (e.g., any antibody or antigen binding fragment described herein), or a functional variant (e.g., substitutional variant) thereof and instructions for use. In certain embodiments, the immunoglobulin-related composition is coupled to one or more detectable labels. In one embodiment, the one or more detectable labels comprise a radioactive label, a fluorescent label, or a chromogenic label.

[0030] Additionally or alternatively, in some embodiments, the kit further comprises a secondary antibody that specifically binds to an anti-CD3 immunoglobulin-related composition described herein. In some embodiments, the secondary antibody is coupled to at least one detectable label selected from the group consisting of a radioactive label, a fluorescent label, or a chromogenic label.

[0031] In one aspect, the present disclosure provides a method for selecting a subject for pretargeted radioimmunotherapy comprising (a) administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that binds to the radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex; (b) detecting radioactive levels emitted by the complex; and (c) selecting the subject for pretargeted radioimmunotherapy when the radioactive levels emitted by the complex are higher than a reference value. In some embodiments, the subject is human.

[0032] In one aspect, the present disclosure provides a method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with cancer comprising administering to the subject an effective amount of a complex comprising a radiolabeled-DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that recognizes and binds to the radiolabeled-DOTA hapten, a CD3 antigen and a tumor antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex.

[0033] In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof comprising administering to the subject an effective amount of a complex comprising a radiolabeled-DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that recognizes and binds to the radiolabeled-DOTA hapten, a CD3 antigen and a tumor antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex.

[0034] In any of the above embodiments of the methods disclosed herein, the complex is administered intravenously, intramuscularly, intraarterially, intrathecally, intracapsularly, intraorbitally, intradermally, intraperitoneally, transtracheally, subcutaneously, intracerebroventricularly, orally, intratumorally, or intranasally. In some embodiments of the methods disclosed herein, the subject is human. Additionally or alternatively, in any of the above embodiments of the methods disclosed herein, the radiolabeled-DOTA hapten comprises ^{213}Bi, ^{211}At, ^{225}Ac, ^{152}Dy, ^{212}Bi, ^{223}Ra , ^{219}Rn, ^{215}Po, ^{211}Bi, ^{221}Fr, ^{217}At, ^{255}Fm, ^{86}Y, ^{90}Y, ^{89}Sr, ^{165}Dy, ^{186}Re, ^{188}Re, ^{177}Lu, ^{67}Cu, ^{111}In, ^{67}Ga, ^{51}Cr, ^{58}Co, ^{99m}Tc, ^{103m}Rh, ^{195m}Pt, ^{119}Sb, ^{161}Ho, ^{189m}Os, ^{192}Ir, ^{201}Tl, ^{203}Pb, ^{68}Ga, ^{227}Th, or ^{64}Cu, and optionally comprises an alpha particle-emitting isotope, a beta particle-emitting isotope, or an Auger-emitter.

[0035] Also disclosed herein is a method for selecting a subject for pretargeted radioimmunotherapy comprising (a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of the present technology that binds to a radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment; (c) detecting radioactive levels emitted by the multi-specific antibody; and (d) selecting the subject for pretargeted radioimmunotherapy when the radioactive levels emitted by the multi-specific antibody are higher than a reference value. In another aspect, the present disclosure provides a method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with cancer comprising (a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of the present technology that binds to a radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; and (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment. In one aspect, the present disclosure provides a method for treating cancer in a subject in need thereof comprising (a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of the present technology that binds to a radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; and (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment. In some embodiments, the methods of the present technology further comprise administering an effective amount of a clearing agent to the subject prior to administration of the radiolabeled-DOTA hapten.

[0036] Additionally or alternatively, in any of the above embodiments of the methods disclosed herein, the radiolabeled-DOTA hapten comprises ^{213}Bi, ^{211}At, ^{225}Ac, ^{152}Dy, ^{212}Bi, ^{223}Ra, ^{219}Rn, ^{215}Po, ^{211}Bi, ^{221}Fr, ^{217}At, ^{255}Fm, ^{86}Y, ^{90}Y, ^{89}Sr, ^{165}Dy, ^{186}Re, ^{188}Re, ^{177}Lu, ^{67}Cu, ^{111}In, ^{67}Ga,

^{51}Cr, ^{58}Co, ^{99m}Tc, ^{103m}Rh, ^{195m}Pt, ^{119}Sb, ^{161}Ho, ^{189m}Os, ^{192}Ir, ^{201}Tl, ^{203}Pb, ^{68}Ga, ^{227}Th, or ^{64}Cu, and optionally comprises an alpha particle-emitting isotope, a beta particle-emitting isotope, or an Auger-emitter. In any of the above embodiments of the methods disclosed herein, the subject is human.

[0037] In any and all embodiments of the methods disclosed herein, the multi-specific antibody or antigen binding fragment binds to CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp 100), GnT-V intron V sequence (N-acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PIGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Le^y) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, or peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pme117, LMP2, or WT1).

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] FIG. **1**A shows a schematic of the modular tetravalent IgG-scFv format comprising an IgG molecule with two binding sites covalently linked to two scFvs providing two additional binding domains.

[0039] FIG. **1**B shows an exemplary analysis of biochemical purity of the BC276 (hOKT3 L2H2) BsAb of the present disclosure. The top panel shows a size-exclusion chromatography-high-performance liquid chromatography (SEC-HPLC) profile. Protein in the eluent was detected based on the absorbance of ultraviolet light having a wavelength of 280 nm. The relative amount of protein in the SEC-HPLC peaks from the chromatogram is displayed in the bottom panel.

[0040] FIG. **2** shows the stability of the humanized OKT3 IgG antibody BC276 (hOKT3 L2H2) at 40° C. The antibody was incubated at 40° C., and aliquots of the same were withdrawn at specified times to assess purity using HPLC. A line graph which plots the stability values as a function of incubation time at 40° C. is shown.

[0041] FIGS. **3**A-**3**B show that BC276 induces potent T cell fratricide in vitro. T cells were cultured with 350 pM BC276 in the presence of interleukin-2 to support T cell proliferation. A CD19 × CD3-specific IgG-L-scFv BsAb, and the humanized OKT3 IgG were used as controls. FIG. **3**A shows the number of CD4 T cell populations at several indicated time points. FIG. **3**B shows the number of CD8 T cell populations at several indicated time points.

[0042] FIGS. **4**A-**4**B show that the BC276 BsAb induces profound T cell depletion in mice. NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally. Treatment with injections of 1 μg of BC276 BsAb was initiated on day 8. Control mice were injected with no antibody (No Ab) or with an anti-CD3 × GD2-BsAb (BC119), which were used as negative controls.

[0043] FIG. **4**A shows the flow cytometry profiles of peripheral blood stained with an anti-human CD45 antibody at indicated time points. FIG. **4**B (left panels) displays line graphs showing quantitation of CD45+ cells per ml of peripheral blood at the indicated time points.

[0044] FIG. **4**B (right panels) display graphs showing quantitation of CD45+ cells per ml of peripheral blood on either day 15 (top panel) and day 22 (bottom panel).

[0045] FIGS. **5**A-**5**B show the dosage effects of BC276 BsAb on T cell depletion in mice. NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally. Treatment with injections of 1 μg or 0.1 μg of BC276 BsAb or an anti-CD3 × GD2-BsAb (BC119, the negative control) was initiated on day 8. FIG. **5**A shows the flow cytometry profiles of peripheral blood stained with an anti-human CD45 antibody on day 15. FIG. **5**B shows graphs showing quantitation of CD45+ cells per ml of peripheral blood on day 15.

[0046] FIGS. **6**A-**6**C demonstrate that both CD4 and CD8 T cells were depleted in vivo upon treatment with BC276 BsAb. NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally. Treatment with injections of 1 μg or 0.1 μg of BC276 BsAb or an anti-CD3 × GD2-BsAb (BC119, the negative control) was initiated on day 8. FIG. **6**A shows the quantitation of CD45+ cells per ml of peripheral blood at the indicated time points. FIG. **6**B shows the quantitation of CD4+ cells per ml of peripheral blood at the indicated time points. FIG. **6**C shows the quantitation of CD8+ cells per ml of peripheral blood at the indicated time points. In FIG. **6**C, CD3BC refers to the BC276 BsAb.

[0047] FIG. **7** demonstrates that depletion of T cells is not associated with clinical side effects. NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors 10 million from each donor) intraperitoneally. Treatment with injections of 1 μg or 0.1 μg of BC276 or an anti-CD3-, and GD2-BsAb (BC119, the negative control) was started on day 8. Shown is a line graph showing body weights of animals receiving 1 μg or 0.1 μg of BC276 or an anti-CD3-, and GD2-BsAb (BC119, the negative control) compared with negative control.

[0048] FIGS. **8**A-**8**B show development of graft-versus-host-disease (GVHD) in BC276-treated mice. NSG mice from the experiments described in FIG. **6**A-**7** were used in the experiment. Antibody injections were discontinued, and a second dose of effector cells (22 million activated T cells per mouse) was injected to the mice. Then antibody injections were resumed as shown. FIG. **8**A shows the line graph showing quantitation of CD4+ cells per ml of peripheral blood at the indicated time points. FIG. **8**B shows the line graph showing quantitation of CD8+ cells per ml of peripheral blood at the indicated time points.

[0049] FIG. **9** shows the graph of GVHD scores in the mice treated with the indicated doses of BC276 or an anti-

CD3-, and GD2-BsAb (BC119, the negative control) antibodies compared to mice receiving no antibody. The mice from the experiments described in FIGS. **8**A-**8**B were randomized in 5 groups and the following treatments were carried out: (1) 30 μg BC276, (2) 10 μg BC276, (3) 3 μg BC276, (4) 10 μg BC119 (CD3×GD2 BsAb), and 5) no antibody (No Ab). GVHD scores were measured at indicated time points and plotted.

[0050] FIG. **10** shows a line graph showing body weights of animals treated with the indicated doses of BC276 or an anti-CD3-, and GD2-BsAb (BC119, the negative control) antibodies compared to mice receiving no antibody. Mice from the experiment described in FIG. **9** were weighed at the indicated time points and their weights were plotted.

[0051] FIG. **11** shows a line graph showing body weights of animals treated with the indicated doses of BC276 or an anti-CD3-, and GD2-BsAb (BC119, the negative control) antibodies compared to mice receiving no antibody. Mice from the experiment described in FIG. **10** were weighed at the indicated time points and their weights were plotted.

[0052] FIG. **12**A shows the amino acid sequences of the murine and humanized OKT3 heavy chain variable domains (SEQ ID NOs: 1, 5, 7-10, and 43-61 respectively). OKT3_VH (SEQ ID NO: 1) is the murine OKT3 heavy chain variable domain sequence. OKT3_VH-1, OKT3 VH-2, OKT3 VH-3, OKT3 VH-4, VH-1 H105, VH-2 H105, VH-3 H105, VH-4 H105, VH-1 H44, VH-2 H44, VH-3 H44, VH-4 H44, VH-1 H100B, VH-2 H100B, VH-3 H100B, VH-4 H100B, VH-1 H100, VH-2 H100, VH-3 H100, VH-4 H100, VH-1 H101, VH-2 H101, VH-3 H101, and VH-4 H101 are variants of the humanized OKT3 heavy chain variable domain. The V_H CDR1 sequence is GYTFTRYT (SEQ ID NO: 2), the V_H CDR2 sequence is INPSRGYT (SEQ ID NO: 3), the V_H CDR3 sequences are ARYYDDHYCLDY (SEQ ID NO: 4), ARYYDDHYSLDY (SEQ ID NO: 6), ARYYDDHYSCDY (SEQ ID NO: 134), ARYYDDHCSLDY (SEQ ID NO: 135), or ARYYDDHYSLCY (SEQ ID NO: 136). The V_H CDR 1-3 sequences are underlined. The CDR sequences of the V_H of humanized anti-CD3 antibody are determined using the IMGT definition.

[0053] FIG. **12**B shows the amino acid sequences of the murine and humanized OKT3 light chain variable domains (SEQ ID NOs: 11, 15-20 and 62-91 respectively). OKT3_VL (SEQ ID NO: 11) is the murine OKT3 light chain variable domain sequence. OKT3_VL-1, OKT3_VL-2, OKT3_VL-3, OKT3_VL-4, OKT3_VL-5, OKT3_VL-6, VL-1 L100, VL-2 L100, VL-3 L100, VL-4 L100, VL-5 L100, VL-6 L100, VL-1 L43, VL-2 L43, VL-3 L43, VL-4 L43, VL-5 L43, VL-6 L43, VL-1 L49, VL-2 L49, VL-3 L49, VL-4 L49, VL-5 L49, VL-6 L49, VL-1 L50, VL-2 L50, VL-3 L50, VL-4 L50, VL-5 L50, VL-6 L50, VL-1 L46, VL-2 L46, VL-3 L46, VL-4 L46, VL-5 L46, and VL-6 L46 are variants of the humanized OKT3 light chain variable domain. The V_L CDR1 sequence is SSVSY (SEQ ID NO: 12), the V_L CDR2 sequence is DT (SEQ ID NO: 13), and the V_L CDR3 sequence is QQWSSNPFT (SEQ ID NO: 14). The V_LCDR 1-3 sequences are underlined. The CDR sequences of the V_L of humanized anti-CD3 antibody are determined using the IMGT definition.

[0054] FIG. **13**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 21-22) of the humanized OKT3 × CD3 BsAb, BC276 (hOKT3 H2L2DS). FIG. **13**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 23-24) of the humanized OKT3 × CD3 BsAbs, BC276 (hOKT3 H2L2DS) or BC276.1 (hOKT3 H2L2) respectively. FIG. **13**C shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 92-93) of the humanized OKT3 × CD3 BsAb, BC276.1 (hOKT3 H2L2). The signal peptide is underlined, the variable domains of the humanized anti-CD3 BsAb are indicated in italicized font, and linker sequences are shown in italicized, underlined boldface font.

[0055] FIG. **14**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 94-95) of the humanized anti-GD2/anti CD3 h3F8 × hOKT3 BsAb. FIG. **14**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 96-97) of the humanized h3F8 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the h3F8 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0056] FIG. **15**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 98-99) of the humanized anti-CD33/anti CD3 hM195 × hOKT3 BsAb. FIG. **15**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 100-101) of the humanized hM195 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the hM195 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0057] FIG. **16**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 102-103) of the humanized anti-glypican-3/anti CD3 hGPC3 x hOKT3 BsAb. FIG. **16**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 104-105) of the humanized hGPC3 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the hGPC3 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0058] FIG. **17**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 106-107) of the humanized anti-CD19/anti CD3 hFMC63 × hOKT3 BsAb. FIG. **17**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 108-109) of the humanized hFMC63 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the hFMC63 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0059] FIG. **18**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 110-111) of the humanized hSTEAP1 × hOKT3 BsAb. FIG. **18**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 112-113) of the humanized hSTEAP1 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the hSTEAP1 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0060] FIG. **19**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 114-115) of the humanized anti-CD33/anti CD3 hHIM34 x hOKT3 BsAb. FIG. **19**B shows the amino acid and nucleotide sequences of the heavy chain (SEQ ID NOs: 116-117) of the humanized hHIM34 × hOKT3 BsAb. The signal peptide is underlined, the variable domains of the hHIM34 × hOKT3 BsAb are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0061] FIGS. **20**A-**20**D show the amino acid sequences of humanized 3F8 × OKT3 BsAb, humanized STEAP1 × OKT3 BsAb, humanized HER2 x OKT3 BsAb, and humanized FMC63 × OKT3 BsAb in the single-chain bispecific tandem fragment variable (scBsTaFv) format (SEQ ID NO: 118-121), respectively. The signal peptide is underlined, the variable domains of the scBsTaFvs are italicized, linker sequences are indicated in boldface font, p53 tetramerization domains are italicized and underlined, and histidine$_6$ tags (SEQ ID NO: 152) are indicated in bold and underlined font.

[0062] FIG. **21**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 122-123) of the humanized h3F8 × hC825 Ab. FIG. **21**B shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 124-125) of the humanized h3F8 × hOKT3 Ab. FIG. **21**C shows the amino acid and nucleotide sequences of the heavy chain K (SEQ ID NOs: 126-127) of the humanized h3F8 Ab. FIG. **21**D shows the amino acid and nucleotide sequences of the heavy chain F (SEQ ID NOs: 137-138) of the humanized h3F8 Ab. The signal peptide is underlined, the variable domains of the heavy and light chains are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0063] FIG. **22**A shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 128-129) of the humanized hSTEAP1 × hC825 Ab. FIG. **22**B shows the amino acid and nucleotide sequences of the light chain (SEQ ID NOs: 130-131) of the humanized hSTEAP1 × hOKT3 Ab. FIG. **22**C shows the amino acid and nucleotide sequences of the heavy chain K (SEQ ID NOs: 132-133) of the humanized hSTEAP1 Ab. FIG. **22**D shows the amino acid and nucleotide sequences of the heavy chain F (SEQ ID NOs: 139-140) of the humanized hSTEAP1 Ab. The signal peptide is underlined, the variable domains of the heavy and light chains are indicated in italicized font, and linker sequences are shown in underlined boldface font.

[0064] FIG. **23**A shows the potency of an anti-GD2 anti-CD3 bispecific antibody (comprising SEQ ID NO: 94 and SEQ ID NO: 96) against a GD2-expressing neuroblastoma cell line (IMR32). FIG. **23**B shows the potency of an anti-GPC3 anti-CD3 bispecific antibody (comprising SEQ ID NO: 102 and SEQ ID NO: 104) against a GPC3-expressing liver cancer cell line (HEPG2).

[0065] FIG. **24**A shows that the CEM-NKR T cell line, which lacks CD3 expression, was not responsive to treatment with the BC276 BsAb. FIG. **24**B shows that HUT78 T cells, which express high levels of CD3, were killed in an antibody dependent T cell mediated cytotoxicity (ADTC) assay when treated with the BC276 BsAb, while the control antibody HER2-BsAb directed at HER2 showed no cytotoxicity. FIG. **24**C shows that JURKAT T cells, which express high levels of CD3, were killed in an antibody dependent T cell mediated cytotoxicity (ADTC) assay when treated with the BC276 BsAb, while the control antibody HER2-BsAb directed at HER2 showed no cytotoxicity. FIG. **24**D shows that 8402 T cells, which express high levels of CD3, were killed in an antibody dependent T cell mediated cytotoxicity (ADTC) assay when treated with the BC276 BsAb, while the control antibody HER2-BsAb directed at HER2 showed no cytotoxicity. FIG. **24**E shows that the MOLT4 T cell line, which lacks CD3 expression, was not responsive to treatment with the BC276 BsAb.

[0066] FIG. **25** demonstrates that signs of distress, such as reduced activity, hunched posture, or ruffled fur, were not observed in animals treated with BC276 BsAb. NSG mice were injected intraperitoneally with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) on day 0. The mice were treated with vehicle only control (no antibody), or with 1 μg or 0.1 μg BC276 BsAb, or 1 μg or 0.1 μg BC119 BsAb starting on day 8. The mice were evaluated for clinical signs of distress (i.e., reduced activity, hunched posture, or ruffled fur).

[0067] FIG. **26** shows 5 GPC3 × CD3 bispecific antibodies (BsAbs) that share the same Fab which binds to Glypican-3 antigen. Each bispecific antibody expresses distinct anti-CD3 scfv attached to the constant light chain. Doted circles indicate the anti-CD3 scFv. BsAb 1-5 express anti-CD3 scFv clone huOKT3, CD3 H2L2, CD3_H2L5, CD3_H4L2 and CD3_H4L5 respectively.

[0068] FIG. **27** shows the amino acid sequences of the anti-CD3 scFv region for each of the 5 GPC3 × CD3 bispecific antibodies (BsAbs) (SEQ ID NOs: 141-145) shown in FIG. **26**.

[0069] FIG. **28** shows the distinct binding affinities of the 5 GPC3 × CD3 BsAbs described in FIG. **26** to ex vivo expanded human T cells using Flow-cytometry. Human T cells activated by anti-CD3/CD28 beads for 21 days were harvested and incubated with BsAb (1×10^6 T cells for each sample) followed by secondary goat-anti human IgG PE. Baseline value (geometric MFI, gMFI) was obtained from T cells incubated with only goat-anti human IgG PE without BsAb. Normalized gMFI values were calculated by deducting gMFI of each sample from baseline value. BsAb #3 shows the highest binding affinity to human T cells followed by BsAb #1, #2, #5 and #4. BsAb #6, which does not contain an anti-CD3 scFv, was included as negative control.

[0070] FIG. **29** shows that the binding affinities of the exemplified BsAbs to human recombinant CD3δ/ε are not drastically different as demonstrated using SPR. Human recombinant CD3 epsilon & CD3 delta heterodimer proteins were immobilized onto the CM5 sensor chip using Amine Coupling Kit, and the BsAbs (diluted in HBS-EP buffer, concentration ranging from 6.25 nM – 100 nM) were injected over the sensor surface at a flow rate of 30 μl/min over 2 min. At the end of each cycle, the surface was regenerated using 10 mM NaOH. Samples were run in Biacore T200 instrument. All data were fitted with a two-state fitting model, KD=kd/ka, using Biacore T200 Evaluation Software. Binding affinity of BsAb to human CD3 antigen as indicated by the KD value shows that BsAb #1, #2, #3 and #5 bind with similar affinities and BsAb #4 showed 1 log lower binding affinity.

[0071] FIGS. **30**-**31** show that the exemplified BsAbs differentially induce surface expression of T cell activation marker CD69 and CD25, respectively. Human T cells activated by anti-CD3/CD28 beads for 21 days were harvested and cocultured with HepG2 cells in a 10:1 ratio (100,000 T cells and 10,000 HepG2) for 3 days at 37° C. After 3 days, cells were harvested and stained for hCD3, hCD4, hCD8, hCD69 and hCD25. Cells were pre-stained with fixable live-dead dye (NIR) prior cell surface staining. Singlet, NIR- and hCD3+ cells were pre-gated and analyzed for CD8 T cells expression for hCD69 or hCD25. BsAb #1, #2, #3 and #5 induced a similar proportion of CD69+ T cells, while BsAb #4 weakly activated CD8 T cell expression of CD69. A similar trend was observed for CD25

expression on CD8 T cells whereby BsAb #4 weakly induced CD25 expression compared to BsAb #1, #2, #3 and #5.

[0072] FIGS. **32**A-**32**B show that the exemplified BsAbs induce robust T cell proliferation. Human T cells activated by anti-CD3/CD28 beads for 14 days were harvested and labelled with CellTrace™ Violet Cell Proliferation Kit (Invitrogen™). T cells were cocultured with HepG2 cells in 10:1 ratio (100,000 T cells and 10,000 HepG2). After 96 hours, cells were harvested and stained for hCD3, hCD4, hCD8. Cells were pre-stained with fixable live-dead dye (NIR) prior cell surface staining. FIG. **32**A top. BsAb #1, #2, #3 and #5 drove robust CD8 T cell proliferation and more than 70% of CD8 T cells underwent active division with as little as 6.4 ng/ml BsAb concentration. BsAb #4 not only weakly induced CD8 T cell activation, there was very little dividing CD8 T cells (15%) at 6.4 ng/ml BsAb concentration. FIG. **32**A bottom. Increasing concentration of BsAb in the T and HepG2 coculture assay did not lead to reduced CD8 T cell viability. Similar CD8 T cell viability (10-20%) was observed among all BsAbs. FIG. **32**B. Singlet, NIR- and hCD3+ cells were pre-gated and analyzed for the intensity of CellTrace violet (Excitation/Emission 405/450) on the CD8 T cells. Undivided CD8 T cells harbor highest intensity of CellTrace dye, whereas each cell division leads to dilution and lower intensity of the dye.

[0073] FIG. **33** shows BsAb-engaged T-cell mediated killing of HepG2 hepatocellular carcinoma cell line. Human T cells activated by anti-CD3/CD28 beads for 14 days were harvested and cocultured with HepG2 cells in 10:1 ratio (50,000 T cells to 5,000 HepG2). Prior incubation with T cells, HepG2 cells were labelled with Cr^{51} for 1 hour at 37 C. Human T cells and HepG2 cells coculture in the presence of respective BsAb were kept in incubator (37 C, 5% CO2) for 4 hours before spinning down at 800×g 10 mins. Supernatants were transferred to microtubes and read in scintillation counter. BsAb #3 and #1 show similar EC50 followed by #2 and #5. BsAb 4 showed lowest EC50. BsAb #6, where Fab is CD33 targeting, was included as negative control (HepG2 is a CD33-negative cancer).

[0074] FIGS. **34**A-**34**B show human T cell engraftment in HepG2 xenograft mice. Human T cells, transduced by luciferase lentivirus, were expanded in the presence of anti-CD3/CD28 beads for 8 days. Each HepG2 xenograft mouse was administered 2×10^7 T-luc cells. Bioluminescence of T-luc cells in the treated mice were acquired using IVIS instrument (Perkin Elmer) on day 1, 4, 7, and 10 after T-luc cells administration. Luciferin (0.3 mg in 100 ul PBS/mouse i.v) was injected 5 mins before imaging. One group of HepG2 xenograft mice was administered neither T-luc cells nor BsAb to obtain baseline value for bioluminescence. Bioluminescence analysis was done using Living Image 2.60 Software. The intensity of bioluminescence correlates with the number of T cell infiltration into the tumor site. BsAb #3 drove the highest number T-luc cells engraftment to HepG2 tumor site followed by BsAb #1 and #2. Dosage of BsAb influenced T-luc cells engraftment, 30 μg BsAb #1 induced higher T-luc infiltration than 3 μg BsAb #1.

DETAILED DESCRIPTION

[0075] It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology.

[0076] The present disclosure generally provides immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof), which can specifically bind to CD3 polypeptides. The immunoglobulin-related compositions of the present technology are useful in methods for detecting or treating CD3-associated pathologies in a subject in need thereof. Accordingly, the various aspects of the present methods relate to the preparation, characterization, and manipulation of anti-CD3 antibodies. The immunoglobulin-related compositions of the present technology are useful alone or in combination with additional therapeutic agents for treating cancer or autoimmune diseases. In some embodiments, the immunoglobulin-related composition is a monoclonal antibody, a humanized antibody, a chimeric antibody, a bispecific antibody, or a multi-specific antibody.

[0077] In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, immunology, microbiology and recombinant DNA are used. See, e.g., Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; the series Ausubel et al. eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson et al. (1991) PCR 1: *A Practical Approach* (IRL Press at Oxford University Press); MacPherson et al. (1995) PCR 2: *A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) Oligonucleotide Synthesis; U.S. Pat. No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg et al. eds (1996) *Weir's Handbook of Experimental Immunology*. Methods to detect and measure levels of polypeptide gene expression products (i.e., gene translation level) are well-known in the art and include the use of polypeptide detection methods such as antibody detection and quantification techniques. (See also, Strachan & Read, *Human Molecular Genetics*, Second Edition. (John Wiley and Sons, Inc., NY, 1999)).

Definitions

[0078] Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. For example, reference to "a cell" includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analy-

tical chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art.

[0079] As used herein, the term "about" in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

[0080] As used herein, the "administration" of an agent or drug to a subject includes any route of introducing or delivering to a subject a compound to perform its intended function. Administration can be carried out by any suitable route, including but not limited to, orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intrathecally, intratumorally or topically. Administration includes self-administration and the administration by another.

[0081] An "adjuvant" refers to one or more substances that cause stimulation of the immune system. In this context, an adjuvant is used to enhance an immune response to one or more vaccine antigens or antibodies. An adjuvant may be administered to a subject before, in combination with, or after administration of the vaccine. Examples of chemical compounds used as adjuvants include aluminum compounds, oils, block polymers, immune stimulating complexes, vitamins and minerals (e.g., vitamin E, vitamin A, selenium, and vitamin B12), Quil A (saponins), bacterial and fungal cell wall components (e.g., lipopolysaccarides, lipoproteins, and glycoproteins), hormones, cytokines, and co-stimulatory factors.

[0082] As used herein, the term "antibody" collectively refers to immunoglobulins or immunoglobulin-like molecules including by way of example and without limitation, IgA, IgD, IgE, IgG and IgM, combinations thereof, and similar molecules produced during an immune response in any vertebrate, for example, in mammals such as humans, goats, rabbits and mice, as well as non-mammalian species, such as shark immunoglobulins. As used herein, "antibodies" (includes intact immunoglobulins) and "antigen binding fragments" specifically bind to a molecule of interest (or a group of highly similar molecules of interest) to the substantial exclusion of binding to other molecules (for example, antibodies and antibody fragments that have a binding constant for the molecule of interest that is at least 10^3 M^{-1} greater, at least 10^4 M^{-1} greater or at least 10^5 M^{-1} greater than a binding constant for other molecules in a biological sample). The term "antibody" also includes genetically engineered forms such as chimeric antibodies (for example, humanized murine antibodies), heteroconjugate antibodies (such as, bispecific antibodies). See also, Pierce Catalog and Handbook, 1994-1995 (Pierce Chemical Co., Rockford, Ill.); Kuby, J., *Immunology*, 3rd Ed., W.H. Freeman & Co., New York, 1997.

[0083] More particularly, antibody refers to a polypeptide ligand comprising at least a light chain immunoglobulin variable region or heavy chain immunoglobulin variable region which specifically recognizes and binds an epitope of an antigen. Antibodies are composed of a heavy and a light chain, each of which has a variable region, termed the variable heavy (V_H) region and the variable light (V_L) region. Together, the V_H region and the V_L region are responsible for binding the antigen recognized by the antibody. Typically, an immunoglobulin has heavy (H) chains and light (L) chains interconnected by disulfide bonds. There are two types of light chain, lambda (λ) and kappa (κ). There are five main heavy chain classes (or isotypes) which determine the functional activity of an antibody molecule: IgM, IgD, IgG, IgA and IgE. Each heavy and light chain contains a constant region and a variable region, (the regions are also known as "domains"). In combination, the heavy and the light chain variable regions specifically bind the antigen. Light and heavy chain variable regions contain a "framework" region interrupted by three hypervariable regions, also called "complementarity-determining regions" or "CDRs". The extent of the framework region and CDRs have been defined (see, Kabat et al., *Sequences of Proteins of Immunological Interest*, U.S. Department of Health and Human Services, 1991, which is hereby incorporated by reference). The Kabat database is now maintained online. The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions.

[0084] The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found. An antibody that binds CD3 protein will have a specific V_H region and the V_L region sequence, and thus specific CDR sequences. Antibodies with different specificities (i.e. different combining sites for different antigens) have different CDRs. Although it is the CDRs that vary from antibody to antibody, only a limited number of amino acid positions within the CDRs are directly involved in antigen binding. These positions within the CDRs are called specificity determining residues (SDRs). "Immunoglobulin-related compositions" as used herein, refers to antibodies (including monoclonal antibodies, polyclonal antibodies, humanized antibodies, chimeric antibodies, recombinant antibodies, multi-specific antibodies, bispecific antibodies, etc.,) as well as antibody fragments. An antibody or antigen binding fragment thereof specifically binds to an antigen.

[0085] As used herein, the term "antibody-related polypeptide" means antigen-binding antibody fragments, including single-chain antibodies, that can comprise the variable region(s) alone, or in combination, with all or part of the following polypeptide elements: hinge region, CH_1, CH_2, and CH_3 domains of an antibody molecule. Also included in the technology are any combinations of variable region(s) and hinge region, CH_1, CH_2, and CH_3 domains. Antibody-related molecules useful in the present methods, e.g., but are not limited to, Fab, Fab′ and $F(ab')_2$, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a V_L or V_H domain. Examples include: (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH_1 domains; (ii) a F(ab

′)$_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH_1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., *Nature* 341: 544-546, 1989), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR). As such "antibody fragments" or "antigen binding fragments" can comprise a portion of a full length antibody, generally the antigen binding or variable region thereof. Examples of antibody fragments or antigen binding fragments include Fab, Fab′, F(ab′)$_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multi-specific antibodies formed from antibody fragments.

[0086] "Bispecific antibody" or "BsAb", as used herein, refers to an antibody that can bind simultaneously to two targets that have a distinct structure, e.g., two different target antigens, two different epitopes on the same target antigen, or a hapten and a target antigen or epitope on a target antigen. A variety of different bispecific antibody structures are known in the art. In some embodiments, each antigen binding moiety in a bispecific antibody includes V_H and/or V_L regions; in some such embodiments, the V_H and/or V_L regions are those found in a particular monoclonal antibody. In some embodiments, the bispecific antibody contains two antigen binding moieties, each including V_H and/or V_L regions from different monoclonal antibodies. In some embodiments, the bispecific antibody contains two antigen binding moieties, wherein one of the two antigen binding moieties includes an immunoglobulin molecule having V_H and/or V_L regions that contain CDRs from a first monoclonal antibody, and the other antigen binding moiety includes an antibody fragment (e.g., Fab, F(ab′), F(ab′)$_2$, Fd, Fv, dAB, scFv, etc.) having V_H and/or V_L regions that contain CDRs from a second monoclonal antibody.

[0087] As used herein, the term "conjugated" refers to the association of two molecules by any method known to those in the art. Suitable types of associations include chemical bonds and physical bonds. Chemical bonds include, for example, covalent bonds and coordinate bonds. Physical bonds include, for instance, hydrogen bonds, dipolar interactions, van der Waal forces, electrostatic interactions, hydrophobic interactions and aromatic stacking.

[0088] As used herein, the term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) in the same polypeptide chain (V_H V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen binding sites. Diabodies are described more fully in, e.g., EP 404,097; WO 93/11161; and Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90: 6444-6448 (1993).

[0089] As used herein, the terms "single-chain antibodies" or "single-chain Fv (scFv)" refer to an antibody fusion molecule of the two domains of the Fv fragment, V_L and V_H. Single-chain antibody molecules may comprise a polymer with a number of individual molecules, for example, dimer, trimer or other polymers. Furthermore, although the two domains of the F_v fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules (known as single-chain F_v (scF$_v$)). Bird et al. (1988) *Science* 242:423-426 and Huston et al. (1988) *Proc. Natl. Acad Sci. USA* 85:5879-5883. Such single-chain antibodies can be prepared by recombinant techniques or enzymatic or chemical cleavage of intact antibodies.

[0090] Any of the above-noted antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for binding specificity and neutralization activity in the same manner as are intact antibodies.

[0091] As used herein, an "antigen" refers to a molecule to which an antibody (or antigen binding fragment thereof) can selectively bind. The target antigen may be a protein, carbohydrate, nucleic acid, lipid, hapten, or other naturally occurring or synthetic compound. In some embodiments, the target antigen may be a polypeptide (e.g., a CD3 polypeptide). An antigen may also be administered to an animal to generate an immune response in the animal.

[0092] The term "antigen binding fragment" refers to a fragment of the whole immunoglobulin structure which possesses a part of a polypeptide responsible for binding to antigen. Examples of the antigen binding fragment useful in the present technology include scFv, (scFv)$_2$, scFvFc, Fab, Fab′ and F(ab′)$_2$, but are not limited thereto.

[0093] By "binding affinity" is meant the strength of the total noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen or antigenic peptide). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by standard methods known in the art, including those described herein. A low-affinity complex contains an antibody that generally tends to dissociate readily from the antigen, whereas a high-affinity complex contains an antibody that generally tends to remain bound to the antigen for a longer duration.

[0094] As used herein, the term "biological sample" means sample material derived from living cells. Biological samples may include tissues, cells, protein or membrane extracts of cells, and biological fluids (e.g., ascites fluid or cerebrospinal fluid (CSF)) isolated from a subject, as well as tissues, cells and fluids present within a subject. Biological samples of the present technology include, but are not limited to, samples taken from breast tissue, renal tissue, the uterine cervix, the endometrium, the head or neck, the gallbladder, parotid tissue, the prostate, the brain, the pituitary gland, kidney tissue, muscle, the esophagus, the stomach, the small intestine, the colon, the liver, the spleen, the pancreas, thyroid tissue, heart tissue, lung tissue, the bladder, adipose tissue, lymph node tissue, the uterus, ovarian tissue, adrenal tissue, testis tissue, the tonsils, thymus, blood, hair, buccal, skin, serum, plasma, CSF, semen, prostate fluid, seminal fluid, urine, feces, sweat, saliva, sputum, mucus, bone marrow, lymph, and tears. Biological samples can also be obtained from biopsies of internal organs or from cancers. Biological samples can be obtained from subjects for diagnosis or research or can be obtained from non-diseased individuals, as controls or for basic research. Samples may be obtained by standard methods including, e.g., venous puncture and surgical biopsy. In certain embodiments, the biological sample is a tissue sample obtained by needle biopsy.

[0095] As used herein, the term "CDR-grafted antibody" means an antibody in which at least one CDR of an "acceptor" antibody is replaced by a CDR "graft" from a "donor" antibody possessing a desirable antigen specificity.

[0096] As used herein, the term "chimeric antibody" means an antibody in which the Fc constant region of a monoclonal antibody from one species (e.g., a mouse Fc constant region) is replaced, using recombinant DNA techniques, with an Fc constant region from an antibody of another species (e.g., a human Fc constant region). See generally, Robinson et al., PCT/US86/02269; Akira et al., European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 0125,023; Better et al., *Science* 240: 1041-1043, 1988; Liu et al., *Proc. Natl. Acad. Sci. USA* 84: 3439-3443, 1987; Liu et al., *J. Immunol* 139: 3521-3526, 1987; Sun et al., *Proc. Natl. Acad. Sci. USA* 84: 214-218, 1987; Nishimura et al., *Cancer Res* 47: 999-1005, 1987; Wood et al., *Nature* 314: 446-449, 1885; and Shaw et al., *J. Natl. Cancer Inst.* 80: 1553-1559, 1988.

[0097] As used herein, the term "consensus FR" means a framework (FR) antibody region in a consensus immunoglobulin sequence. The FR regions of an antibody do not contact the antigen.

[0098] As used herein, a "control" is an alternative sample used in an experiment for comparison purpose. A control can be "positive" or "negative." For example, where the purpose of the experiment is to determine a correlation of the efficacy of a therapeutic agent for the treatment for a particular type of disease, a positive control (a compound or composition known to exhibit the desired therapeutic effect) and a negative control (a subject or a sample that does not receive the therapy or receives a placebo) are typically employed.

[0099] As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, e.g., an amount which results in the prevention of, or a decrease in a disease or condition described herein or one or more signs or symptoms associated with a disease or condition described herein. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will vary depending on the composition, the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compositions may be administered to a subject having one or more signs or symptoms of a disease or condition described herein. As used herein, a "therapeutically effective amount" of a composition refers to composition levels in which the physiological effects of a disease or condition are ameliorated or eliminated. A therapeutically effective amount can be given in one or more administrations.

[0100] As used herein, the term "effector cell" means an immune cell which is involved in the effector phase of an immune response, as opposed to the cognitive and activation phases of an immune response. Exemplary immune cells include a cell of a myeloid or lymphoid origin, e.g., lymphocytes (e.g., B cells and T cells including cytolytic T cells (CTLs)), killer cells, natural killer cells, macrophages, monocytes, eosinophils, neutrophils, polymorphonuclear cells, granulocytes, mast cells, and basophils. Effector cells express specific Fc receptors and carry out specific immune functions. An effector cell can induce antibody-dependent cell-mediated cytotoxicity (ADCC), e.g., a neutrophil capable of inducing ADCC. For example, monocytes, macrophages, neutrophils, eosinophils, and lymphocytes which express FcαR are involved in specific killing of target cells and presenting antigens to other components of the immune system, or binding to cells that present antigens.

[0101] As used herein, the term "epitope" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents. In some embodiments, an "epitope" of the CD3 protein is a region of the protein to which the anti-CD3 antibodies of the present technology specifically bind. In some embodiments, the epitope is a conformational epitope or a non-conformational epitope. To screen for anti-CD3 antibodies which bind to an epitope, a routine cross-blocking assay such as that described in Antibodies, *A Laboratory Manual*, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can be performed. This assay can be used to determine if an anti-CD3 antibody binds the same site or epitope as an anti-CD3 antibody of the present technology. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. In a different method, peptides corresponding to different regions of CD3 protein can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

[0102] As used herein, "expression" includes one or more of the following: transcription of the gene into precursor mRNA; splicing and other processing of the precursor mRNA to produce mature mRNA; mRNA stability; translation of the mature mRNA into protein (including codon usage and tRNA availability); and glycosylation and/or other modifications of the translation product, if required for proper expression and function.

[0103] As used herein, the term "gene" means a segment of DNA that contains all the information for the regulated biosynthesis of an RNA product, including promoters, exons, introns, and other untranslated regions that control expression.

[0104] "Homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a position in each sequence which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. A polynucleotide or polynucleotide region (or a polypeptide or polypeptide region) has a certain percentage (for example, at least 60%, 65%, 70%, 75%,

80%, 85%, 90%, 95%, 98% or 99%) of "sequence identity" to another sequence means that, when aligned, that percentage of bases (or amino acids) are the same in comparing the two sequences. This alignment and the percent homology or sequence identity can be determined using software programs known in the art. In some embodiments, default parameters are used for alignment. One alignment program is BLAST, using default parameters. In particular, programs are BLASTN and BLASTP, using the following default parameters: Genetic code=standard; filter=none; strand=-both; cutoff=60; expect=10; Matrix=BLOSUM62; Descriptions=50 sequences; sort by =HIGH SCORE; Databases=-non-redundant, GenBank+EMBL+DDBJ+PDB+GenBank CDS translations+SwissProtein+SPupdate+PIR. Details of these programs can be found at the National Center for Biotechnology Information. Biologically equivalent polynucleotides are those having the specified percent homology and encoding a polypeptide having the same or similar biological activity. Two sequences are deemed "unrelated" or "non-homologous" if they share less than 40% identity, or less than 25% identity, with each other.

[0105] As used herein, "humanized" forms of non-human (e.g., murine) antibodies are chimeric antibodies which contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins in which hypervariable region residues of the recipient are replaced by hypervariable region residues from a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues which are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance such as binding affinity. Generally, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains (e.g., Fab, Fab′, $F(ab')_2$, or Fv), in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus FR sequence although the FR regions may include one or more amino acid substitutions that improve binding affinity. The number of these amino acid substitutions in the FR are typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally may also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., *Nature* 321:522-525 (1986); Reichmann et al., *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992). See e.g., Ahmed & Cheung, *FEBS Letters* 588(2):288-297 (2014).

[0106] As used herein, the term "hypervariable region" refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g., around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L, and around about 31-35B (H1), 50-65 (H2) and 95-102 (H3) in the V_H (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g., residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L, and 26-32 (H1), 52A-55 (H2) and 96-101 (H3) in the V_H (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)).

[0107] As used herein, the terms "identical" or percent "identity", when used in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues or nucleotides that are the same (i.e., about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region (e.g., nucleotide sequence encoding an antibody described herein or amino acid sequence of an antibody described herein)), when compared and aligned for maximum correspondence over a comparison window or designated region as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (e.g., NCBI web site). Such sequences are then said to be "substantially identical." This term also refers to, or can be applied to, the complement of a test sequence. The term also includes sequences that have deletions and/or additions, as well as those that have substitutions. In some embodiments, identity exists over a region that is at least about 25 amino acids or nucleotides in length, or 50-100 amino acids or nucleotides in length.

[0108] As used herein, the term "intact antibody" or "intact immunoglobulin" means an antibody that has at least two heavy (H) chain polypeptides and two light (L) chain polypeptides interconnected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH_1, CH_2 and CH_3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L. The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxyl-terminus in the following order: FR_1, CDR_1, FR_2, CDR_2, FR_3, CDR_3, FR_4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

[0109] As used herein, the terms "individual", "patient", or "subject" can be an individual organism, a vertebrate, a mammal, or a human. In some embodiments, the individual, patient or subject is a human.

[0110] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. For example, a monoclonal antibody can be an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced. A monoclonal antibody

composition displays a single binding specificity and affinity for a particular epitope. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including, e.g., but not limited to, hybridoma, recombinant, and phage display technologies. For example, the monoclonal antibodies to be used in accordance with the present methods may be made by the hybridoma method first described by Kohler et al., *Nature* 256:495 (1975), or may be made by recombinant DNA methods (See, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., *Nature* 352:624-628 (1991) and Marks et al., *J. Mol. Biol.* 222:581-597 (1991), for example.

[0111] As used herein, the term "pharmaceutically-acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal compounds, isotonic and absorption delaying compounds, and the like, compatible with pharmaceutical administration. Pharmaceutically-acceptable carriers and their formulations are known to one skilled in the art and are described, for example, in Remington's Pharmaceutical Sciences (20^{th} edition, ed. A. Gennaro, 2000, Lippincott, Williams & Wilkins, Philadelphia, Pa.).

[0112] As used herein, the term "polyclonal antibody" means a preparation of antibodies derived from at least two (2) different antibody-producing cell lines. The use of this term includes preparations of at least two (2) antibodies that contain antibodies that specifically bind to different epitopes or regions of an antigen.

[0113] As used herein, the term "polynucleotide" or "nucleic acid" means any RNA or DNA, which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, RNA that is mixture of single-and double-stranded regions, and hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, polynucleotide refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons.

[0114] As used herein, the terms "polypeptide," "peptide" and "protein" are used interchangeably herein to mean a polymer comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. Polypeptide refers to both short chains, commonly referred to as peptides, glycopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. Polypeptides include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature.

[0115] As used herein, the term "recombinant" when used with reference, e.g., to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the material is derived from a cell so modified. Thus, for example, recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all.

[0116] As used herein, the term "separate" therapeutic use refers to an administration of at least two active ingredients at the same time or at substantially the same time by different routes.

[0117] As used herein, the term "sequential" therapeutic use refers to administration of at least two active ingredients at different times, the administration route being identical or different. More particularly, sequential use refers to the whole administration of one of the active ingredients before administration of the other or others commences. It is thus possible to administer one of the active ingredients over several minutes, hours, or days before administering the other active ingredient or ingredients. There is no simultaneous treatment in this case.

[0118] As used herein, "specifically binds" refers to a molecule (e.g., an antibody or antigen binding fragment thereof) which recognizes and binds another molecule (e.g., an antigen), but that does not substantially recognize and bind other molecules. The terms "specific binding," "specifically binds to," or is "specific for" a particular molecule (e.g., a polypeptide, or an epitope on a polypeptide), as used herein, can be exhibited, for example, by a molecule having a K_D for the molecule to which it binds to of about 10^{-4} M, 10^{-5} M, 10^{-6}M, 10^{-7}M, 10^{-8}M, 10^{-9}M, 10^{-10}M, 10^{-11}M, or 10^{-12}M. The term "specifically binds" may also refer to binding where a molecule (e.g., an antibody or antigen binding fragment thereof) binds to a particular polypeptide (e.g., a CD3 polypeptide), or an epitope on a particular polypeptide, without substantially binding to any other polypeptide, or polypeptide epitope.

[0119] As used herein, the term "simultaneous" therapeutic use refers to the administration of at least two active ingredients by the same route and at the same time or at substantially the same time.

[0120] As used herein, the term "therapeutic agent" is intended to mean a compound that, when present in an effective amount, produces a desired therapeutic effect on a subject in need thereof.

[0121] "Treating" or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, i.e., arresting its development; (ii) relieving a disease or disorder, i.e., causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments, treatment means that the symptoms associated with the disease are, e.g., alleviated, reduced, cured, or placed in a state of remission.

[0122] It is also to be appreciated that the various modes of treatment of disorders as described herein are intended to mean "substantial," which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic disease or a single, or few time administrations for the treatment of an acute condition.

[0123] Amino acid sequence modification(s) of the anti-CD3 antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an anti-CD3 antibody are prepared by introducing appropriate nucleotide changes into the antibody nucleic acid, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution is made to obtain the antibody of interest, as long as the obtained antibody possesses the desired properties. The modification also includes the change of the pattern of glycosylation of the protein. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. "Conservative substitutions" are shown in the Table below.

TABLE 1

Amino Acid Substitutions		
Original Residue	Exemplary Substitutions	Conservative Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; asp, lys; arg	gln
Asp (D)	glu; asn	glu
Cys (C)	ser; ala	ser
Gln (Q)	asn; glu	asn
Glu (E)	asp; gln	asp
Gly (G)	ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	tyr
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

[0124] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Specifically, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino acid substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and the antigen. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with similar or superior properties in one or more relevant assays may be selected for further development.

Immunoglobulin-Related Compositions of the Present Technology

[0125] The present technology describes methods and compositions for the generation and use of anti-CD3 immunoglobulin-related compositions (e.g., anti-CD3 antibodies or antigen binding fragments thereof). The anti-CD3 immunoglobulin-related compositions of the present disclosure may be useful in the diagnosis, or treatment of CD3-associated pathologies. Anti-CD3 immunoglobulin-related compositions within the scope of the present technology include, e.g., but are not limited to, monoclonal, chimeric, humanized, bispecific antibodies and diabodies that specifically bind the target polypeptide, a homolog, derivative or a fragment thereof. The present disclosure also provides antigen binding fragments of any of the anti-CD3 antibodies disclosed herein, wherein the antigen binding fragment is selected from the group consisting of Fab, F(ab)'2, Fab', scF_v, and F_v. In one aspect, the present technology provides chimeric and re-humanized variants of Teplizumab, including multi-specific immunoglobulin-related compositions (e.g., bispecific antibody agents). The CDR of the V_H and V_L of humanized CD3 antibody based on the IMGT annotation system are summarized below:

Region	Definition	Sequence Fragment	Residues	Length
CDR-H1	IMGT	GYTFTRYT (SEQ ID NO: 2)	26 - 33	8
CDR-H2	IMGT	INPSRGYT (SEQ ID NO: 3)	51 - 58	8
CDR-H3	IMGT	ARYYDDHYSLDY (SEQ ID NO: 6) ARYYDDHYSCDY (SEQ ID NO: 134), ARYYDDHCSLDY (SEQ ID NO: 135), ARYYDDHYSLCY (SEQ ID NO: 136)	97 - 108	12
CDR-L1	IMGT	SSVSY (SEQ ID NO: 12)	27 -31	5
CDR-L2	IMGT	DT (SEQ ID NO: 13)	49 - 50	2
CDR-L3	IMGT	QQWSSNPFT (SEQ ID NO: 14)	88 - 96	9

[0126] In one aspect, the present disclosure provides an antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein (a) the V_H comprises a V_H-CDR1 sequence of (SEQ ID NO: 2), a V_H-CDR2 sequence of

INPSRGYT

(SEQ ID NO: 3), and a V_H-CDR3 sequence of

ARYYDDHYSLDY

(SEQ ID NO: 6),

ARYYDDHYSCDY

(SEQ ID NO: 134),

ARYYDDHCSLDY

(SEQ ID NO: 135), or

ARYYDDHYSLCY

(SEQ ID NO: 136); and/or; (b) the V_L comprises a V_L-CDR1 sequence of

SSVSY

(SEQ ID NO: 12), a V_L-CDR2 sequence of DT (SEQ ID NO: 13), and a V_L-CDR3 sequence of

QQWSSNPFT

(SEQ ID NO: 14).

[0127] In one aspect, the present disclosure provides an antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein: (a) the V_H comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61; and/or (b) the V_L comprises an amino acid sequence selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0128] In any of the above embodiments, the antibody further comprises a Fc domain of any isotype, e.g., but are not limited to, IgG (including IgG1, IgG2, IgG3, and IgG4), IgA (including IgA_1 and IgA_2), IgD, IgE, or IgM, and IgY. Non-limiting examples of constant region sequences include:

[0129] Human IgD constant region, Uniprot: P01880 (SEQ ID NO: 25)

APTKAPDVFPIISGCRHPKDNSPVVLACLITGYHPTSVTVTWYMGTQSQP
QRTFPEIQRRDSYYMTSSQLSTPLQQWRQGEYKCVVQHTASKSKKEIFRW
PESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEE
QEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDA
HLTWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSLWNAGTSVTCT
LNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWLLCEVSGFS
PPNILLMWLEDQREVNTSGF AP ARPPPQPGSTTFWAWSVLRVPAPPSP

-continued

QPATYTCVVSHEDSRTLLNASRSLEVSYVTDHGPMK

[0130] Human IgG1 constant region, Uniprot: P01857 (SEQ ID NO: 26)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK
EYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTC
LVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW
QQGNVFSCSVMHEALHNHYTQKSLSLSPGK

[0131] Human IgG2 constant region, Uniprot: P01859 (SEQ ID NO: 27)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVER
KCCVECPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKC
KVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG
FYPSDISVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHEALHNHYTQKSLSLSPGK

[0132] Human IgG3 constant region, Uniprot: P01860 (SEQ ID NO: 28)

ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVEL
KTPLGDTTHTCPRCPEPKSCDTPPPCPRCPEPKSCDTPPPCPRCPEPKSC
DTPPPCPRCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED
PEVQFKWYVDGVEVHNAKTKPREEQYNSTFRVVSVLTVLHQDWLNGKEYK
CKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVK
GFYPSDIAVEWESSGQPENNYNTTPPMLDSDGSFFLYSKLTVDKSRWQQG
NIFSCSVMHEALHNRFTQKSLSLSPGK

[0133] Human IgM constant region, Uniprot: P01871 (SEQ ID NO: 29)

GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITLSWKYKNNSDI
SSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPNGNKEKN
VPLPVIAELPPKVSVFVPPRDGFFGNPRKSKLICQATGFSPRQIQVSWLR
EGKQVGSGVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLGQ SMFTCRV
DHRGLTFQQNAS SMC VPDQDTAIRVFAIPPSFASIFLTKSTKLTCLVT
DLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFSAVGEASICEDDWNS
GERFTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRESA
TITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSI
LTVSEEEWNTGETYTCVABEALPNRVTERTVDKSTGKPTLYNVSLVMSDT
AGTCY

[0134] Human IgG4 constant region, Uniprot: P01861 (SEQ ID NO: 30)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGV
HTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVES
KYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYK
CKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVK

-continued

GFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEG
NVFSCSVMHEALHNHYTQKSLSLSLGK

[0135] Human IgA1 constant region, Uniprot: P01876 (SEQ ID NO: 31)

ASPTSPKVFPLSLCSTQPDGNVVIACLVQGFFPQEPLSVTWSESGQGVTA
RNFPPSQDASGDLYTTSSQLTLPATQCLAGKSVTCHVKHYTNPSQDVTVP
CPVPSTPPTPSPSTPPTPSPSCCHPRLSLHRPALEDLLLGSEANLTCTLT
GLRDASGVTFTWTPSSGKSAVQGPPERDLCGCYSVSSVLPGCAEPWNHGK
TFTCTAAYPESKTPLTATLSKSGNTFRPEVHLLPPPSEELALNELVTLTC
LARGFSPKDVLVRWLQGSQELPREKYLTWASRQEPSQGTTTFAVTSILRV
AAEDWKKGDTFSCMVGHEALPLAFTQKTIDRLAGKPTHVNVSVVMAEVDG
TCY

[0136] Human IgA2 constant region, Uniprot: P01877 (SEQ ID NO: 32)

ASPTSPKVFPLSLDSTPQDGNVVVACLVQGFFPQEPLSVTWSESGQNVTA
RNFPPSQDASGDLYTTSSQLTLPATQCPDGKSVTCHVKHYTNPSQDVTVP
CPVPPPPPCCHPRLSLHRPALEDLLLGSEANLTCTLTGLRDASGATFTWT
PSSGKSAVQGPPERDLCGCYSVSSVLPGCAQPWNHGETFTCTAAHPELKT
PLTANITKSGNTFRPEVHLLPPPSEELALNELVTLTCLARGFSPKDVLVR
WLQGSQELPREKYLTWASRQEPSQGTTTFAVTSILRVAAEDWKKGDTFSC
MVGHEALPLAFTQKTIDRMAGKPTHVNVSVVMAEVDGTCY

[0137] Human Ig kappa constant region, Uniprot: P01834 (SEQ ID NO: 33)

TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

[0138] In some embodiments, the immunoglobulin-related compositions of the present technology comprise a heavy chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NOS: 25-32. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions of the present technology comprise a light chain constant region that is at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or is 100% identical to SEQ ID NO: 33.

[0139] In some embodiments, the immunoglobulin-related compositions of the present technology bind to the extracellular domain of a CD3 polypeptide. In certain embodiments, the epitope is a conformational epitope or non-conformational epitope. In some embodiments, the CD3 polypeptide has the amino acid sequence of SEQ ID NO: 42.

[0140] NCBI Ref: NP_000724.1 *Homo sapiens* T-cell surface glycoprotein CD3 epsilon chain precursor (SEQ ID NO: 42)

MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCP
QYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYP
RGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYY
WSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYS
GLNQRRI

[0141] Additionally or alternatively, in some embodiments, the antibody or antigen binding fragment binds to the extracellular domain of a CD3 polypeptide. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop).

[0142] In another aspect, the present disclosure provides an isolated immunoglobulin-related composition (e.g., an antibody or antigen binding fragment thereof) comprising a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 23, SEQ ID NO: 96, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 112, SEQ ID NO: 116, SEQ ID NO: 126, SEQ ID NO: 132, SEQ ID NO: 137, SEQ ID NO: 139, or a variant thereof having one or more conservative amino acid substitutions. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions of the present technology comprise a light chain (LC) amino acid sequence comprising SEQ ID NO: 21, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 98, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 114, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 128, SEQ ID NO: 130, or a variant thereof having one or more conservative amino acid substitutions. In some embodiments, the immunoglobulin-related compositions of the present technology comprise a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of: SEQ ID NO: 23 and SEQ ID NO: 21, SEQ ID NO: 23 and SEQ ID NO: 92, SEQ ID NO: 96 and SEQ ID NO: 94, SEQ ID NO: 100 and SEQ ID NO: 98, SEQ ID NO: 104 and SEQ ID NO: 102, SEQ ID NO: 108 and SEQ ID NO: 106, SEQ ID NO: 112 and SEQ ID NO: 110, and SEQ ID NO: 116 and SEQ ID NO: 114, respectively. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions comprise a first LC amino acid sequence, a second LC amino acid sequence, a first HC amino acid sequence, and a second HC amino acid sequence selected from the group consisting of SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, and SEQ ID NO: 137; and SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 139, respectively.

[0143] In any of the above embodiments of the immunoglobulin-related compositions, the HC and LC immunoglobulin variable domain sequences form an antigen binding site that binds to the extracellular domain of a CD3 polypeptide. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop). In some embodiments, the epitope is a conformational epitope or a non-conformational epitope.

[0144] In some embodiments, the HC and LC immunoglobulin variable domain sequences are components of the same polypeptide chain. In other embodiments, the HC and LC immunoglobulin variable domain sequences are components of different polypeptide chains. In certain embodiments, the antibody is a full-length antibody.

[0145] In some embodiments, the immunoglobulin-related compositions of the present technology bind specifically to at least one CD3 polypeptide. In some embodi-

ments, the immunoglobulin-related compositions of the present technology bind at least one CD3 polypeptide with a dissociation constant (K_D) of about 10^{-3} M, 10^{-4} M, 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M. In certain embodiments, the immunoglobulin-related compositions are monoclonal antibodies, chimeric antibodies, humanized antibodies, bispecific antibodies, or multi-specific antibodies. In some embodiments, the antibodies comprise a human antibody framework region.

[0146] In certain embodiments, the immunoglobulin-related composition includes one or more of the following characteristics: (a) a light chain immunoglobulin variable domain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the light chain immunoglobulin variable domain sequence of any one of SEQ ID NOs: 15-20 or 62-91; and/or (b) a heavy chain immunoglobulin variable domain sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the heavy chain immunoglobulin variable domain sequence of any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61. In another aspect, one or more amino acid residues in the immunoglobulin-related compositions provided herein are substituted with another amino acid. The substitution may be a "conservative substitution" as defined herein.

[0147] In one aspect, the present disclosure provides an immunoglobulin-related composition comprising an amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to an amino acid sequence selected from SEQ ID NOs: 118-121.

[0148] In another aspect, the present disclosure provides an antibody comprising (a) a LC sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the LC sequence present in SEQ ID NO: 21, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 98, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 114, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 128, SEQ ID NO: 130; and/or (b) a HC sequence that is at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to the HC sequence present in SEQ ID NO: 23, SEQ ID NO: 96, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 112, SEQ ID NO: 116, SEQ ID NO: 126, SEQ ID NO: 132, SEQ ID NO: 137, or SEQ ID NO: 139.

[0149] Additionally or alternatively, in some embodiments, the multi-specific antibodies of the present disclosure bind to CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N-acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PlGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Le^y) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pmel17, LMP2, or WT1), or a small molecule DOTA hapten.

[0150] In one aspect, the present disclosure provides a multi-specific antigen binding fragment comprising a first polypeptide chain, wherein: the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (iii) a light chain variable domain of the first immunoglobulin; (iv) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_4$ (SEQ ID NO: 149); (v) a heavy chain variable domain of a second immunoglobulin that is capable of specifically binding to a second epitope; (vi) a flexible peptide linker comprising the amino acid sequence $(GGGGS)_6$ (SEQ ID NO: 148); (vii) a light chain variable domain of the second immunoglobulin; (viii) a flexible peptide linker sequence comprising the amino acid sequence TPLGDTTHT (SEQ ID NO: 150); and (ix) a self-assembly disassembly (SADA) polypeptide, wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0151] In another aspect, the present disclosure provides a multi-specific antigen binding fragment comprising a first polypeptide chain, wherein: the first polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a flexible peptide linker comprising the amino acid sequence (

GGGGS

)$_6$ (SEQ ID NO: 148); (iii) a heavy chain variable domain of the first immunoglobulin; (iv) a flexible peptide linker comprising the amino acid sequence (

GGGGS

)$_4$ (SEQ ID NO: 149); (v) a heavy chain variable domain of a second immunoglobulin that is capable of specifically binding to a second epitope; (vi) a flexible peptide linker comprising the amino acid sequence (

GGGGS

)$_6$ (SEQ ID NO: 148); (vii) a light chain variable domain of the second immunoglobulin; (viii) a flexible peptide linker

sequence comprising the amino acid sequence TPLGDTTHT (SEQ ID NO: 150); and (ix) a self-assembly disassembly (SADA) polypeptide, wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0152] In certain embodiments of the bispecific antigen binding fragments disclosed herein, the SADA polypeptide comprises a tetramerization, pentamerization, or hexamerization domain. In some embodiments, the SADA polypeptide comprises a tetramerization domain of any one of p53, p63, p73, hnRNPC, SNA-23, Stefin B, KCNQ4, and CBFA2T1. Additionally or alternatively, in some embodiments, the bispecific antigen binding fragment comprises an amino acid sequence selected from SEQ ID NOs: 118-121.

[0153] In one aspect, the present disclosure provides a multi-specific antibody comprising a first polypeptide chain, a second polypeptide chain, a third polypeptide chain and a fourth polypeptide chain, wherein the first and second polypeptide chains are covalently bonded to one another, the second and third polypeptide chains are covalently bonded to one another, and the third and fourth polypeptide chain are covalently bonded to one another, and wherein: (a) each of the first polypeptide chain and the fourth polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a light chain variable domain of a first immunoglobulin that is capable of specifically binding to a first epitope; (ii) a light chain constant domain of the first immunoglobulin; (iii) a flexible peptide linker comprising the amino acid sequence (

GGGGS

)$_3$ (SEQ ID NO: 151); and (iv) a light chain variable domain of a second immunoglobulin that is linked to a complementary heavy chain variable domain of the second immunoglobulin, or a heavy chain variable domain of a second immunoglobulin that is linked to a complementary light chain variable domain of the second immunoglobulin, wherein the light chain and heavy chain variable domains of the second immunoglobulin are capable of specifically binding to a second epitope, and are linked together via a flexible peptide linker comprising the amino acid sequence (

GGGGS

)$_6$ (SEQ ID NO: 148) to form a single-chain variable fragment; and (b) each of the second polypeptide chain and the third polypeptide chain comprises in the N-terminal to C-terminal direction: (i) a heavy chain variable domain of the first immunoglobulin that is capable of specifically binding to the first epitope; and (ii) a heavy chain constant domain of the first immunoglobulin; and wherein the heavy chain variable domain of the first immunoglobulin or the heavy chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61, and/or the light chain variable domain of the first immunoglobulin or the light chain variable domain of the second immunoglobulin is selected from any one of SEQ ID NOs: 15-20 or 62-91.

[0154] In certain embodiments, the immunoglobulin-related compositions contain an IgG1 constant region comprising one or more amino acid substitutions selected from the group consisting of N297A and K322A. Additionally or alternatively, in some embodiments, the immunoglobulin-related compositions contain an IgG4 constant region comprising a S228P mutation.

[0155] In some aspects, the anti-CD3 immunoglobulin-related compositions described herein contain structural modifications to facilitate rapid binding and cell uptake and/or slow release. In some aspects, the anti-CD3 immunoglobulin-related composition of the present technology (e.g., an antibody) may contain a deletion in the CH2 constant heavy chain region to facilitate rapid binding and cell uptake and/or slow release. In some aspects, a Fab fragment is used to facilitate rapid binding and cell uptake and/or slow release. In some aspects, a F(ab)′$_2$ fragment is used to facilitate rapid binding and cell uptake and/or slow release.

[0156] In one aspect, the present technology provides a nucleic acid sequence encoding any of the immunoglobulin-related compositions described herein. Also disclosed herein are recombinant nucleic acid sequences encoding any of the antibodies described herein. In some embodiments, the nucleic acid sequence is selected from the group consisting of SEQ ID NOs: 22, 24, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 138, and 140.

[0157] In another aspect, the present technology provides a host cell expressing any nucleic acid sequence encoding any of the immunoglobulin-related compositions described herein.

[0158] The immunoglobulin-related compositions of the present technology (e.g., an anti-CD3 antibody) can be monospecific, bispecific, trispecific or of greater multi-specificity. Multi-specific antibodies can be specific for different epitopes of one or more CD3 polypeptides or can be specific for both the CD3 polypeptide(s) as well as for heterologous compositions, such as a heterologous polypeptide or solid support material. See, e.g., WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt et al., *J. Immunol.* 147: 60-69 (1991); U.S. Pat. Nos. 5,573,920, 4,474,893, 5,601,819, 4,714,681, 4,925,648; 6,106,835; Kostelny et al., *J. Immunol.* 148: 1547-1553 (1992). In some embodiments, the immunoglobulin-related compositions are chimeric. In certain embodiments, the immunoglobulin-related compositions are humanized.

[0159] The immunoglobulin-related compositions of the present technology can further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, the immunoglobulin-related compositions of the present technology can be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, or toxins. See, e.g., WO 92/08495; WO 91/14438; WO 89/12624; U.S. Pat. No. 5,314,995; and EP 0 396 387.

[0160] In any of the above embodiments of the immunoglobulin-related compositions of the present technology, the antibody or antigen binding fragment may be optionally

conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof. For a chemical bond or physical bond, a functional group on the immunoglobulin-related composition typically associates with a functional group on the agent. Alternatively, a functional group on the agent associates with a functional group on the immunoglobulin-related composition.

[0161] The functional groups on the agent and immunoglobulin-related composition can associate directly. For example, a functional group (e.g., a sulfhydryl group) on an agent can associate with a functional group (e.g., sulfhydryl group) on an immunoglobulin-related composition to form a disulfide. Alternatively, the functional groups can associate through a cross-linking agent (i.e., linker). Some examples of cross-linking agents are described below. The cross-linker can be attached to either the agent or the immunoglobulin-related composition. The number of agents or immunoglobulin-related compositions in a conjugate is also limited by the number of functional groups present on the other. For example, the maximum number of agents associated with a conjugate depends on the number of functional groups present on the immunoglobulin-related composition. Alternatively, the maximum number of immunoglobulin-related compositions associated with an agent depends on the number of functional groups present on the agent.

[0162] In yet another embodiment, the conjugate comprises one immunoglobulin-related composition associated to one agent. In one embodiment, a conjugate comprises at least one agent chemically bonded (e.g., conjugated) to at least one immunoglobulin-related composition. The agent can be chemically bonded to an immunoglobulin-related composition by any method known to those in the art. For example, a functional group on the agent may be directly attached to a functional group on the immunoglobulin-related composition. Some examples of suitable functional groups include, for example, amino, carboxyl, sulfhydryl, maleimide, isocyanate, isothiocyanate and hydroxyl.

[0163] The agent may also be chemically bonded to the immunoglobulin-related composition by means of cross-linking agents, such as dialdehydes, carbodiimides, dimaleimides, and the like. Cross-linking agents can, for example, be obtained from Pierce Biotechnology, Inc., Rockford, Ill. The Pierce Biotechnology, Inc. web-site can provide assistance. Additional cross-linking agents include the platinum cross-linking agents described in U.S. Pat. Nos. 5,580,990; 5,985,566; and 6,133,038 of Kreatech Biotechnology, B.V., Amsterdam, The Netherlands.

[0164] Alternatively, the functional group on the agent and immunoglobulin-related composition can be the same. Homobifunctional cross-linkers are typically used to cross-link identical functional groups. Examples of homobifunctional cross-linkers include EGS (i.e., ethylene glycol bis [succinimidylsuccinate]), DSS (i.e., disuccinimidyl suberate), DMA (i.e., dimethyl adipimidate.2HCl), DTSSP (i.e., 3,3′-dithiobis[sulfosuccinimidylpropionate])), DPDPB (i.e., 1,4-di-[3′-(2′-pyridyldithio)-propionamido]butane), and BMH (i.e., bis-maleimidohexane). Such homobifunctional cross-linkers are also available from Pierce Biotechnology, Inc.

[0165] In other instances, it may be beneficial to cleave the agent from the immunoglobulin-related composition. The web-site of Pierce Biotechnology, Inc. described above can also provide assistance to one skilled in the art in choosing suitable cross-linkers which can be cleaved by, for example, enzymes in the cell. Thus the agent can be separated from the immunoglobulin-related composition. Examples of cleavable linkers include SMPT (i.e., 4-succinimidyloxycarbonyl-methyl-α-[2-pyridyldithio]toluene), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), LC-SPDP (i.e., succinimidyl 6-(3-[2-pyridyldithio]-propionamido)hexanoate), Sulfo-LC-SPDP (i.e., sulfosuccinimidyl 6-(3-[2-pyridyldithio]-propionamido) hexanoate), SPDP (i.e., N-succinimidyl 3-[2-pyridyldithio]-propionamidohexanoate), and AEDP (i.e., 3-[(2-aminoethyl)dithio]propionic acid HCl).

[0166] In another embodiment, a conjugate comprises at least one agent physically bonded with at least one immunoglobulin-related composition. Any method known to those in the art can be employed to physically bond the agents with the immunoglobulin-related compositions. For example, the immunoglobulin-related compositions and agents can be mixed together by any method known to those in the art. The order of mixing is not important. For instance, agents can be physically mixed with immunoglobulin-related compositions by any method known to those in the art. For example, the immunoglobulin-related compositions and agents can be placed in a container and agitated, by for example, shaking the container, to mix the immunoglobulin-related compositions and agents.

[0167] The immunoglobulin-related compositions can be modified by any method known to those in the art. For instance, the immunoglobulin-related composition may be modified by means of cross-linking agents or functional groups, as described above.

A. Methods of Preparing Anti-CD3 Antibodies of the Present Technology

[0168] General Overview. Initially, a target polypeptide is chosen to which an antibody of the present technology can be raised. For example, an antibody may be raised against the full-length CD3 protein, or to a portion of the extracellular domain of the CD3 protein. Techniques for generating antibodies directed to such target polypeptides are well known to those skilled in the art. Examples of such techniques include, for example, but are not limited to, those involving display libraries, xeno or human mice, hybridomas, and the like. Target polypeptides within the scope of the present technology include any polypeptide derived from CD3 protein containing the extracellular domain which is capable of eliciting an immune response. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the βC strand), and residues 46ε and 48ε (the C′-D loop).

[0169] It should be understood that recombinantly engineered antibodies and antibody fragments, e.g., antibody-related polypeptides, which are directed to CD3 protein and fragments thereof are suitable for use in accordance with the present disclosure.

[0170] Anti-CD3 antibodies that can be subjected to the techniques set forth herein include monoclonal and polyclonal antibodies, and antibody fragments such as Fab, Fab′, $F(ab')_2$, Fd, scFv, diabodies, antibody light chains, antibody heavy chains and/or antibody fragments. Methods useful for the high yield production of antibody Fv-containing polypeptides, e.g., Fab′ and $F(ab')_2$ antibody fragments have been described. See U.S. Pat. No. 5,648,237.

[0171] Generally, an antibody is obtained from an originating species. More particularly, the nucleic acid or amino acid sequence of the variable portion of the light chain, heavy chain or both, of an originating species antibody having specificity for a target polypeptide antigen is obtained. An originating species is any species which was useful to generate the antibody of the present technology or library of antibodies, e.g., rat, mouse, rabbit, chicken, monkey, human, and the like.

[0172] Phage or phagemid display technologies are useful techniques to derive the antibodies of the present technology. Techniques for generating and cloning monoclonal antibodies are well known to those skilled in the art. Expression of sequences encoding antibodies of the present technology, can be carried out in *E. coli*.

[0173] Due to the degeneracy of nucleic acid coding sequences, other sequences which encode substantially the same amino acid sequences as those of the naturally occurring proteins may be used in the practice of the present technology These include, but are not limited to, nucleic acid sequences including all or portions of the nucleic acid sequences encoding the above polypeptides, which are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. It is appreciated that the nucleotide sequence of an immunoglobulin according to the present technology tolerates sequence homology variations of up to 25% as calculated by standard methods ("Current Methods in Sequence Comparison and Analysis," *Macromolecule Sequencing and Synthesis, Selected Methods and Applications*, pp. 127-149, 1998, Alan R. Liss, Inc.) so long as such a variant forms an operative antibody which recognizes CD3 proteins. For example, one or more amino acid residues within a polypeptide sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Also included within the scope of the present technology are proteins or fragments or derivatives thereof which are differentially modified during or after translation, e.g., by glycosylation, proteolytic cleavage, linkage to an antibody molecule or other cellular ligands, etc. Additionally, an immunoglobulin encoding nucleic acid sequence can be mutated in vitro or in vivo to create and/or destroy translation, initiation, and/or termination sequences or to create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to in vitro site directed mutagenesis, *J. Biol. Chem.* 253:6551, use of Tab linkers (Pharmacia), and the like.

Preparation of Polyclonal Antisera and Immunogens

[0174] Methods of generating antibodies or antibody fragments of the present technology typically include immunizing a subject (generally a non-human subject such as a mouse or rabbit) with a purified CD3 protein or fragment thereof or with a cell expressing the CD3 protein or fragment thereof. An appropriate immunogenic preparation can contain, e.g., a recombinantly-expressed CD3 protein or a chemically-synthesized CD3 peptide. The extracellular domain of the CD3 protein, or a portion or fragment thereof, can be used as an immunogen to generate an anti-CD3 antibody that binds to the CD3 protein, or a portion or fragment thereof using standard techniques for polyclonal and monoclonal antibody preparation. In certain embodiments, the extracellular domain comprises a CD3ε subunit including a linear stretch of sequence on the F-G loop. In some embodiments, the CD3ε subunit may comprise three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the βC strand), and residues 46ε and 48ε (the C′-D loop). The full-length CD3 protein or fragments thereof, are useful as fragments as immunogens. In some embodiments, a CD3 fragment comprises the extracellular domain of the CD3 protein, or a portion or fragment thereof (e.g., a CD3 polypeptide comprising a CD3ε subunit that includes three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the βC strand), and residues 46ε and 48ε (the C′-D loop), such that an antibody raised against the peptide forms a specific immune complex with the CD3 protein. In some embodiments, the antigenic CD3 peptide comprises at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, or at least 100 amino acid residues. Longer antigenic peptides are sometimes desirable over shorter antigenic peptides, depending on use and according to methods well known to those skilled in the art. Multimers of a given epitope are sometimes more effective than a monomer.

[0175] If needed, the immunogenicity of the CD3 protein (or fragment thereof) can be increased by fusion or conjugation to a carrier protein such as keyhole limpet hemocyanin (KLH) or ovalbumin (OVA). Many such carrier proteins are known in the art. One can also combine the CD3 protein with a conventional adjuvant such as Freund's complete or incomplete adjuvant to increase the subject's immune reaction to the polypeptide. Various adjuvants used to increase the immunological response include, but are not limited to, Freund's (complete and incomplete), mineral gels (e.g., aluminum hydroxide), surface active substances (e.g., lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, dinitrophenol, etc.), human adjuvants such as Bacille Calmette-Guerin and *Corynebacterium parvum*, or similar immunostimulatory compounds. These techniques are standard in the art.

[0176] In describing the present technology, immune responses may be described as either "primary" or "secondary" immune responses. A primary immune response, which is also described as a "protective" immune response, refers to an immune response produced in an individual as a result of some initial exposure (e.g., the initial "immunization") to

a particular antigen, e.g., CD3 protein. In some embodiments, the immunization can occur as a result of vaccinating the individual with a vaccine containing the antigen. For example, the vaccine can be a CD3 vaccine comprising one or more CD3 protein-derived antigens. A primary immune response can become weakened or attenuated over time and can even disappear or at least become so attenuated that it cannot be detected. Accordingly, the present technology also relates to a "secondary" immune response, which is also described here as a "memory immune response." The term secondary immune response refers to an immune response elicited in an individual after a primary immune response has already been produced.

[0177] Thus, a secondary immune response can be elicited, e.g., to enhance an existing immune response that has become weakened or attenuated, or to recreate a previous immune response that has either disappeared or can no longer be detected. The secondary or memory immune response can be either a humoral (antibody) response or a cellular response. A secondary or memory humoral response occurs upon stimulation of memory B cells that were generated at the first presentation of the antigen. Delayed type hypersensitivity (DTH) reactions are a type of cellular secondary or memory immune response that are mediated by $CD4^+$ T cells. A first exposure to an antigen primes the immune system and additional exposure(s) results in a DTH.

[0178] Following appropriate immunization, the anti-CD3 antibody can be prepared from the subject's serum. If desired, the antibody molecules directed against the CD3 protein can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as polypeptide A chromatography to obtain the IgG fraction.

[0179] Monoclonal Antibody. In one embodiment of the present technology, the antibody is an anti-CD3 monoclonal antibody. For example, in some embodiments, the anti-CD3 monoclonal antibody may be a human or a mouse anti-CD3 monoclonal antibody. For preparation of monoclonal antibodies directed towards the CD3 protein, or derivatives, fragments, analogs or homologs thereof, any technique that provides for the production of antibody molecules by continuous cell line culture can be utilized. Such techniques include, but are not limited to, the hybridoma technique (See, e.g., Kohler & Milstein, 1975. *Nature* 256: 495-497); the trioma technique; the human B-cell hybridoma technique (See, e.g., Kozbor, et al., 1983. *Immunol. Today* 4: 72) and the EBV hybridoma technique to produce human monoclonal antibodies (See, e.g., Cole, et al., 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies can be utilized in the practice of the present technology and can be produced by using human hybridomas (See, e.g., Cote, et al., 1983. *Proc. Natl. Acad. Sci. USA* 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (See, e.g., Cole, et al., 1985. In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). For example, a population of nucleic acids that encode regions of antibodies can be isolated. PCR utilizing primers derived from sequences encoding conserved regions of antibodies is used to amplify sequences encoding portions of antibodies from the population and then DNAs encoding antibodies or fragments thereof, such as variable domains, are reconstructed from the amplified sequences. Such amplified sequences also can be fused to DNAs encoding other proteins – e.g., a bacteriophage coat, or a bacterial cell surface protein – for expression and display of the fusion polypeptides on phage or bacteria. Amplified sequences can then be expressed and further selected or isolated based, e.g., on the affinity of the expressed antibody or fragment thereof for an antigen or epitope present on the CD3 protein. Alternatively, hybridomas expressing anti-CD3 monoclonal antibodies can be prepared by immunizing a subject and then isolating hybridomas from the subject's spleen using routine methods. See, e.g., Milstein et al., (Galfre and Milstein, *Methods Enzymol* (1981) 73: 3-46). Screening the hybridomas using standard methods will produce monoclonal antibodies of varying specificity (i.e., for different epitopes) and affinity. A selected monoclonal antibody with the desired properties, e.g., CD3 binding, can be used as expressed by the hybridoma, it can be bound to a molecule such as polyethylene glycol (PEG) to alter its properties, or a cDNA encoding it can be isolated, sequenced and manipulated in various ways. Synthetic dendromeric trees can be added to reactive amino acid side chains, e.g., lysine, to enhance the immunogenic properties of CD3 protein. Also, CPG-dinucleotide techniques can be used to enhance the immunogenic properties of the CD3 protein. Other manipulations include substituting or deleting particular amino acyl residues that contribute to instability of the antibody during storage or after administration to a subject, and affinity maturation techniques to improve affinity of the antibody of the CD3 protein.

Hybridoma Technique

[0180] In some embodiments, the antibody of the present technology is an anti-CD3 monoclonal antibody produced by a hybridoma which includes a B cell obtained from a transgenic non-human animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell. Hybridoma techniques include those known in the art and taught in Harlow et al., *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 349 (1988); Hammerling et al., *Monoclonal Antibodies And T-Cell Hybridomas*, 563-681 (1981). Other methods for producing hybridomas and monoclonal antibodies are well known to those of skill in the art.

Phage Display Technique

[0181] As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA and phage display technology. For example, anti-CD3 antibodies, can be prepared using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of a phage particle which carries polynucleotide sequences encoding them. Phages with a desired binding property are selected from a repertoire or combinatorial antibody library (e.g., human or murine) by selecting directly with an antigen, typically an antigen bound or captured to a solid surface or bead. Phages used in these methods are typically filamentous phage including fd and M13 with Fab, Fv or disulfide stabilized Fv antibody domains that are recombinantly fused to either the phage gene III or gene VIII protein. In addition, methods can be adapted for the construc-

tion of Fab expression libraries (See, e.g., Huse, et al., *Science* 246: 1275-1281, 1989) to allow rapid and effective identification of monoclonal Fab fragments with the desired specificity for a CD3 polypeptide, e.g., a polypeptide or derivatives, fragments, analogs or homologs thereof. Other examples of phage display methods that can be used to make the antibodies of the present technology include those disclosed in Huston et al., *Proc. Natl. Acad. Sci U.S.A.*, 85: 5879-5883, 1988; Chaudhary et al., *Proc. Natl. Acad. Sci U.S.A.*, 87: 1066-1070, 1990; Brinkman et al., *J. Immunol. Methods* 182: 41-50, 1995; Ames et al., J. Immunol. Methods 184: 177-186, 1995; Kettleborough et al., *Eur. J. Immunol.* 24: 952-958, 1994; Persic et al., Gene 187: 9-18, 1997; Burton et al., *Advances in Immunology* 57: 191-280, 1994; PCT/GB91/01134; WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; WO 96/06213; WO 92/01047 (Medical Research Council etal.); WO 97/08320 (Morphosys); WO 92/01047 (CAT/MRC); WO 91/17271 (Affymax); and U.S. Pat. Nos. 5,698,426, 5,223,409, 5,403,484, 5,580,717, 5,427,908, 5,750,753, 5,821,047, 5,571,698, 5,427,908, 5,516,637, 5,780,225, 5,658,727 and 5,733,743. Methods useful for displaying polypeptides on the surface of bacteriophage particles by attaching the polypeptides via disulfide bonds have been described by Lohning, U.S. Pat. No. 6,753,136. As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host including mammalian cells, insect cells, plant cells, yeast, and bacteria. For example, techniques to recombinantly produce Fab, Fab′ and F(ab′)$_2$ fragments can also be employed using methods known in the art such as those disclosed in WO 92/22324; Mullinax et al., *BioTechniques* 12: 864-869, 1992; and Sawai et al., *AJRI* 34: 26-34, 1995; and Better et al., *Science* 240: 1041-1043, 1988.

[0182] Generally, hybrid antibodies or hybrid antibody fragments that are cloned into a display vector can be selected against the appropriate antigen in order to identify variants that maintain good binding activity, because the antibody or antibody fragment will be present on the surface of the phage or phagemid particle. See, e.g., Barbas III et al., *Phage Display, A Laboratory Manual* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001). However, other vector formats could be used for this process, such as cloning the antibody fragment library into a lytic phage vector (modified T7 or Lambda Zap systems) for selection and/or screening.

[0183] Expression of Recombinant Anti-CD3 Antibodies. As noted above, the antibodies of the present technology can be produced through the application of recombinant DNA technology. Recombinant polynucleotide constructs encoding an anti-CD3 antibody of the present technology typically include an expression control sequence operably-linked to the coding sequences of anti-CD3 antibody chains, including naturally-associated or heterologous promoter regions. As such, another aspect of the technology includes vectors containing one or more nucleic acid sequences encoding an anti-CD3 antibody of the present technology. For recombinant expression of one or more of the polypeptides of the present technology, the nucleic acid containing all or a portion of the nucleotide sequence encoding the anti-CD3 antibody is inserted into an appropriate cloning vector, or an expression vector (i.e., a vector that contains the necessary elements for the transcription and translation of the inserted polypeptide coding sequence) by recombinant DNA techniques well known in the art and as detailed below. Methods for producing diverse populations of vectors have been described by Lerner et al., U.S. Pat. Nos. 6,291,160 and 6,680,192.

[0184] In general, expression vectors useful in recombinant DNA techniques are often in the form of plasmids. In the present disclosure, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the present technology is intended to include such other forms of expression vectors that are not technically plasmids, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions. Such viral vectors permit infection of a subject and expression of a construct in that subject. In some embodiments, the expression control sequences are eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences encoding the anti-CD3 antibody, and the collection and purification of the anti-CD3 antibody, e.g., cross-reacting anti-CD3 antibodies. See generally, U.S. 2002/0199213. These expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers, e.g., ampicillin-resistance or hygromycin-resistance, to permit detection of those cells transformed with the desired DNA sequences. Vectors can also encode signal peptide, e.g., pectate lyase, useful to direct the secretion of extracellular antibody fragments. See U.S. Pat. No. 5,576,195.

[0185] The recombinant expression vectors of the present technology comprise a nucleic acid encoding a protein with CD3 binding properties in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression that is operably-linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably-linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (e.g., in an in vitro transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Such regulatory sequences are described, e.g., in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of polypeptide desired, etc. Typical regulatory sequences useful as promoters of recombinant polypeptide expression (e.g., anti-CD3 antibody),

include, e.g., but are not limited to, promoters of 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for maltose and galactose utilization. In one embodiment, a polynucleotide encoding an anti-CD3 antibody of the present technology is operably-linked to an ara B promoter and expressible in a host cell. See U.S. Pat. 5,028,530. The expression vectors of the present technology can be introduced into host cells to thereby produce polypeptides or peptides, including fusion polypeptides, encoded by nucleic acids as described herein (e.g., anti-CD3 antibody, etc.).

[0186] Another aspect of the present technology pertains to anti-CD3 antibody-expressing host cells, which contain a nucleic acid encoding one or more anti-CD3 antibodies. The recombinant expression vectors of the present technology can be designed for expression of an anti-CD3 antibody in prokaryotic or eukaryotic cells. For example, an anti-CD3 antibody can be expressed in bacterial cells such as *Escherichia coli*, insect cells (using baculovirus expression vectors), fungal cells, e.g., yeast, yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990). Alternatively, the recombinant expression vector can be transcribed and translated in vitro, e.g., using T7 promoter regulatory sequences and T7 polymerase. Methods useful for the preparation and screening of polypeptides having a predetermined property, e.g., anti-CD3 antibody, via expression of stochastically generated polynucleotide sequences has been previously described. See U.S. Pat. Nos. 5,763,192; 5,723,323; 5,814,476; 5,817,483; 5,824,514; 5,976,862; 6,492,107; 6,569,641.

[0187] Expression of polypeptides in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion polypeptides. Fusion vectors add a number of amino acids to a polypeptide encoded therein, usually to the amino terminus of the recombinant polypeptide. Such fusion vectors typically serve three purposes: (i) to increase expression of recombinant polypeptide; (ii) to increase the solubility of the recombinant polypeptide; and (iii) to aid in the purification of the recombinant polypeptide by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant polypeptide to enable separation of the recombinant polypeptide from the fusion moiety subsequent to purification of the fusion polypeptide. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988. *Gene* 67: 31-40), pMAL (New England Biolabs, Beverly, Mass.) and pRIT5 (Pharmacia, Piscataway, N.J.) that fuse glutathione S-transferase (GST), maltose E binding polypeptide, or polypeptide A, respectively, to the target recombinant polypeptide.

[0188] Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amrann et al., (1988) *Gene* 69: 301-315) and pET 11d (Studier et al., GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 60-89). Methods for targeted assembly of distinct active peptide or protein domains to yield multifunctional polypeptides via polypeptide fusion has been described by Pack et al., U.S. Pat. Nos. 6,294,353; 6,692,935. One strategy to maximize recombinant polypeptide expression, e.g., an anti-CD3 antibody, in E. coli is to express the polypeptide in host bacteria with an impaired capacity to proteolytically cleave the recombinant polypeptide. See, e.g., Gottesman, GENE EXPRESSION TECHNOLOGY: METHODS IN ENZYMOLOGY 185, Academic Press, San Diego, Calif. (1990) 119-128. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in the expression host, e.g., E. coli (See, e.g., Wada, et al., 1992. *Nucl. Acids Res.* 20: 2111-2118). Such alteration of nucleic acid sequences of the present technology can be carried out by standard DNA synthesis techniques.

[0189] In another embodiment, the anti-CD3 antibody expression vector is a yeast expression vector. Examples of vectors for expression in yeast Saccharomyces cerevisiae include pYepSec1 (Baldari, et al., 1987. *EMBO J.* 6: 229-234), pMFa (Kurjan and Herskowitz, *Cell* 30: 933-943, 1982), pJRY88 (Schultz et al., *Gene* 54: 113-123, 1987), pYES2 (Invitrogen Corporation, San Diego, Calif.), and picZ (Invitrogen Corp, San Diego, Calif.). Alternatively, an anti-CD3 antibody can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of polypeptides, e.g., anti-CD3 antibody, in cultured insect cells (e.g., SF9 cells) include the pAc series (Smith, et al., *Mol. Cell. Biol.* 3: 2156-2165, 1983) and the pVL series (Lucklow and Summers, 1989. *Virology* 170: 31-39).

[0190] In yet another embodiment, a nucleic acid encoding an anti-CD3 antibody of the present technology is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include, e.g., but are not limited to, pCDM8 (Seed, *Nature* 329: 840, 1987) and pMT2PC (Kaufman, et al., *EMBO J.* 6: 187-195, 1987). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, adenovirus 2, cytomegalovirus, and simian virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells that are useful for expression of the anti-CD3 antibody of the present technology, see, e.g., Chapters 16 and 17 of Sambrook, et al., MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989.

[0191] In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid in a particular cell type (e.g., tissue-specific regulatory elements). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert, et al., *Genes Dev.* 1: 268-277, 1987), lymphoid-specific promoters (Calame and Eaton, *Adv. Immunol.* 43: 235-275, 1988), promoters of T cell receptors (Winoto and Baltimore, *EMBO J.* 8: 729-733, 1989) and immunoglobulins (Banerji, et al., 1983. *Cell* 33: 729-740; Queen and Baltimore, *Cell* 33: 741-748, 1983.), neuron-specific promoters (e.g., the neurofilament promoter; Byrne and Ruddle, *Proc. Natl. Acad. Sci. USA* 86: 5473-5477, 1989), pancreas-specific promoters (Edlund, et al., 1985. Science 230: 912-

916), and mammary gland-specific promoters (e.g., milk whey promoter; U.S. Pat. No. 4,873,316 and European Application publication No. 264,166). Developmentally-regulated promoters are also encompassed, e.g., the murine hox promoters (Kessel and Gruss, *Science* 249: 374-379, 1990) and the α-fetoprotein promoter (Campes and Tilghman, *Genes* Dev. 3: 537-546, 1989).

[0192] Another aspect of the present methods pertains to host cells into which a recombinant expression vector of the present technology has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0193] A host cell can be any prokaryotic or eukaryotic cell. For example, an anti-CD3 antibody can be expressed in bacterial cells such as E. coli, insect cells, yeast or mammalian cells. Mammalian cells are a suitable host for expressing nucleotide segments encoding immunoglobulins or fragments thereof. See Winnacker, *From Genes To Clones*, (VCH Publishers, NY, 1987). A number of suitable host cell lines capable of secreting intact heterologous proteins have been developed in the art, and include Chinese hamster ovary (CHO) cell lines, various COS cell lines, HeLa cells, L cells and myeloma cell lines. In some embodiments, the cells are non-human. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer, and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Queen et al., *Immunol. Rev.* 89: 49, 1986. Illustrative expression control sequences are promoters derived from endogenous genes, cytomegalovirus, SV40, adenovirus, bovine papillomavirus, and the like. Co et al., *J Immunol.* 148: 1149, 1992. Other suitable host cells are known to those skilled in the art.

[0194] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (e.g., DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, electroporation, biolistics or viral-based transfection. Other methods used to transform mammalian cells include the use of polybrene, protoplast fusion, liposomes, electroporation, and microinjection (See generally, Sambrook et al., *Molecular Cloning*). Suitable methods for transforming or transfecting host cells can be found in Sambrook, et al. (MOLECULAR CLONING: A LABORATORY MANUAL. 2nd ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989), and other laboratory manuals. The vectors containing the DNA segments of interest can be transferred into the host cell by well-known methods, depending on the type of cellular host.

[0195] For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Various selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding the anti-CD3 antibody or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die).

[0196] A host cell that includes an anti-CD3 antibody of the present technology, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (i.e., express) recombinant anti-CD3 antibody. In one embodiment, the method comprises culturing the host cell (into which a recombinant expression vector encoding the anti-CD3 antibody has been introduced) in a suitable medium such that the anti-CD3 antibody is produced. In another embodiment, the method further comprises the step of isolating the anti-CD3 antibody from the medium or the host cell. Once expressed, collections of the anti-CD3 antibody, e.g., the anti-CD3 antibodies or the anti-CD3 antibody-related polypeptides are purified from culture media and host cells. The anti-CD3 antibody can be purified according to standard procedures of the art, including HPLC purification, column chromatography, gel electrophoresis and the like. In one embodiment, the anti-CD3 antibody is produced in a host organism by the method of Boss et al., U.S. Pat. No. 4,816,397. Usually, anti-CD3 antibody chains are expressed with signal sequences and are thus released to the culture media. However, if the anti-CD3 antibody chains are not naturally secreted by host cells, the anti-CD3 antibody chains can be released by treatment with mild detergent. Purification of recombinant polypeptides is well known in the art and includes ammonium sulfate precipitation, affinity chromatography purification technique, column chromatography, ion exchange purification technique, gel electrophoresis and the like (See generally Scopes, Protein Purification (Springer-Verlag, N.Y., 1982).

[0197] Polynucleotides encoding anti-CD3 antibodies, e.g., the anti-CD3 antibody coding sequences, can be incorporated in transgenes for introduction into the genome of a transgenic animal and subsequent expression in the milk of the transgenic animal. See, e.g., U.S. Pat. Nos. 5,741,957, 5,304,489, and 5,849,992. Suitable transgenes include coding sequences for light and/or heavy chains in operable linkage with a promoter and enhancer from a mammary gland specific gene, such as casein or β-lactoglobulin. For production of transgenic animals, transgenes can be microinjected into fertilized oocytes, or can be incorporated into the genome of embryonic stem cells, and the nuclei of such cells transferred into enucleated oocytes.

Single-Chain Antibodies

[0198] In one embodiment, the anti-CD3 antibody of the present technology is a single-chain anti-CD3 antibody. According to the present technology, techniques can be adapted for the production of single-chain antibodies specific to a CD3 protein (See, e.g., U.S. Pat. No. 4,946,778). Examples of techniques which can be used to produce single-chain Fvs and antibodies of the present technology

include those described in U.S. Pat. Nos. 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology*, 203: 46-88, 1991; Shu, L. et al., *Proc. Natl. Acad. Sci. USA*, 90: 7995-7999, 1993; and Skerra et al., *Science* 240: 1038-1040, 1988.

Chimeric and Humanized Antibodies

[0199] In one embodiment, the anti-CD3 antibody of the present technology is a chimeric anti-CD3 antibody. In one embodiment, the anti-CD3 antibody of the present technology is a humanized anti-CD3 antibody. In one embodiment of the present technology, the donor and acceptor antibodies are monoclonal antibodies from different species. For example, the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a "humanized" antibody.

[0200] Recombinant anti-CD3 antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, can be made using standard recombinant DNA techniques, and are within the scope of the present technology. For some uses, including in vivo use of the anti-CD3 antibody of the present technology in humans as well as use of these agents in in vitro detection assays, it is possible to use chimeric or humanized anti-CD3 antibodies. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art. Such useful methods include, e.g., but are not limited to, methods described in International Application No. PCT/US86/02269; U.S. Pat. No. 5,225,539; European Patent No. 184187; European Patent No. 171496; European Patent No. 173494; PCT International Publication No. WO 86/01533; U.S. Pat. Nos. 4,816,567; 5,225,539; European Patent No. 125023; Better, et al., 1988. *Science* 240: 1041-1043; Liu, et al., 1987. *Proc. Natl. Acad. Sci. USA* 84: 3439-3443; Liu, et al., 1987. *J. Immunol.* 139: 3521-3526; Sun, et al., 1987. *Proc. Natl. Acad. Sci. USA* 84: 214-218; Nishimura, et al., 1987. *Cancer Res.* 47: 999-1005; Wood, et al., 1985. *Nature* 314: 446-449; Shaw, etal., 1988. *J. Natl. Cancer Inst.* 80: 1553-1559; Morrison (1985) *Science* 229: 1202-1207; Oi, et al. (1986) *BioTechniques* 4: 214; Jones, et al., 1986. *Nature* 321: 552-525; Verhoeyan, etal., 1988. *Science* 239: 1534; Morrison, *Science* 229: 1202, 1985; Oi et al., *BioTechniques* 4: 214, 1986; Gillies et al., *J. Immunol. Methods*, 125: 191-202, 1989; U.S. Pat. No. 5,807,715; and Beidler, et al., 1988. *J. Immunol.* 141: 4053-4060. For example, antibodies can be humanized using a variety of techniques including CDR-grafting (EP 0 239 400; WO 91/09967; U.S. Pat. No. 5,530,101; 5,585,089; 5,859,205; 6,248,516; EP460167), veneering or resurfacing (EP 0 592 106; EP 0 519 596; Padlan E. A., *Molecular Immunology*, 28: 489-498, 1991; Studnicka et al., *Protein Engineering* 7: 805-814, 1994; Roguska et al., *PNAS* 91: 969-973, 1994), and chain shuffling (U.S. Pat. No. 5,565,332). In one embodiment, a cDNA encoding a murine anti-CD3 monoclonal antibody is digested with a restriction enzyme selected specifically to remove the sequence encoding the Fc constant region, and the equivalent portion of a cDNA encoding a human Fc constant region is substituted (See Robinson et al., PCT/US86/02269; Akira et al., European Patent Application 184,187; Taniguchi, European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better et al. (1988) *Science* 240: 1041-1043; Liu et al. (1987) *Proc. Natl. Acad. Sci. USA* 84: 3439-3443; Liu et al. (1987) *J Immunol* 139: 3521-3526; Sun et al. (1987) *Proc. Natl. Acad. Sci. USA* 84: 214-218; Nishimura et al. (1987) *Cancer Res* 47: 999-1005; Wood et al. (1985) *Nature* 314: 446-449; and Shaw etal. (1988) *J. Natl. Cancer Inst.* 80: 1553-1559; U.S. Pat. No. 6,180,370; U.S. Pat. Nos. 6,300,064; 6,696,248; 6,706,484; 6,828,422.

[0201] In one embodiment, the present technology provides the construction of humanized anti-CD3 antibodies that are unlikely to induce a human anti-mouse antibody (hereinafter referred to as "HAMA") response, while still having an effective antibody effector function. As used herein, the terms "human" and "humanized", in relation to antibodies, relate to any antibody which is expected to elicit a therapeutically tolerable weak immunogenic response in a human subject. In one embodiment, the present technology provides for a humanized anti-CD3 antibodies, heavy and light chain immunoglobulins.

[0202] CDR Antibodies. In some embodiments, the anti-CD3 antibody of the present technology is an anti-CD3 CDR antibody. Generally the donor and acceptor antibodies used to generate the anti-CD3 CDR antibody are monoclonal antibodies from different species; typically the acceptor antibody is a human antibody (to minimize its antigenicity in a human), in which case the resulting CDR-grafted antibody is termed a "humanized" antibody. The graft may be of a single CDR (or even a portion of a single CDR) within a single V_H or V_L of the acceptor antibody, or can be of multiple CDRs (or portions thereof) within one or both of the V_H and V_L. Frequently, all three CDRs in all variable domains of the acceptor antibody will be replaced with the corresponding donor CDRs, though one needs to replace only as many as necessary to permit adequate binding of the resulting CDR-grafted antibody to CD3 protein. Methods for generating CDR-grafted and humanized antibodies are taught by Queen etal. U.S. Pat. No. 5,585,089; U.S. Pat. No. 5,693,761; U.S. Pat. No. 5,693,762; and Winter U.S. 5,225,539; and EP 0682040. Methods useful to prepare V_H and V_L polypeptides are taught by Winter et al., U.S. Pat. Nos. 4,816,397; 6,291,158; 6,291,159; 6,291,161; 6,545,142; EP 0368684; EP0451216; and EP0120694.

[0203] After selecting suitable framework region candidates from the same family and/or the same family member, either or both the heavy and light chain variable regions are produced by grafting the CDRs from the originating species into the hybrid framework regions. Assembly of hybrid antibodies or hybrid antibody fragments having hybrid variable chain regions with regard to either of the above aspects can be accomplished using conventional methods known to those skilled in the art. For example, DNA sequences encoding the hybrid variable domains described herein (i.e., frameworks based on the target species and CDRs from the originating species) can be produced by oligonucleotide synthesis and/or PCR. The nucleic acid encoding CDR regions can also be isolated from the originating species antibodies using suitable restriction enzymes and ligated into the target species framework by ligating with suitable ligation enzymes. Alternatively, the framework regions of the variable chains of the originating species antibody can be changed by site-directed mutagenesis.

[0204] Since the hybrids are constructed from choices among multiple candidates corresponding to each frame-

work region, there exist many combinations of sequences which are amenable to construction in accordance with the principles described herein. Accordingly, libraries of hybrids can be assembled having members with different combinations of individual framework regions. Such libraries can be electronic database collections of sequences or physical collections of hybrids.

[0205] This process typically does not alter the acceptor antibody's FRs flanking the grafted CDRs. However, one skilled in the art can sometimes improve antigen binding affinity of the resulting anti-CD3 CDR-grafted antibody by replacing certain residues of a given FR to make the FR more similar to the corresponding FR of the donor antibody. Suitable locations of the substitutions include amino acid residues adjacent to the CDR, or which are capable of interacting with a CDR (See, e.g., US 5,585,089, especially columns 12-16). Or one skilled in the art can start with the donor FR and modify it to be more similar to the acceptor FR or a human consensus FR. Techniques for making these modifications are known in the art. Particularly if the resulting FR fits a human consensus FR for that position, or is at least 90% or more identical to such a consensus FR, doing so may not increase the antigenicity of the resulting modified anti-CD3 CDR-grafted antibody significantly compared to the same antibody with a fully human FR.

Bispecific Antibodies (BsAbs)

[0206] A bispecific antibody is an antibody that can bind simultaneously to two targets that have a distinct structure, e.g., two different target antigens, two different epitopes on the same target antigen, or a hapten and a target antigen or epitope on a target antigen. BsAbs can be made, for example, by combining heavy chains and/or light chains that recognize different epitopes of the same or different antigen. In some embodiments, by molecular function, a bispecific binding agent binds one antigen (or epitope) on one of its two binding arms (one VH/VL pair), and binds a different antigen (or epitope) on its second arm (a different VH/VL pair). By this definition, a bispecific binding agent has two distinct antigen binding arms (in both specificity and CDR sequences), and is monovalent for each antigen to which it binds.

[0207] Multi-specific antibodies, such as bispecific antibodies (BsAb) and bispecific antibody fragments (BsFab) have at least one arm that specifically binds to, for example, CD3 and at least one other arm that specifically binds to a second target antigen. In some embodiments, the second target antigen is an antigen or epitope of a B-cell, a T-cell, a myeloid cell, a plasma cell, or a mast-cell. Additionally or alternatively, in certain embodiments, the second target antigen is selected from the group consisting of CD3, CD4, CD8, CD20, CD19, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46 and KIR. In certain embodiments, the BsAbs are capable of binding to tumor cells that express CD3 antigen on the cell surface. In some embodiments, the BsAbs have been engineered to facilitate killing of tumor cells by directing (or recruiting) cytotoxic T cells to a tumor site. Other exemplary BsAbs include those with a first antigen binding site specific for CD3 and a second antigen binding site specific for a small molecule hapten (e.g., DTP A, IMP288, DOTA, DOTA-Bn, DOTA-desferrioxamine, other DOTA-chelates described herein, Biotin, fluorescein, or those disclosed in Goodwin, D A. et al, 1994, *Cancer Res.* 54(22):5937-5946).

[0208] A variety of bispecific fusion proteins can be produced using molecular engineering. For example, BsAbs have been constructed that either utilize the full immunoglobulin framework (e.g., IgG), single chain variable fragment (scFv), or combinations thereof. In some embodiments, the bispecific fusion protein is divalent, comprising, for example, a scFv with a single binding site for one antigen and a Fab fragment with a single binding site for a second antigen. In some embodiments, the bispecific fusion protein is divalent, comprising, for example, an scFv with a single binding site for one antigen and another scFv fragment with a single binding site for a second antigen. In other embodiments, the bispecific fusion protein is tetravalent, comprising, for example, an immunoglobulin (e.g., IgG) with two binding sites for one antigen and two identical scFvs for a second antigen. BsAbs composed of two scFv units in tandem have been shown to be a clinically successful bispecific antibody format. In some embodiments, BsAbs comprise two single chain variable fragments (scFvs) in tandem have been designed such that an scFv that binds a tumor antigen (e.g., CD3) is linked with an scFv that engages T cells (e.g., by binding CD3). In this way, T cells are recruited to a tumor site such that they can mediate cytotoxic killing of the tumor cells. See e.g., Dreier et al., *J. Immunol.* 170:4397-4402 (2003); Bargou et al., *Science* 321 :974-977 (2008)). In some embodiments, BsAbs of the present technology comprise two single chain variable fragments (scFvs) in tandem have been designed such that an scFv that binds a tumor antigen (e.g., CD3) is linked with an scFv that engages a small molecule DOTA hapten.

[0209] Recent methods for producing BsAbs include engineered recombinant monoclonal antibodies which have additional cysteine residues so that they crosslink more strongly than the more common immunoglobulin isotypes. See, e.g., FitzGerald et al., *Protein Eng.* 10(10): 1221-1225 (1997). Another approach is to engineer recombinant fusion proteins linking two or more different single-chain antibody or antibody fragment segments with the needed dual specificities. See, e.g., Coloma et al., *Nature Biotech.* 15:159-163 (1997). A variety of bispecific fusion proteins can be produced using molecular engineering.

[0210] Bispecific fusion proteins linking two or more different single-chain antibodies or antibody fragments are produced in a similar manner. Recombinant methods can be used to produce a variety of fusion proteins. In some certain embodiments, a BsAb according to the present technology comprises an immunoglobulin, which immunoglobulin comprises a heavy chain and a light chain, and an scFv. In some certain embodiments, the scFv is linked to the C-terminal end of the heavy chain of any CD3 immunoglobulin disclosed herein. In some certain embodiments, scFvs are linked to the C-terminal end of the light chain of any CD3 immunoglobulin disclosed herein. In various embodiments, scFvs are linked to heavy or light chains via a linker sequence. Appropriate linker sequences necessary for the in-frame connection of the heavy chain Fd to the scFv are introduced into the V_L and V_{kappa} domains through PCR reactions. The DNA fragment encoding the scFv is then ligated into a staging vector containing a DNA sequence encoding the CH1 domain. The resulting scFv-CH1 construct is excised and ligated into a vector containing a DNA sequence encoding the V_H region of a CD3 anti-

body. The resulting vector can be used to transfect an appropriate host cell, such as a mammalian cell for the expression of the bispecific fusion protein.

[0211] In some embodiments, a linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length. In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, but rather provides flexibility to the polypeptide (e.g., first and/or second antigen binding sites). In some embodiments, a linker is employed in a BsAb described herein based on specific properties imparted to the BsAb such as, for example, an increase in stability. In some embodiments, a BsAb of the present technology comprises a G_4S linker (SEQ ID NO: 153). In some certain embodiments, a BsAb of the present technology comprises a $(G_4S)_n$ linker (SEQ ID NO: 154), wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 1 1, 12, 13, 14, 15 or more.

Self Assembly Disassembly (SADA) Conjugates

[0212] In some embodiments, the anti-CD3 antibodies of the present technology comprise one or more SADA domains. SADA domains can be designed and/or tailored to achieve environmentally-dependent multimerization with beneficial kinetic, thermodynamic, and/or pharmacologic properties. For example, it is recognized that SADA domains may be part of a conjugate that permit effective delivery of a payload to a target site of interest while minimizing the risk off-target interactions. The anti-CD3 antibodies of the present technolgy may comprise a SADA domain linked to one or more binding domains. In some embodiments, such conjugates are characterized in that they multimerize to form a complex of a desired size under relevant conditions (e.g., in a solution in which the conjugate is present above a threshold concentration or pH and/or when present at a target site characterized by a relevant level or density of receptors for the payload), and disassemble to a smaller form under other conditions (e.g., absent the relevant environmental multimerization trigger).

[0213] A SADA conjugate may have improved characteristics compared to a conjugate without a SADA domain. In some embodiments, improved characteristics of a multimeric conjugate include: increased avidity /binding to a target, increased specificity for target cells or tissues, and/or extended initial serum half-life. In some embodiments, improved characteristics include that through dissociation to smaller states (e.g., dimeric or monomeric), a SADA conjugate exhibits reduced non-specific binding, decreased toxicity, and/or improved renal clearance. In some embodiments, a SADA conjugate comprises a SADA polypeptide having an amino acid sequence that shows at least 75% identity with that of a human homo-multimerizing polypeptide and is characterized by one or more multimerization dissociation constants (K_D).

[0214] In some embodiments, a SADA conjugate is constructed and arranged so that it adopts a first multimerization state and one or more higher-order multimerization states. In some embodiments, a first multimerization state is less than about ~70 kDa in size. In some embodiments, a first multimerization state is an unmultimerized state (e.g., a monomer or a dimer). In some embodiments, a first multimerization state is a monomer. In some embodiments, a first multimerization state is a dimer. In some embodiments, a first multimerization state is a multimerized state (e.g., a trimer or a tetramer). In some embodiments, a higher-order multimerization states is a homo-tetramer or higher-order homo-multimer greater than 150 kDa in size. In some embodiments, a higher-order homo-multimerized conjugate is stable in aqueous solution when the conjugate is present at a concentration above the SADA polypeptide K_D. In some embodiments, a SADA conjugate transitions from a higher-order multimerization state(s) to a first multimerization state under physiological conditions when the concentration of the conjugate is below the SADA polypeptide K_D.

[0215] In some embodiments, a SADA polypeptide is covalently linked to a binding domain via a linker. Any suitable linker known in the art can be used. In some embodiments, a SADA polypeptide is linked to a binding domain via a polypeptide linker. In some embodiments, a polypeptide linker is a Gly-Ser linker. In some embodiments, a polypeptide linker is or comprises a sequence of (GGGGS)n (SEQ ID NO: 155), where n represents the number of repeating GGGGS (SEQ ID NO: 153) units and is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or more. In some embodiments, a binding domain is directly fused to a SADA polypeptide.

[0216] In some embodiments, a SADA domain is a human polypeptide or a fragment and/or derivative thereof. In some embodiments, a SADA domain is substantially non-immunogenic in a human. In some embodiments, a SADA polypeptide is stable as a multimer. In some embodiments, a SADA polypeptide lacks unpaired cysteine residues. In some embodiments, a SADA polypeptide does not have large exposed hydrophobic surfaces. In some embodiments, a SADA domain has or is predicted to have a structure comprising helical bundles that can associate in a parallel or anti-parallel orientation. In some embodiments, a SADA polypeptide is capable of reversible multimerization. In some embodiments, a SADA domain is a tetramerization domain, a heptamerization domain, a hexamerization domain or an octamerization domain. In certain embodiments, a SADA domain is a tetramerization domain. In some embodiments, a SADA domain is composed of a multimerization domains which are each composed of helical bundles that associate in a parallel or anti- parallel orientation. In some embodiments, a SADA domain is selected from the group of one of the following human proteins: p53, p63, p73, heterogeneous nuclear Ribonucleoprotein C (hnRNPC), N-terminal domain of Synaptosomal-associated protein 23 (SNAP-23), Stefin B (Cystatin B), Potassium voltage-gated channel subfamily KQT member 4 (KCNQ4), or Cyclin-D-related protein (CBFA2T1). Examples of suitable SADA domains are described in PCT/US201 8/03 1235, which is hereby incorporated by reference in its entirety. Provided below are polypeptide sequences for exemplary SADA domains.

[0217] Human p53 tetramerization domain amino acid sequence (321-359)

KPLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEP

(SEQ ID NO: 34)

[0218] Human p63 tetramerization domain amino acid sequence (396-450)

RSPDDELLYLPVRGRETYEMLLKIKESLELMQYLPQHTIETYRQQQQQQH QHLLQKQ

(SEQ ID NO: 35)

[0219] Human p73 tetramerization domain amino acid sequence (348-399)

RHGDEDTYYLQVRGRENFEILMKLKESLELMELVPQPLVDSYRQQQQLLQ RP

(SEQ ID NO: 36).

[0220] Human HNRNPC tetramerization domain amino acid sequence (194-220)

QAIKKELTQIKQKVDSLLENLEKIEKE

(SEQ ID NO: 37)

[0221] Human SNAP-23 tetramerization domain amino acid sequence (23-76)

STRRILGLAIESQDAGIKTITMLDEQKEQLNRIEEGLDQINKDMRETEKT LTEL

(SEQ ID NO: 38)

[0222] Human Stefin B tetramerizaiton domain amino acid sequence (2-98)

MCGAPSATQPATAETQHIADQVRSQLEEKENKKFPVFKAVSFKSQVVAGT NYFIKVHVGDEDFVHLRVFQSLPHENKPLTLSNYQTNKAKHDELTYF

(SEQ ID NO: 39)

[0223] KCNQ4 tetramerizaiton domain amino acid sequence (611-640)

DEISMMGRVVKVEKQVQSIEHKLDLLLGFY

(SEQ ID NO: 40)

[0224] CBFA2T1 tetramerizaiton domain amino acid sequence (462-521)

TVAEAKRQAAEDALAVINQQEDSSESCWNCGRKASETCSGCNTARYCGSF CQHKDWEKHH

(SEQ ID NO: 41)

[0225] In some embodiments, a SADA polypeptide is or comprises a tetramerization domain of p53, p63, p73, heterogeneous nuclear Ribonucleoprotein C (hnRNPC), N-terminal domain of Synaptosomal-associated protein 23 (SNAP-23), Stefin B (Cystatin B), Potassium voltage-gated channel subfamily KQT member 4 (KCNQ4), or Cyclin-D-related protein (CBFA2T1). In some embodiments, a SADA polypeptide is or comprises a sequence that is at least 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% identical to a sequence as set forth in any one of SEQ ID NOs: 34-41.

Fc Modifications

[0226] In some embodiments, the anti-CD3 antibodies of the present technology comprise a variant Fc region, wherein said variant Fc region comprises at least one amino acid modification relative to a wild-type Fc region (or the parental Fc region), such that said molecule has an altered affinity for an Fc receptor (e.g., an FcγR), provided that said variant Fc region does not have a substitution at positions that make a direct contact with Fc receptor based on crystallographic and structural analysis of Fc-Fc receptor interactions such as those disclosed by Sondermann et al., *Nature*, 406:267-273 (2000). Examples of positions within the Fc region that make a direct contact with an Fc receptor such as an FcγR, include amino acids 234-239 (hinge region), amino acids 265-269 (B/C loop), amino acids 297-299 (C7E loop), and amino acids 327-332 (F/G) loop.

[0227] In some embodiments, an anti-CD3 antibody of the present technology has an altered affinity for activating and/or inhibitory receptors, having a variant Fc region with one or more amino acid modifications, wherein said one or more amino acid modification is a N297 substitution with alanine, or a K322 substitution with alanine.

Glycosylation Modifications

[0228] In some embodiments, anti-CD3 antibodies of the present technology have an Fc region with variant glycosylation as compared to a parent Fc region. In some embodiments, variant glycosylation includes the absence of fucose; in some embodiments, variant glycosylation results from expression in GnT1-deficient CHO cells.

[0229] In some embodiments, the antibodies of the present technology, may have a modified glycosylation site relative to an appropriate reference antibody that binds to an antigen of interest (e.g., CD3), without altering the functionality of the antibody, e.g., binding activity to the antigen. As used herein, "glycosylation sites" include any specific amino acid sequence in an antibody to which an oligosaccharide (i.e., carbohydrates containing two or more simple sugars linked together) will specifically and covalently attach.

[0230] Oligosaccharide side chains are typically linked to the backbone of an antibody via either N-or O-linkages. N-linked glycosylation refers to the attachment of an oligosaccharide moiety to the side chain of an asparagine residue. O-linked glycosylation refers to the attachment of an oligosaccharide moiety to a hydroxyamino acid, e.g., serine, threonine. For example, an Fc-glycoform (hCD3-IgGln) that lacks certain oligosaccharides including fucose and terminal N- acetylglucosamine may be produced in special CHO cells and exhibit enhanced ADCC effector function.

[0231] In some embodiments, the carbohydrate content of an immunoglobulin-related composition disclosed herein is modified by adding or deleting a glycosylation site. Methods for modifying the carbohydrate content of antibodies are well known in the art and are included within the present technology, see, e.g., U.S. Pat. No. 6,218,149; EP 0359096B1; U.S. Pat. Publication No. US 2002/0028486; International Patent Application Publication WO 03/035835; U.S. Pat. Publication No. 2003/0115614; U.S. Pat. No. 6,218,149; U.S. Pat. No. 6,472,511; all of which are incorporated herein by reference in their entirety. In some

embodiments, the carbohydrate content of an antibody (or relevant portion or component thereof) is modified by deleting one or more endogenous carbohydrate moieties of the antibody. In some certain embodiments, the present technology includes deleting the glycosylation site of the Fc region of an antibody, by modifying position 297 from asparagine to alanine.

[0232] Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function. Engineered glycoforms may be generated by any method known to one skilled in the art, for example by using engineered or variant expression strains, by co-expression with one or more enzymes, for example N-acetylglucosaminyltransferase III (GnTIII), by expressing a molecule comprising an Fc region in various organisms or cell lines from various organisms, or by modifying carbohydrate(s) after the molecule comprising Fc region has been expressed. Methods for generating engineered glycoforms are known in the art, and include but are not limited to those described in Umana et al., 1999, *Nat. Biotechnol.* 17: 176-180; Davies et al., 2001, *Biotechnol. Bioeng.* 74:288-294; Shields et al., 2002, *J. Biol. Chem.* 277:26733-26740; Shinkawa et al., 2003, *J. Biol. Chem.* 278:3466-3473; U.S. Pat. No. 6,602,684; U.S. Pat. Application Serial No. 10/277,370; U.S. Pat. Application Serial No. 10/113,929; International Patent Application Publications WO 00/61739A1 ; WO 01/292246A1; WO 02/311140A1; WO 02/30954A1; POTILLEGENT™ technology (Biowa, Inc. Princeton, N.J.); GLYCOMAB™ glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland); each of which is incorporated herein by reference in its entirety. See, e.g., International Patent Application Publication WO 00/061739; U.S. Pat. Application Publication No. 2003/0115614; Okazaki et al., 2004, *JMB*, 336: 1239-49.

Fusion Proteins

[0233] In one embodiment, the anti-CD3 antibody of the present technology is a fusion protein. The anti-CD3 antibodies of the present technology, when fused to a second protein, can be used as an antigenic tag. Examples of domains that can be fused to polypeptides include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but can occur through linker sequences. Moreover, fusion proteins of the present technology can also be engineered to improve characteristics of the anti-CD3 antibodies. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of the anti-CD3 antibody to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties can be added to an anti-CD3 antibody to facilitate purification. Such regions can be removed prior to final preparation of the anti-CD3 antibody. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art. The anti-CD3 antibody of the present technology can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In select embodiments, the marker amino acid sequence is a hexa-histidine peptide (SEQ ID NO: 152), such as the tag provided in a pQE vector (QIAGEN, Inc., Chatsworth, Calif), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86: 821-824, 1989, for instance, hexa-histidine (SEQ ID NO: 152) provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. Wilson et al., *Cell* 37: 767, 1984.

[0234] Thus, any of these above fusion proteins can be engineered using the polynucleotides or the polypeptides of the present technology. Also, in some embodiments, the fusion proteins described herein show an increased half-life in vivo.

[0235] Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can be more efficient in binding and neutralizing other molecules compared to the monomeric secreted protein or protein fragment alone. Fountoulakis et al., *J. Biochem.* 270: 3958-3964, 1995.

[0236] Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or a fragment thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, e.g., improved pharmacokinetic properties. See EP-A 0232 262. Alternatively, deleting or modifying the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion can hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, e.g., human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. Bennett et al., *J. Molecular Recognition* 8: 52-58, 1995; Johanson et al., *J. Biol. Chem.*, 270: 9459-9471, 1995.

[0237] Labeled Anti-CD3 antibodies. In one embodiment, the anti-CD3 antibody of the present technology is coupled with a label moiety, i.e., detectable group. The particular label or detectable group conjugated to the anti-CD3 antibody is not a critical aspect of the technology, so long as it does not significantly interfere with the specific binding of the anti-CD3 antibody of the present technology to the CD3 protein. The detectable group can be any material having a detectable physical or chemical property. Such detectable labels have been well-developed in the field of immunoassays and imaging. In general, almost any label useful in such methods can be applied to the present technology. Thus, a label is any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Labels useful in the practice of the present technology include magnetic beads (e.g., Dynabeads™), fluorescent dyes (e.g., fluorescein isothiocyanate, Texas red, rhodamine, and the like), radiolabels (e.g., ^{3}H, ^{14}C, ^{35}S, ^{125}I, $^{121}1$, ^{131}I, ^{112}In, ^{99}mTc), other imaging agents such as microbubbles (for ultrasound imaging), ^{18}F, ^{11}C, ^{15}O, ^{89}Zr (for Positron emission tomography), ^{99m}TC, ^{111}In (for Single photon emission tomography), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and calorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, and the like) beads. Patents that describe the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241, each incorporated herein by reference in their entirety and for all purposes. See also

Handbook of Fluorescent Probes and Research Chemicals (6th Ed., Molecular Probes, Inc., Eugene OR.).

[0238] The label can be coupled directly or indirectly to the desired component of an assay according to methods well known in the art. As indicated above, a wide variety of labels can be used, with the choice of label depending on factors such as required sensitivity, ease of conjugation with the compound, stability requirements, available instrumentation, and disposal provisions.

[0239] Non-radioactive labels are often attached by indirect means. Generally, a ligand molecule (e.g., biotin) is covalently bound to the molecule. The ligand then binds to an anti-ligand (e.g., streptavidin) molecule which is either inherently detectable or covalently bound to a signal system, such as a detectable enzyme, a fluorescent compound, or a chemiluminescent compound. A number of ligands and anti-ligands can be used. Where a ligand has a natural anti-ligand, e.g., biotin, thyroxine, and cortisol, it can be used in conjunction with the labeled, naturally-occurring anti-ligands. Alternatively, any haptenic or antigenic compound can be used in combination with an antibody, e.g., an anti-CD3 antibody.

[0240] The molecules can also be conjugated directly to signal generating compounds, e.g., by conjugation with an enzyme or fluorophore. Enzymes of interest as labels will primarily be hydrolases, particularly phosphatases, esterases and glycosidases, or oxidoreductases, particularly peroxidases. Fluorescent compounds useful as labeling moieties, include, but are not limited to, e.g., fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, and the like. Chemiluminescent compounds useful as labeling moieties, include, but are not limited to, e.g., luciferin, and 2,3-dihydrophthalazinediones, e.g., luminol. For a review of various labeling or signal-producing systems which can be used, see U.S. Pat. No. 4,391,904.

[0241] Means of detecting labels are well known to those of skill in the art. Thus, for example, where the label is a radioactive label, means for detection include a scintillation counter or photographic film as in autoradiography. Where the label is a fluorescent label, it can be detected by exciting the fluorochrome with the appropriate wavelength of light and detecting the resulting fluorescence. The fluorescence can be detected visually, by means of photographic film, by the use of electronic detectors such as charge coupled devices (CCDs) or photomultipliers and the like. Similarly, enzymatic labels can be detected by providing the appropriate substrates for the enzyme and detecting the resulting reaction product. Finally, simple colorimetric labels can be detected simply by observing the color associated with the label. Thus, in various dipstick assays, conjugated gold often appears pink, while various conjugated beads appear the color of the bead.

[0242] Some assay formats do not require the use of labeled components. For instance, agglutination assays can be used to detect the presence of the target antibodies, e.g., the anti-CD3 antibodies. In this case, antigen-coated particles are agglutinated by samples comprising the target antibodies. In this format, none of the components need be labeled and the presence of the target antibody is detected by simple visual inspection.

B. Identifying and Characterizing the Anti-CD3 Antibodies of the Present Technology

Methods for Identifying and/or Screening the Anti-CD3 Antibodies of the Present Technology

[0243] Methods useful to identify and screen antibodies against CD3 polypeptides for those that possess the desired specificity to CD3 protein (e.g., those that bind to the extracellular domain of CD3 protein, in particular, a CDSε subunit comprising three discontinuous regions: residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the βC strand), and residues 46ε and 48ε (the C′-D loop) include any immunologically-mediated techniques known within the art. Components of an immune response can be detected in vitro by various methods that are well known to those of ordinary skill in the art. For example, (1) cytotoxic T lymphocytes can be incubated with radioactively labeled target cells and the lysis of these target cells detected by the release of radioactivity; (2) helper T lymphocytes can be incubated with antigens and antigen presenting cells and the synthesis and secretion of cytokines measured by standard methods (Windhagen A et al., *Immunity*, 2: 373-80, 1995); (3) antigen presenting cells can be incubated with whole protein antigen and the presentation of that antigen on MHC detected by either T lymphocyte activation assays or biophysical methods (Harding et al., *Proc. Natl. Acad. Sci.*, 86: 4230-4, 1989); (4) mast cells can be incubated with reagents that cross-link their Fc-epsilon receptors and histamine release measured by enzyme immunoassay (Siraganian et al., *TIPS*, 4: 432-437, 1983); and (5) enzyme-linked immunosorbent assay (ELISA).

[0244] Similarly, products of an immune response in either a model organism (e.g., mouse) or a human subject can also be detected by various methods that are well known to those of ordinary skill in the art. For example, (1) the production of antibodies in response to vaccination can be readily detected by standard methods currently used in clinical laboratories, e.g., an ELISA; (2) the migration of immune cells to sites of inflammation can be detected by scratching the surface of skin and placing a sterile container to capture the migrating cells over scratch site (Peters et al., *Blood*, 72: 1310-5, 1988); (3) the proliferation of peripheral blood mononuclear cells (PBMCs) in response to mitogens or mixed lymphocyte reaction can be measured using ^{3}H-thymidine; (4) the phagocytic capacity of granulocytes, macrophages, and other phagocytes in PBMCs can be measured by placing PBMCs in wells together with labeled particles (Peters et al., *Blood*, 72: 1310-5, 1988); and (5) the differentiation of immune system cells can be measured by labeling PBMCs with antibodies to CD molecules such as CD4 and CD8 and measuring the fraction of the PBMCs expressing these markers.

[0245] In one embodiment, anti-CD3 antibodies of the present technology are selected using display of CD3 peptides on the surface of replicable genetic packages. See, e.g., U.S. Pat. Nos. 5,514,548; 5,837,500; 5,871,907; 5,885,793; 5,969,108; 6,225,447; 6,291,650; 6,492,160; EP 585 287; EP 605522; EP 616640; EP 1024191; EP 589 877; EP 774 511; EP 844 306. Methods useful for producing/selecting a filamentous bacteriophage particle containing a phagemid genome encoding for a binding molecule with a desired specificity has been described. See, e.g., EP 774 511; US

5871907; US 5969108; US 6225447; US 6291650; US 6492160.

[0246] In some embodiments, anti-CD3 antibodies of the present technology are selected using display of CD3 peptides on the surface of a yeast host cell. Methods useful for the isolation of scFv polypeptides by yeast surface display have been described by Kieke et al., *Protein Eng.* 1997 Nov; 10(11): 1303-10.

[0247] In some embodiments, anti-CD3 antibodies of the present technology are selected using ribosome display. Methods useful for identifying ligands in peptide libraries using ribosome display have been described by Mattheakis et al., *Proc. Natl. Acad. Sci. USA* 91: 9022-26, 1994; and Hanes et al., *Proc. Natl. Acad. Sci. USA* 94: 4937-42, 1997.

[0248] In certain embodiments, anti-CD3 antibodies of the present technology are selected using tRNA display of CD3 peptides. Methods useful for in vitro selection of ligands using tRNA display have been described by Merryman et al., *Chem. Biol.*, 9: 741-46, 2002.

[0249] In one embodiment, anti-CD3 antibodies of the present technology are selected using RNA display. Methods useful for selecting peptides and proteins using RNA display libraries have been described by Roberts et al. *Proc. Natl. Acad. Sci. USA*, 94: 12297-302, 1997; and Nemoto et al., *FEBS Lett.*, 414: 405-8, 1997. Methods useful for selecting peptides and proteins using unnatural RNA display libraries have been described by Frankel et al., *Curr. Opin. Struct. Biol.*, 13: 506-12, 2003.

[0250] In some embodiments, anti-CD3 antibodies of the present technology are expressed in the periplasm of gram negative bacteria and mixed with labeled CD3 protein. See WO 02/34886. In clones expressing recombinant polypeptides with affinity for CD3 protein, the concentration of the labeled CD3 protein bound to the anti-CD3 antibodies is increased and allows the cells to be isolated from the rest of the library as described in Harvey et al., *Proc. Natl. Acad. Sci.* 22: 9193-98 2004 and U.S. Pat. Publication No. 2004/0058403.

[0251] After selection of the desired anti-CD3 antibodies, it is contemplated that said antibodies can be produced in large volume by any technique known to those skilled in the art, e.g., prokaryotic or eukaryotic cell expression and the like. The anti-CD3 antibodies which are, e.g., but not limited to, anti-CD3 hybrid antibodies or fragments can be produced by using conventional techniques to construct an expression vector that encodes an antibody heavy chain in which the CDRs and, if necessary, a minimal portion of the variable region framework, that are required to retain original species antibody binding specificity (as engineered according to the techniques described herein) are derived from the originating species antibody and the remainder of the antibody is derived from a target species immunoglobulin which can be manipulated as described herein, thereby producing a vector for the expression of a hybrid antibody heavy chain.

[0252] Measurement of CD3 Binding. In some embodiments, a CD3 binding assay refers to an assay format wherein CD3 protein and an anti-CD3 antibody are mixed under conditions suitable for binding between the CD3 protein and the anti-CD3 antibody and assessing the amount of binding between the CD3 protein and the anti-CD3 antibody. The amount of binding is compared with a suitable control, which can be the amount of binding in the absence of the CD3 protein, the amount of the binding in the presence of a non-specific immunoglobulin composition, or both. The amount of binding can be assessed by any suitable method. Binding assay methods include, e.g., ELISA, radioimmunoassays, scintillation proximity assays, fluorescence energy transfer assays, liquid chromatography, membrane filtration assays, and the like. Biophysical assays for the direct measurement of CD3 protein binding to anti-CD3 antibody are, e.g., nuclear magnetic resonance, fluorescence, fluorescence polarization, surface plasmon resonance (BIACORE chips) and the like. Specific binding is determined by standard assays known in the art, e.g., radioligand binding assays, ELISA, FRET, immunoprecipitation, SPR, NMR (2D-NMR), mass spectroscopy and the like. If the specific binding of a candidate anti-CD3 antibody is at least 1 percent greater than the binding observed in the absence of the candidate anti-CD3 antibody, the candidate anti-CD3 antibody is useful as an anti-CD3 antibody of the present technology.

Uses of the Anti-CD3 Antibodies of the Present Technology

[0253] General. The anti-CD3 antibodies of the present technology are useful in methods known in the art relating to the localization and/or quantitation of CD3 protein (e.g., for use in measuring levels of the CD3 protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the polypeptide, and the like). Antibodies of the present technology are useful to isolate a CD3 protein by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-CD3 antibody of the present technology can facilitate the purification of natural immunoreactive CD3 proteins from biological samples, e.g., mammalian sera or cells as well as recombinantly-produced immunoreactive CD3 proteins expressed in a host system. Moreover, anti-CD3 antibodies can be used to detect an immunoreactive CD3 protein (e.g., in plasma, a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the immunoreactive polypeptide. The anti-CD3 antibodies of the present technology can be used diagnostically to monitor immunoreactive CD3 protein levels in tissue as part of a clinical testing procedure, e.g., to determine the efficacy of a given treatment regimen. As noted above, the detection can be facilitated by coupling (i.e., physically linking) the anti-CD3 antibodies of the present technology to a detectable substance.

[0254] Detection of CD3 protein. An exemplary method for detecting the presence or absence of an immunoreactive CD3 protein in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with an anti-CD3 antibody of the present technology capable of detecting an immunoreactive CD3 protein such that the presence of an immunoreactive CD3 protein is detected in the biological sample. Detection may be accomplished by means of a detectable label attached to the antibody.

[0255] The term "labeled" with regard to the anti-CD3 antibody is intended to encompass direct labeling of the antibody by coupling (i.e., physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reactivity with another compound that is directly labeled, such as a secondary antibody. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-

labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin.

[0256] In some embodiments, the anti-CD3 antibodies disclosed herein are conjugated to one or more detectable labels. For such uses, anti-CD3 antibodies may be detectably labeled by covalent or non-covalent attachment of a chromogenic, enzymatic, radioisotopic, isotopic, fluorescent, toxic, chemiluminescent, nuclear magnetic resonance contrast agent or other label.

[0257] Examples of suitable chromogenic labels include diaminobenzidine and 4-hydroxyazo-benzene-2-carboxylic acid. Examples of suitable enzyme labels include malate dehydrogenase, staphylococcal nuclease, Δ-5-steroid isomerase, yeast-alcohol dehydrogenase, α-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, β-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

[0258] Examples of suitable radioisotopic labels include ^{3}H, ^{111}In, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{57}To , ^{58}Co, ^{59}Fe, ^{75}Se, ^{152}Eu, ^{90}Y, ^{67}Cu , ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{109}Pd, etc. ^{111}In is an exemplary isotope where in vivo imaging is used since its avoids the problem of dehalogenation of the ^{125}I or ^{131}I-labeled CD3-binding antibodies by the liver. In addition, this isotope has a more favorable gamma emission energy for imaging (Perkins et al, *Eur. J. Nucl. Med.* 70:296-301 (1985); Carasquillo et al., *J. Nucl. Med.* 25:281-287 (1987)). For example, ^{111}In coupled to monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA exhibits little uptake in non-tumorous tissues, particularly the liver, and enhances specificity of tumor localization (Esteban et al., *J. Nucl. Med.* 28:861-870 (1987)). Examples of suitable non-radioactive isotopic labels include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Tr, and ^{56}Fe.

[0259] Examples of suitable fluorescent labels include an ^{152}Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, a Green Fluorescent Protein (GFP) label, an o-phthaldehyde label, and a fluorescamine label. Examples of suitable toxin labels include diphtheria toxin, ricin, and cholera toxin.

[0260] Examples of chemiluminescent labels include a luminol label, an isoluminol label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label. Examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

[0261] The detection method of the present technology can be used to detect an immunoreactive CD3 protein in a biological sample in vitro as well as in vivo. In vitro techniques for detection of an immunoreactive CD3 protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, radioimmunoassay, and immunofluorescence. Furthermore, in vivo techniques for detection of an immunoreactive CD3 protein include introducing into a subject a labeled anti-CD3 antibody. For example, the anti-CD3 antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques. In one embodiment, the biological sample contains CD3 protein molecules from the test subj ect.

Immunoassay and Imaging

[0262] An anti-CD3 antibody of the present technology can be used to assay immunoreactive CD3 protein levels in a biological sample (e.g., human plasma) using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. Jalkanen, M. et al., *J. Cell. Biol.* 101: 976-985, 1985; Jalkanen, M. et al., *J. Cell. Biol.* 105: 3087-3096, 1987. Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes or other radioactive agent, such as iodine (^{125}I, ^{121}I, ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99}mTc), and fluorescent labels, such as fluorescein, rhodamine, and green fluorescent protein (GFP), as well as biotin.

[0263] In addition to assaying immunoreactive CD3 protein levels in a biological sample, anti-CD3 antibodies of the present technology may be used for in vivo imaging of CD3. Antibodies useful for this method include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which can be incorporated into the anti-CD3 antibodies by labeling of nutrients for the relevant scFv clone.

[0264] An anti-CD3 antibody which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (e.g., ^{131}I, ^{112}In, ^{99}mTc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (e.g., parenterally, subcutaneously, or intraperitoneally) into the subject. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99}mTc. The labeled anti-CD3 antibody will then accumulate at the location of cells which contain the specific target polypeptide. For example, labeled anti-CD3 antibodies of the present technology will accumulate within the subject in cells and tissues in which the CD3 protein has localized.

[0265] Thus, the present technology provides a diagnostic method of a medical condition, which involves: (a) assaying the expression of immunoreactive CD3 protein by measuring binding of an anti-CD3 antibody of the present technology in cells or body fluid of an individual; (b) comparing the amount of immunoreactive CD3 protein present in the sample with a standard reference, wherein an increase or decrease in immunoreactive CD3 protein levels compared to the standard is indicative of a medical condition.

Affinity Purification

[0266] The anti-CD3 antibodies of the present technology may be used to purify immunoreactive CD3 protein from a sample. In some embodiments, the antibodies are immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and

such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10 (1986); Jacoby et al., *Meth. Enzym.* 34 Academic Press, N.Y. (1974)).

[0267] The simplest method to bind the antigen to the antibody-support matrix is to collect the beads in a column and pass the antigen solution down the column. The efficiency of this method depends on the contact time between the immobilized antibody and the antigen, which can be extended by using low flow rates. The immobilized antibody captures the antigen as it flows past. Alternatively, an antigen can be contacted with the antibody-support matrix by mixing the antigen solution with the support (e.g., beads) and rotating or rocking the slurry, allowing maximum contact between the antigen and the immobilized antibody. After the binding reaction has been completed, the slurry is passed into a column for collection of the beads. The beads are washed using a suitable washing buffer and then the pure or substantially pure antigen is eluted.

[0268] An antibody or polypeptide of interest can be conjugated to a solid support, such as a bead. In addition, a first solid support such as a bead can also be conjugated, if desired, to a second solid support, which can be a second bead or other support, by any suitable means, including those disclosed herein for conjugation of a polypeptide to a support. Accordingly, any of the conjugation methods and means disclosed herein with reference to conjugation of a polypeptide to a solid support can also be applied for conjugation of a first support to a second support, where the first and second solid support can be the same or different.

[0269] Appropriate linkers, which can be cross-linking agents, for use for conjugating a polypeptide to a solid support include a variety of agents that can react with a functional group present on a surface of the support, or with the polypeptide, or both. Reagents useful as cross-linking agents include homo-bi-functional and, in particular, hetero-bi-functional reagents. Useful bi-functional cross-linking agents include, but are not limited to, N-SIAB, dimaleimide, DTNB, N-SATA, N-SPDP, SMCC and 6-HYNIC. A cross-linking agent can be selected to provide a selectively cleavable bond between a polypeptide and the solid support. For example, a photolabile cross-linker, such as 3-amino-(2-nitrophenyl)propionic acid can be employed as a means for cleaving a polypeptide from a solid support. (Brown et al., *Mol. Divers*, pp, 4-12 (1995); Rothschild et al., *Nucl. Acids Res.*, 24:351-66 (1996); and US. Pat. No. 5,643,722). Other cross-linking reagents are well-known in the art. (See, e.g., Wong (1991), *supra*; and Hermanson (1996), *supra*).

[0270] An antibody or polypeptide can be immobilized on a solid support, such as a bead, through a covalent amide bond formed between a carboxyl group functionalized bead and the amino terminus of the polypeptide or, conversely, through a covalent amide bond formed between an amino group functionalized bead and the carboxyl terminus of the polypeptide. In addition, a bi-functional trityl linker can be attached to the support, e.g., to the 4-nitrophenyl active ester on a resin, such as a Wang resin, through an amino group or a carboxyl group on the resin via an amino resin. Using a bi-functional trityl approach, the solid support can require treatment with a volatile acid, such as formic acid or trifluoroacetic acid to ensure that the polypeptide is cleaved and can be removed. In such a case, the polypeptide can be deposited as a beadless patch at the bottom of a well of a solid support or on the flat surface of a solid support. After addition of a matrix solution, the polypeptide can be desorbed into a MS.

[0271] Hydrophobic trityl linkers can also be exploited as acid-labile linkers by using a volatile acid or an appropriate matrix solution, e.g., a matrix solution containing 3-HPA, to cleave an amino linked trityl group from the polypeptide. Acid lability can also be changed. For example, trityl, monomethoxytrityl, dimethoxytrityl or trimethoxytrityl can be changed to the appropriate p-substituted, or more acid-labile tritylamine derivatives, of the polypeptide, i.e., trityl ether and tritylamine bonds can be made to the polypeptide. Accordingly, a polypeptide can be removed from a hydrophobic linker, e.g., by disrupting the hydrophobic attraction or by cleaving tritylether or tritylamine bonds under acidic conditions, including, if desired, under typical MS conditions, where a matrix, such as 3-HPA acts as an acid.

[0272] Orthogonally cleavable linkers can also be useful for binding a first solid support, e.g., a bead to a second solid support, or for binding a polypeptide of interest to a solid support. Using such linkers, a first solid support, e.g., a bead, can be selectively cleaved from a second solid support, without cleaving the polypeptide from the support; the polypeptide then can be cleaved from the bead at a later time. For example, a disulfide linker, which can be cleaved using a reducing agent, such as DTT, can be employed to bind a bead to a second solid support, and an acid cleavable bi-functional trityl group could be used to immobilize a polypeptide to the support. As desired, the linkage of the polypeptide to the solid support can be cleaved first, e.g., leaving the linkage between the first and second support intact. Trityl linkers can provide a covalent or hydrophobic conjugation and, regardless of the nature of the conjugation, the trityl group is readily cleaved in acidic conditions.

[0273] For example, a bead can be bound to a second support through a linking group which can be selected to have a length and a chemical nature such that high density binding of the beads to the solid support, or high density binding of the polypeptides to the beads, is promoted. Such a linking group can have, e.g., "tree-like" structure, thereby providing a multiplicity of functional groups per attachment site on a solid support. Examples of such linking group; include polylysine, polyglutamic acid, penta-erythrole and tris-hydroxyaminomethane.

Noncovalent Binding Association

[0274] An antibody or polypeptide can be conjugated to a solid support, or a first solid support can also be conjugated to a second solid support, through a noncovalent interaction. For example, a magnetic bead made of a ferromagnetic material, which is capable of being magnetized, can be attracted to a magnetic solid support, and can be released from the support by removal of the magnetic field. Alternatively, the solid support can be provided with an ionic or hydrophobic moiety, which can allow the interaction of an ionic or hydrophobic moiety, respectively, with a polypeptide, e.g., a polypeptide containing an attached trityl group or with a second solid support having hydrophobic character.

[0275] A solid support can also be provided with a member of a specific binding pair and, therefore, can be conju-

gated to a polypeptide or a second solid support containing a complementary binding moiety. For example, a bead coated with avidin or with streptavidin can be bound to a polypeptide having a biotin moiety incorporated therein, or to a second solid support coated with biotin or derivative of biotin, such as iminobiotin.

[0276] It should be recognized that any of the binding members disclosed herein or otherwise known in the art can be reversed. Thus, biotin, e.g., can be incorporated into either a polypeptide or a solid support and, conversely, avidin or other biotin binding moiety would be incorporated into the support or the polypeptide, respectively. Other specific binding pairs contemplated for use herein include, but are not limited to, hormones and their receptors, enzyme, and their substrates, a nucleotide sequence and its complementary sequence, an antibody and the antigen to which it interacts specifically, and other such pairs knows to those skilled in the art.

A. Diagnostic Uses of Anti-CD3 Antibodies of the Present Technology

General

[0277] The anti-CD3 antibodies of the present technology are useful in diagnostic methods. As such, the present technology provides methods using the antibodies in the diagnosis of CD3 activity in a subject. Anti-CD3 antibodies of the present technology may be selected such that they have any level of epitope binding specificity and very high binding affinity to a CD3 protein. In general, the higher the binding affinity of an antibody the more stringent wash conditions can be performed in an immunoassay to remove nonspecifically bound material without removing target polypeptide. Accordingly, anti-CD3 antibodies of the present technology useful in diagnostic assays usually have binding affinities of about 10^8 M^{-1}, 10^9 M^{-1}, 10^{10} M^{-1}, 10^{11} M^{-1} or 10^{12} M^{-1}. Further, it is desirable that anti-CD3 antibodies used as diagnostic reagents have a sufficient kinetic on-rate to reach equilibrium under standard conditions in at least 12 h, at least five (5) h, or at least one (1) hour.

[0278] Anti-CD3 antibodies can be used to detect an immunoreactive CD3 protein in a variety of standard assay formats. Such formats include immunoprecipitation, Western blotting, ELISA, radioimmunoassay, and immunometric assays. See Harlow & Lane, *Antibodies, A Laboratory Manual* (Cold Spring Harbor Publications, New York, 1988); U.S. Pat. Nos. 3,791,932; 3,839,153; 3,850,752; 3,879,262; 4,034,074, 3,791,932; 3,817,837; 3,839,153; 3,850,752; 3,850,578; 3,853,987; 3,867,517; 3,879,262; 3,901,654; 3,935,074; 3,984,533; 3,996,345; 4,034,074; and 4,098,876. Biological samples can be obtained from any tissue or body fluid of a subject. In certain embodiments, the subject is at an early stage of cancer. In one embodiment, the early stage of cancer is determined by the level or expression pattern of CD3 protein in a sample obtained from the subject. In certain embodiments, the sample is selected from the group consisting of urine, blood, serum, plasma, saliva, amniotic fluid, cerebrospinal fluid (CSF), and biopsied body tissue.

[0279] Immunometric or sandwich assays are one format for the diagnostic methods of the present technology. See U.S. Pat. No. 4,376,110, 4,486,530, 5,914,241, and 5,965,375. Such assays use one antibody, e.g., an anti-CD3 antibody or a population of anti-CD3 antibodies immobilized to a solid phase, and another anti-CD3 antibody or a population of anti-CD3 antibodies in solution. Typically, the solution anti-CD3 antibody or population of anti-CD3 antibodies is labeled. If an antibody population is used, the population can contain antibodies binding to different epitope specificities within the target polypeptide. Accordingly, the same population can be used for both solid phase and solution antibody. If anti-CD3 monoclonal antibodies are used, first and second CD3 monoclonal antibodies having different binding specificities are used for the solid and solution phase. Solid phase (also referred to as "capture") and solution (also referred to as "detection") antibodies can be contacted with target antigen in either order or simultaneously. If the solid phase antibody is contacted first, the assay is referred to as being a forward assay. Conversely, if the solution antibody is contacted first, the assay is referred to as being a reverse assay. If the target is contacted with both antibodies simultaneously, the assay is referred to as a simultaneous assay. After contacting the CD3 protein with the anti-CD3 antibody, a sample is incubated for a period that usually varies from about 10 min to about 24 hr and is usually about 1 hr. A wash step is then performed to remove components of the sample not specifically bound to the anti-CD3 antibody being used as a diagnostic reagent. When solid phase and solution antibodies are bound in separate steps, a wash can be performed after either or both binding steps. After washing, binding is quantified, typically by detecting a label linked to the solid phase through binding of labeled solution antibody. Usually for a given pair of antibodies or populations of antibodies and given reaction conditions, a calibration curve is prepared from samples containing known concentrations of target antigen. Concentrations of the immunoreactive CD3 protein in samples being tested are then read by interpolation from the calibration curve (i.e., standard curve). Analyte can be measured either from the amount of labeled solution antibody bound at equilibrium or by kinetic measurements of bound labeled solution antibody at a series of time points before equilibrium is reached. The slope of such a curve is a measure of the concentration of the CD3 protein in a sample.

[0280] Suitable supports for use in the above methods include, e.g., nitrocellulose membranes, nylon membranes, and derivatized nylon membranes, and also particles, such as agarose, a dextran-based gel, dipsticks, particulates, microspheres, magnetic particles, test tubes, microtiter wells, SEPHADEX™ (Amersham Pharmacia Biotech, Piscataway N.J.), and the like. Immobilization can be by absorption or by covalent attachment. Optionally, anti-CD3 antibodies can be joined to a linker molecule, such as biotin for attachment to a surface bound linker, such as avidin.

[0281] In some embodiments, the present disclosure provides an anti-CD3 antibody of the present technology conjugated to a diagnostic agent. The diagnostic agent may comprise a radioactive or non-radioactive label, a contrast agent (such as for magnetic resonance imaging, computed tomography or ultrasound), and the radioactive label can be a gamma-, beta-, alpha-, Auger electron-, or positron-emitting isotope. A diagnostic agent is a molecule which is administered conjugated to an antibody moiety, i.e., antibody or antibody fragment, or subfragment, and is useful

in diagnosing or detecting a disease by locating the cells containing the antigen.

[0282] Useful diagnostic agents include, but are not limited to, radioisotopes, dyes (such as with the biotin-streptavidin complex), contrast agents, fluorescent compounds or molecules and enhancing agents (e.g., paramagnetic ions) for magnetic resonance imaging (MRI). U.S. Pat. No. 6,331,175 describes MRI technique and the preparation of antibodies conjugated to a MRI enhancing agent and is incorporated in its entirety by reference. In some embodiments, the diagnostic agents are selected from the group consisting of radioisotopes, enhancing agents for use in magnetic resonance imaging, and fluorescent compounds. In order to load an antibody component with radioactive metals or paramagnetic ions, it may be necessary to react it with a reagent having a long tail to which are attached a multiplicity of chelating groups for binding the ions. Such a tail can be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which can be bound chelating groups such as, e.g., ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups known to be useful for this purpose. Chelates may be coupled to the antibodies of the present technology using standard chemistries. The chelate is normally linked to the antibody by a group which enables formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking. Other methods and reagents for conjugating chelates to antibodies are disclosed in U.S. Pat. No. 4,824,659. Particularly useful metal-chelate combinations include 2-benzyl-DTPA and its monomethyl and cyclohexyl analogs, used with diagnostic isotopes for radio-imaging. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MRI, when used along with the CD3 antibodies of the present technology.

[0283] Macrocyclic chelates such as NOTA (1,4,7-triazacyclononane-N,N′,N″-triacetic acid), DOTA, and TETA (p-bromoacetamido-benzyl-tetraethylaminetetraacetic acid) are of use with a variety of metals and radiometals, such as radionuclides of gallium, yttrium and copper, respectively. Such metal-chelate complexes can be stabilized by tailoring the ring size to the metal of interest. Examples of other DOTA chelates include (i) DOTA-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-NH_2; (ii) Ac-Lys(HSG)D-Tyr-Lys(HSG)-Lys(Tscg-Cys)-NH_2; (iii) DOTA-D-Asp-D-Lys(HSG)-D-Asp-D-Lys(HSG)-NH_2; (iv) DOTA-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (v) DOTA-D-Tyr-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (vi) DOTA-D-Ala-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (vii) DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH_2; (viii) Ac-D-Phe-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-NH_2; (ix) Ac-D-Phe-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2; (x) Ac-D-Phe-D-Lys(Bz-DTPA)-D-Tyr-D-Lys(Bz-DTPA)-NH_2; (xi) Ac-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2; (xii) DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2; (xiii) (Tscg-Cys)-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(DOTA)-NH_2; (xiv) Tscg-D-Cys-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (xv) (Tscg-Cys)-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (xvi) Ac-D-Cys-D-Lys(DOTA)-D-Tyr-D-Ala-D-Lys(DOTA)-D-Cys-NH_2; (xvii) Ac-D-Cys-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2; (xviii) Ac-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-D-Lys(Tscg-Cys)-NH_2; and (xix) Ac-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-D-Lys(Tscg-Cys)-NH_2.

[0284] Other ring-type chelates such as macrocyclic polyethers, which are of interest for stably binding nuclides, such as ^{223}Ra for RAIT are also contemplated.

B. Therapeutic Use of Anti-CD3 Antibodies of the Present Technology

[0285] In one aspect, the immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof) of the present technology are useful for the treatment of solid tumors or liquid tumors. Non-limiting examples of suitable solid or liquid tumors include adrenal cancers, bladder cancers, blood cancers, bone cancers, brain cancers, breast cancers, carcinoma, cervical cancers, colon cancers, colorectal cancers, corpus uterine cancers, ear, nose and throat (ENT) cancers, endometrial cancers, esophageal cancers, gastrointestinal cancers, head and neck cancers, Hodgkin's disease, intestinal cancers, kidney cancers, larynx cancers, acute and chronic leukemias, liver cancers, lymph node cancers, lymphomas, lung cancers, melanomas, mesothelioma, myelomas, nasopharynx cancers, neuroblastomas, non-Hodgkin's lymphoma, oral cancers, ovarian cancers, pancreatic cancers, penile cancers, pharynx cancers, prostate cancers, rectal cancers, sarcoma, seminomas, skin cancers, stomach cancers, teratomas, testicular cancers, thyroid cancers, uterine cancers, vaginal cancers, vascular tumors, and metastases thereof.

[0286] In one aspect, the immunoglobulin-related compositions (e.g., antibodies or antigen binding fragments thereof) of the present technology are useful for the treatment of CD3-associated pathologies, such as multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus, Celiac disease, Sympathetic ophthalmia, Type 1 diabetes, graft-versus-host disease, precursor T acute lymphoblastic leukemia/lymphoma, anaplastic large-cell lymphoma, lymphomatoid papulosis type A, Mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, Sezary disease, adult T-cell leukemia/lymphoma, cutaneous large T cell lymphoma, pleomorphic T-cell lymphoma, lymphomatoid papulosis type B, secondary cutaneous CD30+ large-cell lymphoma, hepatosplenic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, subcutaneous T-cell lymphoma, large granular lymphocytic leukemia, and acute biphenotypic leukemia. Such treatment can be used in patients identified as having pathologically high levels of the CD3 (e.g., those diagnosed by the methods described herein) or in patients diagnosed with a disease known to be associated with such pathological levels. In one aspect, the present disclosure provides a method for treating a CD3-associated pathology in a subject in need thereof, comprising administering to the subject an effective amount of an antibody (or antigen binding fragment thereof) of the present technology. Examples of CD3-associated pathologies that can be treated by the antibodies of the present technology include, but are not limited to: multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus, Celiac disease, Sympathetic ophthalmia, Type 1 diabetes, graft-versus-host disease, precursor T acute lymphoblastic leukemia/lymphoma, anaplastic large-cell lymphoma, lymphomatoid papulosis

type A, Mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, Sezary disease, adult T-cell leukemia/lymphoma, cutaneous large T cell lymphoma, pleomorphic T-cell lymphoma, lymphomatoid papulosis type B, secondary cutaneous CD30+ large-cell lymphoma, hepatosplenic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, subcutaneous T-cell lymphoma, large granular lymphocytic leukemia, and acute biphenotypic leukemia.

[0287] The compositions of the present technology may be employed in conjunction with other therapeutic agents useful in the treatment of autoimmune diseases or T-cell malignancies. For example, the antibodies of the present technology may be separately, sequentially or simultaneously administered with at least one additional therapeutic agent selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, glucocorticoids, and conventional disease-modifying anti-rheumatic drugs (cDMARDs). Examples of NSAIDs include, but are not limited to, (1) salicylic acid derivatives: acetylsalicylic acid (aspirin), diflunisal and sulfasalazine; (2) para-aminophenol derivatives: acetaminophen; (3) fenamates: mefenamic acid, meclofenamate, flufenamic acid; (4) propionic acid derivatives: ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin; and (5) enolic acid (oxicam) derivatives: piroxicam, tenoxicam.

[0288] Examples of selective COX-2 inhibitors include, but are not limited to, meloxicam, salicylate, nimesulide, celecoxib, ofecoxib, valdecoxib, lumiracoxib, parecoxib, and etoricoxib. Examples of glucocorticoids include, but are not limited to, prednisone/prednisolone, methylprednisolone, and fluorinated glucocorticoids such as dexamethasone and betamethasone. Examples of DMARDS include, but are not limited to, methotrexate, leflunomide, gold compounds, sulfasalazine, azathioprine, cyclophosphamide, antimalarials, d-penicillamine, cyclosporine, hydroxychloroquine, etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol.

[0289] The compositions of the present technology may be employed in conjunction with other therapeutic agents useful in the treatment of CD3-associated cancers. For example, the antibodies of the present technology may be separately, sequentially or simultaneously administered with at least one additional therapeutic agent-selected from the group consisting of alkylating agents, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, bisphosphonate therapy agents and targeted biological therapy agents (e.g., therapeutic peptides described in US 6306832, WO 2012007137, WO 2005000889, WO 2010096603 etc.). In some embodiments, the at least one additional therapeutic agent is a chemotherapeutic agent. Specific chemotherapeutic agents include, but are not limited to, cyclophosphamide, fluorouracil (or 5-fluorouracil or 5-FU), methotrexate, edatrexate (10-ethyl-10-deaza-aminopterin), thiotepa, carboplatin, cisplatin, taxanes, paclitaxel, protein-bound paclitaxel, docetaxel, vinorelbine, tamoxifen, raloxifene, toremifene, fulvestrant, gemcitabine, irinotecan, ixabepilone, temozolmide, topotecan, vincristine, vinblastine, eribulin, mutamycin, capecitabine, anastrozole, exemestane, letrozole, leuprolide, abarelix, buserlin, goserelin, megestrol acetate, risedronate, pamidronate, ibandronate, alendronate, denosumab, zoledronate, trastuzumab, tykerb, anthracyclines (e.g., daunorubicin and doxorubicin), bevacizumab, oxaliplatin, melphalan, etoposide, mechlorethamine, bleomycin, microtubule poisons, annonaceous acetogenins, or combinations thereof.

[0290] The compositions of the present technology may optionally be administered as a single bolus to a subject in need thereof. Alternatively, the dosing regimen may comprise multiple administrations performed at various times after the appearance of tumors.

[0291] Administration can be carried out by any suitable route, including orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intracranially, intratumorally, intrathecally, or topically. Administration includes self-administration and the administration by another. It is also to be appreciated that the various modes of treatment of medical conditions as described are intended to mean "substantial", which includes total but also less than total treatment, and wherein some biologically or medically relevant result is achieved.

[0292] In some embodiments, the antibodies of the present technology comprise pharmaceutical formulations which may be administered to subjects in need thereof in one or more doses. Dosage regimens can be adjusted to provide the desired response (e.g., a therapeutic response).

[0293] Typically, an effective amount of the antibody compositions of the present technology, sufficient for achieving a therapeutic effect, range from about 0.000001 mg per kilogram body weight per day to about 10,000 mg per kilogram body weight per day. Typically, the dosage ranges are from about 0.0001 mg per kilogram body weight per day to about 100 mg per kilogram body weight per day. For administration of anti-CD3 antibodies, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg every week, every two weeks or every three weeks, of the subject body weight. For example, dosages can be 1 mg/kg body weight or 10 mg/kg body weight every week, every two weeks or every three weeks or within the range of 1-10 mg/kg every week, every two weeks or every three weeks. In one embodiment, a single dosage of antibody ranges from 0.1-10,000 micrograms per kg body weight. In one embodiment, antibody concentrations in a carrier range from 0.2 to 2000 micrograms per delivered milliliter. An exemplary treatment regime entails administration once per every two weeks or once a month or once every 3 to 6 months. Anti-CD3 antibodies may be administered on multiple occasions. Intervals between single dosages can be hourly, daily, weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the antibody in the subject. In some methods, dosage is adjusted to achieve a serum antibody concentration in the subject of from about 75 μg/mL to about 125 μg/mL, 100 μg/mL to about 150 μg/mL, from about 125 μg/mL to about 175 μg/mL, or from about 150 μg/mL to about 200 μg/mL. Alternatively, anti-CD3 antibodies can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the antibody in the subject. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at rela-

tively infrequent intervals over a long period of time. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, or until the subject shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

[0294] In another aspect, the present disclosure provides a method for detecting cancer in a subject in vivo comprising (a) administering to the subject an effective amount of an antibody (or antigen binding fragment thereof) of the present technology, wherein the antibody is configured to localize to a cancer cell expressing CD3 and is labeled with a radioisotope; and (b) detecting the presence of a tumor in the subject by detecting radioactive levels emitted by the antibody that are higher than a reference value. In some embodiments, the reference value is expressed as injected dose per gram (%ID/g). The reference value may be calculated by measuring the radioactive levels present in non-tumor (normal) tissues, and computing the average radioactive levels present in non-tumor (normal) tissues ± standard deviation. In some embodiments, the ratio of radioactive levels between a tumor and normal tissue is about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1 or 100:1.

[0295] In some embodiments, the subject is diagnosed with or is suspected of having cancer. Radioactive levels emitted by the antibody may be detected using positron emission tomography or single photon emission computed tomography.

[0296] Additionally or alternatively, in some embodiments, the method further comprises administering to the subject an effective amount of an immunoconjugate comprising an antibody of the present technology conjugated to a radionuclide. In some embodiments, the radionuclide is an alpha particle-emitting isotope, a beta particle-emitting isotope, an Auger-emitter, or any combination thereof. Examples of beta particle-emitting isotopes include ^{86}Y, ^{90}Y, ^{89}Sr, ^{165}Dy, ^{186}Re, ^{188}Re, ^{177}Lu, and ^{67}Cu. Examples of alpha particle-emitting isotopes include ^{213}Bi, ^{211}At, ^{225}Ac, ^{152}Dy, ^{212}Bi, ^{223}Ra, ^{219}Rn, ^{215}Po, ^{211}Bi, ^{221}Fr, ^{217}At, and ^{255}Fm. Examples of Auger-emitters include ^{111}In, ^{67}Ga, ^{51}Cr, ^{58}Co, ^{99m}Tc, ^{103m}Rh, ^{195m}Pt, ^{119}Sb, ^{161}Ho, ^{189m}Os, ^{192}Ir, ^{201}Tl, and ^{203}Pb. In some embodiments of the method, nonspecific FcR-dependent binding in normal tissues is eliminated or reduced (e.g., via N297A mutation in Fc region, which results in aglycosylation). The therapeutic effectiveness of such an immunoconjugate may be determined by computing the area under the curve (AUC) tumor: AUC normal tissue ratio. In some embodiments, the immunoconjugate has a AUC tumor: AUC normal tissue ratio of about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1 or 100:1.

[0297] PRIT. In one aspect, the present disclosure provides a method for detecting tumors in a subject in need thereof comprising (a) administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that binds to the radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex; and (b) detecting the presence of tumors in the subject by detecting radioactive levels emitted by the complex that are higher than a reference value. In some embodiments, the subject is human.

[0298] In one aspect, the present disclosure provides a method for selecting a subject for pretargeted radioimmunotherapy comprising (a) administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that binds to the radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex; (b) detecting radioactive levels emitted by the complex; and (c) selecting the subject for pretargeted radioimmunotherapy when the radioactive levels emitted by the complex are higher than a reference value. In some embodiments, the subject is human.

[0299] Also disclosed herein is a method for selecting a subject for pretargeted radioimmunotherapy comprising (a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of the present technology that binds to a radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment; (c) detecting radioactive levels emitted by the multi-specific antibody; and (d) selecting the subject for pretargeted radioimmunotherapy when the radioactive levels emitted by the multi-specific antibody are higher than a reference value.

[0300] Examples of DOTA haptens include (i) DOTA-Phe-Lys(HSG)-D-Tyr-Lys(HSG)-NH_2; (ii) Ac-Lys(HSG) D-Tyr-Lys(HSG)-Lys(Tscg-Cys)-NH_2; (iii) DOTA-D-Asp-D-Lys(HSG)-D-Asp-D-Lys(HSG)-NH_2; (iv) DOTA-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (v) DOTA-D-Tyr-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (vi) DOTA-D-Ala-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (vii) DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-NH_2; (viii) Ac-D-Phe-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-NH_2; (ix) Ac-D-Phe-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2; (x) Ac-D-Phe-D-Lys(Bz-DTPA)-D-Tyr-D-Lys(Bz-DTPA)-NH_2; (xi) Ac-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2; (xii) DOTA-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(Tscg-Cys)-NH_2; (xiii) (Tscg-Cys)-D-Phe-D-Lys(HSG)-D-Tyr-D-Lys(HSG)-D-Lys(DOTA)-NH_2; (xiv) Tscg-D-Cys-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (xv) (Tscg-Cys)-D-Glu-D-Lys(HSG)-D-Glu-D-Lys(HSG)-NH_2; (xvi) Ac-D-Cys-D-Lys(DOTA)-D-Tyr-D-Ala-D-Lys(DOTA)-D-Cys-NH_2; (xvii) Ac-D-Cys-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-NH_2; (xviii) Ac-D-Lys(DTPA)-D-Tyr-D-Lys(DTPA)-D-Lys(Tscg-Cys)-NH_2; (xix) Ac-D-Lys(DOTA)-D-Tyr-D-Lys(DOTA)-D-Lys(Tscg-Cys)-NH_2 and (xx) DOTA. The radiolabel may be an alpha particle-emitting isotope, a beta particle-emitting isotope, or an Auger-emitter. Examples of radiolabels include ^{213}Bi, ^{211}At, ^{225}Ac, ^{152}Dy, ^{212}Bi, ^{223}Ra, ^{219}Rn, ^{215}Po, ^{211}Bi, ^{221}Fr, ^{217}At, ^{255}Fm, ^{86}Y, ^{90}Y, ^{89}Sr, ^{165}Dy, ^{186}Re, ^{188}Re,

^{177}Lu, ^{67}Cu, ^{111}In, ^{67}Ga, ^{51}Cr, ^{58}Co, ^{99m}Tc, ^{103m}Rh, ^{195m}Pt, ^{119}Sb, ^{161}Ho, ^{189m}Os, ^{192}Ir, ^{201}Tl, ^{203}Pb, ^{68}Ga, ^{227}Th, or ^{64}Cu.

[0301] In some embodiments of the methods disclosed herein, the radioactive levels emitted by the complex are detected using positron emission tomography or single photon emission computed tomography.

[0302] Additionally or alternatively, in some embodiments of the methods disclosed herein, the subject is diagnosed with, or is suspected of having multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus, Celiac disease, Sympathetic ophthalmia, Type 1 diabetes, graft-versus-host disease, precursor T acute lymphoblastic leukemia/lymphoma, anaplastic large-cell lymphoma, lymphomatoid papulosis type A, Mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, Sezary disease, adult T-cell leukemia/lymphoma, cutaneous large T cell lymphoma, pleomorphic T-cell lymphoma, lymphomatoid papulosis type B, secondary cutaneous CD30+ large-cell lymphoma, hepatosplenic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, subcutaneous T-cell lymphoma, large granular lymphocytic leukemia, and acute biphenotypic leukemia. In other embodiments of the methods disclosed herein, the subject is diagnosed with, or is suspected of having adrenal cancers, bladder cancers, blood cancers, bone cancers, brain cancers, breast cancers, carcinoma, cervical cancers, colon cancers, colorectal cancers, corpus uterine cancers, ear, nose and throat (ENT) cancers, endometrial cancers, esophageal cancers, gastrointestinal cancers, head and neck cancers, Hodgkin's disease, intestinal cancers, kidney cancers, larynx cancers, acute and chronic leukemias, liver cancers, lymph node cancers, lymphomas, lung cancers, melanomas, mesothelioma, myelomas, nasopharynx cancers, neuroblastomas, non-Hodgkin's lymphoma, oral cancers, ovarian cancers, pancreatic cancers, penile cancers, pharynx cancers, prostate cancers, rectal cancers, sarcoma, seminomas, skin cancers, stomach cancers, teratomas, testicular cancers, thyroid cancers, uterine cancers, vaginal cancers, vascular tumors, and metastases thereof.

[0303] Additionally or alternatively, in some embodiments of the methods disclosed herein, the complex is administered intravenously, intramuscularly, intraarterially, intrathecally, intracapsularly, intraorbitally, intradermally, intraperitoneally, transtracheally, subcutaneously, intracerebroventricularly, orally, intratumorally, or intranasally. In certain embodiments, the complex is administered into the cerebral spinal fluid or blood of the subj ect.

[0304] In some embodiments of the methods disclosed herein, the radioactive levels emitted by the complex are detected between 2 to 120 hours after the complex is administered. In certain embodiments of the methods disclosed herein, the radioactive levels emitted by the complex are expressed as the percentage injected dose per gram tissue (%ID/g). The reference value may be calculated by measuring the radioactive levels present in non-tumor (normal) tissues, and computing the average radioactive levels present in non-tumor (normal) tissues ± standard deviation. In some embodiments, the reference value is the standard uptake value (SUV). See Thie JA, *J Nucl Med.* 45(9):1431-4 (2004). In some embodiments, the ratio of radioactive levels between a tumor and normal tissue is about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1 or 100:1.

[0305] In another aspect, the present disclosure provides a method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with cancer comprising (a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of the present technology that binds to a radiolabeled DOTA hapten, a tumor antigen, and a CD3 antigen, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; and (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment. In some embodiments, the subject is human.

[0306] The anti-DOTA multi-specific antibody is administered under conditions and for a period of time (e.g., according to a dosing regimen) sufficient for it to saturate tumor cells. In some embodiments, unbound anti-DOTA multi-specific antibody is removed from the blood stream after administration of the anti-DOTA multi-specific antibody. In some embodiments, the radiolabeled-DOTA hapten is administered after a time period that may be sufficient to permit clearance of unbound anti-DOTA multi-specific antibody.

[0307] The radiolabeled-DOTA hapten may be administered at any time between 1 minute to 4 or more days following administration of the anti-DOTA multi-specific antibody. For example, in some embodiments, the radiolabeled-DOTA hapten is administered 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 1 hour, 1.25 hours, 1.5 hours, 1.75 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 5.5 hours, 6 hours, 6.5 hours, 7 hours, 7.5 hours, 8 hours, 8.5 hours, 9 hours, 9.5 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, or any range therein, following administration of the anti-DOTA multi-specific antibody. Alternatively, the radiolabeled-DOTA hapten may be administered at any time after 4 or more days following administration of the anti-DOTA multi-specific antibody.

[0308] Additionally or alternatively, in some embodiments, the method further comprises administering an effective amount of a clearing agent to the subject prior to administration of the radiolabeled-DOTA hapten. A clearing agent can be any molecule (dextran or dendrimer or polymer) that can be conjugated with C825-hapten. In some embodiments, the clearing agent is no more than 2000 kD, 1500 kD, 1000 kD, 900 kD, 800 kD, 700 kD, 600 kD, 500 kD, 400 kD, 300 kD, 200 kD, 100 kD, 90 kD, 80 kD, 70 kD, 60 kD, 50 kD, 40 kD, 30 kD, 20 kD, 10 kD, or 5 kD. In some embodiments, the clearing agent is a 500 kD aminodextran-DOTA conjugate (e.g., 500 kD dextran-DOTA-Bn (Y), 500 kD dextran-DOTA-Bn (Lu), or 500 kD dextran-DOTA-Bn (In) etc.).

[0309] In some embodiments, the clearing agent and the radiolabeled-DOTA hapten are administered without further administration of the anti-DOTA multi-specific antibody or antigen binding fragment of the present technology. For example, in some embodiments, an anti-DOTA multi-speci-

fic antibody or antigen binding fragment of the present technology is administered according to a regimen that includes at least one cycle of: (i) administration of the anti-DOTA multi-specific antibody or antigen binding fragment of the present technology (optionally so that relevant tumor cells are saturated); (ii) administration of a radiolabeled-DOTA hapten and, optionally a clearing agent; (iii) optional additional administration of the radiolabeled-DOTA hapten and/or the clearing agent, without additional administration of the anti-DOTA multi-specific antibody. In some embodiments, the method may comprise multiple such cycles (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more cycles).

[0310] Additionally or alternatively, in some embodiments of the method, the anti-DOTA multi-specific antibody and/or the radiolabeled-DOTA hapten is administered intravenously, intramuscularly, intraarterially, intrathecally, intracapsularly, intraorbitally, intradermally, intraperitoneally, transtracheally, subcutaneously, intracerebroventricularly, intratumorally, orally or intranasally.

[0311] In one aspect, the present disclosure provides a method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with cancer comprising administering to the subject an effective amount of a complex comprising a radiolabeled-DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that recognizes and binds to the radiolabeled-DOTA hapten, a CD3 antigen and a tumor antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment of the complex. The complex may be administered intravenously, intramuscularly, intraarterially, intrathecally, intracapsularly, intraorbitally, intradermally, intraperitoneally, transtracheally, subcutaneously, intracerebroventricularly, orally, intratumorally, or intranasally. In some embodiments, the subject is human.

[0312] In another aspect, the present disclosure provides a method for treating cancer in a subject in need thereof comprising (a) administering an effective amount of an anti-DOTA multi-specific antibody or antigen binding fragment of the present technology to the subject, wherein the anti-DOTA multi-specific antibody is configured to (i) bind to a CD3 antigen, and (ii) bind and localize to a tumor antigen; and (b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the anti-DOTA multi-specific antibody or antigen binding fragment. The anti-DOTA multi-specific antibody is administered under conditions and for a period of time (e.g., according to a dosing regimen) sufficient for it to saturate tumor cells. In some embodiments, unbound anti-DOTA multi-specific antibody is removed from the blood stream after administration of the anti-DOTA multi-specific antibody. In some embodiments, the radiolabeled-DOTA hapten is administered after a time period that may be sufficient to permit clearance of unbound anti-DOTA multi-specific antibody. In some embodiments, the subject is human.

[0313] Accordingly, in some embodiments, the method further comprises administering an effective amount of a clearing agent to the subject prior to administration of the radiolabeled-DOTA hapten. The radiolabeled-DOTA hapten may be administered at any time between 1 minute to 4 or more days following administration of the anti-DOTA multi-specific antibody. For example, in some embodiments, the radiolabeled-DOTA hapten is administered 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 25 minutes, 30 minutes, 35 minutes, 40 minutes, 45 minutes, 50 minutes, 55 minutes, 1 hour, 1.25 hours, 1.5 hours, 1.75 hours, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 5.5 hours, 6 hours, 6.5 hours, 7 hours, 7.5 hours, 8 hours, 8.5 hours, 9 hours, 9.5 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, 24 hours, 48 hours, 72 hours, 96 hours, or any range therein, following administration of the anti-DOTA multi-specific antibody. Alternatively, the radiolabeled-DOTA hapten may be administered at any time after 4 or more days following administration of the anti-DOTA multi-specific antibody.

[0314] The clearing agent may be a 500 kD aminodextran-DOTA conjugate (e.g., 500 kD dextran-DOTA-Bn (Y), 500 kD dextran-DOTA-Bn (Lu), or 500 kD dextran-DOTA-Bn (In) etc.). In some embodiments, the clearing agent and the radiolabeled-DOTA hapten are administered without further administration of the anti-DOTA multi-specific antibody. For example, in some embodiments, an anti-DOTA multi-specific antibody is administered according to a regimen that includes at least one cycle of: (i) administration of the an anti-DOTA multi-specific antibody or antigen binding fragment of the present technology (optionally so that relevant tumor cells are saturated); (ii) administration of a radiolabeled-DOTA hapten and, optionally a clearing agent; (iii) optional additional administration of the radiolabeled-DOTA hapten and/or the clearing agent, without additional administration of the anti-DOTA multi-specific antibody. In some embodiments, the method may comprise multiple such cycles (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more cycles).

[0315] Also provided herein are methods for treating cancer in a subject in need thereof comprising administering to the subject an effective amount of a complex comprising a radiolabeled-DOTA hapten and a multi-specific antibody or antigen binding fragment of the present technology that recognizes and binds to the radiolabeled-DOTA hapten, a CD3 antigen, and a tumor antigen, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody of the complex. The therapeutic effectiveness of such a complex may be determined by computing the area under the curve (AUC) tumor: AUC normal tissue ratio. In some embodiments, the complex has a AUC tumor: AUC normal tissue ratio of about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 15:1, 20:1, 25:1, 30:1, 35:1, 40:1, 45:1, 50:1, 55:1, 60:1, 65:1, 70:1, 75:1, 80:1, 85:1, 90:1, 95:1 or 100:1.

[0316] In any and all embodiments of the methods disclosed herein, the tumor antigen is selected from the group consisting of CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N-acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138,

EGFR, EGP-1, EGP-2, VEGF, PlGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Le^y) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pmel17, LMP2, or WT1), or a small molecule DOTA hapten.

Toxicity

[0317] Optimally, an effective amount (e.g., dose) of an anti-CD3 antibody described herein will provide therapeutic benefit without causing substantial toxicity to the subject. Toxicity of the anti-CD3 antibody described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of the anti-CD3 antibody described herein lies within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the subject's condition. See, e.g., Fingl et al., In: *The Pharmacological Basis of Therapeutics*, Ch. 1 (1975).

[0318] Formulations of Pharmaceutical Compositions. According to the methods of the present technology, the anti-CD3 antibody can be incorporated into pharmaceutical compositions suitable for administration. The pharmaceutical compositions generally comprise recombinant or substantially purified antibody and a pharmaceutically-acceptable carrier in a form suitable for administration to a subject. Pharmaceutically-acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions for administering the antibody compositions (See, e.g., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA 18th ed., 1990). The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[0319] The terms "pharmaceutically-acceptable," "physiologically-tolerable," and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a subject without the production of undesirable physiological effects to a degree that would prohibit administration of the composition. For example, "pharmaceutically-acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. "Pharmaceutically-acceptable salts and esters" means salts and esters that are pharmaceutically-acceptable and have the desired pharmacological properties. Such salts include salts that can be formed where acidic protons present in the composition are capable of reacting with inorganic or organic bases. Suitable inorganic salts include those formed with the alkali metals, e.g., sodium and potassium, magnesium, calcium, and aluminum. Suitable organic salts include those formed with organic bases such as the amine bases, e.g., ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Such salts also include acid addition salts formed with inorganic acids (e.g., hydrochloric and hydrobromic acids) and organic acids (e.g., acetic acid, citric acid, maleic acid, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid). Pharmaceutically-acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the anti-CD3 antibody, e.g., C_{1-6} alkyl esters. When there are two acidic groups present, a pharmaceutically-acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified. An anti-CD3 antibody named in this technology can be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such anti-CD3 antibody is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically-acceptable salts and esters. Also, certain embodiments of the present technology can be present in more than one stereoisomeric form, and the naming of such anti-CD3 antibody is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers. A person of ordinary skill in the art, would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs and compositions of the present technology.

[0320] Examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and compounds for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or compound is incompatible with the anti-CD3 antibody, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0321] A pharmaceutical composition of the present technology is formulated to be compatible with its intended route of administration. The anti-CD3 antibody compositions of the present technology can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intradermal, transdermal, rectal, intracranial, intrathecal, intraperitoneal, intranasal; or intramuscular routes, or as inhalants. The anti-CD3 antibody can optionally be administered in combination with other agents that are at least partly effective in treating various CD3-associated pathologies.

[0322] Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial compounds such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating compounds such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and compounds for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0323] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, e.g., water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, e.g., by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal compounds, e.g., parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be desirable to include isotonic compounds, e.g., sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition a compound which delays absorption, e.g., aluminum monostearate and gelatin.

[0324] Sterile injectable solutions can be prepared by incorporating an anti-CD3 antibody of the present technology in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the anti-CD3 antibody into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The antibodies of the present technology can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[0325] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the anti-CD3 antibody can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding compounds, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating compound such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening compound such as sucrose or saccharin; or a flavoring compound such as peppermint, methyl salicylate, or orange flavoring.

[0326] For administration by inhalation, the anti-CD3 antibody is delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0327] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, e.g., for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the anti-CD3 antibody is formulated into ointments, salves, gels, or creams as generally known in the art.

[0328] The anti-CD3 antibody can also be prepared as pharmaceutical compositions in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0329] In one embodiment, the anti-CD3 antibody is prepared with carriers that will protect the anti-CD3 antibody against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically-acceptable carriers. These can be prepared according to methods known to those skilled in the art, e.g., as described in U.S. Pat. No. 4,522,811.

C. Kits

[0330] The present technology provides kits for the detection and/or treatment of CD3-associated pathologies, comprising at least one immunoglobulin-related composition of the present technology (e.g., any antibody or antigen binding fragment described herein), or a functional variant (e.g., substitutional variant) thereof. Optionally, the above described components of the kits of the present technology are packed in suitable containers and labeled for diagnosis and/or treatment of CD3-associated pathologies. The above-

mentioned components may be stored in unit or multi-dose containers, for example, sealed ampoules, vials, bottles, syringes, and test tubes, as an aqueous, preferably sterile, solution or as a lyophilized, preferably sterile, formulation for reconstitution. The kit may further comprise a second container which holds a diluent suitable for diluting the pharmaceutical composition towards a higher volume. Suitable diluents include, but are not limited to, the pharmaceutically acceptable excipient of the pharmaceutical composition and a saline solution. Furthermore, the kit may comprise instructions for diluting the pharmaceutical composition and/or instructions for administering the pharmaceutical composition, whether diluted or not. The containers may be formed from a variety of materials such as glass or plastic and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper which may be pierced by a hypodermic injection needle). The kit may further comprise more containers comprising a pharmaceutically acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, culture medium for one or more of the suitable hosts. The kits may optionally include instructions customarily included in commercial packages of therapeutic or diagnostic products, that contain information about, for example, the indications, usage, dosage, manufacture, administration, contraindications and/or warnings concerning the use of such therapeutic or diagnostic products.

[0331] The kits are useful for detecting the presence of an immunoreactive CD3 protein in a biological sample, e.g., any body fluid including, but not limited to, e.g., serum, plasma, lymph, cystic fluid, urine, stool, cerebrospinal fluid, ascitic fluid or blood and including biopsy samples of body tissue. For example, the kit can comprise: one or more humanized, chimeric, or bispecific anti-CD3 antibodies of the present technology (or antigen binding fragments thereof) capable of binding a CD3 protein in a biological sample; means for determining the amount of the CD3 protein in the sample; and means for comparing the amount of the immunoreactive CD3 protein in the sample with a standard. One or more of the anti-CD3 antibodies may be labeled. The kit components, (e.g., reagents) can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect the immunoreactive CD3 protein.

[0332] For antibody-based kits, the kit can comprise, e.g., 1) a first antibody, e.g. a humanized, chimeric or bispecific CD3 antibody of the present technology (or an antigen binding fragment thereof), attached to a solid support, which binds to a CD3 protein; and, optionally; 2) a second, different antibody which binds to either the CD3 protein or to the first antibody, and is conjugated to a detectable label.

[0333] The kit can also comprise, e.g., a buffering agent, a preservative or a protein-stabilizing agent. The kit can further comprise components necessary for detecting the detectable-label, e.g., an enzyme or a substrate. The kit can also contain a control sample or a series of control samples, which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit. The kits of the present technology may contain a written product on or in the kit container. The written product describes how to use the reagents contained in the kit, e.g., for detection of a CD3 protein in vitro or in vivo, or for treatment of CD3-associated pathologies in a subject in need thereof. In certain embodiments, the use of the reagents can be according to the methods of the present technology.

EXAMPLES

[0334] The present technology is further illustrated by the following Examples, which should not be construed as limiting in any way. The following Examples demonstrate the preparation, characterization, and use of illustrative anti-CD3 antibodies of the present technology. The following Examples demonstrate the production of chimeric, humanized, and bispecific antibodies of the present technology, and characterization of their binding specificities and in vitro and in vivo biological activities.

Example 1: Humanization of Mouse OKT3

[0335] A bivalent modular platform was chosen to build CD3-BsAb (FIG. **1**A). The anti-CD3 antibody OKT3 was rehumanized to >85% humanness. The CDRs of the heavy and light chains of OKT3 (Arakawa, Kuroki et al., *J Biochem* 120(3): 657-662 (1996)) were grafted onto human IgG1 frameworks based on their homology with human frameworks IGHV1-46*01-IGHJ4*01 for VH, IGKV3-11*01-IGKJ2*02 for VL, respectively.

[0336] FIG. **12**A shows the amino acid sequences of the murine and humanized OKT3 heavy chain variable domains (V_H). The V_H domain of the murine OKT3 is set forth in SEQ ID NO: 1, which comprises V_H CDR1 (SEQ ID NO: 2), V_H CDR2 (SEQ ID NO: 3), and V_H CDR3 (SEQ ID NO: 4) (FIG. **12**A). SEQ ID NO: 7-10 are the humanized versions of V_H domain of the murine OKT3. The sequences OKT3_VH-1 (SEQ ID NO: 7), OKT3_VH-2 (SEQ ID NO: 8), OKT3 VH-3 (SEQ ID NO: 9), and OKT3 VH-4 (SEQ ID NO: 10), are four variants of the humanized OKT3 heavy chain variable domain disclosed herein, which feature >85% humanness (FIG. **12**A). FIG. **12**B shows the amino acid sequences of the murine and humanized OKT3 light chain variable domains (V_L). The V_L domain of the murine OKT3 is set forth in SEQ ID NO: 11, which comprises V_L CDR1 (SEQ ID NO: 12), V_L CDR2 (SEQ ID NO: 13), and V_L CDR3 (SEQ ID NO: 14) (FIG. **12**B). SEQ ID NO: 15-20 are the humanized versions of V_L domain of the OKT3. The sequences OKT3_VL-1 (SEQ ID NO: 15), OKT3 VL-2 (SEQ ID NO: 16), OKT3 VL-3 (SEQ ID NO: 17), OKT3 VL-4 (SEQ ID NO: 18), OKT3 VL-5 (SEQ ID NO: 19), and OKT3_VL-6 (SEQ ID NO: 20), are six variants of the humanized OKT3 light chain variable domain disclosed herein, which feature >85% humanness (FIG. **12**B). From 4 heavy chain and 6 light chain designs, 24 versions of huOKT3 were gene synthesized and expressed in CHO cells.

[0337] To remove glycosylation, N297A mutation in a standard hIgG1 Fc region was introduced. The light chain was constructed by extending a humanized OKT3 IgG1 light chain with a C-terminal $(G_4S)_3$ linker (SEQ ID NO: 151) followed by huOKT3 scFv. The DNA encoding both heavy chain and light chain was inserted into a mammalian expression vector, transfected into CHO-S cells, and stable clones of highest expression were selected. Supernatants

were collected from shaker flasks and purified on protein A affinity chromatography.

[0338] FIGS. **13**A and **13**B shows the amino acid sequences of the light chain (SEQ ID NO: 21) and heavy chain (SEQ ID NOs: 23) of humanized anti-CD3 BC276 BsAb amino acid sequence that combines OKT3_VL-2 and OKT3_VH-2 humanized variable domains disclosed herein.

[0339] Stability data for the humanized anti-CD3 antibodies of the present disclosure are provided below:

Purity (% Monomer)	d0	Freeze/ Thaw	d7	d14	d21	d35
OKT3_chimeric	97.167	95.195	85.107	71.562	66.550	54.716
H1L1	98.911	97.130	87.702	73.940	67.174	57.858
H2L1	98.311	94.636	89.481	79.366	73.448	2.112
H3L1	98.879	94.941	89.394	80.855	76.026	43.174
H4L1	99.117	95.354	88.865	79.596	73.511	6.051
H1L2	99.257	94.914	89.493	79.413	73.706	65.794
H2L2	98.745	96.477	89.741	80.149	74.550	66.956
H3L2	98.975	94.622	89.325	80.395	75.236	67.692
H4L2	99.085	96.501	89.479	79.377	73.820	66.121
H1L3	98.780	95.147	88.727	78.807	72.946	64.919
H2L3	98.599	93.875	88.988	80.022	73.249	67.448
H3L3	98.576	97.163	87.473	77.227	71.828	65.601
H4L3	98.363	95.911	88.739	76.896	70.038	61.683
H1L4	98.777	97.094	89.323	78.744	72.074	65.72
H2L4	98.602	94.111	89.896	79.950	73.826	68.576
H3L4	98.513	94.354	90.852	81.446	75.523	67.451
H4L4	98.724	95.816	89.976	81.340	75.740	67.003
H1L5	98.280	97.315	88.376	79.650	74.166	65.259
H2L5	98.071	93.511	91.210	83.919	78.548	72.478
H3L5	98.834	94.797	90.545	82.885	77.388	69.212
H4L5	98.881	96.257	90.091	82.402	76.822	69.652
H1L6	98.677	93.978	90.680	81.383	75.808	68.983
H2L6	98.313	94.649	90.072	81.125	75.779	70.764
H3L6	98.243	93.905	89.035	78.658	73.129	65.674
H4L6	98.444	94.746	89.662	81.076	73.013	65.524

[0340] Binding affinity data for the humanized anti-CD3 antibodies of the present disclosure are provided below:

CD3 Ab	ka (1/Ms)	kd (1/s)	ka2 (1/s)	kd2 (1/s)	KD (M)
OKT3-chimeric	3.44E+07	1.38E-01	1.05E-02	1.94E-03	6.22E-10
H1L1	2.96E+06	1.06E-01	2.36E-02	8.28E-04	1.21E-09
H1L2	2.55E+06	1.26E-01	2.52E-02	1.09E-03	2.05E-09
H1L3	5.53E+06	2.11E-01	1.92E-02	7.82E-04	1.50E-09
H1L4	2.61E+06	1.14E-01	2.37E-02	9.10E-04	1.61E-09
H1L5	3.52E+06	6.43E-02	6.57E-03	4.21E-03	7.15E-09
H1L6	3.19E+06	8.70E-02	4.33E-03	2.36E-03	9.62E-09
H2L1	3.52E+06	9.79E-02	2.60E-02	7.79E-04	8.08E-10
H2L2	3.26E+06	9.86E-02	2.68E-02	8.14E-04	8.92E-10
H2L3	6.42E+06	1.30E-01	2.28E-02	7.19E-04	6.19E-10
H2L4	3.54E+06	8.14E-02	2.34E-02	6.71E-04	6.42E-10
H2L5	5.02E+06	5.67E-02	1.27E-02	3.69E-03	2.55E-09
H2L6	4.10E+06	6.38E-02	1.01E-02	5.81E-03	5.68E-09
H3L1	4.67E+06	1.55E-01	2.29E-02	8.31E-04	1.16E-09
H3L2	3.06E+06	1.39E-01	2.34E-02	9.39E-04	1.75E-09
H3L3	1.19E+07	4.02E-01	1.91E-02	8.15E-04	1.38E-09
H3L4	3.03E+06	1.19E-01	2.13E-02	7.44E-04	1.33E-09
H3L5	3.51E+06	6.47E-02	7.09E-03	4.96E-03	7.60E-09
H3L6	3.05E+06	8.14E-02	4.91E-03	2.43E-03	8.84E-09
H4L1	1.77E+06	1.76E-01	2.82E-02	2.30E-03	7.49E-09
H4L2	1.44E+06	2.17E-01	2.60E-02	2.94E-03	1.53E-08

-continued

CD3 Ab	ka (1/Ms)	kd (1/s)	ka2 (1/s)	kd2 (1/s)	KD (M)
H4L3	1.88E+06	2.64E-01	2.05E-02	2.38E-03	1.47E-08
H4L4	1.75E+06	2.48E-01	2.12E-02	2.30E-03	1.39E-08
H4L5	2.17E+06	1.41E-01	4.10E-03	7.44E-04	9.96E-09
H4L6	2.02E+06	2.51E-01	5.34E-03	5.94E-04	1.24E-08

Example 2: Purification and Biochemical Characterization of Anti-CD3 Immunoglobulin-Related Compositions of the Present Disclosure

[0341] To characterize the humanized antibodies, culture supernatants were collected from shaker flasks and purified using protein A affinity chromatography. The purified antibodies were subjected to biochemical purity analysis. To determine the biochemical purity of the BsAbs of the present disclosure, the purified BsAbs were resolved using size-exclusion chromatography-high-performance liquid chromatography (SEC-HPLC). The protein in the eluate was detected based on absorbance of UV light at 280 nm. An exemplary SEC-HPLC chromatogram is shown in FIG. **1**B. The BsAb peaks were identified based on the retention time on SEC-HPLC. Biochemical purity was assessed based on area of the BsAb peak.

[0342] The humanized antibodies were incubated at 40° C., and aliquots of the same were withdrawn at specified times to assess purity using HPLC. As shown in FIG. **2**, the humanized OKT3 IgG antibody was > 75% intact after three weeks at 40° C. These results demonstrate that the immunoglobulin-related compositions of the present technology have purity and stability properties that are pharmacologically acceptable.

Example 3: Anti-CD3 Immunoglobulin-Related Compositions of the Present Disclosure Induce Potent T Cell Fratricide in Vitro

[0343] T cells were cultured with 350 pM BC276 BsAb in the presence of interleukin-2 to support T cell proliferation. Two different antibodies were used as controls. The first control antibody was an IgG-L-scFv BsAb specific for CD19 (two Fab arms of the IgG) and CD3 (two scFvs connected to the C-terminal of the IgG CL). The second control antibody was the humanized OKT3 IgG. Both the control antibodies are monospecific to CD3. As shown in FIGS. **3**A-**3**B, BC276 BsAb induced strong T cell fratricide among both CD4 (FIG. **3**A) and CD8 (FIG. **3**B) at doses as low as 350 pM. T cell populations although T cell death was more prominent among CD4 T cells. Importantly, neither of the control antibodies induced a significant or durable T cell depletion response and T cells ultimately proliferated in the presence of the control antibodies (FIGS. **3**A-**3**B).

[0344] These results demonstrate that the immunoglobulin-related compositions of the present technology exhibit potent anti-T cell activity. Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 4: Anti-CD3 Immunoglobulin-Related Compositions of the Present Disclosure Induces Profound T Cell Depletion In Vivo

[0345] NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally. Peripheral blood was stained for the presence of T cells on day 7 and treatment was initiated on day 8. Treatment comprised injection of 1 μg of BC276 BsAb or BC119, a CD3 × GD2-specific BsAb, or vehicle only (no antibody). On day 15 and day 22, peripheral blood was stained with an anti-human CD45 antibody and subjected to flow cytometry analysis. As shown in FIG. **4**A, treatment with BC276 BsAb caused near complete loss of CD45+ population seen on the right hand side of the flow cytometry dot plots. The effect of BC119 BsAb was comparable to the no-antibody group. The number of CD45+ cells from the three treatment groups were quantitated. As shown in FIG. **4**B, treatment with BC276 BsAb induced profound T cell depletion in mice. In contrast, BC119 BsAb caused a modest effect compared to the no-antibody group. BC276 induced more potent T cell depletion compared to BC119.

[0346] To further evaluate the potency of BC276 BsAb in inducing T cell depletion in vivo, the effects of the BC276 BsAb at 1 μg and 0.1 μg doses were assessed. NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally. Peripheral blood was stained for the presence of T cells on day 7 and treatment was initiated on day 8. Treatment comprised injection of 1 μg or 0.1 μg BC276 BsAb, or 1 μg or 0.1 μg BC119. On day 15, peripheral blood was stained with an anti-human CD45 antibody and subjected to flow cytometry analysis.

[0347] As shown in FIG. **5**A, CD45+ populations were observed in animals treated with either 1 μg or 0.1 μg of BC119 BsAb, as seen on the right hand side of the flow cytometry dot plots. In contrast, treatment with both 1 μg and 0.1 μg of BC276 BsAb led to diminished CD45+ population. As shown in FIG. **5**B, following treatment with either 1 μg or 0.1 μg of BC119 BsAb, the average CD45+ cell numbers ranged between about 300 and 400/ μl of peripheral blood. In contrast, the average CD45+ cell numbers were about 10/ μl and about 35/ μl of peripheral blood following treatment with either 1 μg or 0.1 μg of BC276 BsAb, respectively (FIG. **5**B), with the 1 μg dose eliciting a more profound T cell depletion in mice compared to the 0.1 μg dose.

[0348] NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally on day 0, and the mice were treated with 1 μg or 0.1 μg BC276 BsAb, or 1 μg or 0.1 μg BC119 BsAb. A no-antibody control was used as a negative control. On days 8, 15, and 22, peripheral blood was stained with an anti-human CD45, anti-human CD4, or anti-human CD8 antibodies and subjected to flow cytometry analysis. As shown in FIG. **6**A, a severe depletion of CD45+ cells was observed on days 15 and 22 following treatment with either 1 μg or 0.1 μg of BC276 BsAb, compared to the no-antibody control, or BC119 BsAb. Treatment with both 1 μg and 0.1 μg of BC119 BsAb had a modest effect on CD45+ cells on day 22 compared to the no-antibody control (FIG. **6**A). Further analysis of T cell subpopulations revealed that both CD4 and CD8 T cells were severely depleted in vivo following treatment with 1 μg or 0.1 μg of BC276 (FIGS. **6**B-**6**C) compared with BC119 BsAb or no-antibody controls.

[0349] These results demonstrate that the immunoglobulin-related compositions of the present technology exhibit potent anti-T cell activity. Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 5: BC276-Induced Depletion of T Cells is not Associated with Clinical Side Effects in Mice

[0350] NSG mice were injected with 30 million PBMCs (a mix of PBMCs from 3 different donors, 10 million cells from each donor) intraperitoneally on day 0. The mice were treated with vehicle only control (no antibody), or with 1 μg or 0.1 μg BC276 BsAb, or 1 μg or 0.1 μg BC119 BsAb starting on day 8. The mice were evaluated for clinical signs of distress such as weight loss, reduced activity, hunched posture, or ruffled fur. The body weights of animals receiving any of the antibody treatments were comparable to those treated with the no antibody control. See FIG. **7**. Other signs of distress, such as reduced activity, hunched posture, or ruffled fur, were also not observed in animals treated with BC276 BsAb. See FIG. **25**.

[0351] These results demonstrate that the immunoglobulin-related compositions of the present technology exhibit potent anti-T cell activity. Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 6 Anti-CD3 Immunoglobulin-Related Compositions of the Present Disclosure can Reduce GVHD Signs and Extend Survival

[0352] To accelerate the development of graft-versus-host-disease (GVHD) in the mice described in Examples 6 and 7, antibody injection was discontinued and a second dose of effector cells (22 million activated T cells per mouse) was injected into the mice. Antibody injections(1 μg or 0.1 μg BC276 BsAb, 1 μg or 0.1 μg BC119 BsAb) were resumed on day 35. Vehicle only (no antibody) was used as a negative control. On days 8, 15, 22, 28 and 44, peripheral blood was stained with anti-human CD4, or anti-human CD8 antibodies and subjected to flow cytometry analysis.

[0353] As shown in FIGS. **8**A-**8**B, both 0.1 μg and 1 μg of BC276 BsAb depleted both CD4+ (FIG. **8**A) and CD8+ (FIG. **8**B) T cells compared to no-antibody control until day 22. Likewise, BC119 exhibited a moderate effect on CD4+ cells till day 22 compared to the no-antibody control (FIG. **8**A). However, after day 22, BC276 BsAb (or BC119 BsAb) was no longer sufficient to deplete either CD4+ (FIG. **8**A) or CD8+ (FIG. **8**B) T cells in mice. Thus, the mice served as a model of graft-versus-host-disease (GVHD).

[0354] The mice were again randomized into 5 groups and were treated with 30 μg BC276 BsAb, 10 μg BC276 BsAb, 3 μg BC276 BsAb, 10 μg BC119 BsAb, or no antibody.

Dead mice were assigned a GVHD score of 5. As shown in FIG. **9**, treatment of the mice with 30 μg and 10 μg BC276 BsAb reduced the score of GVHD from 2 to 0.12 ($p<0.0001$) and from 1.8 to 0.12 ($p<0.0003$), respectively. In contrast, the GVHD score in the mice treated with only 3 μg of BC276 BsAb, those treated with 10 μg of the control BsAb, and untreated mice increased. As shown in FIG. **10**, the mice in the BC276 BsAb group (30 μg and 10 μg) gained weight while the mice in the other groups lost weight providing further evidence of the therapeutic effects of higher doses of BC276 BsAb against GVHD (FIG. **10**). As shown in FIG. **11**, all mice that received 30 μg and 10 μg BC276 BsAb survived, while those in the other groups succumbed to GVHD.

[0355] These results demonstrate that the immunoglobulin-related compositions of the present technology exhibit potent anti-T cell activity. Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 7: Use of the Immunoglobulin-Related Compositions of the Present Disclosure to Treat Cancer

[0356] FIGS. **23**A-**23**B show results from multiple T-cell cytotoxicity assays using various cancer target cells. Human activated T-cells and the targeted human tumor cells were incubated with bispecific antibodies targeting a tumor antigen and CD3 for four hours to measure anti-tumor cytotoxicity, using an anti-GD2 × CD3 BsAb comprising SEQ ID NO: 94 and SEQ ID NO: 96 sequences, or an anti-GPC3 × CD3 BsAb comprising SEQ ID NO: 102 and SEQ ID NO: 104 sequences from the present disclosure. FIG. **23**A specifically shows the potency of an anti-GD2 anti-CD3 bispecific antibody against a GD2-expressing neuroblastoma cell line (IMR32). FIG. **23**B shows the potency of an anti-GPC3 anti-CD3 bispecific antibody against a GPC3-expressing liver cancer cell line (HEPG2).

[0357] Naïve T cells were purified from human normal volunteer PBMC using Pan T cell isolation kit (Miltenyi Biotec, Bergisch Gladbach, Germany). These T cells were activated and expanded by CD3/CD28 Dynabeads (Invitrogen, Carlsbad CA) for 7 to 14 days in the presence of 30 IU/mL of IL-2 according to manufacturer's protocol. ^{51}Cr release assay as described in Xu H et al., *Cancer Immunol Res* 3 :266-77 (2015) was performed and EC_{50} was calculated using SigmaPlot software. Tumor cell lines were cultured in RPMI-1640 (Cellgro, Swedesboro, NJ) supplemented with 10% fetal bovine serum (FBS, Life Technologies, Carlsbad CA) and harvested with EDTA/Trypsin. Target tumor cells were labeled with sodium ^{51}Cr chromate (Amersham, Arlington Height, IL) at 100 uCi/10^6 cells at 37° C. for 1 hour. After the cells were washed twice, target tumor cells were plated at 5000 cells per well in a 96-well plate; at a E:T ratio of 10:1, BC276 BsAb was titrated down 10 fold from starting concentration of 0.1 μg/ml. After incubation at 37° C. for 4 hours, the released ^{51}Cr was measured by a gamma counter (Packed Instrument, Downers Grove, IL). Percentage of specific lysis was calculated using the formula 100% (experimental cpm- background cpm)/ (total cpm-background cpm), where cpm represented counts per minute of ^{51}Cr released. Total release of ^{51}Cr was assessed by lysis with 10% SDS (Sigma, St Louis, Mo) and background release was measured in the absence of effector cells and antibodies. As shown in FIGS. **24**A-**24**E and Table 2, T cell lines with CD3 expression were killed in the ADTC assay, while the control antibody HER2-BsAb directed at HER2 showed no cytotoxicity.

TABLE 2

	CD3 Expression	CD3-BsAb	HER2 expression	HER2-BsAb
CEM-NKR	-	No killing	-	No killing
HUT78	++	Yes killing	-	No killing
JURKAT	++	Yes killing	-	No killing
8402	++	Yes killing	-	No killing
MOLT4	-	No killing	-	No killing

[0358] These results demonstrate that the anti-CD3 immunoglobulin-related compositions of the present technology can be used to retarget polyclonal T-cells against a variety of tumor antigens and tumor types.

Example 8: Use of Immunoglobulin-Related Compositions of the Present Disclosure to Treat Autoimmune Diseases and Type 1 Diabetes Mellitus

[0359] Animal models will be used to assess the therapeutic effects of the anti-CD3 antibodies or antigen binding fragments of the present technology in vivo. Examples of rodent models of autoimmune diseases and Type 1 diabetes mellitus have been developed. Vudattu et al., *J Immunol.* 193(2):587-96 (2014); Turley et al., *Proc Natl Acad Sci USA.* 102(49): 17729-17733 (2005).

[0360] Type 1 diabetes mellitus is a T-cell mediated autoimmune destruction of the pancreatic ß cells that are responsible for secretion of insulin. Roep, *Diabetologia*, 46: 305-321 (2003). To investigate the effect of BC276 BsAb treatment on Type-I diabetes via eliminating T-cells, three transgenic mouse models will be used: i) OT-I mice (C57BL/6-Tg(TcraTcrb)1100Mjb/J), which express a transgenic T cell receptor recognizing ovalbumin peptide residues 257-264 ($OVA_{257-264}$); ii) RIP-mOVA mice (C57BL/6-Tg(Ins2-TFRC/OVA)296Wehi/WehiJ), which exhibit strong expression of ovalbumin in pancreatic ß cells (which secrete insulin) and kidney proximal tubular cells; and iii) human CD3 transgenic (B6.Cg-Tg(CD3E)600Cpt/J) mice, in which murine T cells express human CD3e domain and therefore are able to bind T-cell bispecific antibodies.

[0361] OT-I mice will be crossed with CD3 transgenic mice. The progenies that have T-cell expressing OT-I T-cell receptor and also a human CD3E gene will be used as T-cell donors. T-cells may be harvested from spleen and lymph nodes of these mice. In a second step, the harvested T-cells will be injected to the RIP-mOVA mice, wherein a prior lymphodepletion may help engraftment of the donor cells. The occurrence and progression of diabetes will be monitored by checking blood glucose. As soon as the blood sugar surpasses 200 mg/dl, treatment with different doses of BC276 BsAb and the control antibodies will be initiated. The severity of diabetes can be monitored through blood glucose levels. At completion of the assay, pancreatic

immunohistochemistry will show the extent of T-cell infiltration into the ß cells.

[0362] It is anticipated that the immunoglobulin-related compositions of the present technology will reduce the symptoms of autoimmune diseases and/or Type 1 diabetes mellitus in the animal models.

[0363] Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 9: Use of Immunoglobulin-Related Compositions of the Present Disclosure to Treat T Cell Malignancies

[0364] Animal models will be used to assess the therapeutic effects of the anti-CD3 antibodies or antigen binding fragments of the present technology in vivo. Examples of rodent models of T-cell malignancies, such as T-cell lymphomas (TCLs) and T-cell leukemias, have been developed. Kohnken et al., *Front Oncol.* 7: 22 (2017). To test the effect of BC276 BsAb treatment on T-cell cancers, immunodeficient mice will be inoculated with T-cell cancers (such as CCRF-CEM, TALL-104, J45.01, and Jurkat Clone E6-1) that are optionally transduced with luciferase. Tumor progression will be monitored by bioluminescent imaging (BLI). Based on the kinetics of tumor growth in mice, human T cells will be injected at different time points with or without different doses of BC276 BsAb or the control antibodies. The BLI signal and mouse weight and survival will be used as a surrogate of treatment effectiveness

[0365] It is anticipated that the immunoglobulin-related compositions of the present technology will reduce the symptoms of T-cell malignancies in the animal models.

[0366] Accordingly, the immunoglobulin-related compositions of the present technology are useful to treat diseases caused by activation of T cells, including graft-versus-host-disease (GVHD), autoimmune diseases (directly induced by T cells or where T cells have a role in activation of B cells to generate autoantibodies), and T cell malignancies.

Example 10: Use of Immunoglobulin-Related Compositions of the Present Disclosure to Treat Cancer

[0367] It is anticipated that the immunoglobulin-related compositions of the present technology comprising SADA domains (e.g., SEQ ID NOs: 118-121) will effectively recruit T-cells to kill solid or liquid tumors. See FIGS. **20**A-**20**D.

[0368] It is anticipated that heterodimeric anti-tumor immunoglobulin-related compositions of the present technology comprising anti-DOTA antibody domains (e.g., BsAbs comprising SEQ ID NOs: 122, 124, 126, and 137 or SEQ ID NOs: 128, 130, 132, and 139) will permit both imaging of T-cells in patients with cancer (using imaging isotopes), as well as delivery of therapeutic payloads to tumors (using therapeutic isotopes). See FIGS. **21**A-**21**D and FIGS. **22**A-**22**D.

Example 11: Comparison of Functional Activities of Bispecific Antibodies With Different Anti-CD3 Sequences

[0369] FIG. **27** shows the amino acid sequences of the anti-CD3 scFv region for each of the 5 GPC3 × CD3 bispecific antibodies (BsAbs) (SEQ ID NOs: 141-145) shown in FIG. **26**. The light chain and heavy chain sequences of the anti-GPC-3 immunoglobulin are:

DIVMTQSPSSLVVSIGERIlTMNCKSSQSLLYSSNQKNYLAWYQQKPGQS
PKLLIYWASSRESGVPDRFSGSGSGTDFTLTISSVKAEDVAVYYCQQYYN
YPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE
AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGECTS

(SEQ ID NO: 146); and

EVQLVESGGGLVQPEGSLKLSCAASGFTFNKNAMNWVRQAPGKGLEWVAR
IRNKTNNYATYYADSVKARFTISRDDSQSMLYLQMNSLKIEDTAMYYCVA
GNSFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTY
RVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYT
LPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

(SEQ ID NO: 147), respectively.

[0370] As shown in FIG. **28**, BsAb #3 shows the highest binding affinity to ex vivo expanded human T cells followed by BsAb #1, #2, #5 and #4. FIG. **29** shows that the binding affinities of the exemplified BsAbs to human recombinant CD3δ/ε are not drastically different as demonstrated using SPR. BsAb #1, #2, #3 and #5 bind with similar affinities whereas BsAb #4 shows 1 log lower binding affinity.

[0371] FIGS. **30**-**31** show that the exemplified BsAbs differentially induce surface expression of T cell activation marker CD69 and CD25, respectively. BsAb #1, #2, #3 and #5 induced a similar proportion of CD69+ T cells, whereas BsAb #4 weakly activated CD8 T cell expression of CD69. A similar trend was observed for CD25 expression on CD8 T cells whereby BsAb #4 weakly induced CD25 expression compared to BsAb #1, #2, #3 and #5.

[0372] BsAb #1, #2, #3 and #5 drove robust CD8 T cell proliferation and more than 70% of CD8 T cells underwent active division with as little as 6.4 ng/ml BsAb concentration. BsAb #4 not only weakly induced CD8 T cell activation, there is very little dividing CD8 T cells (15%) at 6.4 ng/ml BsAb concentration. See FIG. **32**A. Increasing concentration of BsAb in the T and HepG2 coculture assay did not lead to reduced CD8 T cell viability. Similar CD8 T cell viability (10-20%) was observed among all BsAbs.

[0373] FIG. **33** shows BsAb-engaged T-cell mediated killing of HepG2 hepatocellular carcinoma cell line. BsAb #3 and #1 show similar EC50 followed by #2 and #5, whereas BsAb 4 showed lowest EC50.

[0374] FIGS. **34**A-**34**B show human T cell engraftment in HepG2 xenograft mice. BsAb #3 drove the highest number of T-luc cells engraftment to HepG2 tumor site followed by BsAb #1 and #2. Dosage of BsAb influenced T-luc cells engraftment. For instance, 30 μg BsAb #1 induced higher T-luc infiltration than 3 μg BsAb #1.

EQUIVALENTS

[0375] The present technology is not to be limited in terms of the particular embodiments described in this application,

which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, 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 be limiting.

[0376] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0377] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a nonlimiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

[0378] All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

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Lys Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala Tyr
65                  70                  75                  80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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35 40 45

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

Gln Gly Arg Ala Thr Leu Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
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Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
            20                  25                  30

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 8
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 8

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 9
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 9

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

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

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

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 10
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 10

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

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

-continued

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 11
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 11

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

Glu Lys Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

Asn Trp Tyr Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr
        35                  40                  45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu
65                  70                  75                  80

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 12
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic peptide

<400> SEQUENCE: 12

Ser Ser Val Ser Tyr
1               5


<210> SEQ ID NO 13
<211> LENGTH: 2
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
```

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<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 13

Asp Thr
1

<210> SEQ ID NO 14
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 14

Gln Gln Trp Ser Ser Asn Pro Phe Thr
1 5

<210> SEQ ID NO 15
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 15

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 16
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 16

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

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```
Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 17
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 17

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 18
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 18

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

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

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

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```
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 19
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 19

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 20
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 20

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

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

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

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

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80
```

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 21
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 21

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
            20                  25                  30

Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val
        35                  40                  45

Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
    50                  55                  60

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

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met
                85                  90                  95

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn
            100                 105                 110

Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg Thr Val
        115                 120                 125

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
    130                 135                 140

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
145                 150                 155                 160

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

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
            180                 185                 190

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
        195                 200                 205

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
    210                 215                 220

Lys Ser Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
                245                 250                 255

Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
            260                 265                 270
```

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```
Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln
        275                 280                 285

Ala Pro Gly Gln Cys Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg
    290                 295                 300

Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr
305                 310                 315                 320

Arg Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg
                325                 330                 335

Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
            340                 345                 350

Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
        355                 360                 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
385                 390                 395                 400

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
                405                 410                 415

Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp
            420                 425                 430

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr
        435                 440                 445

Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    450                 455                 460

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe
465                 470                 475                 480

Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly
                485                 490                 495

Cys Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505


<210> SEQ ID NO 22
<211> LENGTH: 1515
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 22

atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcgt gcactccgac       60

atccagatga cccagtctcc tagctccctg agcgcctccg tgggcgatag ggtgaccatg      120

acatgctctg cctctagctc cgtgagctac atgaactggt atcagcagaa gcccggcaag      180

gcccctaagc tgctgatcta cgacacatct aagctggcca gcggcgtgcc ctccagattc      240

tctggcagcg gctccggcac cgactttacc ctgacaatct ctagcatgca gccagaggat      300

ttcgccacat actattgtca gcagtggtcc tctaacccct tcacctttgg ctccggcaca      360

aagctggaga tcaatcggac cgtggccgcc ccctccgtgt tcatcttccc cccctccgac      420
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gagcagctga agtccggcac cgcctccgtg gtgtgcctgc tgaacaactt ctacccccgg 480

gaggccaagg tgcagtggaa ggtggacaac gccctgcagt ccggcaactc ccaggagtcc 540

gtgaccgagc aggactccaa ggactccacc tactccctgt cctccaccct gaccctgtcc 600

aaggccgact acgagaagca caaggtgtac gcctgcgagg tgacccacca gggcctgtcc 660

tcccccgtga ccaagtcctt caaccggggc gagtgcacta gtggcggcgg cggctctgga 720

ggaggaggca gcggcggagg aggctcccag gtgcagctgc agcagtccgg cgccgaggtg 780

gcaaagccag gagccagcgt gaaggtgtcc tgcaaggcct ctggctacac cttcacacgg 840

tataccatgc actgggtgag acaggcccca ggccagtgtc tggagtggat gggctacatc 900

aaccccagcc ggggctacac aaactataat cagaagttta aggacagggc caccctgaca 960

cgcgataagt ctatcagcac cgcctatatg gagctgagcc ggctgagatc cgacgataca 1020

gccgtgtact attgcgcccg gtactatgac gatcactact ccctggacta ttggggccag 1080

ggcaccacac tgaccgtgag ctccggagga ggaggctctg gcggcggcgg cagcggcggc 1140

ggaggctccg gaggcggcgg ctctgggggga ggcggcagcg gcggcggcgg ctccgacatc 1200

cagatgacac agagcccatc tagcctgtcc gcctctgtgg gcgatagggt gaccatgaca 1260

tgttctgcct cctctagcgt gagctacatg aattggtatc agcagaagcc cggcaaggcc 1320

cctaagctgc tgatctacga tacctctaag ctggccagcg gagtgccttc ccgcttcagc 1380

ggctccggct ctggaaccga ctttaccctg acaatctcct ctatgcagcc tgaggatttc 1440

gccacatact attgccagca gtggagctcc aacccattca cctttggctg tggcacaaag 1500

ctggagatca ataga 1515

<210> SEQ ID NO 23
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 23

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Ala Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn
65 70 75 80

Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser
85 90 95

Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
100 105 110

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```
Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp
        115                 120                 125

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
                245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

-continued

<210> SEQ ID NO 24
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 24

atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcgt gcacagccag 60

gtgcagctgc agcagtccgg agcagaggtg gcaaagccag gagcctccgt gaaggtgtct 120

tgcaaggcca gcggctacac cttcacacgg tataccatgc actgggtgag acaggcacca 180

ggacagggcc tggagtggat gggctacatc aacccttcta ggggctacac aaactataat 240

cagaagttta aggacagggc caccctgaca cgcgataagt ctatcagcac cgcctatatg 300

gagctgtccc ggctgagatc tgacgataca gccgtgtact attgtgccag atactatgac 360

gatcactaca gcctggacta ttggggccag ggcaccacac tgaccgtgag ctccgcctcc 420

accaagggcc cctctgtgtt tcctctggcc ccctccagca agtccacctc tggtggaaca 480

gccgccctgg gctgcctcgt gaaggactac tttcccgagc ccgtgaccgt gtcctggaac 540

tctggcgctc tgacctctgg cgtgcacacc ttccctgctg tgctgcagtc tagcggcctg 600

tactccctgt cctccgtcgt gacagtgccc tccagctctc tgggcaccca gacctacatc 660

tgcaacgtga accacaagcc ctccaatacc aaggtggaca agcgggtgga acccaagtcc 720

tgcgacaaga cccacacctg tccccttgt cctgcccctg aactgctggg cggaccttcc 780

gtgttcctgt tccccccaaa gcccaaggac accctgatga tctcccggac ccccgaagtg 840

acctgcgtgg tggtggatgt gtcccacgag gaccctgaag tgaagttcaa ttggtacgtg 900

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta cgcctccacc 960

taccgggtgg tgtccgtgct gacagtgctg caccaggact ggctgaacgg caaagagtac 1020

aagtgcgccg tgtccaacaa ggccctgcct gcccccatcg aaaagaccat ctccaaggcc 1080

aagggccagc cccgggaacc ccaggtgtac acactgcccc ctagcaggga cgagctgacc 1140

aagaaccagg tgtccctgac ctgtctcgtg aaaggcttct acccctccga tatcgccgtg 1200

gaatgggagt ccaacggcca gcctgagaac aactacaaga ccacccccc tgtgctggac 1260

tccgacggct cattcttcct gtacagcaag ctgaccgtgg acaagtcccg gtggcagcag 1320

ggcaacgtgt tctcctgctc cgtgatgcac gaggccctgc acaaccacta cacccagaag 1380

tccctgtccc tgagccccgg caaa 1404

<210> SEQ ID NO 25
<211> LENGTH: 384
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Ala Pro Thr Lys Ala Pro Asp Val Phe Pro Ile Ile Ser Gly Cys Arg
1 5 10 15

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```
His Pro Lys Asp Asn Ser Pro Val Val Leu Ala Cys Leu Ile Thr Gly
            20                  25                  30

Tyr His Pro Thr Ser Val Thr Val Thr Trp Tyr Met Gly Thr Gln Ser
        35                  40                  45

Gln Pro Gln Arg Thr Phe Pro Glu Ile Gln Arg Arg Asp Ser Tyr Tyr
    50                  55                  60

Met Thr Ser Ser Gln Leu Ser Thr Pro Leu Gln Gln Trp Arg Gln Gly
65                  70                  75                  80

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

Ile Phe Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro
            100                 105                 110

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

Pro Ala Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys
    130                 135                 140

Glu Lys Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu
145                 150                 155                 160

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

Val Gln Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val
            180                 185                 190

Val Gly Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly
        195                 200                 205

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

Asn Gly Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu
225                 230                 235                 240

Trp Asn Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu
                245                 250                 255

Pro Pro Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro
            260                 265                 270

Val Lys Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala
        275                 280                 285

Ala Ser Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile
    290                 295                 300

Leu Leu Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe
305                 310                 315                 320

Ala Pro Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala
                325                 330                 335

Trp Ser Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr
            340                 345                 350

Tyr Thr Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala
        355                 360                 365

Ser Arg Ser Leu Glu Val Ser Tyr Val Thr Asp His Gly Pro Met Lys
    370                 375                 380
```

-continued

<210> SEQ ID NO 26
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65 70 75 80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
100 105 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
115 120 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
130 135 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145 150 155 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
165 170 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
180 185 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
195 200 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
210 215 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225 230 235 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
245 250 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
260 265 270

Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
275 280 285

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
290 295 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305 310 315 320

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```
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330


<210> SEQ ID NO 27
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110

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

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
    130                 135                 140

Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145                 150                 155                 160

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
                165                 170                 175

Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
            180                 185                 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
        195                 200                 205

Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
    210                 215                 220

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225                 230                 235                 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
                245                 250                 255

Ser Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
            260                 265                 270

Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
        275                 280                 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
    290                 295                 300
```

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```
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305                 310                 315                 320

Ser Leu Ser Pro Gly Lys
                325


<210> SEQ ID NO 28
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Thr Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Leu Lys Thr Pro Leu Gly Asp Thr Thr His Thr Cys Pro
            100                 105                 110

Arg Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg
        115                 120                 125

Cys Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys
    130                 135                 140

Pro Glu Pro Lys Ser Cys Asp Thr Pro Pro Pro Cys Pro Arg Cys Pro
145                 150                 155                 160

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                165                 170                 175

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            180                 185                 190

Val Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Lys Trp Tyr
        195                 200                 205

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    210                 215                 220

Gln Tyr Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Leu His
225                 230                 235                 240

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                245                 250                 255

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln
            260                 265                 270

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
        275                 280                 285
```

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```
Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    290                 295                 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
305                 310                 315                 320

Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
                325                 330                 335

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
            340                 345                 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
        355                 360                 365

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    370                 375


<210> SEQ ID NO 29
<211> LENGTH: 452
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Gly Ser Ala Ser Ala Pro Thr Leu Phe Pro Leu Val Ser Cys Glu Asn
1               5                   10                  15

Ser Pro Ser Asp Thr Ser Ser Val Ala Val Gly Cys Leu Ala Gln Asp
            20                  25                  30

Phe Leu Pro Asp Ser Ile Thr Leu Ser Trp Lys Tyr Lys Asn Asn Ser
        35                  40                  45

Asp Ile Ser Ser Thr Arg Gly Phe Pro Ser Val Leu Arg Gly Gly Lys
    50                  55                  60

Tyr Ala Ala Thr Ser Gln Val Leu Leu Pro Ser Lys Asp Val Met Gln
65                  70                  75                  80

Gly Thr Asp Glu His Val Val Cys Lys Val Gln His Pro Asn Gly Asn
                85                  90                  95

Lys Glu Lys Asn Val Pro Leu Pro Val Ile Ala Glu Leu Pro Pro Lys
            100                 105                 110

Val Ser Val Phe Val Pro Pro Arg Asp Gly Phe Phe Gly Asn Pro Arg
        115                 120                 125

Lys Ser Lys Leu Ile Cys Gln Ala Thr Gly Phe Ser Pro Arg Gln Ile
    130                 135                 140

Gln Val Ser Trp Leu Arg Glu Gly Lys Gln Val Gly Ser Gly Val Thr
145                 150                 155                 160

Thr Asp Gln Val Gln Ala Glu Ala Lys Glu Ser Gly Pro Thr Thr Tyr
                165                 170                 175

Lys Val Thr Ser Thr Leu Thr Ile Lys Glu Ser Asp Trp Leu Gly Gln
            180                 185                 190

Ser Met Phe Thr Cys Arg Val Asp His Arg Gly Leu Thr Phe Gln Gln
        195                 200                 205

Asn Ala Ser Ser Met Cys Val Pro Asp Gln Asp Thr Ala Ile Arg Val
    210                 215                 220
```

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```
Phe Ala Ile Pro Pro Ser Phe Ala Ser Ile Phe Leu Thr Lys Ser Thr
225                 230                 235                 240

Lys Leu Thr Cys Leu Val Thr Asp Leu Thr Thr Tyr Asp Ser Val Thr
                245                 250                 255

Ile Ser Trp Thr Arg Gln Asn Gly Glu Ala Val Lys Thr His Thr Asn
            260                 265                 270

Ile Ser Glu Ser His Pro Asn Ala Thr Phe Ser Ala Val Gly Glu Ala
        275                 280                 285

Ser Ile Cys Glu Asp Asp Trp Asn Ser Gly Glu Arg Phe Thr Cys Thr
    290                 295                 300

Val Thr His Thr Asp Leu Pro Ser Pro Leu Lys Gln Thr Ile Ser Arg
305                 310                 315                 320

Pro Lys Gly Val Ala Leu His Arg Pro Asp Val Tyr Leu Leu Pro Pro
                325                 330                 335

Ala Arg Glu Gln Leu Asn Leu Arg Glu Ser Ala Thr Ile Thr Cys Leu
            340                 345                 350

Val Thr Gly Phe Ser Pro Ala Asp Val Phe Val Gln Trp Met Gln Arg
        355                 360                 365

Gly Gln Pro Leu Ser Pro Glu Lys Tyr Val Thr Ser Ala Pro Met Pro
    370                 375                 380

Glu Pro Gln Ala Pro Gly Arg Tyr Phe Ala His Ser Ile Leu Thr Val
385                 390                 395                 400

Ser Glu Glu Glu Trp Asn Thr Gly Glu Thr Tyr Thr Cys Val Ala His
                405                 410                 415

Glu Ala Leu Pro Asn Arg Val Thr Glu Arg Thr Val Asp Lys Ser Thr
            420                 425                 430

Gly Lys Pro Thr Leu Tyr Asn Val Ser Leu Val Met Ser Asp Thr Ala
        435                 440                 445

Gly Thr Cys Tyr
    450


<210> SEQ ID NO 30
<211> LENGTH: 327
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1               5                   10                  15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
```

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```
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320

Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> SEQ ID NO 31
<211> LENGTH: 353
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

```
Ala Ser Pro Thr Ser Pro Lys Val Phe Pro Leu Ser Leu Cys Ser Thr
1               5                   10                  15

Gln Pro Asp Gly Asn Val Val Ile Ala Cys Leu Val Gln Gly Phe Phe
            20                  25                  30

Pro Gln Glu Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Gly Val
        35                  40                  45

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

-continued

```
Thr Thr Ser Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Leu Ala Gly
65                  70                  75                  80

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

Val Thr Val Pro Cys Pro Val Pro Ser Thr Pro Pro Thr Pro Ser Pro
            100                 105                 110

Ser Thr Pro Pro Thr Pro Ser Pro Ser Cys Cys His Pro Arg Leu Ser
        115                 120                 125

Leu His Arg Pro Ala Leu Glu Asp Leu Leu Leu Gly Ser Glu Ala Asn
    130                 135                 140

Leu Thr Cys Thr Leu Thr Gly Leu Arg Asp Ala Ser Gly Val Thr Phe
145                 150                 155                 160

Thr Trp Thr Pro Ser Ser Gly Lys Ser Ala Val Gln Gly Pro Pro Glu
                165                 170                 175

Arg Asp Leu Cys Gly Cys Tyr Ser Val Ser Ser Val Leu Pro Gly Cys
            180                 185                 190

Ala Glu Pro Trp Asn His Gly Lys Thr Phe Thr Cys Thr Ala Ala Tyr
        195                 200                 205

Pro Glu Ser Lys Thr Pro Leu Thr Ala Thr Leu Ser Lys Ser Gly Asn
    210                 215                 220

Thr Phe Arg Pro Glu Val His Leu Leu Pro Pro Pro Ser Glu Glu Leu
225                 230                 235                 240

Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg Gly Phe Ser
                245                 250                 255

Pro Lys Asp Val Leu Val Arg Trp Leu Gln Gly Ser Gln Glu Leu Pro
            260                 265                 270

Arg Glu Lys Tyr Leu Thr Trp Ala Ser Arg Gln Glu Pro Ser Gln Gly
        275                 280                 285

Thr Thr Thr Phe Ala Val Thr Ser Ile Leu Arg Val Ala Ala Glu Asp
    290                 295                 300

Trp Lys Lys Gly Asp Thr Phe Ser Cys Met Val Gly His Glu Ala Leu
305                 310                 315                 320

Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Leu Ala Gly Lys Pro
                325                 330                 335

Thr His Val Asn Val Ser Val Val Met Ala Glu Val Asp Gly Thr Cys
            340                 345                 350

Tyr
```

<210> SEQ ID NO 32
<211> LENGTH: 340
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

```
Ala Ser Pro Thr Ser Pro Lys Val Phe Pro Leu Ser Leu Asp Ser Thr
1               5                   10                  15

Pro Gln Asp Gly Asn Val Val Val Ala Cys Leu Val Gln Gly Phe Phe
            20                  25                  30
```

-continued

```
Pro Gln Glu Pro Leu Ser Val Thr Trp Ser Glu Ser Gly Gln Asn Val
        35                  40                  45

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

Thr Thr Ser Ser Gln Leu Thr Leu Pro Ala Thr Gln Cys Pro Asp Gly
65                  70                  75                  80

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

Val Thr Val Pro Cys Pro Val Pro Pro Pro Pro Pro Cys Cys His Pro
            100                 105                 110

Arg Leu Ser Leu His Arg Pro Ala Leu Glu Asp Leu Leu Leu Gly Ser
        115                 120                 125

Glu Ala Asn Leu Thr Cys Thr Leu Thr Gly Leu Arg Asp Ala Ser Gly
    130                 135                 140

Ala Thr Phe Thr Trp Thr Pro Ser Ser Gly Lys Ser Ala Val Gln Gly
145                 150                 155                 160

Pro Pro Glu Arg Asp Leu Cys Gly Cys Tyr Ser Val Ser Ser Val Leu
                165                 170                 175

Pro Gly Cys Ala Gln Pro Trp Asn His Gly Glu Thr Phe Thr Cys Thr
            180                 185                 190

Ala Ala His Pro Glu Leu Lys Thr Pro Leu Thr Ala Asn Ile Thr Lys
        195                 200                 205

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

Glu Glu Leu Ala Leu Asn Glu Leu Val Thr Leu Thr Cys Leu Ala Arg
225                 230                 235                 240

Gly Phe Ser Pro Lys Asp Val Leu Val Arg Trp Leu Gln Gly Ser Gln
                245                 250                 255

Glu Leu Pro Arg Glu Lys Tyr Leu Thr Trp Ala Ser Arg Gln Glu Pro
            260                 265                 270

Ser Gln Gly Thr Thr Thr Phe Ala Val Thr Ser Ile Leu Arg Val Ala
        275                 280                 285

Ala Glu Asp Trp Lys Lys Gly Asp Thr Phe Ser Cys Met Val Gly His
    290                 295                 300

Glu Ala Leu Pro Leu Ala Phe Thr Gln Lys Thr Ile Asp Arg Met Ala
305                 310                 315                 320

Gly Lys Pro Thr His Val Asn Val Ser Val Val Met Ala Glu Val Asp
                325                 330                 335

Gly Thr Cys Tyr
            340


<210> SEQ ID NO 33
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33
```

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```
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
1               5                   10                  15

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

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
        35                  40                  45

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
    50                  55                  60

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
65                  70                  75                  80

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

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
            100                 105


<210> SEQ ID NO 34
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu
1               5                   10                  15

Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp
            20                  25                  30

Ala Gln Ala Gly Lys Glu Pro
        35


<210> SEQ ID NO 35
<211> LENGTH: 57
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

Arg Ser Pro Asp Asp Glu Leu Leu Tyr Leu Pro Val Arg Gly Arg Glu
1               5                   10                  15

Thr Tyr Glu Met Leu Leu Lys Ile Lys Glu Ser Leu Glu Leu Met Gln
            20                  25                  30

Tyr Leu Pro Gln His Thr Ile Glu Thr Tyr Arg Gln Gln Gln Gln Gln
        35                  40                  45

Gln His Gln His Leu Leu Gln Lys Gln
    50                  55


<210> SEQ ID NO 36
<211> LENGTH: 52
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Arg His Gly Asp Glu Asp Thr Tyr Tyr Leu Gln Val Arg Gly Arg Glu
1               5                   10                  15
```

-continued

```
Asn Phe Glu Ile Leu Met Lys Leu Lys Glu Ser Leu Glu Leu Met Glu
            20                  25                  30

Leu Val Pro Gln Pro Leu Val Asp Ser Tyr Arg Gln Gln Gln Gln Leu
        35                  40                  45

Leu Gln Arg Pro
    50


<210> SEQ ID NO 37
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Gln Ala Ile Lys Lys Glu Leu Thr Gln Ile Lys Gln Lys Val Asp Ser
1               5                   10                  15

Leu Leu Glu Asn Leu Glu Lys Ile Glu Lys Glu
            20                  25


<210> SEQ ID NO 38
<211> LENGTH: 54
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Ser Thr Arg Arg Ile Leu Gly Leu Ala Ile Glu Ser Gln Asp Ala Gly
1               5                   10                  15

Ile Lys Thr Ile Thr Met Leu Asp Glu Gln Lys Glu Gln Leu Asn Arg
            20                  25                  30

Ile Glu Glu Gly Leu Asp Gln Ile Asn Lys Asp Met Arg Glu Thr Glu
        35                  40                  45

Lys Thr Leu Thr Glu Leu
    50


<210> SEQ ID NO 39
<211> LENGTH: 97
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Cys Gly Ala Pro Ser Ala Thr Gln Pro Ala Thr Ala Glu Thr Gln
1               5                   10                  15

His Ile Ala Asp Gln Val Arg Ser Gln Leu Glu Glu Lys Glu Asn Lys
            20                  25                  30

Lys Phe Pro Val Phe Lys Ala Val Ser Phe Lys Ser Gln Val Val Ala
        35                  40                  45

Gly Thr Asn Tyr Phe Ile Lys Val His Val Gly Asp Glu Asp Phe Val
    50                  55                  60

His Leu Arg Val Phe Gln Ser Leu Pro His Glu Asn Lys Pro Leu Thr
65                  70                  75                  80

Leu Ser Asn Tyr Gln Thr Asn Lys Ala Lys His Asp Glu Leu Thr Tyr
                85                  90                  95
```

-continued

Phe

<210> SEQ ID NO 40
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown: KCNQ4
tetramerizaiton domain sequence

<400> SEQUENCE: 40

Asp Glu Ile Ser Met Met Gly Arg Val Val Lys Val Glu Lys Gln Val
1 5 10 15

Gln Ser Ile Glu His Lys Leu Asp Leu Leu Leu Gly Phe Tyr
20 25 30

<210> SEQ ID NO 41
<211> LENGTH: 60
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Description of Unknown: CBFA2T1
tetramerizaiton domain sequence

<400> SEQUENCE: 41

Thr Val Ala Glu Ala Lys Arg Gln Ala Ala Glu Asp Ala Leu Ala Val
1 5 10 15

Ile Asn Gln Gln Glu Asp Ser Ser Glu Ser Cys Trp Asn Cys Gly Arg
20 25 30

Lys Ala Ser Glu Thr Cys Ser Gly Cys Asn Thr Ala Arg Tyr Cys Gly
35 40 45

Ser Phe Cys Gln His Lys Asp Trp Glu Lys His His
50 55 60

<210> SEQ ID NO 42
<211> LENGTH: 207
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Met Gln Ser Gly Thr His Trp Arg Val Leu Gly Leu Cys Leu Leu Ser
1 5 10 15

Val Gly Val Trp Gly Gln Asp Gly Asn Glu Glu Met Gly Gly Ile Thr
20 25 30

Gln Thr Pro Tyr Lys Val Ser Ile Ser Gly Thr Thr Val Ile Leu Thr
35 40 45

Cys Pro Gln Tyr Pro Gly Ser Glu Ile Leu Trp Gln His Asn Asp Lys
50 55 60

Asn Ile Gly Gly Asp Glu Asp Asp Lys Asn Ile Gly Ser Asp Glu Asp
65 70 75 80

His Leu Ser Leu Lys Glu Phe Ser Glu Leu Glu Gln Ser Gly Tyr Tyr
85 90 95

Val Cys Tyr Pro Arg Gly Ser Lys Pro Glu Asp Ala Asn Phe Tyr Leu
100 105 110

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```
Tyr Leu Arg Ala Arg Val Cys Glu Asn Cys Met Glu Met Asp Val Met
        115                 120                 125

Ser Val Ala Thr Ile Val Ile Val Asp Ile Cys Ile Thr Gly Gly Leu
    130                 135                 140

Leu Leu Leu Val Tyr Tyr Trp Ser Lys Asn Arg Lys Ala Lys Ala Lys
145                 150                 155                 160

Pro Val Thr Arg Gly Ala Gly Ala Gly Gly Arg Gln Arg Gly Gln Asn
                165                 170                 175

Lys Glu Arg Pro Pro Pro Val Pro Asn Pro Asp Tyr Glu Pro Ile Arg
            180                 185                 190

Lys Gly Gln Arg Asp Leu Tyr Ser Gly Leu Asn Gln Arg Arg Ile
        195                 200                 205


<210> SEQ ID NO 43
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 43

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Cys Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 44
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 44

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

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

-continued

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

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Cys Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 45
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 45

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Cys Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 46
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 46

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

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

-continued

```
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Ile
        35                  40                  45

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 47
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 47

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 48
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 48

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

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

-continued

```
Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Cys Leu Glu Trp Ile
        35                  40                  45

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 49
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 49

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 50
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 50

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Cys Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 51
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 51

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Cys Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 52
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 52

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

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

-continued

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

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Cys Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 53
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 53

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Cys Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 54
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 54

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Cys Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 55
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 55

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Cys Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 56
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 56

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

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

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

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Cys Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 57
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 57

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Cys Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 58
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 58

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Cys Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 59
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 59

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Cys Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 60
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 60

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

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

-continued

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

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

Lys Asp Arg Ala Thr Met Thr Thr Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Cys Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 61
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 61

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Cys Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser
        115


<210> SEQ ID NO 62
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 62

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30
```

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

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

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

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 63
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 63

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 64
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 64

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

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

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

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60
```

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```
Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 65
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 65

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

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

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

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

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

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 66
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 66

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

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

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

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

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

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 67
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 67

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

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

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

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

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

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

Phe Gly Cys Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 68
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 68

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 69
<211> LENGTH: 107

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 69

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 70
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 70

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 71
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

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<400> SEQUENCE: 71

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 72
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 72

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

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

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Cys Pro Lys Arg Trp Ile Tyr
35 40 45

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 73
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 73

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

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```
Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 74
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 74

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 75
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 75

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Cys
        35                  40                  45
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Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 76
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 76

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 77
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 77

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

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

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

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

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu
65                  70                  75                  80
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```
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85                  90                  95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 78
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 78

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 79
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 79

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

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

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

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

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

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

-continued

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 80
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 80

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 81
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 81

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
20 25 30

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 82
<211> LENGTH: 107

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 82

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

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

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 83
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 83

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

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

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 84
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

-continued

<400> SEQUENCE: 84

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

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

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 85
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 85

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

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

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

Cys Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
50 55 60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
100 105

<210> SEQ ID NO 86
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 86

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

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```
Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 87
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 87

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

Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            20                  25                  30

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 88
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 88

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

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

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile Tyr
        35                  40                  45
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```
Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 89
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 89

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 90
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 90

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

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

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

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

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu
65                  70                  75                  80
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```
Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                85                  90                  95

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 91
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 91

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

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

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

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

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

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

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            100                 105


<210> SEQ ID NO 92
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 92

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
            20                  25                  30

Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val
        35                  40                  45

Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu
    50                  55                  60

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

Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met
                85                  90                  95

Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn
            100                 105                 110
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Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg Thr Val
        115                 120                 125

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
    130                 135                 140

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
145                 150                 155                 160

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

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
            180                 185                 190

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
        195                 200                 205

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
    210                 215                 220

Lys Ser Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
                245                 250                 255

Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
            260                 265                 270

Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln
        275                 280                 285

Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg
    290                 295                 300

Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr
305                 310                 315                 320

Arg Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg
                325                 330                 335

Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
            340                 345                 350

Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
        355                 360                 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
385                 390                 395                 400

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
                405                 410                 415

Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp
            420                 425                 430

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr
        435                 440                 445

Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    450                 455                 460

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe
465                 470                 475                 480
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Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly
485 490 495

Ser Gly Thr Lys Leu Glu Ile Asn Arg
500 505

<210> SEQ ID NO 93
<211> LENGTH: 1515
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 93

atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcgt gcactccgac 60

atccagatga cccagtctcc tagctccctg agcgcctccg tgggcgatag ggtgaccatg 120

acatgctctg cctctagctc cgtgagctac atgaactggt atcagcagaa gcccggcaag 180

gcccctaagc tgctgatcta cgacacatct aagctggcca gcggcgtgcc ctccagattc 240

tctggcagcg gctccggcac cgactttacc ctgacaatct ctagcatgca gccagaggat 300

ttcgccacat actattgtca gcagtggtcc tctaacccct tcacctttgg ctccggcaca 360

aagctggaga tcaatcggac cgtggccgcc ccctccgtgt tcatcttccc cccctccgac 420

gagcagctga agtccggcac cgcctccgtg gtgtgcctgc tgaacaactt ctacccccgg 480

gaggccaagg tgcagtggaa ggtggacaac gccctgcagt ccggcaactc ccaggagtcc 540

gtgaccgagc aggactccaa ggactccacc tactccctgt cctccaccct gaccctgtcc 600

aaggccgact acgagaagca caaggtgtac gcctgcgagg tgacccacca gggcctgtcc 660

tcccccgtga ccaagtcctt caaccggggc gagtgcacta gtggcggcgg aggatctggc 720

ggaggtggaa gtgggggagg cggatctcag gtgcagctgc agcagtccgg agcagaggtg 780

gcaaagccag gagccagcgt gaaggtgtcc tgcaaggcct ctggctacac cttcacacgg 840

tataccatgc actgggtgag acaggcacca ggacagggcc tggagtggat gggctacatc 900

aacccctctc ggggctacac aaactataat cagaagttta aggacagggc caccctgaca 960

cgcgataagt ctatcagcac cgcctatatg gagctgagcc ggctgagatc cgacgataca 1020

gccgtgtact attgtgcccg gtactatgac gatcactaca gcctggacta ttggggccag 1080

ggcaccacac tgaccgtgag ctctggcggc ggcggctctg gaggaggagg cagcggcgga 1140

ggaggctccg gaggaggcgg ctctggcggc ggcggcagcg gcggcggcgg ctccgacatc 1200

cagatgacac agtccccatc tagcctgtcc gcctctgtgg gcgatagggt gaccatgaca 1260

tgctctgcct cctctagcgt gagctacatg aattggtatc agcagaagcc cggcaaggcc 1320

cctaagctgc tgatctacga tacctctaag ctggccagcg gagtgccttc ccgcttcagc 1380

ggctccggct ctggaaccga ctttaccctg acaatctcct ctatgcagcc tgaggatttc 1440

gccacatact attgtcagca gtggagctcc aacccattca cctttggcag cggcacaaag 1500

ctggagatca ataga 1515

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<210> SEQ ID NO 94
<211> LENGTH: 500
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 94

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
20 25 30

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
35 40 45

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
50 55 60

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
65 70 75 80

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
85 90 95

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
100 105 110

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
130 135 140

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
145 150 155 160

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

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

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

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

Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
225 230 235 240

Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Ala
245 250 255

Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr
260 265 270

Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly
275 280 285

Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr
290 295 300

Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile
305 310 315 320

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Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala
                325                 330                 335

Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr
            340                 345                 350

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser
        355                 360                 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser
385                 390                 395                 400

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys
                405                 410                 415

Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro
            420                 425                 430

Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser
        435                 440                 445

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
    450                 455                 460

Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys
465                 470                 475                 480

Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu
                485                 490                 495

Glu Ile Asn Arg
            500
```

<210> SEQ ID NO 95
<211> LENGTH: 1500
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 95

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atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga gatcgtgatg       60

acacagaccc ctgccaccct gtccgtgtct gctggcgaga gagtgaccat tacctgcaag      120

gcctcccagt ccgtgtccaa cgacgtgacc tggtatcagc agaagcccgg ccaggccccc      180

agactgctga tctactccgc ctccaaccgg tactctggcg tgcccgctag attctccggc      240

tctggctacg gcaccgagtt taccttcacc atctcctccg tgcagtccga ggacttcgcc      300

gtgtacttct gtcagcaaga ctactccagc ttcggccagg gcaccaagct ggaaatcaag      360

cggaccgtgg ccgctccctc cgtgttcatc ttcccacctt ccgacgagca gctgaagtcc      420

ggcaccgctt ctgtcgtgtg cctgctgaac aacttctacc cccgcgaggc caaggtgcag      480

tggaaggtgg acaacgccct gcagtccggc aactcccagg aatccgtgac cgagcaggac      540

tccaaggaca gcacctactc cctgtcctcc accctgaccc tgtccaaggc cgactacgag      600

aagcacaagg tgtacgcctg cgaagtgacc caccagggcc tgtctagccc cgtgaccaag      660
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tctttcaacc ggggcgagtg cactagtggc ggcggaggat ctggcggagg tggaagtggg 720

ggaggcggat ctcaggtgca gctgcagcag tccggagcag aggtggcaaa gccaggagcc 780

agcgtgaagg tgtcctgcaa ggcctctggc tacaccttca cacggtatac catgcactgg 840

gtgagacagg caccaggaca gggcctggag tggatgggct acatcaaccc ctctcggggc 900

tacacaaact ataatcagaa gtttaaggac agggccaccc tgacacgcga taagtctatc 960

agcaccgcct atatggagct gagccggctg agatccgacg atacagccgt gtactattgt 1020

gcccggtact atgacgatca ctacagcctg gactattggg gccagggcac cacactgacc 1080

gtgagctctg gcggcggcgg ctctggagga ggaggcagcg gcggaggagg ctccggagga 1140

ggcggctctg gcggcggcgg cagcggcggc ggcggctccg acatccagat gacacagtcc 1200

ccatctagcc tgtccgcctc tgtgggcgat agggtgacca tgacatgctc tgcctcctct 1260

agcgtgagct acatgaattg gtatcagcag aagcccggca aggcccctaa gctgctgatc 1320

tacgatacct ctaagctggc cagcggagtg ccttcccgct tcagcggctc cggctctgga 1380

accgacttta ccctgacaat ctcctctatg cagcctgagg atttcgccac atactattgt 1440

cagcagtgga gctccaaccc attcaccttt ggcagcggca caaagctgga gatcaataga 1500

<210> SEQ ID NO 96
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 96

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln
20 25 30

Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ser Val
35 40 45

Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu
50 55 60

Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser
65 70 75 80

Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr
85 90 95

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr
100 105 110

Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu Asp Tyr Trp
115 120 125

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145 150 155 160

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Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
               165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
               245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
               325                 330                 335

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
               405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> SEQ ID NO 97
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

-continued

<400> SEQUENCE: 97

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt gcacagccag 60

gtgcagctgg tggagtccgg ccccggcgtg gtgcagcccg gccggtccct gcggatctcc 120

tgcgccgtgt ccggcttctc cgtgaccaac tacggcgtgc actgggtgcg acagcctcca 180

ggcaagggcc tggagtggct gggcgtgatc tgggccggcg gcatcaccaa ctacaactcc 240

gccttcatgt cccggctgac catctccaag gacaactcca agaacaccgt gtacctgcag 300

atgaactccc tgcgggccga ggacaccgcc atgtactact gcgcctcccg gggcggccac 360

tacggctacg ccctggacta ctggggccag ggcaccctgg tgaccgtgtc ctccgcctcc 420

accaagggcc cctctgtgtt tcctctggcc ccctccagca agtccacctc tggtggaaca 480

gccgccctgg gctgcctcgt gaaggactac tttcccgagc ccgtgaccgt gtcctggaac 540

tctggcgctc tgacctctgg cgtgcacacc ttccctgctg tgctgcagtc tagcggcctg 600

tactccctgt cctccgtcgt gacagtgccc tccagctctc tgggcaccca gacctacatc 660

tgcaacgtga accacaagcc ctccaatacc aaggtggaca agcgggtgga acccaagtcc 720

tgcgacaaga cccacacctg tccccttgt cctgccctg aactgctggg cggaccttcc 780

gtgttcctgt tcccccaaa gcccaaggac accctgatga tctcccggac ccccgaagtg 840

acctgcgtgg tggtggatgt gtcccacgag gaccctgaag tgaagttcaa ttggtacgtg 900

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta cgcctccacc 960

taccgggtgg tgtccgtgct gacagtgctg caccaggact ggctgaacgg caaagagtac 1020

aagtgcgccg tgtccaacaa ggccctgcct gcccccatcg aaaagaccat ctccaaggcc 1080

aagggccagc cccgggaacc ccaggtgtac acactgcccc ctagcaggga cgagctgacc 1140

aagaaccagg tgtccctgac ctgtctcgtg aaaggcttct acccctccga tatcgccgtg 1200

gaatgggagt ccaacggcca gcctgagaac aactacaaga ccacccccc tgtgctggac 1260

tccgacggct cattcttcct gtacagcaag ctgaccgtgg acaagtcccg gtggcagcag 1320

ggcaacgtgt tctcctgctc cgtgatgcac gaggccctgc acaaccacta cacccagaag 1380

tccctgtccc tgagccccgg caaa 1404

<210> SEQ ID NO 98
<211> LENGTH: 507
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 98

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Leu Gly
20 25 30

Glu Arg Ala Thr Ile Ser Cys Arg Ala Ser Glu Ser Val Asp Asn Tyr
35 40 45

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Gly Ile Ser Phe Met Asn Trp Phe Gln Gln Lys Pro Gly Gln Pro Pro
    50                  55                  60

Arg Leu Leu Ile Tyr Ala Ala Ser Asn Gln Gly Ser Gly Val Pro Ala
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Pro Gly Thr Asp Phe Thr Leu Thr Ile Ser
                85                  90                  95

Ser Met Glu Pro Glu Asp Phe Ala Met Tyr Phe Cys Gln Gln Ser Lys
            100                 105                 110

Glu Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
    130                 135                 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly
225                 230                 235                 240

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln
                245                 250                 255

Gln Ser Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser
            260                 265                 270

Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val
        275                 280                 285

Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro
    290                 295                 300

Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr
305                 310                 315                 320

Leu Thr Arg Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg
                325                 330                 335

Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp
            340                 345                 350

Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
        355                 360                 365

Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
385                 390                 395                 400

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
                405                 410                 415
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Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met
            420                 425                 430

Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        435                 440                 445

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    450                 455                 460

Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu
465                 470                 475                 480

Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr
                485                 490                 495

Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505


<210> SEQ ID NO 99
<211> LENGTH: 1521
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 99

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga gatcgtgctg       60

actcagtctc ctgccaccct gtccgtgtcc ctgggcgaga gagccaccat ctcttgcaga      120

gcctccgagt ccgtggacaa ctacggcatc tccttcatga actggttcca gcagaagccc      180

ggccagcctc ctcggctgct gatctacgcc gcttccaatc agggctctgg cgtgcccgct      240

agattctccg gatctggccc tggcaccgac tttaccctga ccatctcctc catggaaccc      300

gaggacttcg ccatgtactt ttgccagcag tccaaagagg tgccctggac ctttggcgga      360

ggcaccaagc tggaaatcaa gcggaccgtg gccgctccct ccgtgttcat cttcccacct      420

tccgacgagc agctgaagtc cggcaccgct tctgtcgtgt gcctgctgaa caacttctac      480

ccccgcgagg ccaaggtgca gtggaaggtg gacaacgccc tgcagtccgg caactcccag      540

gaatccgtga ccgagcagga ctccaaggac agcacctact ccctgtcctc caccctgacc      600

ctgagcaagg ccgactacga gaagcacaag gtgtacgcct gcgaagtgac ccaccagggc      660

ctgtctagcc ccgtgaccaa gtctttcaac cggggcgagt gcactagtgg cggcggagga      720

tctggcggag gtggaagtgg gggaggcgga tctcaggtgc agctgcagca gtccggagca      780

gaggtggcaa agccaggagc cagcgtgaag gtgtcctgca aggcctctgg ctacaccttc      840

acacggtata ccatgcactg ggtgagacag gcaccaggac agggcctgga gtggatgggc      900

tacatcaacc cctctcgggg ctacacaaac tataatcaga agtttaagga cagggccacc      960

ctgacacgcg ataagtctat cagcaccgcc tatatggagc tgagccggct gagatccgac     1020

gatacagccg tgtactattg tgcccggtac tatgacgatc actacagcct ggactattgg     1080

ggccagggca ccacactgac cgtgagctct ggcggcggcg gctctggagg aggaggcagc     1140

ggcggaggag gctccggagg aggcggctct ggcggcggcg gcagcggcgg cggcggctcc     1200
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gacatccaga tgacacagtc cccatctagc ctgtccgcct ctgtgggcga tagggtgacc     1260

atgacatgct ctgcctcctc tagcgtgagc tacatgaatt ggtatcagca gaagcccggc     1320

aaggccccta agctgctgat ctacgatacc tctaagctgg ccagcggagt gccttcccgc     1380

ttcagcggct ccggctctgg aaccgacttt accctgacaa tctcctctat gcagcctgag     1440

gatttcgcca catactattg tcagcagtgg agctccaacc cattcacctt tggcagcggc     1500

acaaagctgg agatcaatag a                                               1521
```

<210> SEQ ID NO 100
<211> LENGTH: 462
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 100

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Glu Val Gln Leu Val Gln Ser Gly Pro Glu Val Val Lys Pro Gly Ala
            20                  25                  30

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
        35                  40                  45

Asn Met His Trp Val Arg Gln Ala His Gly Gln Ser Leu Glu Trp Ile
    50                  55                  60

Gly Tyr Ile Tyr Pro Tyr Asn Gly Gly Thr Gly Tyr Asn Gln Lys Phe
65                  70                  75                  80

Lys Ser Arg Ala Thr Leu Thr Val Asp Asn Ser Ala Ser Thr Ala Tyr
                85                  90                  95

Met Glu Val Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
            100                 105                 110

Ala Arg Gly Arg Pro Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val
        115                 120                 125

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

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240
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```
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
            420                 425                 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
        435                 440                 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 101
<211> LENGTH: 1386
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 101

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga ggtgcagctg       60

gtgcagtctg gacccgaggt cgtgaagcct ggcgcctccg tgaagatctc ctgcaaggcc      120

tccggctaca ccttcaccga ctacaacatg cactgggtgc gacaggccca cggccagtcc      180

ctggaatgga tcggctacat ctaccctac aacggcggca ccggctacaa ccagaagttc      240

aagtctcggg ccaccctgac cgtggacaac tctgcctcta ccgcctacat ggaagtgtcc      300

tccctgagat ccgaggacac cgccgtgtac tactgcgcca gaggcagacc cgccatggac      360

tattggggcc agggcaccct cgtgaccgtg tctagcgctt ctaccaaggg cccctctgtg      420

tttcctctgg ccccctccag caagtccacc tctggtggaa cagccgccct gggctgcctc      480
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gtgaaggact actttcccga gcccgtgacc gtgtcctgga actctggcgc tctgacctct 540

ggcgtgcaca ccttccctgc tgtgctgcag tctagcggcc tgtactccct gtcctccgtc 600

gtgacagtgc cctccagctc tctgggcacc cagacctaca tctgcaacgt gaaccacaag 660

ccctccaata ccaaggtgga caagcgggtg gaacccaagt cctgcgacaa gacccacacc 720

tgtccccctt gtcctgcccc tgaactgctg ggcggacctt ccgtgttcct gttccccccа 780

aagcccaagg acaccctgat gatctcccgg acccccgaag tgacctgcgt ggtggtggat 840

gtgtcccacg aggaccctga agtgaagttc aattggtacg tggacggcgt ggaagtgcac 900

aacgccaaga ccaagcctag agaggaacag tacgcctcca cctaccgggt ggtgtccgtg 960

ctgacagtgc tgcaccagga ctggctgaac ggcaaagagt acaagtgcgc cgtgtccaac 1020

aaggccctgc ctgcccccat cgaaaagacc atctccaagg ccaagggcca gccccgggaa 1080

ccccaggtgt acacactgcc ccctagcagg gacgagctga ccaagaacca ggtgtccctg 1140

acctgtctcg tgaaaggctt ctacccctcc gatatcgccg tggaatggga gtccaacggc 1200

cagcctgaga acaactacaa gaccaccccc cctgtgctgg actccgacgg ctcattcttc 1260

ctgtacagca agctgaccgt ggacaagtcc cggtggcagc agggcaacgt gttctcctgc 1320

tccgtgatgc acgaggccct gcacaaccac tacacccaga agtccctgtc cctgagcccc 1380

ggcaaa 1386

<210> SEQ ID NO 102
<211> LENGTH: 509
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 102

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Val Val Ser Ile Gly
20 25 30

Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
35 40 45

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

Ser Pro Lys Leu Leu Ile Tyr Trp Ala Ser Ser Arg Glu Ser Gly Val
65 70 75 80

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Val Lys Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
100 105 110

Tyr Tyr Asn Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
115 120 125

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
130 135 140

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Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
145                 150                 155                 160

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
                165                 170                 175

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
            180                 185                 190

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
        195                 200                 205

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
    210                 215                 220

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly
225                 230                 235                 240

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
                245                 250                 255

Leu Gln Gln Ser Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys
            260                 265                 270

Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His
        275                 280                 285

Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile
    290                 295                 300

Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg
305                 310                 315                 320

Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu
                325                 330                 335

Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr
            340                 345                 350

Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu
        355                 360                 365

Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    370                 375                 380

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
385                 390                 395                 400

Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser
                405                 410                 415

Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser
            420                 425                 430

Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp
        435                 440                 445

Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser
    450                 455                 460

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln
465                 470                 475                 480

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro
                485                 490                 495

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505
```

-continued

<210> SEQ ID NO 103
<211> LENGTH: 1527
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 103

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga catcgtgatg 60

acccagtccc cctcctccct ggtggtgtcc attggcgagc gcgtgaccat gaactgcaag 120

tcctcccagt ccctgctgta ctcctccaac cagaagaact acctggcctg gtatcagcag 180

aagcccggcc agtcccctaa gctgctgatc tactgggcct ccagccgcga gtctggcgtg 240

cccgatagat tctccggctc tggctctggc accgacttta ccctgaccat ctcctccgtg 300

aaggccgagg acgtggccgt gtactactgc cagcagtact acaactaccc cctgaccttc 360

ggcgctggca ccaagctgga actgaagaga accgtggccg ctccctccgt gttcatcttc 420

ccaccttccg acgagcagct gaagtccggc accgcttctg tcgtgtgcct gctgaacaac 480

ttctaccccc gcgaggccaa ggtgcagtgg aaggtggaca acgccctgca gtccggcaac 540

tcccaggaat ccgtgaccga gcaggactcc aaggacagca cctactccct gtcctccacc 600

ctgaccctgt ccaaggccga ctacgagaag cacaaggtgt acgcctgcga agtgacccac 660

cagggcctgt ctagccccgt gaccaagtct ttcaaccggg gcgagtgcac tagtggcggc 720

ggaggatctg gcggaggtgg aagtgggga ggcggatctc aggtgcagct gcagcagtcc 780

ggagcagagg tggcaaagcc aggagccagc gtgaaggtgt cctgcaaggc ctctggctac 840

accttcacac ggtataccat gcactgggtg agacaggcac caggacaggg cctggagtgg 900

atgggctaca tcaacccctc tcggggctac acaaactata atcagaagtt taaggacagg 960

gccaccctga cacgcgataa gtctatcagc accgcctata tggagctgag ccggctgaga 1020

tccgacgata cagccgtgta ctattgtgcc agatactatg acgatcacta cagcctggac 1080

tattggggcc agggcaccac actgaccgtg agctctggcg gcggcggctc tggaggagga 1140

ggcagcggcg gaggaggctc cggaggaggc ggctctggcg gcggcggcag cggcggcggc 1200

ggctccgaca tccagatgac acagtcccca tctagcctgt ccgcctctgt gggcgatagg 1260

gtgaccatca catgctctgc ctcctctagc gtgagctaca tgaattggta tcagcagaag 1320

cccggcaagg cccctaagag gtggatctac gatacctcta agctggccag cggagtgcct 1380

tcccgcttca gcggctccgg ctctggaacc gactttaccc tgacaatctc ctctctgcag 1440

cctgaggatt tcgccacata ctattgtcag cagtggagct ccaacccatt caccttggc 1500

agcggcacaa agctggagat caatcgg 1527

<210> SEQ ID NO 104
<211> LENGTH: 463
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 104

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Glu Gly
            20                  25                  30

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Asn
        35                  40                  45

Ala Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
    50                  55                  60

Ala Arg Ile Arg Asn Lys Thr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
65                  70                  75                  80

Ser Val Lys Ala Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
                85                  90                  95

Leu Tyr Leu Gln Met Asn Ser Leu Lys Ile Glu Asp Thr Ala Met Tyr
            100                 105                 110

Tyr Cys Val Ala Gly Asn Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu
        115                 120                 125

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

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
145                 150                 155                 160

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
                165                 170                 175

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
            180                 185                 190

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
        195                 200                 205

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
    210                 215                 220

Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His
225                 230                 235                 240

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
                245                 250                 255

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
            260                 265                 270

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
        275                 280                 285

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
    290                 295                 300

Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser
305                 310                 315                 320

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
                325                 330                 335
```

-continued

```
Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
            340                 345                 350

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
        355                 360                 365

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
    370                 375                 380

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
385                 390                 395                 400

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
                405                 410                 415

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
            420                 425                 430

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
        435                 440                 445

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455                 460


<210> SEQ ID NO 105
<211> LENGTH: 1389
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 105

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga ggtgcagctg       60

gtggaatctg gcggaggact ggtgcagcct gagggctccc tgaagctgtc ttgtgccgcc      120

tccggcttca ccttcaacaa gaacgccatg aactgggtgc gacaggcccc tggcaagggc      180

ctggaatggg tggcccggat cagaaacaag accaacaact acgccaccta ctacgccgac      240

tccgtgaagg cccggttcac catctctcgg gacgactccc agtccatgct gtacctgcag      300

atgaacagcc tgaagatcga ggacaccgcc atgtactact gcgtggccgg caactccttc      360

gcctattggg gccagggcac cctcgtgacc gtgtcctctg cttctaccaa gggcccctct      420

gtgtttcctc tggcccccctc cagcaagtcc acctctggtg gaacagccgc cctgggctgc      480

ctcgtgaagg actactttcc cgagcccgtg accgtgtcct ggaactctgg cgctctgacc      540

tctggcgtgc acaccttccc tgctgtgctg cagtctagcg gcctgtactc cctgtcctcc      600

gtcgtgacag tgccctccag ctctctgggc acccagacct acatctgcaa cgtgaaccac      660

aagccctcca ataccaaggt ggacaagcgg gtggaaccca agtcctgcga caagacccac      720

acctgtcccc cttgtcctgc ccctgaactg ctgggcggac cttccgtgtt cctgttcccc      780

ccaaagccca aggacaccct gatgatctcc cggacccccg aagtgacctg cgtggtggtg      840

gatgtgtccc acgaggaccc tgaagtgaag ttcaattggt acgtggacgg cgtggaagtg      900

cacaacgcca agaccaagcc tagagaggaa cagtacgcct ccacctaccg ggtggtgtcc      960

gtgctgacag tgctgcacca ggactggctg aacggcaaag agtacaagtg cgccgtgtcc     1020
```

-continued

```
aacaaggccc tgcctgcccc catcgaaaag accatctcca aggccaaggg ccagccccgg     1080

gaaccccagg tgtacacact gccccctagc agggacgagc tgaccaagaa ccaggtgtcc     1140

ctgacctgtc tcgtgaaagg cttctacccc tccgatatcg ccgtggaatg ggagtccaac     1200

ggccagcctg agaacaacta caagaccacc ccccctgtgc tggactccga cggctcattc     1260

ttcctgtaca gcaagctgac cgtggacaag tcccggtggc agcagggcaa cgtgttctcc     1320

tgctccgtga tgcacgaggc cctgcacaac cactacaccc agaagtccct gtccctgagc     1380

cccggcaaa                                                            1389
```

<210> SEQ ID NO 106
<211> LENGTH: 503
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 106

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
            20                  25                  30

Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Lys Tyr
        35                  40                  45

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Val Lys Leu Leu Ile
    50                  55                  60

Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
65                  70                  75                  80

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
                85                  90                  95

Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
            100                 105                 110

Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Arg Thr Val Ala Ala
        115                 120                 125

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
    130                 135                 140

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
145                 150                 155                 160

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

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
            180                 185                 190

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
        195                 200                 205

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
    210                 215                 220

Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240
```

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```
Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala
                245                 250                 255

Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
            260                 265                 270

Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro
        275                 280                 285

Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr
    290                 295                 300

Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp
305                 310                 315                 320

Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser
            340                 345                 350

Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
        355                 360                 365

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
385                 390                 395                 400

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                405                 410                 415

Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln
            420                 425                 430

Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys
        435                 440                 445

Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
    450                 455                 460

Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr
465                 470                 475                 480

Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly
                485                 490                 495

Thr Lys Leu Glu Ile Asn Arg
            500
```

<210> SEQ ID NO 107
<211> LENGTH: 1509
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 107

```
atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcga catccagatg       60

acccagtctc caagctccct gtccgcctct gtgggcgaca gggtgaccat cacatgccag      120

gccagccagg atatctccaa gtacctgaac tggtatcagc agaagccagg caaggccgtg      180

aagctgctga tctaccacac atctcggctg cacagcggag tgccatccag attcagcggc      240
```

-continued

```
tccggctctg gcaccgacta taccctgaca atctctagcc tgcagcccga ggatatcgcc      300

acatacttct gtcagcaggg caataccctg ccttatacat ttggcggcgg caccaagctg      360

gagatcacac ggaccgtggc cgccccctcc gtgttcatct tccccccctc cgacgagcag      420

ctgaagtccg gcaccgcctc cgtggtgtgc ctgctgaaca acttctaccc ccgggaggcc      480

aaggtgcagt ggaaggtgga caacgccctg cagtccggca actcccagga gtccgtgacc      540

gagcaggact ccaaggactc cacctactcc ctgtcctcca ccctgaccct gtccaaggcc      600

gactacgaga agcacaaggt gtacgcctgc gaggtgaccc accagggcct gtcctccccc      660

gtgaccaagt ccttcaaccg gggcgagtgc actagtggcg gcggaggatc tggcggaggt      720

ggaagtgggg gaggcggatc tcaggtgcag ctgcagcagt ccggagcaga ggtggcaaag      780

ccaggagcca gcgtgaaggt gtcctgcaag gcctctggct acaccttcac acggtatacc      840

atgcactggg tgagacaggc accaggacag ggcctggagt ggatgggcta catcaacccc      900

tctcggggct acacaaacta taatcagaag tttaaggaca gggccaccct gacacgcgat      960

aagtctatca gcaccgccta tatggagctg agccggctga gatccgacga tacagccgtg     1020

tactattgtg ccagatacta tgacgatcac tacagcctgg actattgggg ccagggcacc     1080

acactgaccg tgagctctgg cggcggcggc tctggaggag gaggcagcgg cggaggaggc     1140

tccggaggag gcggctctgg cggcggcggc agcggcggcg gcggctccga catccagatg     1200

acacagtccc catctagcct gtccgcctct gtgggcgata gggtgaccat cacatgctct     1260

gcctcctcta gcgtgagcta catgaattgg tatcagcaga agcccggcaa ggcccctaag     1320

aggtggatct acgatacctc taagctggcc agcggagtgc cttcccgctt cagcggctcc     1380

ggctctggaa ccgactttac cctgacaatc tcctctctgc agcctgagga tttcgccaca     1440

tactattgtc agcagtggag ctccaaccca ttcacctttg gcagcggcac aaagctggag     1500

atcaatcgg                                                             1509
```

<210> SEQ ID NO 108
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 108

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
            20                  25                  30

Thr Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
        35                  40                  45

Gly Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
    50                  55                  60

Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Pro Ser Leu Lys
65                  70                  75                  80
```

-continued

```
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Val Ser Leu
                85                  90                  95

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
            100                 105                 110

Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
        115                 120                 125

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

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145                 150                 155                 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp
225                 230                 235                 240

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445
```

-continued

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460

Gly Lys
465

<210> SEQ ID NO 109
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 109

atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcca ggtgcagctg 60

caggagtccg gcccaggcct ggtgaagcca tctgagaccc tgagcgtgac ctgcacagtg 120

tccggcgtgt ctctgcctga ctatggcgtg tcttggatca gacagccacc tggcaagggc 180

ctggagtgga tcggcgtgat ctggggcagc gagaccacat actataaccc cagcctgaag 240

tccagagtga ccatctccgt ggacacatct aagaatcagg tgtctctgaa gctgagctcc 300

gtgaccgccg ccgatacagc cgtgtactat tgtgccaagc actactatta cggcggcagc 360

tatgctatgg actactgggg ccagggcacc tccgtgacag tgtctagcgc ctccaccaag 420

ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc 480

ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc 540

gccctgacca gcggcgtgca caccttcccg gccgtcctac agtcctcagg actctactcc 600

ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac 660

gtgaatcaca agcccagcaa caccaaggtg gacaagagag ttgagcccaa atcttgtgac 720

aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc gtcagtcttc 780

ctcttccccc caaaacccaa ggacaccctc atgatctccc ggaccccctga ggtcacatgc 840

gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta cgtggacggc 900

gtggaggtgc ataacgccaa gaccaagcct agagaggaac agtacgcctc cacctaccgg 960

gtggtgtccg tgctgacagt gctgcaccag gactggctga acggcaaaga gtacaagtgc 1020

gccgtgtcca acaaggccct gcctgccccc atcgaaaaga ccatctccaa ggccaagggc 1080

cagccccggg aaccccaggt gtacacactg ccccctagca gggacgagct gaccaagaac 1140

caggtgtccc tgacctgtct cgtgaaaggc ttctaccccct ccgatatcgc cgtggaatgg 1200

gagtccaacg gccagcctga gaacaactac aagaccaccc cccctgtgct ggactccgac 1260

ggctcattct tcctgtacag caagctgacc gtggacaagt cccggtggca gcagggcaac 1320

gtgttctcct gctccgtgat gcacgaggcc ctgcacaacc actacaccca gaagtccctg 1380

tccctgagcc ccggcaaa 1398

<210> SEQ ID NO 110
<211> LENGTH: 512
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 110

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Tyr Arg Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Gln Tyr Tyr Asn Tyr Pro Arg Thr Phe Gly Gly Gly Thr Lys
115 120 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130 135 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145 150 155 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Thr
225 230 235 240

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

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Ala Lys Pro Gly Ala
260 265 270

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
275 280 285

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
290 295 300

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
305 310 315 320

Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser Thr Ala Tyr
325 330 335

-continued

```
Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
            340                 345                 350

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
385                 390                 395                 400

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
                405                 410                 415

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
            420                 425                 430

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
        435                 440                 445

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
    450                 455                 460

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
465                 470                 475                 480

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
                485                 490                 495

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505                 510
```

<210> SEQ ID NO 111
<211> LENGTH: 1536
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 111

```
atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccatagcgac       60

atcgtgatga cccagagccc tgatagcctg gccgtgagcg tgggggaaag agtgacaatg      120

aactgtaaga gcagccagtc cctgctgtac cggtctaacc agaagaatta cctggcctgg      180

tatcagcaga agccaggcca gccccctaag ctgctgatct attgggcctc taccagggag      240

agcggagtgc cagacagatt ctctggcagc ggctccggca cagacttcac cctgacaatc      300

agctccgtgc aggcagagga cgtggccgtg tactattgtc agcagtatta caactacccc      360

agaacttttg gaggcggcac taaggtggaa atcaagcgga ccgtggccgc tccctccgtg      420

ttcatcttcc caccttccga cgagcagctg aagtccggca ccgcttctgt cgtgtgcctg      480

ctgaacaact tctacccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag      540

tccggcaact cccaggaatc cgtgaccgag caggactcca aggacagcac ctactccctg      600

tcctccaccc tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa      660

gtgacccacc agggcctgtc tagccccgtg accaagtctt tcaaccgggg cgagtgcact      720

agtggcggcg gaggatctgg cggaggtgga agtgggggag gcggatctca ggtgcagctg      780
```

-continued

```
cagcagtccg gagcagaggt ggcaaagcca ggagccagcg tgaaggtgtc ctgcaaggcc      840

tctggctaca ccttcacacg gtataccatg cactgggtga gacaggcacc aggacagggc      900

ctggagtgga tgggctacat caacccctct cggggctaca caaactataa tcagaagttt      960

aaggacaggg ccaccctgac acgcgataag tctatcagca ccgcctatat ggagctgagc     1020

cggctgagat ccgacgatac agccgtgtac tattgtgcca gatactatga cgatcactac     1080

agcctggact attggggcca gggcaccaca ctgaccgtga gctctggcgg cggcggctct     1140

ggaggaggag gcagcggcgg aggaggctcc ggaggaggcg gctctggcgg cggcggcagc     1200

ggcggcggcg gctccgacat ccagatgaca cagtccccat ctagcctgtc cgcctctgtg     1260

ggcgataggg tgaccatcac atgctctgcc tcctctagcg tgagctacat gaattggtat     1320

cagcagaagc ccggcaaggc ccctaagagg tggatctacg atacctctaa gctggccagc     1380

ggagtgcctt cccgcttcag cggctccggc tctggaaccg actttaccct gacaatctcc     1440

tctctgcagc ctgaggattt cgccacatac tattgtcagc agtggagctc caacccattc     1500

acctttggca gcggcacaaa gctggagatc aatcgg                               1536
```

<210> SEQ ID NO 112
<211> LENGTH: 473
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 112

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Asp Val Gln Val Gln Glu Ser Gly Pro Gly Leu Val Lys
            20                  25                  30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile
        35                  40                  45

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

Leu Glu Trp Met Gly Tyr Ile Ser Asn Ser Gly Ser Thr Ser Tyr Asn
65                  70                  75                  80

Pro Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn
                85                  90                  95

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Arg Asn Tyr Asp Tyr Asp Asp Tyr Tyr Tyr
        115                 120                 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ala Ala
    130                 135                 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145                 150                 155                 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
                165                 170                 175
```

-continued

```
Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
            180                 185                 190

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

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
    210                 215                 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
225                 230                 235                 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                245                 250                 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470


<210> SEQ ID NO 113
<211> LENGTH: 1419
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 113

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccactccgat       60
```

-continued

```
gtgcaggtgc aggaaagcgg cccaggactg gtgaagccct cccagactct gtctctgact      120

tgtaccgtga ccggctacag catcacctcc gactatgcct ggaactggat cagacagcca      180

cctggcaagg gcctggagtg gatgggctac atctctaaca gcggctccac atcttataat      240

ccctctctga agagcaggat caccatctcc cgcgatacat ctaagaacca gttcagcctg      300

aagctgagct ccgtgaccgc agcagacaca gccgtgtact attgcgcccg ggagagaaat      360

tacgattatg atgactacta ttatgctatg gattactggg gacaggggac tactctgacc      420

gtctccgccg cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc      480

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg      540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggccgtccta      600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc      660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga      720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc      780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc      840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag      900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag      960

cagtacgcca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg     1020

aatggcaagg agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa     1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gccccatcc      1140

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc     1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg     1260

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag     1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac     1380

cactacacgc agaagagcct ctccctgtct ccgggtaaa                            1419
```

<210> SEQ ID NO 114
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 114

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
            20                  25                  30

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile
        35                  40                  45

Asn Lys Tyr Ile Ala Trp Tyr Gln His Lys Pro Gly Lys Ala Pro Lys
    50                  55                  60
```

-continued

```
Leu Leu Ile Tyr Tyr Ala Ser Asn Leu Gln Pro Gly Val Pro Ser Arg
65                  70                  75                  80

Phe Ser Gly Ser Gly Ser Gly Arg Asp Phe Thr Phe Thr Ile Ser Ser
                85                  90                  95

Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Leu Gln Tyr Asp Asn
            100                 105                 110

Leu Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val
        115                 120                 125

Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys
    130                 135                 140

Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg
145                 150                 155                 160

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

Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser
            180                 185                 190

Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys
        195                 200                 205

Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
    210                 215                 220

Lys Ser Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly
225                 230                 235                 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
                245                 250                 255

Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
            260                 265                 270

Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln
        275                 280                 285

Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg
    290                 295                 300

Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr
305                 310                 315                 320

Arg Asp Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg
                325                 330                 335

Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
            340                 345                 350

Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
        355                 360                 365

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
385                 390                 395                 400

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
                405                 410                 415

Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp
            420                 425                 430
```

-continued

```
Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr
        435                 440                 445

Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
    450                 455                 460

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe
465                 470                 475                 480

Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly
                485                 490                 495

Ser Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505


<210> SEQ ID NO 115
<211> LENGTH: 1515
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 115

atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcgt gcacagcgac       60

atccagatga cccagtcccc tagctccctg tccgcctctg tgggcgacag ggtgaccatc      120

acatgcaagg cctcccagga tatcaacaag tacatcgcct ggtatcagca caagccaggc      180

aaggccccca agctgctgat ctactatgcc tctaatctgc agccaggagt gcctagccgg      240

ttcagcggct ccggctctgg aagagatttc acctttacaa tctctagcct gcagcccgag      300

gacatcgcca catactattg tctgcagtac gataacctgc tgacctttgg cgccggcaca      360

aagctggagc tgaagcggac cgtggccgcc ccctccgtgt tcatcttccc cccctccgac      420

gagcagctga agtccggcac cgcctccgtg gtgtgcctgc tgaacaactt ctacccccgg      480

gaggccaagg tgcagtggaa ggtggacaac gccctgcagt ccggcaactc ccaggagtcc      540

gtgaccgagc aggactccaa ggactccacc tactccctgt cctccaccct gaccctgtcc      600

aaggccgact acgagaagca caaggtgtac gcctgcgagg tgacccacca gggcctgtcc      660

tcccccgtga ccaagtcctt caaccggggc gagtgcacta gtggcggcgg aggatctggc      720

ggaggtggaa gtgggggagg cggatctcag gtgcagctgc agcagtccgg agcagaggtg      780

gcaaagccag gagccagcgt gaaggtgtcc tgcaaggcct ctggctacac cttcacacgg      840

tataccatgc actgggtgag acaggcacca ggacagggcc tggagtggat gggctacatc      900

aacccctctc ggggctacac aaactataat cagaagttta aggacagggc caccctgaca      960

cgcgataagt ctatcagcac cgcctatatg gagctgagcc ggctgagatc cgacgataca     1020

gccgtgtact attgtgccag atactatgac gatcactaca gcctggacta ttggggccag     1080

ggcaccacac tgaccgtgag ctctggcggc ggcggctctg gaggaggagg cagcggcgga     1140

ggaggctccg gaggaggcgg ctctggcggc ggcggcagcg gcggcggcgg ctccgacatc     1200

cagatgacac agtccccatc tagcctgtcc gcctctgtgg gcgatagggt gaccatcaca     1260

tgctctgcct cctctagcgt gagctacatg aattggtatc agcagaagcc cggcaaggcc     1320
```

-continued

```
cctaagaggt ggatctacga tacctctaag ctggccagcg gagtgccttc ccgcttcagc     1380

ggctccggct ctggaaccga ctttaccctg acaatctcct ctctgcagcc tgaggatttc     1440

gccacatact attgtcagca gtggagctcc aacccattca cctttggcag cggcacaaag     1500

ctggagatca atcgg                                                      1515
```

<210> SEQ ID NO 116
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 116

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Val Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ser Phe
        35                  40                  45

Thr Asp Tyr Asn Met Tyr Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Tyr Ile Asp Pro Tyr Lys Gly Gly Thr Ile Tyr Asn
65                  70                  75                  80

Gln Lys Phe Gln Gly Arg Ala Thr Leu Thr Arg Asp Thr Ser Ile Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Arg Glu Met Ile Thr Ala Tyr Tyr Phe Asp Tyr Trp
        115                 120                 125

Gly Gln Gly Ser Ser Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
    130                 135                 140

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
                245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270
```

-continued

```
Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> SEQ ID NO 117
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 117

```
atgggctggt cctgcatcat cctgttcctg gtggccaccg ccaccggcgt gcacagccag       60

gtgcagctgc agcagtccgg agcagaggtg gtgaagccag gagcctctgt gaaggtgagc      120

tgcaaggcca gcggctactc cttcaccgac tacaacatgt attgggtgcg gcaggcacca      180

ggacagggcc tggagtggat gggctacatc gacccttata agggcggcac aatctacaat      240

cagaagtttc agggaagggc caccctgaca agggacacct ccatctctac agcctatatg      300

gagctgtccc ggctgagatc tgacgatacc gccgtgtact attgtgccag ggagatgatc      360

acagcctact atttcgatta ttggggccag ggcagctccg tgaccgtgtc tagcgcctcc      420

accaagggcc cctctgtgtt tcctctggcc ccctccagca agtccacctc tggtggaaca      480

gccgccctgg gctgcctcgt gaaggactac tttcccgagc ccgtgaccgt gtcctggaac      540

tctggcgctc tgacctctgg cgtgcacacc ttccctgctg tgctgcagtc tagcggcctg      600
```

-continued

```
tactccctgt cctccgtcgt gacagtgccc tccagctctc tgggcaccca gacctacatc      660

tgcaacgtga accacaagcc ctccaatacc aaggtggaca agcgggtgga acccaagtcc      720

tgcgacaaga cccacacctg tccccttgt cctgcccctg aactgctggg cggaccttcc      780

gtgttcctgt tccccccaaa gcccaaggac accctgatga tctcccggac ccccgaagtg      840

acctgcgtgg tggtggatgt gtcccacgag gaccctgaag tgaagttcaa ttggtacgtg      900

gacggcgtgg aagtgcacaa cgccaagacc aagcctagag aggaacagta cgcctccacc      960

taccgggtgg tgtccgtgct gacagtgctg caccaggact ggctgaacgg caaagagtac     1020

aagtgcgccg tgtccaacaa ggccctgcct gcccccatcg aaaagaccat ctccaaggcc     1080

aagggccagc cccgggaacc ccaggtgtac acactgcccc ctagcaggga cgagctgacc     1140

aagaaccagg tgtccctgac ctgtctcgtg aaaggcttct acccctccga tatcgccgtg     1200

gaatgggagt ccaacggcca gcctgagaac aactacaaga ccacccccc tgtgctggac     1260

tccgacggct cattcttcct gtacagcaag ctgaccgtgg acaagtcccg gtggcagcag     1320

ggcaacgtgt tctcctgctc cgtgatgcac gaggccctgc acaaccacta cacccagaag     1380

tccctgtccc tgagccccgg caaa                                            1404
```

<210> SEQ ID NO 118
<211> LENGTH: 609
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 118

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
            20                  25                  30

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
        35                  40                  45

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
    50                  55                  60

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
65                  70                  75                  80

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
                85                  90                  95

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
            100                 105                 110

Cys Gly Thr Lys Leu Glu Ile Lys Arg Gly Gly Gly Gly Ser Gly Gly
        115                 120                 125

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    130                 135                 140

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Val Glu Ser Gly Pro
145                 150                 155                 160
```

-continued

```
Gly Val Val Gln Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val Ser
                165                 170                 175

Gly Phe Ser Val Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro Pro
            180                 185                 190

Gly Lys Cys Leu Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile Thr
        195                 200                 205

Asn Tyr Asn Ser Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp Asn
    210                 215                 220

Ser Lys Asn Thr Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
225                 230                 235                 240

Thr Ala Met Tyr Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr Ala
                245                 250                 255

Leu Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly
            260                 265                 270

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

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

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

Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu
                325                 330                 335

Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln
            340                 345                 350

Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser Thr
        355                 360                 365

Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr
    370                 375                 380

Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly
385                 390                 395                 400

Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
                405                 410                 415

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
            420                 425                 430

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
        435                 440                 445

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala
    450                 455                 460

Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys
465                 470                 475                 480

Ala Pro Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val
                485                 490                 495

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
            500                 505                 510

Ile Ser Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
        515                 520                 525
```

-continued

```
Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
    530                 535                 540

Asn Arg Thr Pro Leu Gly Asp Thr Thr His Thr Ser Gly Lys Pro Leu
545                 550                 555                 560

Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu Arg Phe Glu
                565                 570                 575

Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp Ala Gln Ala
            580                 585                 590

Gly Lys Glu Pro Gly Gly Ser Gly Gly Ala Pro His His His His His
        595                 600                 605

His
```

<210> SEQ ID NO 119
<211> LENGTH: 625
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 119

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Tyr Arg Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110

Cys Gln Gln Tyr Tyr Asn Tyr Pro Arg Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
    130                 135                 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
145                 150                 155                 160

Gly Ser Asp Val Gln Val Gln Glu Ser Gly Pro Gly Leu Val Lys Pro
                165                 170                 175

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

Ser Asp Tyr Ala Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu
        195                 200                 205

Glu Trp Met Gly Tyr Ile Ser Asn Ser Gly Ser Thr Ser Tyr Asn Pro
    210                 215                 220
```

-continued

```
Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln
225                 230                 235                 240

Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr
                245                 250                 255

Tyr Cys Ala Arg Glu Arg Asn Tyr Asp Tyr Asp Asp Tyr Tyr Tyr Ala
            260                 265                 270

Met Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ala Gly Gly
        275                 280                 285

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    290                 295                 300

Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Ala Lys Pro
305                 310                 315                 320

Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
                325                 330                 335

Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu
            340                 345                 350

Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln
        355                 360                 365

Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser Thr
    370                 375                 380

Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr
385                 390                 395                 400

Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly
                405                 410                 415

Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
            420                 425                 430

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
        435                 440                 445

Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser
    450                 455                 460

Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala
465                 470                 475                 480

Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys
                485                 490                 495

Ala Pro Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val
            500                 505                 510

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
        515                 520                 525

Ile Ser Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
    530                 535                 540

Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile
545                 550                 555                 560

Asn Arg Thr Pro Leu Gly Asp Thr Thr His Thr Ser Gly Lys Pro Leu
                565                 570                 575

Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg Glu Arg Phe Glu
            580                 585                 590
```

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```
Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys Asp Ala Gln Ala
        595                 600                 605

Gly Lys Glu Pro Gly Gly Ser Gly Gly Ala Pro His His His His His
    610                 615                 620

His
625


<210> SEQ ID NO 120
<211> LENGTH: 613
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 120

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
            20                  25                  30

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn Thr Ala
        35                  40                  45

Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
    50                  55                  60

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

Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
                85                  90                  95

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
            100                 105                 110

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu
145                 150                 155                 160

Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys
                165                 170                 175

Ala Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Arg
            180                 185                 190

Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr
        195                 200                 205

Asn Gly Tyr Thr Arg Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile
    210                 215                 220

Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu
225                 230                 235                 240

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp
                245                 250                 255
```

-continued

```
Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
            260                 265                 270

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

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

Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly
305                 310                 315                 320

Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly
                325                 330                 335

Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr
            340                 345                 350

Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys
        355                 360                 365

Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp Asp
    370                 375                 380

Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu
385                 390                 395                 400

Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly Gly
                405                 410                 415

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
            420                 425                 430

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
        435                 440                 445

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Met
    450                 455                 460

Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
465                 470                 475                 480

Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu
                485                 490                 495

Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
            500                 505                 510

Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr
        515                 520                 525

Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr
    530                 535                 540

Lys Leu Glu Ile Asn Arg Thr Pro Leu Gly Asp Thr Thr His Thr Ser
545                 550                 555                 560

Gly Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile Arg Gly Arg
                565                 570                 575

Glu Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu Glu Leu Lys
            580                 585                 590

Asp Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Gly Gly Ala Pro His
        595                 600                 605

His His His His His
    610
```

-continued

<210> SEQ ID NO 121
<211> LENGTH: 616
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 121

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
20 25 30

Ser Val Gly Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile
35 40 45

Ser Lys Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Val Lys
50 55 60

Leu Leu Ile Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg
65 70 75 80

Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser
85 90 95

Leu Gln Pro Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr
100 105 110

Leu Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr Arg Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
130 135 140

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
145 150 155 160

Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser
165 170 175

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

Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Val Ile
195 200 205

Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Pro Ser Leu Lys Ser Arg Val
210 215 220

Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Val Ser Leu Lys Leu Ser
225 230 235 240

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Lys His Tyr
245 250 255

Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
260 265 270

Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
275 280 285

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser
290 295 300

Gly Ala Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys
305 310 315 320

-continued

```
Ala Ser Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln
                325                 330                 335

Ala Pro Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg
            340                 345                 350

Gly Tyr Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr
        355                 360                 365

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

Ser Asp Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His
385                 390                 395                 400

Tyr Ser Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
                405                 410                 415

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
            420                 425                 430

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile
        435                 440                 445

Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg
    450                 455                 460

Val Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp
465                 470                 475                 480

Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr
                485                 490                 495

Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser
            500                 505                 510

Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe
        515                 520                 525

Ala Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly
    530                 535                 540

Ser Gly Thr Lys Leu Glu Ile Asn Arg Thr Pro Leu Gly Asp Thr Thr
545                 550                 555                 560

His Thr Ser Gly Lys Pro Leu Asp Gly Glu Tyr Phe Thr Leu Gln Ile
                565                 570                 575

Arg Gly Arg Glu Arg Phe Glu Met Phe Arg Glu Leu Asn Glu Ala Leu
            580                 585                 590

Glu Leu Lys Asp Ala Gln Ala Gly Lys Glu Pro Gly Gly Ser Gly Gly
        595                 600                 605

Ala Pro His His His His His His
    610                 615


<210> SEQ ID NO 122
<211> LENGTH: 503
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 122
```

-continued

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val Ser Ala Gly
            20                  25                  30

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val Ser Asn Asp
        35                  40                  45

Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
    50                  55                  60

Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
65                  70                  75                  80

Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
                85                  90                  95

Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
            100                 105                 110

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

Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
    130                 135                 140

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
145                 150                 155                 160

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

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

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

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

Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
225                 230                 235                 240

Gly Gly Gly Ser His Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val
                245                 250                 255

Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser
            260                 265                 270

Leu Thr Asp Tyr Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly
        275                 280                 285

Leu Glu Trp Leu Gly Val Ile Trp Ser Gly Gly Gly Thr Ala Tyr Asn
    290                 295                 300

Thr Ala Leu Ile Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
305                 310                 315                 320

Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val
                325                 330                 335

Tyr Tyr Cys Ala Arg Arg Gly Ser Tyr Pro Tyr Asn Tyr Phe Asp Ala
            340                 345                 350

Trp Gly Cys Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser
        355                 360                 365
```

-continued

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
    370                 375                 380

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ala Val Val Thr Gln Glu
385                 390                 395                 400

Pro Ser Leu Thr Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly
                405                 410                 415

Ser Ser Thr Gly Ala Val Thr Ala Ser Asn Tyr Ala Asn Trp Val Gln
            420                 425                 430

Gln Lys Pro Gly Gln Cys Pro Arg Gly Leu Ile Gly Gly His Asn Asn
        435                 440                 445

Arg Pro Pro Gly Val Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly
    450                 455                 460

Lys Ala Ala Leu Thr Leu Leu Gly Ala Gln Pro Glu Asp Glu Ala Glu
465                 470                 475                 480

Tyr Tyr Cys Ala Leu Trp Tyr Ser Asp His Trp Val Ile Gly Gly Gly
                485                 490                 495

Thr Lys Leu Thr Val Leu Gly
            500
```

<210> SEQ ID NO 123
<211> LENGTH: 1509
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 123

```
atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga gatcgtgatg       60

acacagaccc ctgccaccct gtccgtgtct gctggcgaga gagtgaccat tacctgcaag      120

gcctcccagt ccgtgtccaa cgacgtgacc tggtatcagc agaagcccgg ccaggccccc      180

agactgctga tctactccgc ctccaaccgg tactctggcg tgcccgctag attctccggc      240

tctggctacg gcaccgagtt taccttcacc atctcctccg tgcagtccga ggacttcgcc      300

gtgtacttct gtcagcaaga ctactccagc ttcggccagg gcaccaagct ggaaatcaag      360

cggaccgtgg ccgctccctc cgtgttcatc ttcccacctt ccgacgagca gctgaagtcc      420

ggcaccgctt ctgtcgtgtg cctgctgaac aacttctacc cccgcgaggc caaggtgcag      480

tggaaggtgg acaacgccct gcagtccggc aactcccagg aatccgtgac cgagcaggac      540

tccaaggaca gcacctactc cctgtcctcc accctgaccc tgtccaaggc cgactacgag      600

aagcacaagg tgtacgcctg cgaagtgacc caccagggcc tgtctagccc cgtgaccaag      660

tctttcaacc ggggcgagtg cactagtggc ggcggaggat ctggcggagg tggaagtggg      720

ggaggcggat ctcatgtgca gctggtggaa agcggaggcg gcctggtgca gcctgggggga      780

tctctgagac tgtcttgtgc cgccagcggc ttctccctga ccgattatgg cgtgcactgg      840

gtgcgacagg cccctggcaa aggactggaa tggctgggag tgatttggag tggcggaggc      900

accgcctaca acaccgccct gatctcccgg ttcaccatca gccgggacaa ctccaagaac      960
```

-continued

```
accctgtacc tgcagatgaa ctccctgcgg gccgaggaca ccgctgtgta ctactgcgcc     1020

agacggggct cctaccccta caactacttc gacgcttggg gctgcggcac cctcgtgaca     1080

gtgtctagcg gaggggggagg ttctgggggc ggaggttcag gtggtggtgg ttccgggggt     1140

ggtggctctg gtggcggtgg ttctggcggt ggcggatctc aggctgtcgt gacccaggaa     1200

cccagcctga ctgtgtctcc tggcggaacc gtgaccctga cctgcggatc ttctaccggc     1260

gctgtgaccg ccagcaacta cgccaattgg gtgcagcaga aacctggaca gtgccctaga     1320

ggcctgatcg gcggccacaa caacagacct ccaggcgtgc cagcccggtt ctctggatct     1380

ctgctgggcg gaaaggccgc tctgacactg ctgggtgctc agcctgagga cgaggccgag     1440

tactactgtg ccctgtggta ctccgaccac tgggtcatcg gaggcgggac caagctgacc     1500

gtgctggga                                                             1509


<210> SEQ ID NO 124
<211> LENGTH: 503
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 124

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                   10                  15

Val His Ser Glu Ile Val Met Thr Gln Thr Pro Ala Thr Leu Ser Val
            20                  25                  30

Ser Ala Gly Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Ser Val
        35                  40                  45

Ser Asn Asp Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg
    50                  55                  60

Leu Leu Ile Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg
65                  70                  75                  80

Phe Ser Gly Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser
                85                  90                  95

Val Gln Ser Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser
            100                 105                 110

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

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
    130                 135                 140

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
145                 150                 155                 160

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

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
            180                 185                 190

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
        195                 200                 205
```

-continued

```
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
    210                 215                 220

Phe Asn Arg Gly Glu Cys Thr Ser Gly Gly Gly Gly Ser Gly Gly Gly
225                 230                 235                 240

Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln Gln Ser Gly Ala
                245                 250                 255

Glu Val Ala Lys Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser
            260                 265                 270

Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro
        275                 280                 285

Gly Gln Gly Leu Glu Trp Met Gly Tyr Ile Asn Pro Ser Arg Gly Tyr
    290                 295                 300

Thr Asn Tyr Asn Gln Lys Phe Lys Asp Arg Ala Thr Leu Thr Arg Asp
305                 310                 315                 320

Lys Ser Ile Ser Thr Ala Tyr Met Glu Leu Ser Arg Leu Arg Ser Asp
                325                 330                 335

Asp Thr Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Ser
            340                 345                 350

Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly
        355                 360                 365

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
    370                 375                 380

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met
385                 390                 395                 400

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
                405                 410                 415

Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln
            420                 425                 430

Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Thr Ser Lys
        435                 440                 445

Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr
    450                 455                 460

Asp Phe Thr Leu Thr Ile Ser Ser Met Gln Pro Glu Asp Phe Ala Thr
465                 470                 475                 480

Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser Gly
                485                 490                 495

Thr Lys Leu Glu Ile Asn Arg
            500
```

<210> SEQ ID NO 125
<211> LENGTH: 1500
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 125

```
atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcga gatcgtgatg       60
```

-continued

```
acacagaccc ctgccaccct gtccgtgtct gctggcgaga gagtgaccat tacctgcaag      120

gcctcccagt ccgtgtccaa cgacgtgacc tggtatcagc agaagcccgg ccaggccccc      180

agactgctga tctactccgc ctccaaccgg tactctggcg tgcccgctag attctccggc      240

tctggctacg gcaccgagtt taccttcacc atctcctccg tgcagtccga ggacttcgcc      300

gtgtacttct gtcagcaaga ctactccagc ttcggccagg gcaccaagct ggaaatcaag      360

cggaccgtgg ccgctccctc cgtgttcatc ttcccacctt ccgacgagca gctgaagtcc      420

ggcaccgctt ctgtcgtgtg cctgctgaac aacttctacc cccgcgaggc caaggtgcag      480

tggaaggtgg acaacgccct gcagtccggc aactcccagg aatccgtgac cgagcaggac      540

tccaaggaca gcacctactc cctgtcctcc accctgaccc tgtccaaggc cgactacgag      600

aagcacaagg tgtacgcctg cgaagtgacc caccagggcc tgtctagccc cgtgaccaag      660

tctttcaacc ggggcgagtg cactagtggc ggcggaggat ctggcggagg tggaagtggg      720

ggaggcggat ctcaggtgca gctgcagcag tccggagcag aggtggcaaa gccaggagcc      780

agcgtgaagg tgtcctgcaa ggcctctggc tacaccttca cacggtatac catgcactgg      840

gtgagacagg caccaggaca gggcctggag tggatgggct acatcaaccc ctctcggggc      900

tacacaaact ataatcagaa gtttaaggac agggccaccc tgacacgcga taagtctatc      960

agcaccgcct atatggagct gagccggctg agatccgacg atacagccgt gtactattgt     1020

gcccggtact atgacgatca ctacagcctg gactattggg gccagggcac cacactgacc     1080

gtgagctctg gcggcggcgg ctctggagga ggaggcagcg gcggaggagg ctccggagga     1140

ggcggctctg gcggcggcgg cagcggcggc ggcggctccg acatccagat gacacagtcc     1200

ccatctagcc tgtccgcctc tgtgggcgat agggtgacca tgacatgctc tgcctcctct     1260

agcgtgagct acatgaattg gtatcagcag aagcccggca aggcccctaa gctgctgatc     1320

tacgatacct ctaagctggc cagcggagtg ccttcccgct tcagcggctc cggctctgga     1380

accgacttta ccctgacaat ctcctctatg cagcctgagg atttcgccac atactattgt     1440

cagcagtgga gctccaaccc attcaccttt ggcagcggca caaagctgga gatcaataga     1500
```

<210> SEQ ID NO 126
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 126

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ser Val
        35                  40                  45
```

-continued

```
Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser
65                  70                  75                  80

Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr
                85                  90                  95

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr
            100                 105                 110

Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu Asp Tyr Trp
        115                 120                 125

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
                245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                325                 330                 335

Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415
```

-continued

```
Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> SEQ ID NO 127
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 127

```
atgggctggt cctgcatcat cctgttcctg gtggccacca ccaccggcgt gcacagccag       60

gtgcagctgg tggagtccgg ccccggcgtg gtgcagcccg gccggtccct gcggatctcc      120

tgcgccgtgt ccggcttctc cgtgaccaac tacggcgtgc actgggtgcg acagcctcca      180

ggcaagggcc tggagtggct gggcgtgatc tgggccggcg gcatcaccaa ctacaactcc      240

gccttcatgt cccggctgac catctccaag gacaactcca agaacaccgt gtacctgcag      300

atgaactccc tgcgggccga ggacaccgcc atgtactact gcgcctcccg gggcggccac      360

tacggctacg ccctggacta ctggggccag ggcaccctgg tgaccgtgtc ctccgcctcc      420

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca      480

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac      540

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggccg tcctacagtc ctcaggactc      600

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc      660

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct      720

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca      780

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc      840

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg      900

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta cgccagcacg      960

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac     1020

aagtgcgcgg tctccaacaa agccctccca gccccccatcg agaaaaccat ctccaaagcc     1080

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga tgagctgacc     1140

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg     1200

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac     1260

tccgacggct ccttcttcct ctacagcagg ctcaccgtgg acaagagcag gtggcagcag     1320

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag     1380
```

-continued

agcctctccc tgtctccggg taaa 1404

<210> SEQ ID NO 128
<211> LENGTH: 515
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 128

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
20 25 30

Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu
35 40 45

Leu Tyr Arg Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
50 55 60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
65 70 75 80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
85 90 95

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr
100 105 110

Cys Gln Gln Tyr Tyr Asn Tyr Pro Arg Thr Phe Gly Gly Gly Thr Lys
115 120 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
130 135 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145 150 155 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
165 170 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
195 200 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
210 215 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Thr
225 230 235 240

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

His Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
260 265 270

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Thr Asp Tyr
275 280 285

Gly Val His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
290 295 300

-continued

```
Gly Val Ile Trp Ser Gly Gly Gly Thr Ala Tyr Asn Thr Ala Leu Ile
305                 310                 315                 320

Ser Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
                325                 330                 335

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
            340                 345                 350

Arg Arg Gly Ser Tyr Pro Tyr Asn Tyr Phe Asp Ala Trp Gly Cys Gly
        355                 360                 365

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
385                 390                 395                 400

Gly Gly Gly Gly Ser Gln Ala Val Val Thr Gln Glu Pro Ser Leu Thr
                405                 410                 415

Val Ser Pro Gly Gly Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly
            420                 425                 430

Ala Val Thr Ala Ser Asn Tyr Ala Asn Trp Val Gln Gln Lys Pro Gly
        435                 440                 445

Gln Cys Pro Arg Gly Leu Ile Gly Gly His Asn Asn Arg Pro Pro Gly
    450                 455                 460

Val Pro Ala Arg Phe Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu
465                 470                 475                 480

Thr Leu Leu Gly Ala Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Ala
                485                 490                 495

Leu Trp Tyr Ser Asp His Trp Val Ile Gly Gly Gly Thr Lys Leu Thr
            500                 505                 510

Val Leu Gly
        515
```

<210> SEQ ID NO 129
<211> LENGTH: 1545
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 129

```
atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccatagcgac       60

atcgtgatga cccagagccc tgatagcctg gccgtgagcg tgggggaaag agtgacaatg      120

aactgtaaga gcagccagtc cctgctgtac cggtctaacc agaagaatta cctggcctgg      180

tatcagcaga agccaggcca gccccctaag ctgctgatct attgggcctc taccagggag      240

agcggagtgc cagacagatt ctctggcagc ggctccggca cagacttcac cctgacaatc      300

agctccgtgc aggcagagga cgtggccgtg tactattgtc agcagtatta caactacccc      360

agaacttttg gaggcggcac taaggtggaa atcaagcgga ccgtggccgc tccctccgtg      420

ttcatcttcc caccttccga cgagcagctg aagtccggca ccgcttctgt cgtgtgcctg      480
```

-continued

```
ctgaacaact tctacccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag      540

tccggcaact cccaggaatc cgtgaccgag caggactcca aggacagcac ctactccctg      600

tcctccaccc tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa      660

gtgacccacc agggcctgtc tagccccgtg accaagtctt tcaaccgggg cgagtgcact      720

agtggcggcg gaggatctgg cggaggtgga agtgggggag gcggatctca tgtgcagctg      780

gtggaaagcg gaggcggcct ggtgcagcct gggggatctc tgagactgtc ttgtgccgcc      840

agcggcttct ccctgaccga ttatggcgtg cactgggtgc gacaggcccc tggcaaagga      900

ctggaatggc tgggagtgat ttggagtggc ggaggcaccg cctacaacac cgccctgatc      960

tcccggttca ccatcagccg ggacaactcc aagaacaccc tgtacctgca gatgaactcc     1020

ctgcgggccg aggacaccgc tgtgtactac tgcgccagac ggggctccta cccctacaac     1080

tacttcgacg cttggggctg cggcaccctc gtgacagtgt ctagcggagg gggaggttct     1140

gggggcggag gttcaggtgg tggtggttcc gggggtggtg gctctggtgg cggtggttct     1200

ggcggtggcg gatctcaggc tgtcgtgacc caggaaccca gcctgactgt gtctcctggc     1260

ggaaccgtga ccctgacctg cggatcttct accggcgctg tgaccgccag caactacgcc     1320

aattgggtgc agcagaaacc tggacagtgc cctagaggcc tgatcggcgg ccacaacaac     1380

agacctccag gcgtgccagc ccggttctct ggatctctgc tgggcggaaa ggccgctctg     1440

acactgctgg gtgctcagcc tgaggacgag gccgagtact actgtgccct gtggtactcc     1500

gaccactggg tcatcggagg cgggaccaag ctgaccgtgc tggga                     1545
```

<210> SEQ ID NO 130
<211> LENGTH: 512
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 130

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1               5                  10                  15

Val His Ser Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val
            20                  25                  30

Ser Val Gly Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu
        35                  40                  45

Leu Tyr Arg Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys
    50                  55                  60

Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
                85                  90                  95

Thr Leu Thr Ile Ser Ser Val Gln Ala Glu Asp Val Ala Val Tyr Tyr
            100                 105                 110
```

-continued

```
Cys Gln Gln Tyr Tyr Asn Tyr Pro Arg Thr Phe Gly Gly Gly Thr Lys
        115                 120                 125

Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro
    130                 135                 140

Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp
                165                 170                 175

Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys
        195                 200                 205

Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln
    210                 215                 220

Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Thr
225                 230                 235                 240

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

Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Val Ala Lys Pro Gly Ala
            260                 265                 270

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Arg Tyr
        275                 280                 285

Thr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
    290                 295                 300

Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn Tyr Asn Gln Lys Phe
305                 310                 315                 320

Lys Asp Arg Ala Thr Leu Thr Arg Asp Lys Ser Ile Ser Thr Ala Tyr
                325                 330                 335

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
            340                 345                 350

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
        355                 360                 365

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    370                 375                 380

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
385                 390                 395                 400

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
                405                 410                 415

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
            420                 425                 430

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
        435                 440                 445

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
    450                 455                 460

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
465                 470                 475                 480
```

-continued

```
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
                485                 490                 495

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
            500                 505                 510


<210> SEQ ID NO 131
<211> LENGTH: 1536
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 131

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccatagcgac       60

atcgtgatga cccagagccc tgatagcctg gccgtgagcg tgggggaaag agtgacaatg      120

aactgtaaga gcagccagtc cctgctgtac cggtctaacc agaagaatta cctggcctgg      180

tatcagcaga agccaggcca gccccctaag ctgctgatct attgggcctc taccagggag      240

agcggagtgc cagacagatt ctctggcagc ggctccggca cagacttcac cctgacaatc      300

agctccgtgc aggcagagga cgtggccgtg tactattgtc agcagtatta caactacccc      360

agaacttttg gaggcggcac taaggtggaa atcaagcgga ccgtggccgc tccctccgtg      420

ttcatcttcc caccttccga cgagcagctg aagtccggca ccgcttctgt cgtgtgcctg      480

ctgaacaact tctacccccg cgaggccaag gtgcagtgga aggtggacaa cgccctgcag      540

tccggcaact cccaggaatc cgtgaccgag caggactcca aggacagcac ctactccctg      600

tcctccaccc tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa      660

gtgacccacc agggcctgtc tagccccgtg accaagtctt tcaaccgggg cgagtgcact      720

agtggcggcg gaggatctgg cggaggtgga agtgggggag gcggatctca ggtgcagctg      780

cagcagtccg gagcagaggt ggcaaagcca ggagccagcg tgaaggtgtc ctgcaaggcc      840

tctggctaca ccttcacacg gtataccatg cactgggtga gacaggcacc aggacagggc      900

ctggagtgga tgggctacat caacccctct cggggctaca caaactataa tcagaagttt      960

aaggacaggg ccaccctgac acgcgataag tctatcagca ccgcctatat ggagctgagc     1020

cggctgagat ccgacgatac agccgtgtac tattgtgcca gatactatga cgatcactac     1080

agcctggact attggggcca gggcaccaca ctgaccgtga gctctggcgg cggcggctct     1140

ggaggaggag gcagcggcgg aggaggctcc ggaggaggcg gctctggcgg cggcggcagc     1200

ggcggcggcg gctccgacat ccagatgaca cagtccccat ctagcctgtc cgcctctgtg     1260

ggcgataggg tgaccatcac atgctctgcc tcctctagcg tgagctacat gaattggtat     1320

cagcagaagc ccggcaaggc ccctaagagg tggatctacg atacctctaa gctggccagc     1380

ggagtgcctt cccgcttcag cggctccggc tctggaaccg actttaccct gacaatctcc     1440

tctctgcagc ctgaggattt cgccacatac tattgtcagc agtggagctc caacccattc     1500

acctttggca gcggcacaaa gctggagatc aatcgg                               1536
```

-continued

<210> SEQ ID NO 132
<211> LENGTH: 473
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 132

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Val Gln Val Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile
35 40 45

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

Leu Glu Trp Met Gly Tyr Ile Ser Asn Ser Gly Ser Thr Ser Tyr Asn
65 70 75 80

Pro Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn
85 90 95

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Glu Arg Asn Tyr Asp Tyr Asp Asp Tyr Tyr Tyr
115 120 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ala Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

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

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
225 230 235 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
245 250 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
260 265 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
275 280 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
290 295 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305 310 315 320

-continued

```
Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
            420                 425                 430

Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470
```

<210> SEQ ID NO 133
<211> LENGTH: 1419
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 133

```
atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccactccgat       60

gtgcaggtgc aggaaagcgg cccaggactg gtgaagccct cccagactct gtctctgact      120

tgtaccgtga ccggctacag catcacctcc gactatgcct ggaactggat cagacagcca      180

cctggcaagg gcctggagtg gatgggctac atctctaaca gcggctccac atcttataat      240

ccctctctga agagcaggat caccatctcc cgcgatacat ctaagaacca gttcagcctg      300

aagctgagct ccgtgaccgc agcagacaca gccgtgtact attgcgcccg ggagagaaat      360

tacgattatg atgactacta ttatgctatg gattactggg gacaggggac tactctgacc      420

gtctccgccg cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc      480

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg      540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggccgtccta      600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc      660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga      720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc      780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc      840
```

-continued

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag 900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag 960

cagtacgcca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg 1020

aatggcaagg agtacaagtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa 1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc 1140

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc 1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg 1260

cctcccgtgc tggactccga cggctccttc ttcctctaca gcaggctcac cgtggacaag 1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac 1380

cactacacgc agaagagcct ctccctgtct ccgggtaaa 1419

<210> SEQ ID NO 134
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 134

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Cys Asp Tyr
1 5 10

<210> SEQ ID NO 135
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 135

Ala Arg Tyr Tyr Asp Asp His Cys Ser Leu Asp Tyr
1 5 10

<210> SEQ ID NO 136
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 136

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Cys Tyr
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 468
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 137

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Thr Thr Gly
1               5                  10                  15

Val His Ser Gln Val Gln Leu Val Glu Ser Gly Pro Gly Val Val Gln
            20                  25                  30

Pro Gly Arg Ser Leu Arg Ile Ser Cys Ala Val Ser Gly Phe Ser Val
        35                  40                  45

Thr Asn Tyr Gly Val His Trp Val Arg Gln Pro Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Leu Gly Val Ile Trp Ala Gly Gly Ile Thr Asn Tyr Asn Ser
65                  70                  75                  80

Ala Phe Met Ser Arg Leu Thr Ile Ser Lys Asp Asn Ser Lys Asn Thr
                85                  90                  95

Val Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr
            100                 105                 110

Tyr Cys Ala Ser Arg Gly Gly His Tyr Gly Tyr Ala Leu Asp Tyr Trp
        115                 120                 125

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

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
145                 150                 155                 160

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
                165                 170                 175

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
            180                 185                 190

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
        195                 200                 205

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
    210                 215                 220

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
225                 230                 235                 240

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
                245                 250                 255

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
            260                 265                 270

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
        275                 280                 285

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
    290                 295                 300

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr
305                 310                 315                 320

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
                325                 330                 335
```

-continued

```
Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro
            340                 345                 350

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
        355                 360                 365

Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val
    370                 375                 380

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
385                 390                 395                 400

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
                405                 410                 415

Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu Tyr Ser Lys Leu Thr
            420                 425                 430

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
        435                 440                 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
    450                 455                 460

Ser Pro Gly Lys
465
```

<210> SEQ ID NO 138
<211> LENGTH: 1404
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polynucleotide

<400> SEQUENCE: 138

```
atgggctggt cctgcatcat cctgttcctg gtggccacca ccaccggcgt gcacagccag       60

gtgcagctgg tggagtccgg ccccggcgtg gtgcagcccg gccggtccct gcggatctcc      120

tgcgccgtgt ccggcttctc cgtgaccaac tacggcgtgc actgggtgcg acagcctcca      180

ggcaagggcc tggagtggct gggcgtgatc tgggccggcg gcatcaccaa ctacaactcc      240

gccttcatgt cccggctgac catctccaag gacaactcca agaacaccgt gtacctgcag      300

atgaactccc tgcgggccga ggacaccgcc atgtactact gcgcctcccg gggcggccac      360

tacggctacg ccctggacta ctggggccag ggcaccctgg tgaccgtgtc ctccgcctcc      420

accaagggcc catcggtctt ccccctggca ccctcctcca agagcacctc tgggggcaca      480

gcggccctgg gctgcctggt caaggactac ttccccgaac cggtgacggt gtcgtggaac      540

tcaggcgccc tgaccagcgg cgtgcacacc ttcccggccg tcctacagtc ctcaggactc      600

tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca gacctacatc      660

tgcaacgtga atcacaagcc cagcaacacc aaggtggaca agagagttga gcccaaatct      720

tgtgacaaaa ctcacacatg cccaccgtgc ccagcacctg aactcctggg gggaccgtca      780

gtcttcctct tccccccaaa acccaaggac accctcatga tctcccggac ccctgaggtc      840

acatgcgtgg tggtggacgt gagccacgaa gaccctgagg tcaagttcaa ctggtacgtg      900

gacggcgtgg aggtgcataa tgccaagaca aagccgcggg aggagcagta cgccagcacg      960
```

-continued

taccgtgtgg tcagcgtcct caccgtcctg caccaggact ggctgaatgg caaggagtac 1020

aagtgcgcgg tctccaacaa agccctccca gcccccatcg agaaaaccat ctccaaagcc 1080

aaagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga tgagctgacc 1140

aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg 1200

gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac 1260

tccgacggct ccttcctcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag 1320

gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag 1380

agcctctccc tgtctccggg taaa 1404

<210> SEQ ID NO 139
<211> LENGTH: 473
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 139

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr Gly
1 5 10 15

Val His Ser Asp Val Gln Val Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Thr Gly Tyr Ser Ile
35 40 45

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

Leu Glu Trp Met Gly Tyr Ile Ser Asn Ser Gly Ser Thr Ser Tyr Asn
65 70 75 80

Pro Ser Leu Lys Ser Arg Ile Thr Ile Ser Arg Asp Thr Ser Lys Asn
85 90 95

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Glu Arg Asn Tyr Asp Tyr Asp Asp Tyr Tyr Tyr
115 120 125

Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ala Ala
130 135 140

Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser
145 150 155 160

Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe
165 170 175

Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly
180 185 190

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

Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr
210 215 220

-continued

```
Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg
225                 230                 235                 240

Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro
                245                 250                 255

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
            260                 265                 270

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
        275                 280                 285

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
    290                 295                 300

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
305                 310                 315                 320

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
                325                 330                 335

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Ala Val Ser Asn Lys
            340                 345                 350

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
        355                 360                 365

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
    370                 375                 380

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
385                 390                 395                 400

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
                405                 410                 415

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Leu Leu
            420                 425                 430

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
        435                 440                 445

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
    450                 455                 460

Lys Ser Leu Ser Leu Ser Pro Gly Lys
465                 470


<210> SEQ ID NO 140
<211> LENGTH: 1419
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polynucleotide

<400> SEQUENCE: 140

atgggctggt cctgcatcat cctgtttctg gtggctaccg ccaccggcgt ccactccgat       60

gtgcaggtgc aggaaagcgg cccaggactg gtgaagccct cccagactct gtctctgact      120

tgtaccgtga ccggctacag catcacctcc gactatgcct ggaactggat cagacagcca      180

cctggcaagg gcctggagtg gatgggctac atctctaaca gcggctccac atcttataat      240

ccctctctga agagcaggat caccatctcc cgcgatacat ctaagaacca gttcagcctg      300
```

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```
aagctgagct ccgtgaccgc agcagacaca gccgtgtact attgcgcccg ggagagaaat      360

tacgattatg atgactacta ttatgctatg gattactggg gacaggggac tactctgacc      420

gtctccgccg cctccaccaa gggcccatcg gtcttccccc tggcaccctc ctccaagagc      480

acctctgggg gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg      540

acggtgtcgt ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggccgtccta      600

cagtcctcag gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc      660

acccagacct acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaga      720

gttgagccca aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc      780

ctgggggggac cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc      840

cggacccctg aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag      900

ttcaactggt acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag      960

cagtacgcca gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg     1020

aatggcaagg agtacaagtg cgcggtctcc aacaaagccc tcccagcccc catcgagaaa     1080

accatctcca aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc     1140

cgggatgagc tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc     1200

agcgacatcg ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg     1260

cctcccgtgc tggactccga cggctccttc ctcctctaca gcaagctcac cgtggacaag     1320

agcaggtggc agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac     1380

cactacacgc agaagagcct ctccctgtct ccgggtaaa                            1419
```

<210> SEQ ID NO 141
<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 141

```
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                  10                  15

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

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

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

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

Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr Gly Val Tyr Phe Cys
                85                  90                  95

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110
```

-continued

```
Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
145                 150                 155                 160

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
                165                 170                 175

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Thr Pro Gly Lys Ala Pro
            180                 185                 190

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
        195                 200                 205

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Phe Thr Ile Ser
    210                 215                 220

Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
225                 230                 235                 240

Ser Asn Pro Phe Thr Phe Gly Cys Gly Thr Lys Leu Gln Ile Thr Arg
                245                 250                 255


<210> SEQ ID NO 142
<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 142

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
145                 150                 155                 160
```

-continued

```
Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser
                165                 170                 175

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
            180                 185                 190

Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
        195                 200                 205

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
    210                 215                 220

Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
225                 230                 235                 240

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
                245                 250                 255


<210> SEQ ID NO 143
<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 143

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

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

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

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

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

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
145                 150                 155                 160

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
                165                 170                 175

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
            180                 185                 190

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
        195                 200                 205
```

-continued

```
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
    210                 215                 220

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
225                 230                 235                 240

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
                245                 250                 255


<210> SEQ ID NO 144
<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 144

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
            100                 105                 110

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
        115                 120                 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
    130                 135                 140

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
145                 150                 155                 160

Ser Ala Ser Val Gly Asp Arg Val Thr Met Thr Cys Ser Ala Ser Ser
                165                 170                 175

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
            180                 185                 190

Lys Leu Leu Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
        195                 200                 205

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
    210                 215                 220

Ser Met Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
225                 230                 235                 240

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
                245                 250                 255


<210> SEQ ID NO 145
```

-continued

<211> LENGTH: 256
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 145

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

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

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

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

Lys Asp Arg Val Thr Leu Thr Thr Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Tyr Tyr Asp Asp His Tyr Ser Leu Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
130 135 140

Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
145 150 155 160

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser
165 170 175

Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
180 185 190

Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser
195 200 205

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
210 215 220

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Trp Ser
225 230 235 240

Ser Asn Pro Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Asn Arg
245 250 255

<210> SEQ ID NO 146
<211> LENGTH: 222
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 146

-continued

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

Glu Arg Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
            20                  25                  30

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

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

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

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

Tyr Tyr Asn Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
        115                 120                 125

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

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

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

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

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

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


<210> SEQ ID NO 147
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
      Synthetic polypeptide

<400> SEQUENCE: 147

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Lys Asn
            20                  25                  30

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

Ala Arg Ile Arg Asn Lys Thr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp
    50                  55                  60

Ser Val Lys Ala Arg Phe Thr Ile Ser Arg Asp Asp Ser Gln Ser Met
65                  70                  75                  80
```

-continued

```
Leu Tyr Leu Gln Met Asn Ser Leu Lys Ile Glu Asp Thr Ala Met Tyr
                85                  90                  95

Tyr Cys Val Ala Gly Asn Ser Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

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

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

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

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

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

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

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

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Ala Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
```

-continued

<210> SEQ ID NO 148
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<400> SEQUENCE: 148

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

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

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 149

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

Gly Gly Gly Ser
20

<210> SEQ ID NO 150
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 150

Thr Pro Leu Gly Asp Thr Thr His Thr
1 5

<210> SEQ ID NO 151
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 151

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

<210> SEQ ID NO 152
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic 6xHis tag

-continued

<400> SEQUENCE: 152

His His His His His His
1 5

<210> SEQ ID NO 153
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic peptide

<400> SEQUENCE: 153

Gly Gly Gly Gly Ser
1 5

<210> SEQ ID NO 154
<211> LENGTH: 75
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (1)..(75)
<223> OTHER INFORMATION: This sequence may encompass 1-15 "Gly Gly
Gly Gly Ser" repeating units

<220> FEATURE:
<223> OTHER INFORMATION: See specification as filed for detailed
description of substitutions and preferred embodiments

<400> SEQUENCE: 154

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

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

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75

<210> SEQ ID NO 155
<211> LENGTH: 150
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence:
Synthetic polypeptide

<220> FEATURE:
<221> NAME/KEY: SITE
<222> LOCATION: (1)..(150)
<223> OTHER INFORMATION: This sequence may encompass 1-20, 25 or 30
"Gly Gly Gly Gly Ser" repeating units

-continued

<220> FEATURE:
<223> OTHER INFORMATION: See specification as filed for detailed description of substitutions and preferred embodiments

<400> SEQUENCE: 155

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

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

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

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
65 70 75 80

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
115 120 125

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
130 135 140

Ser Gly Gly Gly Gly Ser
145 150

1. An antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein

(a) the V_H comprises a V_H-CDR1 sequence of GYTFTRYT (SEQ ID NO: 2), a V_H-CDR2 sequence of INPSRGYT (SEQ ID NO: 3), and a V_H-CDR3 sequence of ARYYDDHYSLDY (SEQ ID NO: 6), ARYYDDHYSCDY (SEQ ID NO: 134), ARYYDDHCSLDY (SEQ ID NO: 135), or ARYYDDHYSLCY (SEQ ID NO: 136); and;

(b) the V_L comprises a V_L-CDR1 sequence of SSVSY (SEQ ID NO: 12), a V_L-CDR2 sequence of DT (SEQ ID NO: 13), and a V_L-CDR3 sequence of QQWSSNPFT (SEQ ID NO: 14), optionally wherein

the antibody or antigen binding fragment binds to a CD3ε subunit that includes residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop); or

the antigen binding fragment is selected from the group consisting of Fab, $F(ab')_2$, Fab′, scF_v, and F_v; or

the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or multi-specific antibody, optionally wherein the multi-specific antibody or antigen binding fragment binds to T cells, B-cells, myeloid cells, plasma cells, mast-cells, CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N- acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PlGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Ley) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pmel17, LMP2, or WT1), or a small molecule DOTA hapten; or

the antibody or antigen binding fragment further comprising a Fc domain of an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1,

IgA2, IgM, IgD, and IgE, optionally wherein IgG1 comprises one or more amino acid substitutions selected from the group consisting of N297A and K322A; or IgG4 comprises a S228P mutation; or the antibody lacks α-1,6-fucose modifications.

2. An antibody or antigen binding fragment thereof comprising a heavy chain immunoglobulin variable domain (V_H) and a light chain immunoglobulin variable domain (V_L), wherein:

(a) the V_H comprises an amino acid sequence selected from any one of SEQ ID NOs: 5, 7, 8, 9, 10, or 43-61; and

(b) the V_L comprises an amino acid sequence selected from any one of SEQ ID NOs: 15-20 or 62-91), optionally wherein

the antibody or antigen binding fragment binds to a CD3ε subunit that includes residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop); or

the antigen binding fragment is selected from the group consisting of Fab, $F(ab')_2$, Fab′, scF_v, and F_v; or

the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or multi-specific antibody, optionally wherein the multi-specific antibody or antigen binding fragment binds to T cells, B-cells, myeloid cells, plasma cells, mast-cells, CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N- acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PlGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Le^y) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pmel17, LMP2, or WT1), or a small molecule DOTA hapten; or

wherein the antibody or antigen binding fragment comprises an amino acid sequence selected from any one of SEQ ID NOs: 118-121.

3. The antibody or antigen binding fragment of claim **2**, further comprising a Fc domain of an isotype selected from the group consisting of IgG1, IgG2, IgG3, IgG4, IgA1, IgA2, IgM, IgD, and IgE, optionally wherein

IgG1 comprises one or more amino acid substitutions selected from the group consisting of N297A and K322A; or

IgG4 comprises a S228P mutation; or

the antibody lacks α-1,6-fucose modifications.

4. (canceled)

5. (canceled)

6. (canceled)

7. (canceled)

8. (canceled)

9. An antibody comprising a heavy chain (HC) amino acid sequence comprising SEQ ID NO: 23, SEQ ID NO: 96, SEQ ID NO: 100, SEQ ID NO: 104, SEQ ID NO: 108, SEQ ID NO: 112, SEQ ID NO: 116, SEQ ID NO: 126, SEQ ID NO: 132, SEQ ID NO: 137, SEQ ID NO: 139 , and a light chain (LC) amino acid sequence comprising SEQ ID NO: 21, SEQ ID NO: 92, SEQ ID NO: 94, SEQ ID NO: 98, SEQ ID NO: 102, SEQ ID NO: 106, SEQ ID NO: 110, SEQ ID NO: 114, SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 128, SEQ ID NO: 130, optionally wherein

the antibody or antigen binding fragment binds to a CD3ε subunit that includes residues 79ε-85ε (the F-G loop), residue 34ε (the first residue of the ßC strand), and residues 46ε and 48ε (the C′-D loop); or

the antibody lacks α-1,6-fucose modifications; or

the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody, a bispecific antibody, or multi-specific antibody, optionally wherein the multi-specific antibody or antigen binding fragment binds to T cells, B-cells, myeloid cells, plasma cells, mast-cells, CD3, GPA33, HER2/neu, GD2, MAGE-1, MAGE-3, BAGE, GAGE-1, GAGE-2, MUM-1, CDK4, N-acetylglucosaminyltransferase, p15, gp75, beta-catenin, ErbB2, cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), RAGE, MART (melanoma antigen), MUC-1, MUC-2, MUC-3, MUC-4, MUC-5ac, MUC-16, MUC-17, tyrosinase, Pmel 17 (gp100), GnT-V intron V sequence (N- acetylglucoaminyltransferase V intron V sequence), Prostate cancer psm, PRAME (melanoma antigen), β-catenin, EBNA (Epstein-Barr Virus nuclear antigen) 1-6, LMP2, p53, lung resistance protein (LRP), Bcl-2, prostate specific antigen (PSA), Ki-67, CEACAM6, colon-specific antigen-p (CSAp), HLA-DR, CD40, CD74, CD138, EGFR, EGP-1, EGP-2, VEGF, PlGF, insulin-like growth factor (ILGF), tenascin, platelet-derived growth factor, IL-6, CD20, CD19, PSMA, CD33, CD123, MET, DLL4, Ang-2, HER3, IGF-1R, CD30, TAG-72, SPEAP, CD45, L1-CAM, Lewis Y (Ley) antigen, E-cadherin, V-cadherin, GPC3, EpCAM, CD4, CD8, CD21, CD23, CD46, CD80, HLA-DR, CD74, CD22, CD14, CD15, CD16, CD123, TCR gamma/delta, NKp46, KIR, CD56, DLL3, PD-1, PD-L1, CD28, CD137, CD99, GloboH, CD24, STEAP1, B7H3, Polysialic Acid, OX40, OX40-ligand, peptide MHC complexes (with peptides derived from TP53, KRAS, MYC, EBNA1-6, PRAME, MART, tyronsinase, MAGEA1-A6, pmel17, LMP2, or WT1), or a small molecule DOTA hapten.

10. The antibody of claim **9**, comprising a HC amino acid sequence and a LC amino acid sequence selected from the group consisting of:

SEQ ID NO: 23 and SEQ ID NO: 21,

SEQ ID NO: 23 and SEQ ID NO: 92,

SEQ ID NO: 96 and SEQ ID NO: 94,

SEQ ID NO: 100 and SEQ ID NO: 98,
SEQ ID NO: 104 and SEQ ID NO: 102,
SEQ ID NO: 108 and SEQ ID NO: 106,
SEQ ID NO: 112 and SEQ ID NO: 110, and
SEQ ID NO: 116 and SEQ ID NO: 114, respectively.

11. The antibody of claim **9**, comprising a first LC amino acid sequence, a second LC amino acid sequence, a first HC amino acid sequence, and a second HC amino acid sequence selected from the group consisting of SEQ ID NO: 122, SEQ ID NO: 124, SEQ ID NO: 126, and SEQ ID NO: 137; and SEQ ID NO: 128, SEQ ID NO: 130, SEQ ID NO: 132, and SEQ ID NO: 139, respectively.

12. (canceled)
13. (canceled)
14. (canceled)
15. (canceled)
16. (canceled)
17. (canceled)
18. (canceled)
19. (canceled)

20. A recombinant nucleic acid sequence encoding the antibody or antigen binding fragment of claim **2**, optionally wherein the recombinant nucleic acid sequence is selected from the group consisting of: SEQ ID NOs: 22, 24, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, 113, 115, 117, 123, 125, 127, 129, 131, 133, 138, and 140.

21. (canceled)

22. A host cell or vector comprising the recombinant nucleic acid sequence of claim **20**.

23. A composition comprising the antibody or antigen binding fragment of claim **2** and a pharmaceutically-acceptable carrier, wherein the antibody or antigen binding fragment is optionally conjugated to an agent selected from the group consisting of isotopes, dyes, chromagens, contrast agents, drugs, toxins, cytokines, enzymes, enzyme inhibitors, hormones, hormone antagonists, growth factors, radionuclides, metals, liposomes, nanoparticles, RNA, DNA or any combination thereof.

24. (canceled)
25. (canceled)
26. (canceled)
27. (canceled)
28. (canceled)

29. A method for treating a CD3-associated autoimmune disease in a subject in need thereof, comprising administering to the subject an effective amount of the antibody of claim **10** or a bispecific antibody or antigen binding fragment comprising an amino acid sequence selected from any one of SEQ ID NOs: 118-121, optionally wherein the CD3-associated autoimmune disease is selected from the group consisting of multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus, Celiac disease, Sympathetic ophthalmia, Type 1 diabetes, and graft-versus-host disease.

30. (canceled)

31. A method for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of the antibody of claim **10** or a bispecific antibody or antigen binding fragment comprising an amino acid sequence selected from any one of SEQ ID NOs: 118-121.

32. (canceled)

33. The method of claim **31**, wherein the cancer is selected from the group consisting of precursor T acute lymphoblastic leukemia/lymphoma, anaplastic large-cell lymphoma, lymphomatoid papulosis type A, Mycosis fungoides, pagetoid reticulosis, granulomatous slack skin, Sezary disease, adult T-cell leukemia/lymphoma, cutaneous large T cell lymphoma, pleomorphic T-cell lymphoma, lymphomatoid papulosis type B, secondary cutaneous CD30+ large-cell lymphoma, hepatosplenic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, enteropathy-associated T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, subcutaneous T-cell lymphoma, large granular lymphocytic leukemia, acute biphenotypic leukemia, adrenal cancers, bladder cancers, blood cancers, bone cancers, brain cancers, breast cancers, carcinoma, cervical cancers, colon cancers, colorectal cancers, corpus uterine cancers, ear, nose and throat (ENT) cancers, endometrial cancers, esophageal cancers, gastrointestinal cancers, head and neck cancers, Hodgkin's disease, intestinal cancers, kidney cancers, larynx cancers, acute and chronic leukemias, liver cancers, lymph node cancers, lymphomas, lung cancers, melanomas, mesothelioma, myelomas, nasopharynx cancers, neuroblastomas, non-Hodgkin's lymphoma, oral cancers, ovarian cancers, pancreatic cancers, penile cancers, pharynx cancers, prostate cancers, rectal cancers, sarcoma, seminomas, skin cancers, stomach cancers, teratomas, testicular cancers, thyroid cancers, uterine cancers, vaginal cancers, vascular tumors, and metastases thereof.

34. The method of claim **31**, wherein the antibody or antigen binding fragment is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent, optionally wherein the additional therapeutic agent is one or more of alkylating agents, platinum agents, taxanes, vinca agents, anti-estrogen drugs, aromatase inhibitors, ovarian suppression agents, VEGF/VEGFR inhibitors, EGF/EGFR inhibitors, PARP inhibitors, cytostatic alkaloids, cytotoxic antibiotics, antimetabolites, endocrine/hormonal agents, and bisphosphonate therapy agents.

35. (canceled)

36. The method of claim **29**, wherein the antibody or antigen binding fragment is administered to the subject separately, sequentially or simultaneously with an additional therapeutic agent, optionally wherein the additional therapeutic agent is one or more of non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, glucocorticoids, and conventional disease-modifying anti-rheumatic drugs (cDMARDs).

37. A method for detecting cancer in a subject in vivo comprising

(a) administering to the subject an effective amount of the antibody or antigen binding fragment of claim **2**, wherein the antibody or antigen binding fragment is configured to localize to a cancer cell expressing CD3 and is labeled with a radioisotope; and
(b) detecting the presence of a tumor in the subject by detecting radioactive levels emitted by the antibody or antigen binding fragment that are higher than a reference value, optionally wherein the subject is diagnosed with or is suspected of having cancer, or wherein the radioactive levels emitted by the antibody or antigen binding fragment are detected using positron emission tomography or single photon emission computed tomography.

38. (canceled)
39. (canceled)
40. (canceled)
41. (canceled)
42. (canceled)
43. (canceled)
44. (canceled)

45. (canceled)
46. (canceled)
47. (canceled)
48. (canceled)
49. (canceled)
50. (canceled)
51. The multi-specific antibody or antigen binding fragment of claim **9** or a bispecific antibody or antigen binding fragment comprising an amino acid sequence selected from any one of SEQ ID NOs: 118-121, wherein the multi-specific antibody binds to a radiolabeled DOTA hapten, a tumor antigen and a CD3 antigen.
52. (canceled)
53. A method for selecting a subject for pretargeted radioimmunotherapy comprising
(a) administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and the multi-specific antibody or antigen binding fragment of claim **51**, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment;
(b) detecting radioactive levels emitted by the complex; and
(c) selecting the subject for pretargeted radioimmunotherapy when the radioactive levels emitted by the complex are higher than a reference value.
54. A method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with cancer or treating cancer in a subject in need thereof comprising administering to the subject an effective amount of a complex comprising a radiolabeled DOTA hapten and the multi-specific antibody or antigen binding fragment of claim **51**, wherein the complex is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment.
55. (canceled)
56. (canceled)
57. A method for increasing tumor sensitivity to radiation therapy in a subject diagnosed with a cancer or treating cancer in a subject in need thereof comprising
(a) administering to the subject an effective amount of the multi-specific antibody or antigen binding fragment of claim **51**, wherein the multi-specific antibody is configured to localize to a tumor expressing the tumor antigen recognized by the multi-specific antibody or antigen binding fragment; and
(b) administering an effective amount of a radiolabeled-DOTA hapten to the subject, wherein the radiolabeled-DOTA hapten is configured to bind to the multi-specific antibody or antigen binding fragment.
58. (canceled)
59. The method of claim **57**, further comprising administering an effective amount of a clearing agent to the subject prior to administration of the radiolabeled-DOTA hapten.
60. (canceled)
61. (canceled)
62. (canceled)
63. (canceled)

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