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(12) **United States Patent**
Gliniak et al.(10) **Patent No.:** **US 7,521,048 B2**(45) **Date of Patent:** **Apr. 21, 2009**(54) **TRAIL RECEPTOR-2 POLYPEPTIDES AND ANTIBODIES**

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U.S.C. 154(b) by 0 days.(21) Appl. No.: **11/512,051**(22) Filed: **Aug. 28, 2006**(65) **Prior Publication Data**

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filed on Aug. 31, 2005.(51) **Int. Cl.****C12P 21/08** (2006.01)**A61K 39/00** (2006.01)(52) **U.S. Cl.** **424/133.1**; 530/388.22(58) **Field of Classification Search** 424/133.1
See application file for complete search history.(56) **References Cited****U.S. PATENT DOCUMENTS**

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Ran(57) **ABSTRACT**

Polypeptides are provided. Antibodies or antigen binding domains are provided which bind such polypeptides. Also provided are methods of obtaining an antibody that binds tumor necrosis factor (TNF)-related apoptosis-inducing ligand ("TRAIL") Receptor-2 (TR-2) comprising administering at least one of such polypeptides to an animal and obtaining an antibody that binds TR-2 from the animal. Antibodies reactive with TR-2 are provided. Also provided are cells producing antibodies reactive with TR-2, pharmaceutical compositions comprising antibodies reactive with TR-2, methods using antibodies reactive with TR-2, and kits comprising antibodies reactive with TR-2. Also provided are methods of decreasing or preventing binding of an antibody to TR-2 by administering such a polypeptide.

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XENOMOUSE IMMUNIZATION SCHEDULE

Group #	Mode of Imm.	Strain	# of mice	1st Inj.	1st boost	2nd boost	3rd boost	Bleed	4th boost	5th boost	Bleed	6th boost	7th boost	8th boost	9th boost	Fusion
1	Footpad	XMG2	7	10 ug /mouse Thiormax Gold Day 0	10 ug /mouse Alum Gel Day 5	10 ug /mouse Alum Gel Day 11	10 ug /mouse Alum Gel Day 14	Day 16	10 ug /mouse Alum Gel Day 18	10 ug /mouse Thiormax Gold Day 24	Day 28	10 ug /mouse Alum Gel Day 28	10 ug /mouse Alum Gel Day 34	10 ug /mouse Alum Gel Day 42	10 ug /mouse D-PBS Day 46	Day 48

Group #	Mode of Imm.	Strain	# of mice	1st Inj.	1st boost	2nd boost	3rd boost	Bleed	4th boost	5th boost	Bleed	6th boost	7th boost	Fusion
2	Footpad	3C-1	8	10 ug /mouse Thiormax Gold Day 0	10 ug /mouse Alum Gel Day 3	10 ug /mouse Alum Gel Day 7	10 ug /mouse Alum Gel Day 10	Day 14	10 ug /mouse Alum Gel Day 14	10 ug /mouse Thiormax Gold Day 17	Day 23	10 ug /mouse Alum Gel Day 24	10 ug /mouse D-PBS Day 27	Day 31

Group #	Mode of Imm.	Strain	# of mice	1st inj.	1st boost	2nd boost	3rd boost	Bleed	4th boost	5th boost	Bleed	6th boost	7th boost	Fusion
3	Footpad	XMG2	8	10 ug /mouse Titanmax Gold Day 0	10 ug /mouse Alum Gel Day 5	10 ug /mouse Alum Gel Day 8	10 ug /mouse Alum Gel Day 15	Day 21	10 ug /mouse Alum Gel Day 21	10 ug /mouse Alum Gel Day 26	Day 30	10 ug /mouse Alum Gel Day 30	10 ug /mouse D-PBS Day 33	Day 37

Group #	Mode of Imm.	Strain	# of mice	1st Inj.	1st boost	2nd boost	Bleed	Bleed	4th boost	Bleed	8th boost	Fusion
4	B/P	XMG2	10	10 ug /mouse CFA Day 0	10 ug /mouse IFA Day 14	10 ug /mouse IFA Day 28	Day 37		10 ug /mouse IFA Day 42	10 ug /mouse IFA Day 58	Day 54	Day 76

Group #	Mode of Imm.	Strain	# of mice	1st Inj.	1st boost	2nd boost	Bleed	Bleed	4th boost	Bleed	5th boost	Fusion
5	B/P	XMG2	5	10 ug /mouse CFA Day 0	10 ug /mouse IFA Day 14	10 ug /mouse IFA Day 28	Day 37		10 ug /mouse IFA Day 42	10 ug /mouse IFA Day 56	Day 54	Day 76

FIGURE 1

Group 1 Immunized XenoMice

Mouse ID	Day 18 bleed (after 4 Inj.)	Day 28 bleed (after 6 Inj.)	Day 46 fusion (after 10 Inj.)
	Reactivity to TR-2 Titers via hlgG		
M560-1	60	1,000	-
M560-2	24,000	40,000	73,000
M560-3	400	12,000	80,000
M560-4	2,500	16,000	80,000
M560-5	200	16,000	150,000
M560-6	1,200	50,000	300,000
M560-7	<100	1,000	-
NC	40	50	210
PC	4,100	3,500	24,000

Group 2 Immunized XenoMice

Mouse ID	Day 14 bleed (after 4 Inj.)	Day 23 bleed (after 6 Inj.)
	Reactivity to TR-2 Titers via hlgG	
L475-6	75	350
L568-7	50	175
L569-7	50	<100
M050-4	50	25
M057-6	50	40
M184-3	50	110
M230-5	50	25
M365-4	50	<100
NC	50	<100
PC	3,500	11,000

Group 3 Immunized XenoMice

Mouse ID	Day 21 bleed (after 4 Inj.)
	Reactivity to TR-2 Titers via hlgG
M712-1	75
M712-2	2,400
M712-3	800
M712-4	2,700
M712-5	1,800
M712-6	290
M712-7	7,500
M712-8	800
NC	<100
PC	24,000

Group 5 Immunized XenoMice

Mouse ID	Day 37 bleed (after 3 Inj.)
	Reactivity to TR-2 Titers via hlgG
M564-1	100
M564-2	100,000
M564-3	200
M564-4	80
M564-5	60
NC	210
PC	24,000

Group 4 Immunized XenoMice

Mouse ID	Day 37 bleed (after 3 Inj.)
	Reactivity to TR-2 Titers via hlgG
M563-1	300
M563-2	100
M563-3	200
M563-4	250,000
M563-5	700
M563-6	<100
M563-7	120
M563-8	130
M563-9	<100
M563-10	<100
NC	225
PC	36,000

Negative Control (NC)

bleed from mouse
not immunized with
TR-2

Positive Control (PC)

TR-2+ 1:50 bleed
from group 1 mouse

FIGURE 2

ANTIBODY A**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGCCTC
AGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTCACCAGTTATGATAT
CAACTGGGTGCGACAGGCCACTGGACAAGGGCTTGAGTGGATGGGATGG
ATGAACCCTAACAGTGATAACACAGGCTATGCACAGAAGTTCAGGGCAG
AGTCACCATGACCAGGAACACCTCCATAAGCACAGCCTACATGGAGTTGA
GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGATGGAAT
CACTATGGTTTCGGGGAGTCATTTTGA TACTGGGGCCAGGGAACCCTGGT
CACCGTCTCCTCA (SEQ ID NO: 1)

Protein sequence of the heavy chain variable region:

QVQLVQSGAEVKKPGASVKVSKASGYTFTSYDINWVRQATGQGLEWMGW
MNPNSDNTGYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARWNH
YGSGSHFDYWQGGLVTVSS (SEQ ID NO: 2)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCATTTATTTAAA
TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTG
CATCCAGTTTGCAAAGTGGGGTCCCATTAAGGTTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATATTGC
AACTTACTACTGTCAACAGAGTTACAAAACCCCGCTCACTTTCGGCGGAG
GGACCAAGGTGGAGATCAAA (SEQ ID NO: 35)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVITICRASQSISYLNWYQQKPGKAPKLLIYAASSL
QSGVPLRFSGSGSDFTLTISLQPEDATYYCQSYKTPLTFGGGTKVEIK
(SEQ ID NO: 36)

FIGURE 3

ANTIBODY B**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTCA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCT
GAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTATTGTGCGAGAGATG
ACAGCAGTGGCTGGGGTTTTGACTACTGGGGCCAGGGAATCCTGGTCACC
GTCTCCTCA (SEQ ID NO: 3)

Protein sequence of the heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGHYWSWIRQHPGKGLEWIGYI
YYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDSSGW
GFDYWGGQILVTVSS (SEQ ID NO: 4)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGGGCCTTAGAAATGATTTAGG
CTGGTTTCAGCAGAAACCAGGGAAAGTCACTAAGCGCCTGATCTATGCTG
CATCCAGTTTGCAAAGAGGGGTCCCATCAAGGTTCAAGCGCAGTGGATCT
GGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGC
AACTTATTACTGTCTACAGCATTATAGTTTCCCGTGGACGTTTCGGCCAAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 37)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGLRNDLGWFQQKPGKVTKRLIYAASS
LQRGVPSRFSGSGSGTEFTLTISLQPEDFATYYCLQHYSFPWTFGQGTKVEIK
(SEQ ID NO: 38)

FIGURE 4

ANTIBODY C**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTCA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCGCCTACTACAACCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCT
GAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGATG
ACAGCAGTGGCTGGGGTTTTGACTACTGGGGCCAGGGAATCCTGGTCACC
GTCTCCTCA (SEQ ID NO: 5)

Protein sequence of the heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGHYWSWIRQHPGKGLEWIGYI
YYSGSAYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDSSGW
GFDYWGQGILVTVSS (SEQ ID NO: 6)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGGGCCTTAGAAATGATTTAGG
CTGGTTTCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG
CATCCAGTTTGCAAAGAGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCT
GGGACAGAATTCCTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTAC
AACTTATTTCTGTCTACAGCATAATAGTTTCCCGTGGACGTTCCGCCAAGG
GACCAAGGTGGAAATCAAA (SEQ ID NO: 39)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGLRNDLGWFQQKPGKAPKRLIYAASS
LQRGVPSRFSGSGSGTEFTLTISLQPEDFTTYFCLQHNSFPWTFGQGTKVEIK
(SEQ ID NO: 40)

FIGURE 5

ANTIBODY D**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTCA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCGCCTACTACAACCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCT
GAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGATG
ACAGCAGTGGCTGGGGTTTTGACTACTGGGGCCAGGGAATCCTGGTCACC
GTCTCCTCA (SEQ ID NO: 7)

Protein sequence of the heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGGHYWSWIRQHPGKGLEWIGYI
YYSGSAYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDSSGW
GFDYWGQGILVTVSS (SEQ ID NO: 8)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGGGCCTTAGAAATGATTTAGG
CTGGTTTCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTG
CATCCAGTTTGCAAAGAGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCT
GGGACAGAATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTAC
AACTTATTTCTGTCTACAGCATAATAGTTTCCCGTGGACGTTTCGGCCAAGG
GACCAAGGTGGAAATCAAA (SEQ ID NO: 41)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRTITCRASQGLRNDLGWFQQKPGKAPKRLIYAASS
LQRGVPSRFSGSGSGTEFTLTISLQPEDFTTYFCLQHNSFPWTFGQGTKVEIK
(SEQ ID NO: 42)

FIGURE 6

ANTIBODY E**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTC
CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTGACTACTACAT
GAACTGGATCCGCCAGGCTCCAGGGAAGGGACTGGAGTGGGTTTCACACA
TTAGTAGTAGTGGTAGTATCTTAGACTACGCAGACTCTGTGAAGGGCCGA
TTCACCATCTCCAGGGACAACGCCAAGAACTCACTGTATCTGCAAATGAA
CAGCCTGAGAGTCGAGGACACGGCCGTGTATTACTGTGCGAGAGATGGGG
CTGCAGCTGGTACGGATGCTTTTGATCTCTGGGGCCAAGGGACAATGGTC
ACCGTCTCTTCA (SEQ ID NO: 9)

Protein sequence of the heavy chain variable region:

QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYMNVIRQAPGKGLEWVSHIS
SSGSILDYADSVKGRFTISRDNANKNSLYLQMNSLRVEDTAVYYCARDGAAAG
TDAFDLWGQGTMTVSS (SEQ ID NO: 10)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGTCAAGTCAGAGCATTAGTAACTATATAAA
TTGGTATCAACAGAGACCAGGGAAAGCCCCGAACCTCCTGATCCATGATG
TATCCAGTTTCCAAAGTGCGGTCCCATCAAGGTTTCAGTCGCAGTGGATCTG
GGACAGTTTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAA
CTTACTTCTGTCAACAGACTTACATTACCCCATTCACCTTCGGCCCTGGGA
CCAAAGTGGATATCAAA (SEQ ID NO: 43)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRSSQSISNYINWYQQRPGKAPNLLIHDVSSF
QSAVPSRFSRSGSGTVFTLTISLQPEDFATYFCQQTITPFTFGPGTKVDIK
(SEQ ID NO: 44)

FIGURE 7

ANTIBODY F**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTTACTATGGCAT
ACACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA
TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA
TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAA
CAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGGAGGT
ATAGCAGCTCGTCCTGGTGGTACTTCGATCTCTGGGGCCGTGGCACCCCTGG
TCACTGTCTCCTCA (SEQ ID NO: 11)

Protein sequence of the heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYYGIHWVRQAPGKGLEWVAVI
WYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGRYS
SSSWWYFDLWGRGTLVTVSS (SEQ ID NO: 12)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCGAGTCAGGGCATTAGCAATTATTTAGC
CTGGTATCAGCAGAAACCAGGGAAAGTTCCTAAGCTCCTGATCTATGCTG
CATCCACTTTGCAATCAGGGGTCCCATCTCGGTTTCAGTGGCAGTGGATCTG
GGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATGTTGCA
ACTTATTACTGTCAAAAGTATAACAGTGCCCCGCTCACTTTCGGCGGAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 45)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWYQQKPGKVPKLLIYAAS
T LQSGVPSRFSGSGSGTDFTLTISSLQPEDVATYYCQKYN S APLTFGGG TKVEIK
(SEQ ID NO: 46)

FIGURE 8

ANTIBODY G**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGGCTGAGCAGTCGGGCCAGGACTGGTGAAGCCTTCGGAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAATTACTACTG
GAGCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTAT
ATCTATTACAGTGGGAGCACCAAGTACAACCCCTCCCTCAAGAGTCGAGT
CACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTAACCT
CTGTGACCACTGCGGACACGGCCGTGTATTACTGTGCGAGAGACTCCCCT
CGTGGATTTAGTGGCTACGAGGCTTTTGACTCCTGGGGCCAGGGAACCCT
GGTCACCGTCTCCTCA (SEQ ID NO: 13)

Protein sequence of the heavy chain variable region:

QVQAEQSGPGLVKPSETLSLTCTVSGGSISNYWWSWIRQPPGKGLEWIGYIYY
SGSTKYNPSLKSRTISVDTSKNQFSLKLTSVTTADTAVYYCARDSPRGFSGY
EAFDSWGQGLVTVSS (SEQ ID NO: 14)

Nucleotide sequence of the light chain variable region:

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGGTCCAA
CAATAAGATCTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCTA
AGCTGCTCATTTACTGGGCATCGACCCGGAATCCGGGGTCCCTGACCGA
TTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCT
GCTGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACTCC
ATTCACCTTTCGGCCCTGGGACCAAAGTGGATATCAAA (SEQ ID NO: 47)

Protein sequence of the light chain variable region:

DIVMTQSPDSLAVSLGERATINCKSSQSVLYRSNNKIYLAWYQQKPGQPPKLL
IYWASTRESGVDPDRFSGSGSGTDFLTISLLAEDVAVYYCQQYYSTPFTFGPG
TKVDIK (SEQ ID NO: 48)

FIGURE 9

ANTIBODY H**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGATAATTA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCT
GAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGGAG
TTAACTGGAAC TTTCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCG
TCTCTTCA (SEQ ID NO: 15)

Protein sequence of the heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSDNYYWSWIRQHPGKGLEWIGYI
YYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARGVNWNF
LFDIWGQGTMVTVSS (SEQ ID NO: 16)

Nucleotide sequence of the light chain variable region:

GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCCCGTCACCCCTGGAGAG
CCGGCCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCGTCGTAATGGA
TACAACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAGTCTCCACAAC
CCTGATCTATTTGGGTTCTAATCGGGCCTCCGGGGTCCCAGACAGGTTTCAG
TGGCAGTGGATCAGGCACAGATTTTACACTGAAAATCAGCAGAGTGGAGG
CTGAGGATGTTGGGGTTTATTACTGCATGCAAGCTCTACAAACTCCGCTCA
CTTTCGGCGGAGGGACCGAGGTGGAGATCAAA (SEQ ID NO: 49)

Protein sequence of the light chain variable region:

DIVMTQSPLSLPVTPGEPASISCRSSQSLRRNGYNYLDWYLQKPGQSPQLLIY
LGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQALQTPLTFGGG
TEVEIK (SEQ ID NO: 50)

FIGURE 10

ANTIBODY I**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCAAGCCTGGAGGGTC
CCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTGACTACTACAT
GAGCTGGATCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTTTCATACA
TTAGTAGAAGTGGTAGTACCATATACTACGCAGACTCTGTGAAGGGCCGA
TTCACCATCTCCAGGGACAACGCCAAGAAGTCACTGTATCTGCAAATGAA
CAGCCTGAGAGCCGAGGACACGGCCGTGTATTACTGTGCGAGATCTTTAG
GCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
(SEQ ID NO: 17)

Protein sequence of the heavy chain variable region:

QVQLVESGGGLVKPGGSLRLSCAASGFTFSDYYSWIRQAPGKGLEWVSYIS
RSGSTIYYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARSLGGMD
VWGQGTTVTVSS (SEQ ID NO: 18)

Nucleotide sequence of the light chain variable region:

GACATCGTGATGACCCAGTTTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTACACAGCTCCAA
CAATAAGAACTACTTAACTTGGTACCAGCTGAAACCAGGACAGCCTCCTA
AGTTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCGAT
TCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCCTG
CAGGCTGAAGATGTGGCAGTTTATTACTGTCACCAATATTATAGTACTCCG
TCCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAA (SEQ ID NO: 51)

Protein sequence of the light chain variable region:

DIVMTQFPDSLAVSLGERATINCKSSQSVLHSSNNKNYLTWYQLKPGQPPKLL
IYWASTRESGVPDRFSGSGSGTDFTLTISLQAEDVAVYYCHQYYSTPSSFGQ
GTKLEIK (SEQ ID NO: 52)

FIGURE 11

ANTIBODY J**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAATAACTATGGCAT
GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA
TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA
TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAA
CAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATAGGA
CCGTATATAGCAACTCGTCACCTTTTACTACTACTACTACGGTATGGACG
TCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO: 19)

Protein sequence of the heavy chain variable region:

QVQLVESGGGVVQGRSLRLSCAASGFTFNNGMHWVRQAPGKGLEWVAV
IWYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRT
VYSNSSPFYYYYYGMDVWGQGTITVTVSS (SEQ ID NO: 20)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTTGGAGAC
AGAGTCACCATCACTTGCCGGACAAGTCAGAGCATTAGCACCTATTTAAA
TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTCTGCTA
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCA
ACTTACTACTGTCAACAGAGTTACAGTACCCCGCTCACTTTCGGCGGAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 53)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRTS QSISTYLNWYQQKPGKAPKLLISATSSL
QSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIK
(SEQ ID NO: 54)

FIGURE 12

ANTIBODY K**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTC
CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTACCTATGGCAT
GCACTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTA
TATGGTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGA
TTCACCATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAA
CAGCCTGAGAGCCGAGGACACGGCTGTGTATTATTGTGCGAGAGATAGGA
CCGTATATAGCAGCTCGTCACCTTTTACTACTACTACTACGGTATGGACG
TCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO: 21)

Protein sequence of the heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSTYGMHWVRQAPGKGLEWVAVI
WYDGSNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARDRTV
YSSSPFYYYYYYGM DVWGQGTTVTVSS (SEQ ID NO: 22)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAA
TTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTCTGCTA
CATCCAGTTTTCAAAGTGGGGTCCCATCAAGGTTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCA
GCTTACTACTGTCAACAGAGTTACAGTACCCCGCTCACTTTCGGCGGAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 55)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLISATSSF
QSGVPSRFS GSGSGTDFLTISLQPEDFAAYYCQQSYSTPLTFGGGTKVEIK
(SEQ ID NO: 56)

FIGURE 13

ANTIBODY L**Nucleotide sequence of the heavy chain variable region:**

CAGGTGCAGCTACAGCAGTGGGGCGCACGACTGTTGAAGCCTTCGGAGAC
CCTGTCCCTCACCTGCGCTGTCTATGGTGGGTCCTTCAGTGGTTACTACTG
GAGCTGGATCCGCCAGCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAA
ATCAATCATAGTGGAAGCACCAACTACAACCCGTCCCTCAAGAGTCGAGT
CACCATATCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGGT
CTGTGACCGCCGCGGACACGGCTGTGTATTACTGTGCGAGAGGGGGAAGC
AGTGGCTACTGGTACTTCGATCTCTGGGGCCGTGGCACCCCTGGTCACTGTC
TCCTCA (SEQ ID NO: 23)

Protein sequence of the heavy chain variable region:

QVQLQQWGARLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEIN
HSGSTNYPNPSLKSRVTISVDTSKNQFSLKLRSVTAADTAVYYCARGGSSGYW
YFDLWGRGTLVTVSS (SEQ ID NO: 24)

Nucleotide sequence of the light chain variable region:

GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGAG
AGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTACACAGCTCCAA
CAATAAGAATTATTTAGTTTGGTACCAGCAGAAACCAGGACAGCCTCCTA
AGCTGCTCATTTACTGGGCATCTACCCGGAATCCGGGGTCCCTGACCGAT
TCAGTGGCAGCGGGTCTGGGACAGATTCTCACTCTCACCATCAGCAGCCTG
CAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACTCCT
CTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA (SEQ ID NO: 57)

Protein sequence of the light chain variable region:

DIVMTQSPDSLAVSLGERATINCKSSQSVLHSSNNKNYLVWYQQKPGQPPL
LIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTPLTFG
GGTKVEIK (SEQ ID NO: 58)

FIGURE 14

ANTIBODY M**Nucleotide sequence of the heavy chain variable region:**

GAGGTGCAGGTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGGGT
CCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCTATAGCA
TGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCATCC
ATTAGTAGTAGTAGTAGTTACATATACTACGCAGACTCAGTGAAGGGCCG
ATTCACCATCTCCAGAGACAACGCCAAGAAGTCACTGTATCTGCAAATGA
ACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGGGGGGGC
AGCAGCTGGTACGGGGACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGT
CACCGTCTCCTCA (SEQ ID NO: 25)

Protein sequence of the heavy chain variable region:

EVQVVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSIS
SSSYIYYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCARGGSSWY
GDWFDPWGQGLVTVSS (SEQ ID NO: 26)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGTCTGGGCGAGTCAGGGTATTAGCAGCTGGTTAGT
CTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTG
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGC
AACTTACTATTGTCAGCAGGCTAACAGTTTCCCTTTCACTTTTCGGCGGAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 59)

Protein sequence of the light chain variable region:

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLVWYQQKPGKAPKLLIYAASS
LQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPFTFGGGTKVEIK
(SEQ ID NO: 60)

FIGURE 15

ANTIBODY N**Nucleotide sequence of the heavy chain variable region:**

CAGCTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAG
ACTCTCCTGTGCAGCGTCTGGATTACCTTCAGTAGCTATGGCATGCACTG
GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATGGT
ATGATGGAAGAAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC
ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCT
GAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGAAGTGGGATATT
GTACTAATGGTGTATGCTCCTACTACTACTACGGTATGGACGTCTGGGGCC
AAGGGACCACGGTCACCGTCTCCTCA (SEQ ID NO: 27)

Protein sequence of the heavy chain variable region:

QLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWY
DGRNKYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAREVGYCT
NGVCSYYYYGMDVWGQGT TVTVSS (SEQ ID NO: 28)

Nucleotide sequence of the light chain variable region:

GACATCCAGATGACCCAGTCTCCATCCTCACTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGTCGGGCGAGTCAGGGCATTAGCAATTATTTAGC
CTGGTTTCAGCAGAAACCAGGGAAAGCCCCCTAAGTCCCTGATCTATGCTG
CATCCAGTTTGCAAAGTGGGGTCCCATCAAAATTCAGCGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGC
AACTTATTACTGCCAACAGTATAATAGTTACCCTCTCACTTTCGGCGGAGG
GACCAAGGTGGAGATCAAA (SEQ ID NO: 61)

Protein sequence of the light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGISNYLAWFQQKPGKAPKSLIYAASSL
QSGVPSKFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKVEIK
(SEQ ID NO: 62)

FIGURE 16

ANTIBODY O**Nucleotide sequence of heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTA
CTTCTGGAGCTGGATCCGCCAGCTCCCAGGGAAGGGCCTGGAGTGCATTG
GGCACATCCATAACAGTGGGACCACCTACTACAATCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTAGACACGTCTAAGAAGCAGTTCTCCCTGAGGCT
GAGTTCTGTGACTGCCGCGGACACGCCGTATATTACTGTGCGAGAGATC
GAGGGGGTGACTACTACTATGGTATGGACGTCTGGGGCCAAGGGACCACG
GTCACCGTCTCCTCA (SEQ ID NO: 29)

Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCTVSGGSISSGDYFWSWIRQLPGKGLECIGHIH
NSGTTYYNPSLKSRTISVDTSKKQFSLRLSSVTAADTAVYYCARDRGGDYY
YGMVDVWGQGTTVTVSS (SEQ ID NO: 30)

Nucleotide sequence of light chain variable region:

GAAATTGTGTTGACGCACTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAA
AGAGCCACCCTCTCCTGCAGGGCCAGTCAGGGTATTAGTAGAAGCTACTT
AGCCTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGCCTCCTCATCTATG
GTGCATCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGG
TCTGGG
ACAGACTTCACTCTCACCATCAGCAGACTGGAGCCTGAAGATTTTGCAGT
GTATTACTGTCAACAATTTGGTAGTTCACCGTGGACGTTCGGCCAAGGGA
CCAAGGTGGAAATCAAA (SEQ ID NO: 63)

Amino acid sequence of light chain variable region:

EIVLTQSPGTLSPGERATLSCRASQGISRSYLAWYQQKPGQAPSLLIYGASS
RATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQFGSSPWTFGQGTKVEIK
(SEQ ID NO: 64)

FIGURE 17

ANTIBODY P**Nucleotide sequence of heavy chain variable region:**

CAGGTGCAGCTGCAGGAGTCGGGCCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCAGTGTCTCTGGTGGCTCCATCAGCAGTGGTGGTTA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCACCTACTGCAACCCGTCCCTCAAGAGT
CGAGTTACCATATCAGTCGACACGTCTAAGAACCAGTTCTCCCTGAAGCT
GAGCTCTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGACA
ATGGTTCGGGGAGTTATGACTGGTTCGACCCCTGGGGCCAGGGAATCCTG
GTCACCGTCTCCTCA (SEQ ID NO: 31)

Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSQTLSTCSVSGGSISSGGYYWSWIRQHPGKGLEWIGYI
YYSGSTYCNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDNGSGSY
DWFDPWGQGILVTVSS (SEQ ID NO: 32)

Nucleotide sequence of light chain variable region:

GACATTCAGATGACCCAGTCTCCATCCTCCGTGTCTGCATCTGTAGGAGAC
AGAGTCACCATCACTTGTCGGGGCGAGTCAGGGTATTAGCAGCTGGTTAGC
CTGGTATCAGCAGAAACCAGGGAAAGCCCCAAAGTTCCTGATCTTTGTTG
CATCCAGTTTCCAAAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGC
AACTTACTATTGTCAACAGGCTAACAGTTTCCCTCGGACGTTTCGGCCAAGG
GACCAAGGTGGAAATCAAA (SEQ ID NO: 65)

Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASVGDRVITICRASQGISSWLAWYQQKPGKAPKFLIFVASS
FQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPRTFGQGTKVEIK
(SEQ ID NO: 66)

FIGURE 18

ANTIBODY Q**Nucleotide sequence of heavy chain variable region:**

CAGGTGCAGATGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCACAGAC
CCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGATTA
CTACTGGAGCTGGATCCGCCAGCACCCAGGGAAGAACCTGGAGTGGATTG
GGTACATCTATTACAGTGGGAGCACCTACTACAACCCGTCCCTCAAGAGT
CGAGT
TACCATATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAAGCTGAGCT
CTGTGACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGACAATGGT
TCGGGGAGTTATGACTGGTTCGACCCCTGGGGCCAGGGAACCCTGGTCAC
CGTCTCCTCA (SEQ ID NO: 33)

Amino acid sequence of heavy chain variable region:

QVQMQESGPGLVKPSQTLSTCTVSGGSISSGDYYWSWIRQHPGKNLEWIGYI
YYSGSTYYNPSLKSRTISVDTSKNQFSLKLSSVTAADTAVYYCARDNGSGS
YDWFDPWGQGLVTVSS (SEQ ID NO: 34)

Nucleotide sequence of light chain variable region:

GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTGCATCTGTTGGAGAC
AGAGTCACCATCACTTGTCGGGCGAGTCAGGGTATTAGCAGCTGGTTAGC
CTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGTTCCTGATCTTTGTTG
CATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTTCAGCGGCAGTGGATCT
GGG
ACAGATTTCACTCTCACCATCAGCAGCCTGCAGCCTGAAGATTTTGCAACT
TACTATTGTCAACAGGCTAACAGTTTCCCTCGGACGTTTCGGCCAAGGGAC
CAAGGTGGAAATCAAA (SEQ ID NO: 67)

Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASVGDRVITICRASQGISSWLAWYQQKPGKAPKFLIFVASS
LQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQANSFPRTFGQGTKVEIK
(SEQ ID NO: 68)

FIGURE 19

Antibody	V	D	J	Seq. ID No	FR1	CDR1	FR2
A	VH1-8	Germline D3-10	JH4B	177 2	QVQLVQSGAEVKKPGASVKVCKAS -----	GYTFTSYDIN -----	WVRQATGQGLEWMG -----
B	VH4-31	Germline D6-19	JH4B	178 4	QVQLQESGPGLVKPKSQTLSTCTVS -----	GGSISSGGYYWS -----H-----	WIRQHPGKLEWIG -----
C	"	"	"	6	-----	-----H-----	-----
D	"	"	"	8	-----	-----H-----	-----
E	VH3-11	Germline D6-13	JH3B	179 10	QVQLVESGGGLVKKPGGSLRLSCAAS -----	GFTFSDYYMS -----N-----	WIRQAPGKLEWVS -----
F	VH3-33	Germline D6-6	JH2	180 12	QVQLVESGGGVVQPGRSRLRLSCAAS -----	GFTFSSYGMH -----Y--I-----	WVRQAPGKLEWVA -----
G	VH4-59	Germline D5-12	JH4B	181 14	QVQLQESGPGLVKPKSETLSLTCTVS ---AEQ-----	GGSISSYYWS -----N-----	WIRQPPGKLEWIG -----
H	VH4-31	Germline D1-7	JH3B	182 16	QVQLQESGPGLVKPKSQTLSTCTVS -----	GGSISSGGYYWS -----DN-----	WIRQHPGKLEWIG -----
I	VH3-11	Germline - NA -	JH6B	183 18	QVQLVESGGGLVKKPGGSLRLSCAAS -----	GFTFSDYYMS -----	WIRQAPGKLEWVS -----
J	VH3-33	Germline D6-6	JH6B	184 20	QVQLVESGGGVVQPGRSRLRLSCAAS -----	GFTFSSYGMH -----NN-----	WVRQAPGKLEWVA -----
K	"	"	"	22	-----	-----T-----	-----
L	VH4-34	Germline D6-19	JH2	185 24	QVQLQQMAGLLKPKSETLSLTCAVY -----R-----	GGSPSGYYWS -----	WIRQPPGKLEWIG -----
M	VH3-21	Germline D6-13	JH5B	186 26	EVQLVESGGGLVKKPGGSLRLSCAAS ---V-----	GFTFSSYSMN -----	WVRQAPGKLEWVS -----
N	VH3-33	Germline D2-8	JH6B	187 28	QVQLVESGGGVVQPGRSRLRLSCAAS ##-----	GFTFSSYGMH -----	WVRQAPGKLEWVA -----
O	VH4-31	Germline - NA -	JH6B	188 30	QVQLQESGPGLVKPKSQTLSTCTVS -----	GGSISSGGYYWS -----D-F-----	WIRQHPGKLEWIG -----C-----
P	VH4-31	Germline D3-10	JH5B	189 32	QVQLQESGPGLVKPKSQTLSTCTVS -----S-----	GGSISSGGYYWS -----	WIRQHPGKLEWIG -----
Q	"	"	"	34	---M-----	-----D-----	-----N-----

FIGURE 20A

CDR2	FR3	CDR3	FR4
WMNPNGNTGYAQKFG	RVTMTNTSISTAYMELSSLSRSEDTAVYYCAR	##YSGGS#FDY	WQGGLTLVTVSSA
-----D-----	-----	WNH-----H---	-----
YIYSGSTYVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	##SSGW#FDY	WQGGLTLVTVSSA
-----	-----	DD-----G---	-----I-----
-----A-----	-----	DD-----G---	-----I-----
-----A-----	-----	DD-----G---	-----I-----
YISSSGSTIYYADSVKG	RFTISRDNANKNSLYLQMNLSLRAEDTAVYYCAR	##AAAG##AFDI	WQGGLTLVTVSSA
H-----ILD-----	-----V-----	DGA---TD---L	-----
VIWYDGSNKYYADSVKG	RFTISRDNASKNTLYLQMNLSLRAEDTAVYYCAR	##YSSS##WYFDL	WGRGLTLVTVSSA
-----	-----	GR-----SW-----	-----
YIYSGSTVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	##GYSGY#FDY	WQGGLTLVTVSSA
-----K-----	-----T---T-----	DSPR-F---EA--S	-----
YIYSGSTYVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	##NNNN##FDI	WQGGLTLVTVSSA
-----	-----	GV---FL---	-----
YISSSGSTIYYADSVKG	RFTISRDNANKNSLYLQMNLSLRAEDTAVYYCAR	##GMDV	WQGGLTLVTVSSA
-----R-----	-----	SLG-----	-----
VIWYDGSNKYYADSVKG	RFTISRDNASKNTLYLQMNLSLRAEDTAVYYCAR	###YSSS##YYYYYGMDV	WQGGLTLVTVSSA
-----	-----	DRTV--N-SPP-----	-----
-----	-----	DRTV---~SPP-----	-----
EINHSGSTVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	##SSGYWYFOL	WGRGLTLVTVSSA
-----	-----R-----	GG-----	-----
SISSSSYIYYADSVKG	RFTISRDNANKNSLYLQMNLSLRAEDTAVYYCA#	##SSWY##WFDP	WQGGLTLVTVSSA
-----	-----R-----	GG-----GD-----	-----
VIWYDGSNKYYADSVKG	RFTISRDNASKNTLYLQMNLSLRAEDTAVYYCAR	##GYCTNGVC#YYYYYGMDV	WQGGLTLVTVSSA
-----R-----	-----	EV-----S-----	-----
YIYSGSTYVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	###YYYGMDV	WQGGLTLVTVSSA
H-HN--T-----	-----K---R-----	DRGD-----	-----
YIYSGSTYVNP SLKS	RVTISVDTSKNQFSLKLSVTAADTAVYYCAR	##GSGSY#WFDP	WQGGLTLVTVSSA
-----C-----	-----	DN-----D-----	-----I-----
-----	-----	DN-----D-----	-----

FIGURE 20B

Antibody	V	J	Seq. ID No	FR1	CDR1	FR2
J	O12	Germline	190	DIQMTQSPSSLSASVGDRVITTC	RASQSISSYLN	WYQQKPGKAPKLLIY
K	"	JK4	54	-----	-T-----	-----S
A	"	"	56	-----	-----	-----S
	"	"	36	-----	-----I-----	-----
E	O12	Germline	191	DIQMTQSPSSLSASVGDRVITTC	RASQSISSYLN	WYQQKPGKAPKLLIY
	"	JK3	44	-----	-S-----N-I-	-----R-----N-----H
H	A3	Germline	192	DIVMTQSPPLSLPVPGPASISC	RSSQSLHSNGVNYLD	WYQQKPGQSPQLLIY
	"	JK4	50	-----	-----RR-----	-----
M	L5	Germline	193	DIQMTQSPSSVSASVGDRVITTC	RASQGISWLA	WYQQKPGKAPKLLIY
	"	JK4	60	-----	-----V	-----
D	A30	Germline	194	DIQMTQSPSSLSASVGDRVITTC	RASQIRNDLG	WYQQKPGKAPKRLIY
C	"	JK1	42	-----	-----L-----	-F-----
B	"	"	40	-----	-----L-----	-F-----
	"	"	38	-----	-----L-----	-F-----VT-----
N	L1	Germline	195	DIQMTQSPSSLSASVGDRVITTC	RASQGISNYLA	WYQQKPGKAPKSLIY
	"	JK4	62	-----	-----	-----
L	B3	Germline	196	DIVMTQSPDLSAVSLGERATINC	KSSQSVLYSSNNKNVLA	WYQQKPGQPPKLLIY
	"	JK4	58	-----	-----H-----V	-----
G	B3	Germline	197	DIVMTQSPDLSAVSLGERATINC	KSSQSVLYSSNNKNVLA	WYQQKPGQPPKLLIY
	"	JK3	48	-----	-----R-----I-----	-----
F	A20	Germline	198	DIQMTQSPSSLSASVGDRVITTC	RASQGISNYLA	WYQQKPGKVPKLLIY
	"	JK4	46	-----	-----	-----
I	B3	Germline	199	DIVMTQSPDLSAVSLGERATINC	KSSQSVLYSSNNKNVLA	WYQQKPGQPPKLLIY
	"	JK1	52	-----F-----	-----H-----T	-----L-----
O	A27	Germline	200	EIVLTQSPGTLSLSPGERATLSC	RASQSVSSSYLA	WYQQKPGQAPRLLIY
	"	JK1	64	-----	-----GI-R-----	-----S-----
P	L5	Germline	201	DIQMTQSPSSVSASVGDRVITTC	RASQGISWLA	WYQQKPGKAPKLLIY
	"	JK1	66	-----	-----	-----F-----F
Q	"	"	68	-----	-----	-----F-----F

FIGURE 21A

CDR2	FR3	CDR3	FR4
AASSLQS	GVPSRFGSGSGTDFTLTISLQPEDFATYYC	QQSYST##T	FGGGTKVEIKR
-T-----	-----	-----PL-	-----
-T--F--	-----A--	-----PL-	-----
-----	---L-----I-----	---K-PL-	-----
AASSLQS	GVPSRFGSGSGTDFTLTISLQPEDFATYYC	QQSYSTPFT	FGPGTKVDIKR
DV--F--	A-----R-----V-----F-	--T-I----	-----
LGSNRAS	GVPSRFGSGSGTDFTLKISRVEAEDVGVYYC	MQALQT##T	FGGGTKVEIKR
-----	-----	-----PL-	---E----
AASSLQS	GVPSRFGSGSGTDFTLTISLQPEDFATYYC	QQANSFP#T	FGGGTKVEIK#
-----	-----	-----F-	-----R
AASSLQS	GVPSRFGSGSGTEFTLTISLQPEDFATYYC	LQHNS##WT	FGQGTKVEIKR
-----R	-----T--F-	-----FP--	-----
---R	-----T--F-	-----FP--	-----
-----R	-----	---Y-FP--	-----
AASSLQS	GVPSRFGSGSGTDFTLTISLQPEDFATYYC	QQVNSYPLT	FGGGTKVEIKR
-----	---K-----	-----	-----
WASTRES	GVPSRFGSGSGTDFTLTISLQAEDEVAVYYC	QQYSTPLT	FGGGTKVEIKR
-----	-----	-----	-----
WASTRES	GVPSRFGSGSGTDFTLTISLQAEDEVAVYYC	QQYSTPFT	FGPGTKVDIKR
-----	-----L-----	-----	-----
AASTLQS	GVPSRFGSGSGTDFTLTISLQPEDVATYYC	QKNSA##T	FGGGTKVEIKR
-----	-----	-----PL-	-----
WASTRES	GVPSRFGSGSGTDFTLTISLQAEDEVAVYYC	QQYST##	FGQGTKLEIKR
-----	-----	K-----PSS	-----
GASSRAT	GIPDRFGSGSGTDFTLTISRLEPEDFVYYC	QQYSSPWT	FGQGTKVEIKR
-----	-----	---F-----	-----
AASSLQS	GVPSRFGSGSGTDFTLTISLQPEDFATYYC	QQANSFPRT	FGQGTKVEIKR
V--F--	-----	-----	-----
V-----	-----	-----	-----

FIGURE 21B

Epitope Binding Groups of Certain Human Anti-TR-2 Antibodies

Group 1	Group 2	Group 3	Group 4
Ab B	Ab A	Ab G	Ab N
Ab C	Ab E	Ab O	
Ab D	Ab H		
Ab F			
Ab I			
Ab J			
Ab K			
Ab L			
Ab M			

FIGURE 22

N-Avidin-TR2 Truncations for epitope mapping

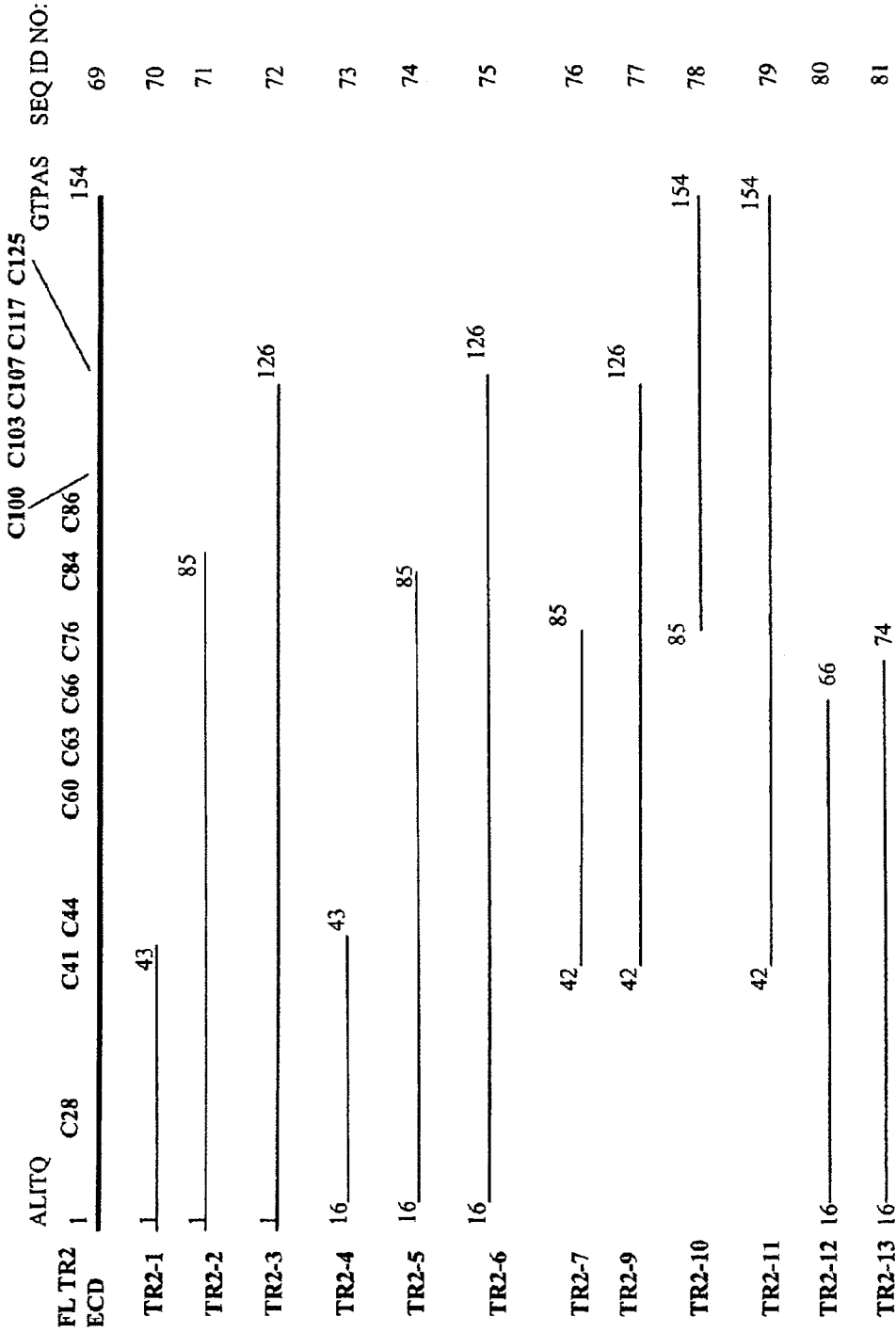
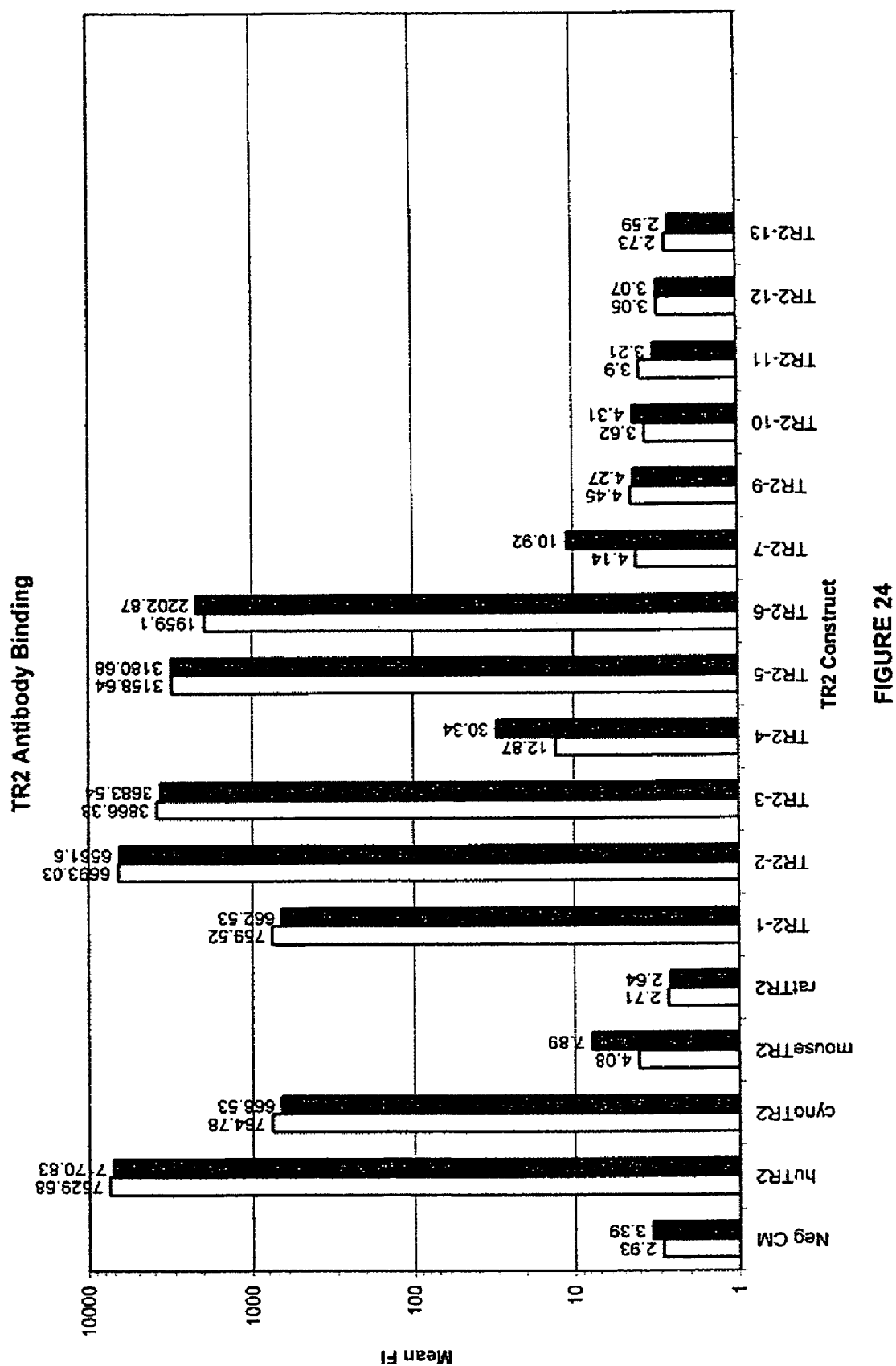


FIGURE 23



Cyno Truncations and Cyno/Human TR-2 Chimeras

Cyno TR-2 (short)	<u>1 APTT</u>	<u>RIQT132</u>
Cyno TR-2 (long)	<u>1 APTT</u>	<u>TPAS 154</u>
Cyno TR-2 1-85	<u>1 APTT</u>	<u>TVCQ85</u>
Cyno TR-2 16-85	<u>16 PQOK</u>	<u>TVCQ85</u>
Cyno TR-2 16-154 (long)	<u>16 PQOK</u>	<u>TPAS 154</u>
CynoTR-2 1-16, hu17-85	<u>1 APTT AAP16 17 QOKR</u>	<u>TVCQ85</u>
CynoTR-2 1-16, hu17-154	<u>1 APTT AAP16 17 QOKR</u>	<u>TPAS 154</u>
Hu TR-21-16, Cyno TR-2 17-85	<u>1 ALIT AAP16 17 QOKR</u>	<u>TVCQ85</u>
Hu TR-2 1-16, Cyno TR-2 17-end (long)	<u>1 ALIT AAP16 17 QOKR</u>	<u>TPAS 154</u>

Legend: Cyno sequences are single line, human are double line.

FIGURE 25

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1
Cyno_TR2_Pep -APITRQSLD PQRRAAPQOK RSSPTEGLCP PGHHISEDGR DCISCKYGQD
huTR2_ECD_Pe -ALITQQDLA PQQRAAPQOK RSSPSEGLCP PGHHISEDGR DCISCKYGQD
muTR2_ECD --PVTANP.A HNRPAQLQRP EESPSRGPCL AGQYLSE..G NCKPCREGID

51
Cyno_TR2_Pep YSTHWNDLF. FCLRCTKCDS GEVEVSSCTT TRNTVCQCEE GTFREEDSPE
huTR2_ECD_Pe YSTHWNDLL. FCLRCTRCDS GEVELSPCTT TRNTVCQCEE GTFREEDSPE
muTR2_ECD YTSHSNHSLD SCILCTVCKE DKVVETRCNI TTNTVCRCKP GTFEDKDSPE

101
Cyno_TR2_Pep ICRKCRTGCP RGMVKVKDCT PWSDIECVHK E-----
huTR2_ECD_Pe MCRKCRTGCP RGMVKVGDCT PWSDIECVHK ESGTKHSGEA PAVEETVTSS
muTR2_ECD ICQSC.SNCT DGEEELTST PRENRKCVSK TAWASWHKL~

151
Cyno_TR2_Pep ----- SEQ ID NO: 202
huTR2_ECD_Pe PGTPAS SEQ ID NO: 203
muTR2_ECD ----- SEQ ID NO: 204
```

FIGURE 26

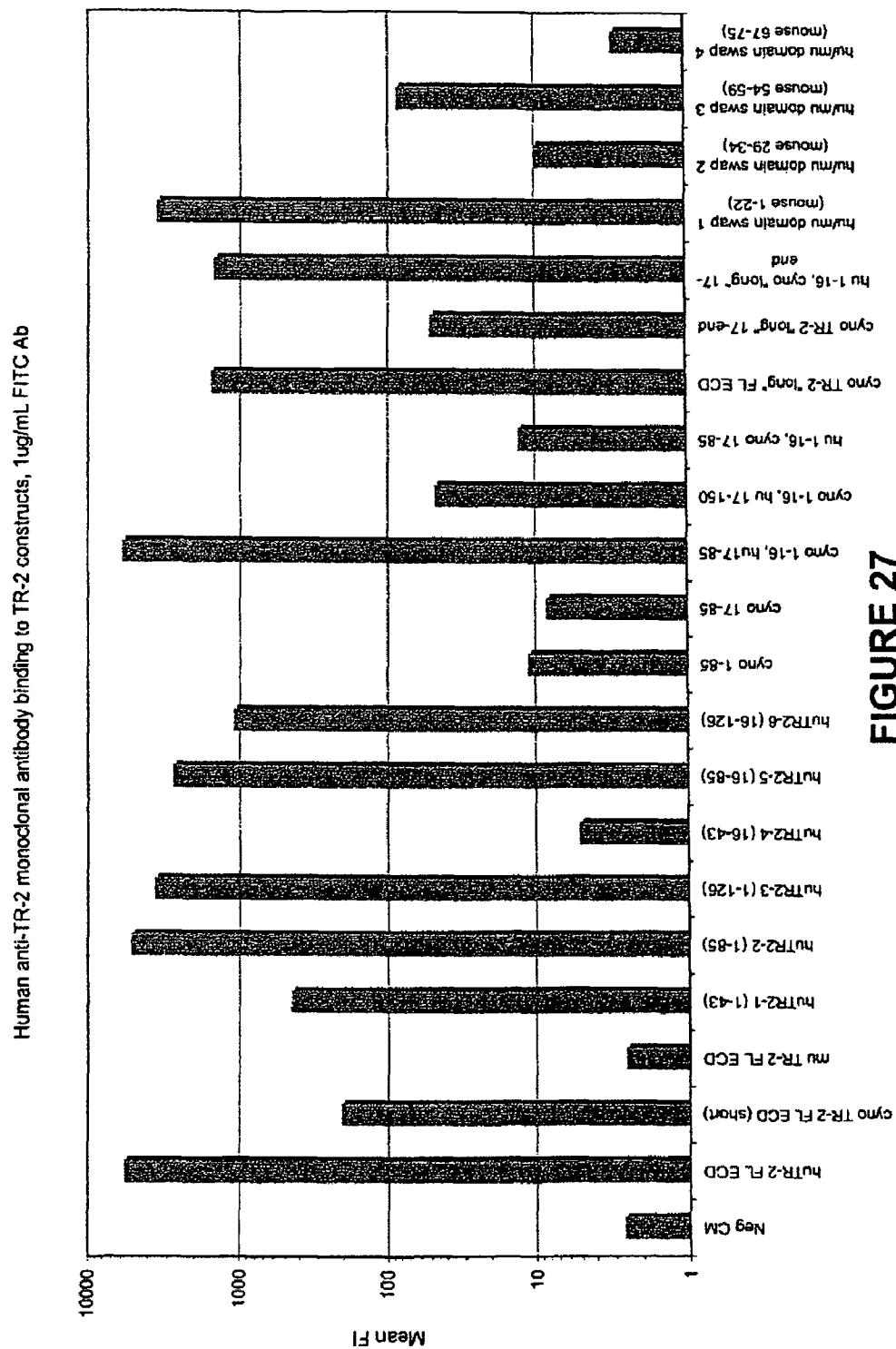


FIGURE 27

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TRAIL RECEPTOR-2 POLYPEPTIDES AND ANTIBODIES

This application claims the benefit of U.S. Provisional Application No. 60/713,433, filed Aug. 31, 2005, and U.S. Provisional Application No. 60/713,478, filed Aug. 31, 2005. U.S. Provisional Application Nos. 60/713,433 and 60/713,478 are incorporated by reference herein in their entirety for any purpose.

FIELD

Polypeptides are provided. Antibodies or antigen binding domains are provided which bind such polypeptides. Also provided are methods of obtaining an antibody that binds tumor necrosis factor (TNF)-related apoptosis-inducing ligand ("TRAIL") Receptor-2 (TR-2) comprising administering at least one of such polypeptides to an animal and obtaining an antibody that binds TR-2 from the animal. Antibodies reactive with TR-2 are provided. Also provided are cells producing antibodies reactive with TR-2, pharmaceutical compositions comprising antibodies reactive with TR-2, methods using antibodies reactive with TR-2, and kits comprising antibodies reactive with TR-2. Also provided are methods of decreasing or preventing binding of an antibody to TR-2 by administering such a polypeptide.

BACKGROUND

The interaction between TR-2 and its ligand, TRAIL, plays a role in the induction of apoptosis (see, for example, Almasan et al., Cytokine & Growth Factor Reviews 14: 337-348 (2003)). TRAIL, also known as Apo2 ligand, is a homomeric ligand that interacts with four members of the TNF-receptor superfamily (TRAIL receptors ("TR") 1 to 4), as well as with the related, soluble, osteoprotegerin ("OPG") receptor. Binding of TRAIL to TR-1 or TR-2 at the surface of a cell triggers apoptosis of that cell. After initial binding of TRAIL to TR-1 or TR-2, intracellular proteins are recruited to the intracellular death domain of the receptor, forming a signaling complex. Certain intracellular caspases are recruited to the complex; where they autoactivate and in turn activate additional caspases and the intracellular apoptosis cascade. TR-3 and TR-4 and OPG lack the intracellular domain responsible for transmitting the apoptosis signal. Thus, binding of TRAIL to TR-3, TR-4, or OPG does not trigger apoptosis. TR-3 and TR-4 are also referred to as "decoy" receptors, and their overexpression has been shown to protect cells from apoptotic induction by TRAIL. TR-2 is expressed in a variety of cells, including liver, brain, breast, kidney, colon, lung, spleen, thymus, peripheral blood lymphocytes, prostate, testis, ovary, uterus, and various tissues along the gastro-intestinal tract. (See, for example, Walczak et al., EMBO J. 16: 5386-5397 (1997); Spierings et al., J. Histochem. Cytochem. 52: 821-831 (2004)). Though TRAIL and TRAIL receptors are widely expressed, they are most active in inducing apoptosis in transformed cells. (See, for example, Daigle et al., Swiss Med. Wkly. 131: 231-237 (2001)).

SUMMARY

In certain embodiments, an isolated polypeptide is provided comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a:

wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid

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b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present;

wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present; wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is

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not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and

wherein the polypeptide, in association with an antibody light chain, binds TRAIL receptor-2 (TR-2).

In certain embodiments, an isolated polypeptide is provided comprising at least one complementarity determining region (CDR) selected from:

amino acids 26 to 35 of SEQ ID NO: 2;
amino acids 50 to 66 of SEQ ID NO: 2;
amino acids 99 to 110 of SEQ ID NO: 2;
amino acids 26 to 37 of SEQ ID NO: 4;
amino acids 52 to 67 of SEQ ID NO: 4;
amino acids 100 to 109 of SEQ ID NO: 4;
amino acids 26 to 37 of SEQ ID NO: 6;
amino acids 52 to 67 of SEQ ID NO: 6;
amino acids 100 to 109 of SEQ ID NO: 6;
amino acids 26 to 37 of SEQ ID NO: 8;
amino acids 52 to 67 of SEQ ID NO: 8;
amino acids 100 to 109 of SEQ ID NO: 8;
amino acids 26 to 35 of SEQ ID NO: 10;
amino acids 50 to 66 of SEQ ID NO: 10;
amino acids 99 to 110 of SEQ ID NO: 10;
amino acids 26 to 35 of SEQ ID NO: 12;
amino acids 50 to 66 of SEQ ID NO: 12;
amino acids 99 to 111 of SEQ ID NO: 12;
amino acids 26 to 35 of SEQ ID NO: 14;
amino acids 50 to 65 of SEQ ID NO: 14;
amino acids 98 to 111 of SEQ ID NO: 14;
amino acids 26 to 37 of SEQ ID NO: 16;
amino acids 52 to 67 of SEQ ID NO: 16;
amino acids 100 to 109 of SEQ ID NO: 16;
amino acids 26 to 35 of SEQ ID NO: 18;
amino acids 50 to 66 of SEQ ID NO: 18;
amino acids 99 to 105 of SEQ ID NO: 18;
amino acids 26 to 35 of SEQ ID NO: 20;
amino acids 50 to 66 of SEQ ID NO: 20;
amino acids 99 to 118 of SEQ ID NO: 20;
amino acids 26 to 35 of SEQ ID NO: 22;
amino acids 50 to 66 of SEQ ID NO: 22;
amino acids 99 to 118 of SEQ ID NO: 22;
amino acids 26 to 35 of SEQ ID NO: 24;
amino acids 50 to 65 of SEQ ID NO: 24;
amino acids 98 to 108 of SEQ ID NO: 24;
amino acids 26 to 35 of SEQ ID NO: 26;
amino acids 50 to 66 of SEQ ID NO: 26;
amino acids 99 to 110 of SEQ ID NO: 26;
amino acids 26 to 35 of SEQ ID NO: 28;
amino acids 50 to 66 of SEQ ID NO: 28;
amino acids 99 to 117 of SEQ ID NO: 28;
amino acids 26 to 37 of SEQ ID NO: 30;
amino acids 52 to 67 of SEQ ID NO: 30;
amino acids 100 to 111 of SEQ ID NO: 30;
amino acids 26 to 37 of SEQ ID NO: 32;
amino acids 52 to 67 of SEQ ID NO: 32;
amino acids 100 to 111 of SEQ ID NO: 32;
amino acids 26 to 37 of SEQ ID NO: 34;
amino acids 52 to 67 of SEQ ID NO: 34; and
amino acids 100 to 111 of SEQ ID NO: 34;

wherein the polypeptide, in association with an antibody light chain, binds TR-2.

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In certain embodiments, an isolated polypeptide is provided comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b:

wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present;

wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine;

wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and

wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an isolated polypeptide is provided comprising at least one complementarity determining region (CDR) selected from:

amino acids 24 to 34 of SEQ ID NO: 36;
amino acids 50 to 56 of SEQ ID NO: 36;
amino acids 89 to 97 of SEQ ID NO: 36;
amino acids 24 to 34 of SEQ ID NO: 38;
amino acids 50 to 56 of SEQ ID NO: 38;
amino acids 89 to 97 of SEQ ID NO: 38;
amino acids 24 to 34 of SEQ ID NO: 40;
amino acids 50 to 56 of SEQ ID NO: 40;
amino acids 89 to 97 of SEQ ID NO: 40;
amino acids 24 to 34 of SEQ ID NO: 42;
amino acids 50 to 56 of SEQ ID NO: 42;

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amino acids 89 to 97 of SEQ ID NO: 42;
 amino acids 24 to 34 of SEQ ID NO: 44;
 amino acids 50 to 56 of SEQ ID NO: 44;
 amino acids 89 to 97 of SEQ ID NO: 44;
 amino acids 24 to 34 of SEQ ID NO: 46;
 amino acids 50 to 56 of SEQ ID NO: 46;
 amino acids 89 to 97 of SEQ ID NO: 46;
 amino acids 24 to 40 of SEQ ID NO: 48;
 amino acids 56 to 62 of SEQ ID NO: 48;
 amino acids 95 to 103 of SEQ ID NO: 48;
 amino acids 24 to 39 of SEQ ID NO: 50;
 amino acids 55 to 61 of SEQ ID NO: 50;
 amino acids 94 to 102 of SEQ ID NO: 50;
 amino acids 24 to 40 of SEQ ID NO: 52;
 amino acids 56 to 62 of SEQ ID NO: 52;
 amino acids 95 to 103 of SEQ ID NO: 52;
 amino acids 24 to 34 of SEQ ID NO: 54;
 amino acids 50 to 56 of SEQ ID NO: 54;
 amino acids 89 to 97 of SEQ ID NO: 54;
 amino acids 24 to 34 of SEQ ID NO: 56;
 amino acids 50 to 56 of SEQ ID NO: 56;
 amino acids 89 to 97 of SEQ ID NO: 56;
 amino acids 24 to 40 of SEQ ID NO: 58;
 amino acids 56 to 62 of SEQ ID NO: 58;
 amino acids 95 to 103 of SEQ ID NO: 58;
 amino acids 24 to 34 of SEQ ID NO: 60;
 amino acids 50 to 56 of SEQ ID NO: 60;
 amino acids 89 to 97 of SEQ ID NO: 60;
 amino acids 24 to 34 of SEQ ID NO: 62;
 amino acids 50 to 56 of SEQ ID NO: 62;
 amino acids 89 to 97 of SEQ ID NO: 62;
 amino acids 24 to 35 of SEQ ID NO: 64;
 amino acids 51 to 57 of SEQ ID NO: 64;
 amino acids 90 to 88 of SEQ ID NO: 64;
 amino acids 24 to 34 of SEQ ID NO: 66;
 amino acids 50 to 57 of SEQ ID NO: 66;
 amino acids 89 to 97 of SEQ ID NO: 66;
 amino acids 24 to 34 of SEQ ID NO: 68;
 amino acids 50 to 56 of SEQ ID NO: 68; and
 amino acids 89 to 97 of SEQ ID NO: 68;

wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an isolated polynucleotide is provided comprising a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a:

wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present;

wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from

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methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present;

wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and

wherein the polypeptide, in association with an antibody light chain, binds TR-2.

In certain embodiments, an isolated polynucleotide is provided comprising a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b:

wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine;

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amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present;

wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine; wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and

wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an isolated anti-TR-2 antibody comprising a variable region and a constant region is provided, wherein the antibody comprises:

- (i) a first polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a,

wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine,

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serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present;

wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present;

wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and

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wherein the first polypeptide, in association with an antibody light chain, binds TR-2; and
 (ii) a second polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b

wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present;

wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine;

wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and

wherein the second polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an isolated anti-TR-2 antibody comprising a variable region and a constant region is provided, wherein the antibody comprises:

a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 2 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 36; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 4 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 38; a first polypeptide comprising complementarity determining regions

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(CDRs) as set forth in SEQ ID NO: 6 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 40; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 8 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 42; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 10 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 44; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 12 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 46; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 14 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 48; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 16 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 50; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 18 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 52; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 20 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 54; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 22 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 56; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 24 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 58; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 26 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 60; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 28 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 62; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 30 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 64; a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 32 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 66; or a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 34 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 68.

In certain embodiments, a cell is provided, comprising:

(a) a first polynucleotide comprising a sequence encoding a first polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a, wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected

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from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present;

wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present;

wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; wherein the first polypeptide, in association with an antibody light chain, binds TR-2; and

(b) a second polynucleotide comprising a sequence encoding a second polypeptide comprising at least one

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complementarity determining region (CD R) selected from CDR1b, CDR2b, and CDR3b,

wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 ml n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid ml is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present;

wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine;

wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; wherein the second polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an isolated antibody is provided that specifically binds to an epitope that is specifically bound by at least one antibody selected from: Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q.

In certain embodiments, a polypeptide is provided comprising at least one amino acid sequence selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96.

In certain embodiments, a polypeptide is provided consisting essentially of at least one amino acid sequence selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96.

In certain embodiments, an antibody or antigen binding domain is provided which binds at least one amino acid sequence selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96.

In certain embodiments, a method of obtaining an antibody that binds TR-2 is provided comprising administering at least

one polypeptide selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96 to an animal and obtaining an antibody that binds TR-2 from the animal.

In certain embodiments, a method of decreasing or preventing binding of an antibody to TR-2 by administering a polypeptide comprising at least one amino acid sequence selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96 is provided.

In certain embodiments, a method of decreasing or preventing binding of an antibody to TR-2 by administering a polypeptide consisting of at least one amino acid sequence selected from SEQ ID NO: 94, SEQ ID NO: 95, and SEQ ID NO: 96 is provided.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows the immunization schedule used in Example 1 for a TR-2-His construct in transgenic mice expressing human immunoglobulin genes, via either footpad inoculation (groups 1, 2, and 3) or via intraperitoneal injection (groups 4 and 5).

FIG. 2 shows the results of an ELISA assay to measure the reactivity of certain blood samples from selected mice described in FIG. 1 to the antigen TR-2, according to work described in Example 1.

FIG. 3 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 1) and light chain (SEQ ID NO: 35) variable regions of anti-TR-2 antibody A, and the amino acid sequences of the heavy chain (SEQ ID NO: 2) and the light chain (SEQ ID NO: 36) variable regions of that antibody.

FIG. 4 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 3) and light chain (SEQ ID NO: 37) variable regions of anti-TR-2 antibody B, and the amino acid sequences of the heavy chain (SEQ ID NO: 4) and the light chain (SEQ ID NO: 38) variable regions of that antibody.

FIG. 5 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 5) and light chain (SEQ ID NO: 39) variable regions of anti-TR-2 antibody C, and the amino acid sequences of the heavy chain (SEQ ID NO: 6) and the light chain (SEQ ID NO: 40) variable regions of that antibody.

FIG. 6 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 7) and light chain (SEQ ID NO: 41) variable regions of anti-TR-2 antibody D, and the amino acid sequences of the heavy chain (SEQ ID NO: 8) and the light chain (SEQ ID NO: 42) variable regions of that antibody.

FIG. 7 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 9) and light chain (SEQ ID NO: 43) variable regions of anti-TR-2 antibody E, and the amino acid sequences of the heavy chain (SEQ ID NO: 10) and the light chain (SEQ ID NO: 44) variable regions of that antibody.

FIG. 8 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 11) and light chain (SEQ ID NO: 45) variable regions of anti-TR-2 antibody F, and the amino acid sequences of the heavy chain (SEQ ID NO: 12) and the light chain (SEQ ID NO: 46) variable regions of that antibody.

FIG. 9 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 13) and light chain (SEQ ID NO: 47) variable regions of anti-TR-2 antibody G, and the amino acid sequences of the heavy chain (SEQ ID NO: 14) and the light chain (SEQ ID NO: 48) variable regions of that antibody.

FIG. 10 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 15) and light chain (SEQ ID NO: 49) variable regions of anti-TR-2 antibody H, and the amino acid sequences of the heavy chain (SEQ ID NO: 16) and the light chain (SEQ ID NO: 50) variable regions of that antibody.

FIG. 11 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 17) and light chain (SEQ ID NO:

51) variable regions of anti-TR-2 antibody I, and the amino acid sequences of the heavy chain (SEQ ID NO: 18) and the light chain (SEQ ID NO: 52) variable regions of that antibody.

FIG. 12 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 19) and light chain (SEQ ID NO: 53) variable regions of anti-TR-2 antibody J, and the amino acid sequences of the heavy chain (SEQ ID NO: 20) and the light chain (SEQ ID NO: 54) variable regions of that antibody.

FIG. 13 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 21) and light chain (SEQ ID NO: 55) variable regions of anti-TR-2 antibody K, and the amino acid sequences of the heavy chain (SEQ ID NO: 22) and the light chain (SEQ ID NO: 56) variable regions of that antibody.

FIG. 14 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 23) and light chain (SEQ ID NO: 57) variable regions of anti-TR-2 antibody L, and the amino acid sequences of the heavy chain (SEQ ID NO: 24) and the light chain (SEQ ID NO: 58) variable regions of that antibody.

FIG. 15 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 25) and light chain (SEQ ID NO: 59) variable regions of anti-TR-2 antibody M, and the amino acid sequences of the heavy chain (SEQ ID NO: 26) and the light chain (SEQ ID NO: 60) variable regions of that antibody.

FIG. 16 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 27) and light chain (SEQ ID NO: 61) variable regions of anti-TR-2 antibody N, and the amino acid sequences of the heavy chain (SEQ ID NO: 28) and the light chain (SEQ ID NO: 62) variable regions of that antibody.

FIG. 17 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 29) and light chain (SEQ ID NO: 63) variable regions of anti-TR-2 antibody O, and the amino acid sequences of the heavy chain (SEQ ID NO: 30) and the light chain (SEQ ID NO: 64) variable regions of that antibody.

FIG. 18 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 31) and light chain (SEQ ID NO: 65) variable regions of anti-TR-2 antibody P, and the amino acid sequences of the heavy chain (SEQ ID NO: 32) and the light chain (SEQ ID NO: 66) variable regions of that antibody.

FIG. 19 shows the nucleotide sequences encoding the heavy chain (SEQ ID NO: 33) and light chain (SEQ ID NO: 67) variable regions of anti-TR-2 antibody Q, and the amino acid sequences of the heavy chain (SEQ ID NO: 34) and the light chain (SEQ ID NO: 68) variable regions of that antibody.

FIG. 20 is an alignment of the amino acid sequences of the heavy chain variable regions for anti-TR-2 antibodies A to Q (SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, and 34). Framework regions 1 through 3 (FR1, FR2, and FR3) and complementarity determining regions 1 through 3 (CDR1, CDR2, and CDR3) for each sequence are shown.

FIG. 21 is an alignment of the amino acid sequences of the light chain variable regions for anti-TR-2 antibodies A to Q (SEQ ID NOs: 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, and 68). Framework regions 1 through 3 (FR1, FR2, and FR3) and complementarity determining regions 1 through 3 (CDR1, CDR2, and CDR3) for each sequence are shown.

FIG. 22 is a table showing the classification of certain human anti-TR-2 antibodies into one of four reactivity groups according to the ability of each to bind to the truncated and chimeric N-avidin TR-2 proteins, according to work described in Example 5.

FIG. 23 shows schematic representations of the thirteen truncations of human N-avidin-TR-2 used in epitope mapping, according to the work described in Example 6.

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FIG. 24 is a bar graph showing the binding of certain human anti-TR-2 antibodies to the N-avidin-TR-2 truncations according to work described in Example 6.

FIG. 25 shows schematic representations of N-avidin-cyno TR-2 truncations and N-avidin-cyno/human TR-2 chimeras used in epitope mapping, according to work described in Example 6.

FIG. 26 is an alignment of the human TR-2, cyno TR-2 (short form), and mouse TR-2 sequences, according to work described in Example 6.

FIG. 27 is a bar graph showing the binding of certain human anti-TR-2 antibodies to the N-avidin-TR-2 truncations, chimeras, and domain replacements according to work described in Example 6.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents or portions of documents cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are expressly incorporated by reference herein in their entirety for any purpose.

Definitions

Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g., Sambrook et al. *Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients.

In this application, the use of the singular includes the plural unless specifically stated otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including", as well as other forms, such as "includes" and "included", is not limiting. Also, terms such as "element" or "component" encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise.

As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

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The terms "polynucleotide" and "oligonucleotide" are used interchangeably, and as referred to herein mean a polymeric form of nucleotides of at least 10 bases in length. In certain embodiments, the bases may comprise at least one of ribonucleotides, deoxyribonucleotides, and a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA. The term "polynucleotide" also encompasses sequences that comprise one or more of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, and 67. In certain embodiments, polynucleotides have nucleotide sequences that are about 90 percent, or about 95 percent, or about 96 percent, or about 97 percent, or about 98 percent, or about 99 percent identical to nucleotide sequences shown in FIGS. 3-19. In certain embodiments, polynucleotides complementary to specific polynucleotides that encode certain polypeptides described herein are provided.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a, wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present; wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present; wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine,

aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and wherein the polypeptide, in association with an antibody light chain, binds TR-2.

In certain embodiments, a polynucleotide comprises a sequence encoding CDR2a, wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present.

In certain embodiments, a polynucleotide comprises a sequence encoding CDR3a comprising the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline,

aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least two complementarity determining regions (CDR) selected from CDR1a, CDR2a, and CDR3a, wherein the polypeptide, in association with an antibody light chain, binds TR-2. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising CDR1a, CDR2a, and CDR3a, wherein the polypeptide, in association with an antibody light chain, binds TR-2.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising an antibody heavy chain variable region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a human antibody heavy chain variable region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a heavy chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a human heavy chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a non-human heavy chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a heavy chain constant region of a species other than human.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from amino acids 26 to 35 of SEQ ID NO: 2; amino acids 50 to 66 of SEQ ID NO: 2; amino acids 99 to 110 of SEQ ID NO: 2; amino acids 26 to 37 of SEQ ID NO: 4; amino acids 52 to 67 of SEQ ID NO: 4; amino acids 100 to 109 of SEQ ID NO: 4; amino acids 26 to 37 of SEQ ID NO: 6; amino acids 52 to 67 of SEQ ID NO: 6; amino acids 100 to 109 of SEQ ID NO: 6; amino acids 26 to 37 of SEQ ID NO: 8; amino acids 52 to 67 of SEQ ID NO: 8; amino acids 100 to 109 of SEQ ID NO: 8; amino acids 26 to 35 of SEQ ID NO: 10; amino acids 50 to 66 of SEQ ID NO: 10; amino acids 99 to 110 of SEQ ID NO: 10; amino acids 26 to 35 of SEQ ID NO: 12; amino acids 50 to 66 of SEQ ID NO: 12; amino acids 99 to 111 of SEQ ID NO: 12; amino acids 26 to 35 of SEQ ID NO: 14; amino acids 50 to 65 of SEQ ID NO: 14; amino acids 98 to 111 of SEQ ID NO: 14; amino acids 26 to 37 of SEQ ID NO: 16; amino acids 52 to 67 of SEQ ID NO: 16; amino acids 100 to 109 of SEQ ID NO: 16; amino acids 26 to 35 of SEQ ID NO: 18; amino acids 50 to 66 of SEQ ID NO: 18; amino acids 99 to 105 of SEQ ID NO: 18; amino acids 26 to 35 of SEQ ID NO: 20; amino acids 50 to 66

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of SEQ ID NO: 20; amino acids 99 to 118 of SEQ ID NO: 20; amino acids 26 to 35 of SEQ ID NO: 22; amino acids 50 to 66 of SEQ ID NO: 22; amino acids 99 to 118 of SEQ ID NO: 22; amino acids 26 to 35 of SEQ ID NO: 24; amino acids 50 to 65 of SEQ ID NO: 24; amino acids 98 to 108 of SEQ ID NO: 24; amino acids 26 to 35 of SEQ ID NO: 26; amino acids 50 to 66 of SEQ ID NO: 26; amino acids 99 to 110 of SEQ ID NO: 26; amino acids 26 to 35 of SEQ ID NO: 28; amino acids 50 to 66 of SEQ ID NO: 28; amino acids 99 to 117 of SEQ ID NO: 28; amino acids 26 to 37 of SEQ ID NO: 30; amino acids 52 to 67 of SEQ ID NO: 30; amino acids 100 to 111 of SEQ ID NO: 30; amino acids 26 to 37 of SEQ ID NO: 32; amino acids 52 to 67 of SEQ ID NO: 32; amino acids 100 to 111 of SEQ ID NO: 32; amino acids 26 to 37 of SEQ ID NO: 34; amino acids 52 to 67 of SEQ ID NO: 34; and amino acids 100 to 111 of SEQ ID NO: 34, wherein the polypeptide, in association with an antibody light chain, binds TR-2. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least two of the CDRs of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 34. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising three of the CDRs of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 34.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 2, amino acids 50 to 66 of SEQ ID NO: 2, and amino acids 99 to 110 of SEQ ID NO: 2. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 4, amino acids 52 to 67 of SEQ ID NO: 4, and amino acids 100 to 109 of SEQ ID NO: 4. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 6, amino acids 52 to 67 of SEQ ID NO: 6, and amino acids 100 to 109 of SEQ ID NO: 6. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 8, amino acids 52 to 67 of SEQ ID NO: 8, and amino acids 100 to 109 of SEQ ID NO: 8. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 10, amino acids 50 to 66 of SEQ ID NO: 10, and amino acids 99-110 of SEQ ID NO: 10. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 12, amino acids 50 to 66 of SEQ ID NO: 12, and amino acids 99-111 of SEQ ID NO: 12. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 14, amino acids 50 to 65 of SEQ ID NO: 14, and amino acids 98 to 111 of SEQ ID NO: 14. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 16, amino acids 52 to 67 of SEQ ID NO: 16, and amino acids 100 to 109 of SEQ ID NO: 16. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 18, amino acids 50 to 66 of SEQ ID NO: 18, and amino acids 99 to 105 of SEQ ID NO: 18. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 20, amino acids 50 to 66 of SEQ ID NO: 20, and amino acids 99 to 118 of SEQ ID NO: 20. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide

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comprising amino acids 26 to 35 of SEQ ID NO: 24, amino acids 50 to 65 of SEQ ID NO: 24, and amino acids 98 to 108 of SEQ ID NO: 24. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 26, amino acids 50 to 66 of SEQ ID NO: 26, and amino acids 99 to 110 of SEQ ID NO: 26. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 35 of SEQ ID NO: 28, amino acids 50 to 66 of SEQ ID NO: 28, and amino acids 99 to 117 of SEQ ID NO: 28. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 30, amino acids 52 to 67 of SEQ ID NO: 30, and amino acids 100 to 111 of SEQ ID NO: 30. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 32, amino acids 52 to 67 of SEQ ID NO: 32, and amino acids 100 to 111 of SEQ ID NO: 32. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 26 to 37 of SEQ ID NO: 34, amino acids 52 to 67 of SEQ ID NO: 34, and amino acids 100 to 111 of SEQ ID NO: 34.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b, wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present; wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine; wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and

amino acid g1' is selected from threonine or serine; and wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least two complementarity determining regions (CDR) selected from CDR1b, CDR2b, and CDR3b, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising CDR1b, CDR2b, and CDR3b, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising an antibody light chain variable region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a human antibody light chain variable region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a light chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a human light chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, or SEQ ID NO: 68. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a non-human light chain constant region. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising a light chain constant region of a species other than human.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from amino acids 24 to 34 of SEQ ID NO: 36; amino acids 50 to 56 of SEQ ID NO: 36; amino acids 89 to 97 of SEQ ID NO: 36; amino acids 24 to 34 of SEQ ID NO: 38; amino acids 50 to 56 of SEQ ID NO: 38; amino acids 89 to 97 of SEQ ID NO: 38; amino acids 24 to 34 of SEQ ID NO: 40; amino acids 50 to 56 of SEQ ID NO: 40; amino acids 89 to 97 of SEQ ID NO: 40; amino acids 24 to 34 of SEQ ID NO: 42; amino acids 50 to 56 of SEQ ID NO: 42; amino acids 89 to 97 of SEQ ID NO: 42; amino acids 24 to 34 of SEQ ID NO: 44; amino acids 50 to 56 of SEQ ID NO: 44; amino acids 89 to 97 of SEQ ID NO: 44; amino acids 24 to 34 of SEQ ID NO: 46; amino acids 50 to 56 of SEQ ID NO: 46; amino acids 89 to 97 of SEQ ID NO: 46; amino acids 24 to 40 of SEQ ID NO: 48; amino acids 56 to 62 of SEQ ID NO: 48; amino acids 95 to 103 of SEQ ID NO: 48; amino acids 24 to 39 of SEQ ID NO: 50; amino acids 55 to 61 of SEQ ID NO: 50; amino acids 94 to 102 of SEQ ID NO: 50; amino acids 24 to 40 of SEQ ID NO: 52; amino acids 56 to 62 of SEQ ID NO: 52; amino acids 95 to 103 of SEQ ID NO: 52; amino acids 24 to 34 of SEQ ID NO: 54; amino acids 50 to 56 of SEQ ID NO: 54; amino acids 89 to 97 of SEQ ID NO: 54; amino acids 24 to 34 of SEQ ID NO: 56; amino acids 50 to 56 of SEQ ID NO: 56; amino acids 89 to 97 of SEQ ID NO: 56; amino acids 24 to 40 of SEQ ID NO: 58; amino acids 56 to 62 of SEQ ID NO: 58; amino acids 95 to 103 of SEQ ID NO: 58; amino acids 24 to 34 of SEQ ID NO: 60; amino acids 50 to 56 of SEQ ID NO: 60; amino acids 89 to 97 of SEQ ID NO: 60; amino acids 24 to 34 of SEQ ID NO: 62; amino acids 50 to 56 of SEQ ID NO: 62; amino acids 89 to 97 of SEQ ID NO: 62; amino acids 24 to 35 of SEQ ID NO: 64; amino acids 51 to 57 of SEQ ID NO: 64; amino acids 90 to 88 of SEQ ID NO: 64;

amino acids 24 to 34 of SEQ ID NO: 66; amino acids 50 to 57 of SEQ ID NO: 66; amino acids 89 to 97 of SEQ ID NO: 66; amino acids 24 to 34 of SEQ ID NO: 68; amino acids 50 to 56 of SEQ ID NO: 68; and amino acids 89 to 97 of SEQ ID NO: 68, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising at least two of the CDRs of SEQ ID NOS. 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, or 68. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising three of the CDRs of SEQ ID NOS. 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, or 68.

In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 36, amino acids 50 to 56 of SEQ ID NO: 36, and amino acids 89-97 of SEQ ID NO: 36. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 38, amino acids 50 to 56 of SEQ ID NO: 38, and amino acids 89 to 97 of SEQ ID NO: 38. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 40, amino acids 50 to 56 of SEQ ID NO: 40, and amino acids 89 to 97 of SEQ ID NO: 40. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 42, amino acids 50 to 56 of SEQ ID NO: 42, and amino acids 89 to 97 of SEQ ID NO: 42. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 44, amino acids 50 to 56 of SEQ ID NO: 44, and amino acids 89-97 of SEQ ID NO: 44. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 46, amino acids 50 to 56 of SEQ ID NO: 46, and amino acids 89 to 97 of SEQ ID NO: 46. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 40 of SEQ ID NO: 48, amino acids 56 to 62 of SEQ ID NO: 48, and amino acids 95 to 103 of SEQ ID NO: 48. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 39 of SEQ ID NO: 50, amino acids 55 to 61 of SEQ ID NO: 50, and amino acids 94 to 102 of SEQ ID NO: 50. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 40 of SEQ ID NO: 52, amino acids 56 to 62 of SEQ ID NO: 52, and amino acids 95 to 103 of SEQ ID NO: 52. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising 24 to 34 of SEQ ID NO: 54, amino acids 50 to 56 of SEQ ID NO: 54, and amino acids 89 to 97 of SEQ ID NO: 54. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 56, amino acids 50 to 56 of SEQ ID NO: 56, and amino acids 89 to 97 of SEQ ID NO: 56. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 40 of SEQ ID NO: 58, amino acids 56 to 62 of SEQ ID NO: 58, and amino acids 95 to 103 of SEQ ID NO: 58. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 60, amino acids 50 to 56 of SEQ ID NO: 60, and amino acids 89-97 of SEQ ID NO: 60. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 62, amino acids 50 to 56 of SEQ ID NO: 62, and amino acids 89 to 97 of SEQ ID NO: 62. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide

comprising amino acids 24 to 35 of SEQ ID NO: 64, amino acids 51 to 57 of SEQ ID NO: 64, and amino acids 90 to 88 of SEQ ID NO: 64. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 66, amino acids 50 to 57 of SEQ ID NO: 66, and amino acids 89 to 97 of SEQ ID NO: 66. In certain embodiments, a polynucleotide comprises a sequence encoding a polypeptide comprising amino acids 24 to 34 of SEQ ID NO: 68, amino acids 50 to 56 of SEQ ID NO: 68, and amino acids 89 to 97 of SEQ ID NO: 68.

In certain embodiments, this application discusses certain polynucleotides encoding antibody heavy and light chains. In certain embodiments, this application discusses certain polynucleotides encoding an antibody heavy chain variable region. In certain embodiments, this application discusses certain polynucleotides encoding a human antibody heavy chain variable region. In certain embodiments, this application discusses certain polynucleotides encoding antibody light chain variable regions. In certain embodiments, this application discusses certain polynucleotides encoding a human antibody light chain variable region. In certain embodiments, this application discusses certain polynucleotides encoding an antibody heavy chain constant region. In certain embodiments, this application discusses certain polynucleotides encoding a human antibody heavy chain constant region. In certain embodiments, this application discusses certain polynucleotides encoding an antibody heavy chain constant region of a species other than human. In certain embodiments, this application discusses certain polynucleotides encoding antibody light chain constant regions. In certain embodiments, this application discusses certain polynucleotides encoding a human antibody light chain constant region. In certain embodiments, this application discusses certain polynucleotides encoding an antibody light chain constant region of a species other than human. In certain embodiments, this application discusses certain polynucleotides encoding a single-chain antibody.

In certain embodiments, these antibody heavy and light chain polynucleotides and polypeptides are human antibody heavy and light chain polynucleotides and polypeptides. In certain embodiments a polynucleotide comprises a nucleotide sequence as set forth in SEQ ID NOS. SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, or 67. In certain embodiments, a polynucleotide comprises a nucleotide sequence that has one or more deletions, additions, and/or substitutions of one or more nucleotides of those sequences. In certain embodiments, a polynucleotide comprises a nucleotide sequence encoding an amino acid sequence comprising an amino acid sequence as set forth in SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68. In certain embodiments, variable region sequences comprising complementarity determining regions (CDRs), e.g., CDR1 through CDR3, are provided. In certain embodiments, variable region polynucleotides and polypeptides are human variable region polynucleotides and polypeptides.

The term "naturally occurring nucleotides" includes deoxyribonucleotides and ribonucleotides. Deoxyribonucleotides include, but are not limited to, adenosine, guanine, cytosine, and thymidine. Ribonucleotides include, but are not limited to, adenosine, cytosine, thymidine, and uracil. The term "modified nucleotides" includes, but is not limited to, nucleotides with modified or substituted sugar groups and the like. The term "polynucleotide linkages" includes, but is not limited to, polynucleotide linkages such as phosphorothioate,

phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoraniladate, phosphoramidate, and the like. See, e.g., LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984); Stein et al. *Nucl. Acids Res.* 16:3209 (1988); Zon et al. *Anti-Cancer Drug Design* 6:539 (1991); Zon et al. *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Pat. No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990). In certain embodiments, a polynucleotide can include a label for detection.

The term "isolated polypeptide" refers to any polypeptide that (1) is free of at least some proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

The terms "polypeptide," "peptide," and "protein" are used interchangeably herein and refer to a polymer of two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. The terms apply to amino acid polymers containing naturally occurring amino acids as well as amino acid polymers in which one or more amino acid residues is a non-naturally occurring amino acid or a chemical analogue of a naturally occurring amino acid. An amino acid polymer may contain one or more amino acid residues that has been modified by one or more natural processes, such as post-translational processing, and/or one or more amino acid residues that has been modified by one or more chemical modification techniques known in the art.

A "fragment" of a reference polypeptide refers to a contiguous stretch of amino acids from any portion of the reference polypeptide. A fragment may be of any length that is less than the length of the reference polypeptide.

A "variant" of a reference polypeptide refers to a polypeptide having one or more amino acid substitutions, deletions, or insertions relative to the reference polypeptide. In certain embodiments, a variant of a reference polypeptide has an altered post-translational modification site (i.e., a glycosylation site). In certain embodiments, both a reference polypeptide and a variant of a reference polypeptide are specific binding agents. In certain embodiments, both a reference polypeptide and a variant of a reference polypeptide are antibodies.

Variants of a reference polypeptide include, but are not limited to, glycosylation variants. Glycosylation variants include variants in which the number and/or type of glycosylation sites have been altered as compared to the reference polypeptide. In certain embodiments, glycosylation variants of a reference polypeptide comprise a greater or a lesser number of N-linked glycosylation sites than the reference polypeptide. In certain embodiments, an N-linked glycosylation site is characterized by the sequence Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. In certain embodiments, glycosylation variants of a reference polypeptide comprise a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created.

Variants of a reference polypeptide include, but are not limited to, cysteine variants. In certain embodiments, cysteine variants include variants in which one or more cysteine residues of the reference polypeptide are replaced by one or more non-cysteine residues; and/or one or more non-cysteine residues of the reference polypeptide are replaced by one or more cysteine residues. Cysteine variants may be useful, in

certain embodiments, when a particular polypeptide must be refolded into a biologically active conformation, e.g., after the isolation of insoluble inclusion bodies. In certain embodiments, cysteine variants of a reference polypeptide have fewer cysteine residues than the reference polypeptide. In certain embodiments, cysteine variants of a reference polypeptide have an even number of cysteines to minimize interactions resulting from unpaired cysteines. In certain embodiments, cysteine variants have more cysteine residues than the native protein.

A “derivative” of a reference polypeptide refers to: a polypeptide: (1) having one or more modifications of one or more amino acid residues of the reference polypeptide; and/or (2) in which one or more peptidyl linkages has been replaced with one or more non-peptidyl linkages; and/or (3) in which the N-terminus and/or the C-terminus has been modified. Certain exemplary modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. In certain embodiments, both a reference polypeptide and a derivative of a reference polypeptide are specific binding agents. In certain embodiments, both a reference polypeptide and a derivative of a reference polypeptide are antibodies.

Polypeptides include, but are not limited to, 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. In certain embodiments, modifications may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. In certain such embodiments, the modifications may be present to the same or varying degrees at several sites in a given polypeptide. In certain embodiments, a given polypeptide contains many types of modifications such as deletions, additions, and/or substitutions of one or more amino acids of a native sequence. In certain embodiments, polypeptides may be branched and/or cyclic. Cyclic, branched and branched cyclic polypeptides may result from post-translational natural processes (including, but not limited to, ubiquitination) or may be made by synthetic methods. The term “polypeptide” also encompasses sequences that comprise the amino acid sequences of the heavy chain and/or light chain of an antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q, as described below (see SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, and 68). The term “polypeptide” also encompasses sequences that have one or more deletions, additions, and/or substitutions of one or more amino acids of those sequences. In certain embodiments, certain polypeptide sequences comprise at least one complementarity determining region (CDR).

In certain embodiments, a polypeptide comprises at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a wherein CDR1a com-

prises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present; wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present; wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine,

or is not present; and amino acid w' is valine or is not present; and wherein the polypeptide, in association with an antibody light chain, binds TR-2.

In certain embodiments, a polypeptide comprises at least two complementarity determining regions (CDR) selected from CDR1a, CDR2a, and CDR3a, wherein the polypeptide, in association with an antibody light chain, binds TR-2. In certain embodiments, a polypeptide comprises CDR1a, CDR2a, and CDR3a, wherein the polypeptide, in association with an antibody light chain, binds TR-2.

In certain embodiments, a polypeptide comprises an antibody heavy chain variable region. In certain embodiments, a polypeptide comprises a human antibody heavy chain variable region. In certain embodiments, a polypeptide comprises a heavy chain constant region. In certain embodiments, a polypeptide comprises a human heavy chain constant region. In certain embodiments, a polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, or SEQ ID NO: 34. In certain embodiments, a polypeptide comprises a non-human heavy chain constant region. In certain embodiments, a polypeptide comprises a heavy chain constant region of a species other than human.

In certain embodiments, a polypeptide comprises at least one complementarity determining region (CDR) selected from amino acids 26 to 35 of SEQ ID NO: 2; amino acids 50 to 66 of SEQ ID NO: 2; amino acids 99 to 110 of SEQ ID NO: 2; amino acids 26 to 37 of SEQ ID NO: 4; amino acids 52 to 67 of SEQ ID NO: 4; amino acids 100 to 109 of SEQ ID NO: 4; amino acids 26 to 37 of SEQ ID NO: 6; amino acids 52 to 67 of SEQ ID NO: 6; amino acids 100 to 109 of SEQ ID NO: 6; amino acids 26 to 37 of SEQ ID NO: 8; amino acids 52 to 67 of SEQ ID NO: 8; amino acids 100 to 109 of SEQ ID NO: 8; amino acids 26 to 35 of SEQ ID NO: 10; amino acids 50 to 66 of SEQ ID NO: 10; amino acids 99-110 of SEQ ID NO: 10; amino acids 26 to 35 of SEQ ID NO: 12; amino acids 50 to 66 of SEQ ID NO: 12; amino acids 99-111 of SEQ ID NO: 12; amino acids 26 to 35 of SEQ ID NO: 14; amino acids 50 to 65 of SEQ ID NO: 14; amino acids 98 to 111 of SEQ ID NO: 14; amino acids 26 to 37 of SEQ ID NO: 16; amino acids 52 to 67 of SEQ ID NO: 16; amino acids 100 to 109 of SEQ ID NO: 16; amino acids 26 to 35 of SEQ ID NO: 18; amino acids 50 to 66 of SEQ ID NO: 18; amino acids 99 to 105 of SEQ ID NO: 18; amino acids 26 to 35 of SEQ ID NO: 20; amino acids 50 to 66 of SEQ ID NO: 20; amino acids 99 to 118 of SEQ ID NO: 20; amino acids 26 to 35 of SEQ ID NO: 22; amino acids 50 to 66 of SEQ ID NO: 22; amino acids 99 to 118 of SEQ ID NO: 22; amino acids 26 to 35 of SEQ ID NO: 24; amino acids 50 to 65 of SEQ ID NO: 24; amino acids 98 to 108 of SEQ ID NO: 24; amino acids 26 to 35 of SEQ ID NO: 26; amino acids 50 to 66 of SEQ ID NO: 26; amino acids 99 to 110 of SEQ ID NO: 26; amino acids 26 to 35 of SEQ ID NO: 28; amino acids 50 to 66 of SEQ ID NO: 28; amino acids 99 to 117 of SEQ ID NO: 28; amino acids 26 to 37 of SEQ ID NO: 30; amino acids 52 to 67 of SEQ ID NO: 30; amino acids 100 to 111 of SEQ ID NO: 30; amino acids 26 to 37 of SEQ ID NO: 32; amino acids 52 to 67 of SEQ ID NO: 32; amino acids 100 to 111 of SEQ ID NO: 32; amino acids 26 to 37 of SEQ ID NO: 34; amino acids 52 to 67 of SEQ ID NO: 34; and amino acids 100 to 111 of SEQ ID NO: 34, wherein the polypeptide, in association with an antibody light chain, binds TR-2. In certain embodiments, a polypeptide comprises at least two of the CDRs of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 34. In certain embodiments, a polypeptide comprises at

least three of the CDRs of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, or 34.

In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 2, amino acids 50 to 66 of SEQ ID NO: 2, and amino acids 99 to 110 of SEQ ID NO: 2. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 4, amino acids 52 to 67 of SEQ ID NO: 4, and amino acids 100 to 109 of SEQ ID NO: 4. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 6, amino acids 52 to 67 of SEQ ID NO: 6, and amino acids 100 to 109 of SEQ ID NO: 6. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 8, amino acids 52 to 67 of SEQ ID NO: 8, and amino acids 100 to 109 of SEQ ID NO: 8. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 10, amino acids 50 to 66 of SEQ ID NO: 10, and amino acids 99-110 of SEQ ID NO: 10. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 12, amino acids 50 to 66 of SEQ ID NO: 12, and amino acids 99-111 of SEQ ID NO: 12. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 14, amino acids 50 to 65 of SEQ ID NO: 14, and amino acids 98 to 111 of SEQ ID NO: 14. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 16, amino acids 52 to 67 of SEQ ID NO: 16, and amino acids 100 to 109 of SEQ ID NO: 16. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 18, amino acids 50 to 66 of SEQ ID NO: 18, and amino acids 99 to 105 of SEQ ID NO: 18. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 20, amino acids 50 to 66 of SEQ ID NO: 20, and amino acids 99 to 118 of SEQ ID NO: 20. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 22, amino acids 50 to 66 of SEQ ID NO: 22, and amino acids 99 to 118 of SEQ ID NO: 22. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 24, amino acids 50 to 65 of SEQ ID NO: 24, and amino acids 98 to 108 of SEQ ID NO: 24. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 26, amino acids 50 to 66 of SEQ ID NO: 26, and amino acids 99 to 110 of SEQ ID NO: 26. In certain embodiments, a polypeptide comprises amino acids 26 to 35 of SEQ ID NO: 28, amino acids 50 to 66 of SEQ ID NO: 28, and amino acids 99 to 117 of SEQ ID NO: 28. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 30, amino acids 52 to 67 of SEQ ID NO: 30, and amino acids 100 to 111 of SEQ ID NO: 30. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 32, amino acids 52 to 67 of SEQ ID NO: 32, and amino acids 100 to 111 of SEQ ID NO: 32. In certain embodiments, a polypeptide comprises amino acids 26 to 37 of SEQ ID NO: 34, amino acids 52 to 67 of SEQ ID NO: 34, and amino acids 100 to 111 of SEQ ID NO: 34.

In certain embodiments, a polypeptide comprises at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b, wherein CDR1b comprises a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or

serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present; wherein CDR2b comprises the amino acid r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine; wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, a polypeptide comprises at least two complementarity determining regions (CDR) selected from CDR1b, CDR2b, and CDR3b, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2. In certain embodiments, a polypeptide comprises CDR1b, CDR2b, and CDR3b, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, a polypeptide comprises an antibody light chain variable region. In certain embodiments, a polypeptide comprises a human antibody light chain variable region. In certain embodiments, a polypeptide comprises a light chain constant region. In certain embodiments, a polypeptide comprises a human light chain constant region. In certain embodiments, a polypeptide comprises an amino acid sequence as set forth in SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 62, SEQ ID NO: 64, SEQ ID NO: 66, or SEQ ID NO: 68. In certain embodiments, a polypeptide comprises a non-human light chain constant region. In certain embodiments, a polypeptide comprises a light chain constant region of a species other than human.

In certain embodiments, a polypeptide which comprises at least one complementarity determining region (CDR) selected from amino acids 24 to 34 of SEQ ID NO: 36; amino acids 50 to 56 of SEQ ID NO: 36; amino acids 89-97 of SEQ ID NO: 36; amino acids 24 to 34 of SEQ ID NO: 38; amino acids 50 to 56 of SEQ ID NO: 38; amino acids 89 to 97 of SEQ ID NO: 38; amino acids 24 to 34 of SEQ ID NO: 40; amino acids 50 to 56 of SEQ ID NO: 40; amino acids 89 to 97 of SEQ ID NO: 40; amino acids 24 to 34 of SEQ ID NO: 42; amino acids 50 to 56 of SEQ ID NO: 42; amino acids 89 to 97 of SEQ ID NO: 42; amino acids 24 to 34 of SEQ ID NO: 44; amino acids 50 to 56 of SEQ ID NO: 44; amino acids 89-97 of SEQ

ID NO: 44; amino acids 24 to 34 of SEQ ID NO: 46; amino acids 50 to 56 of SEQ ID NO: 46; amino acids 89 to 97 of SEQ ID NO: 46; amino acids 24 to 40 of SEQ ID NO: 48; amino acids 56 to 62 of SEQ ID NO: 48; amino acids 95 to 103 of SEQ ID NO: 48; amino acids 24 to 39 of SEQ ID NO: 50; amino acids 55 to 61 of SEQ ID NO: 50; amino acids 94 to 102 of SEQ ID NO: 50; amino acids 24 to 40 of SEQ ID NO: 52; amino acids 56 to 62 of SEQ ID NO: 52; amino acids 95 to 103 of SEQ ID NO: 52; 24 to 34 of SEQ ID NO: 54; amino acids 50 to 56 of SEQ ID NO: 54; amino acids 89 to 97 of SEQ ID NO: 54; amino acids 24 to 34 of SEQ ID NO: 56; amino acids 50 to 56 of SEQ ID NO: 56; amino acids 89 to 97 of SEQ ID NO: 56; amino acids 24 to 40 of SEQ ID NO: 58; amino acids 56 to 62 of SEQ ID NO: 58; amino acids 95 to 103 of SEQ ID NO: 58; amino acids 24 to 34 of SEQ ID NO: 60; amino acids 50 to 56 of SEQ ID NO: 60; amino acids 89 to 97 of SEQ ID NO: 60; amino acids 24 to 34 of SEQ ID NO: 62; amino acids 50 to 56 of SEQ ID NO: 62; amino acids 89 to 97 of SEQ ID NO: 62; amino acids 24 to 35 of SEQ ID NO: 64; amino acids 51 to 57 of SEQ ID NO: 64; amino acids 90 to 88 of SEQ ID NO: 64; amino acids 24 to 34 of SEQ ID NO: 66; amino acids 50 to 57 of SEQ ID NO: 66; amino acids 89 to 97 of SEQ ID NO: 66; amino acids 24 to 34 of SEQ ID NO: 68; amino acids 50 to 56 of SEQ ID NO: 68; and amino acids 89 to 97 of SEQ ID NO: 68, wherein the polypeptide, in association with an antibody heavy chain, binds TR-2. In certain embodiments, a polypeptide comprises at least two of the CDRs of SEQ ID NOS. 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68. In certain embodiments, a polypeptide comprises at least three of the CDRs of SEQ ID NOS. 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, or 68.

In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 36, amino acids 50 to 56 of SEQ ID NO: 36, and amino acids 89-97 of SEQ ID NO: 36. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 38, amino acids 50 to 56 of SEQ ID NO: 38, and amino acids 89 to 97 of SEQ ID NO: 38. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 40, amino acids 50 to 56 of SEQ ID NO: 40, and amino acids 89 to 97 of SEQ ID NO: 40. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 42, amino acids 50 to 56 of SEQ ID NO: 42, and amino acids 89 to 97 of SEQ ID NO: 42. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 44, amino acids 50 to 56 of SEQ ID NO: 44, and amino acids 89-97 of SEQ ID NO: 44. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 46, amino acids 50 to 56 of SEQ ID NO: 46, and amino acids 89 to 97 of SEQ ID NO: 46. In certain embodiments, a polypeptide comprises amino acids 24 to 40 of SEQ ID NO: 48, amino acids 56 to 62 of SEQ ID NO: 48, and amino acids 95 to 103 of SEQ ID NO: 48. In certain embodiments, a polypeptide comprises amino acids 24 to 39 of SEQ ID NO: 50, amino acids 55 to 61 of SEQ ID NO: 50, and amino acids 94 to 102 of SEQ ID NO: 50. In certain embodiments, a polypeptide comprises amino acids 24 to 40 of SEQ ID NO: 52, amino acids 56 to 62 of SEQ ID NO: 52, and amino acids 95 to 103 of SEQ ID NO: 52. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 54, amino acids 50 to 56 of SEQ ID NO: 54, and amino acids 89 to 97 of SEQ ID NO: 54. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 56, amino acids 50 to 56 of SEQ ID NO: 56, and amino acids 89 to 97 of SEQ ID NO: 56. In certain embodiments, a polypeptide comprises amino acids 24 to 40 of SEQ ID NO: 58, amino acids 56 to 62 of SEQ ID NO: 58,

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and amino acids 95 to 103 of SEQ ID NO: 58. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 60, amino acids 50 to 56 of SEQ ID NO: 60, and amino acids 89-97 of SEQ ID NO: 60. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 62, amino acids 50 to 56 of SEQ ID NO: 62, and amino acids 89 to 97 of SEQ ID NO: 62. In certain embodiments, a polypeptide comprises amino acids 24 to 35 of SEQ ID NO: 64, amino acids 51 to 57 of SEQ ID NO: 64, and amino acids 90 to 88 of SEQ ID NO: 64. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 66, amino acids 50 to 57 of SEQ ID NO: 66, and amino acids 89 to 97 of SEQ ID NO: 66. In certain embodiments, a polypeptide comprises amino acids 24 to 34 of SEQ ID NO: 68, amino acids 50 to 56 of SEQ ID NO: 68, and amino acids 89 to 97 of SEQ ID NO: 68.

The term “naturally-occurring” as applied to an object means that an object can be found in nature. For example, a polypeptide or polynucleotide that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring.

The term “operably linked” as used herein refers to components that are in a relationship permitting them to function in their intended manner. For example, in the context of a polynucleotide sequence, a control sequence may be “operably linked” to a coding sequence when the control sequence and coding sequence are in association with each other in such a way that expression of the coding sequence is achieved under conditions compatible with the functioning of the control sequence.

The term “control sequence” refers to polynucleotide sequences which may effect the expression and processing of coding sequences with which they are in association. The nature of such control sequences may differ depending upon the host organism. Certain exemplary control sequences for prokaryotes include, but are not limited to, promoters, ribosomal binding sites, and transcription termination sequences. Certain exemplary control sequences for eukaryotes include, but are not limited to, promoters, enhancers, and transcription termination sequences. In certain embodiments, “control sequences” can include leader sequences and/or fusion partner sequences.

In certain embodiments, a first polynucleotide coding sequence is operably linked to a second polynucleotide coding sequence when the first and second polynucleotide coding sequences are transcribed into a single contiguous mRNA that can be translated into a single contiguous polypeptide.

In the context of polypeptides, two or more polypeptides are “operably linked” if each linked polypeptide is able to function in its intended manner. A polypeptide that is able to function in its intended manner when operably linked to another polypeptide may or may not be able to function in its intended manner when not operably linked to another polypeptide. For example, in certain embodiments, a first polypeptide may be unable to function in its intended manner when unlinked, but may be stabilized by being linked to a second polypeptide such that it becomes able to function in its intended manner. Alternatively, in certain embodiments, a first polypeptide may be able to function in its intended manner when unlinked, and may retain that ability when operably linked to a second polypeptide.

As used herein, two or more polypeptides are “fused” when the two or more polypeptides are linked by translating them as a single contiguous polypeptide sequence or by synthesizing them as a single contiguous polypeptide sequence. In certain embodiments, two or more fused polypeptides may have been

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translated in vivo from two or more operably linked polynucleotide coding sequences. In certain embodiments, two or more fused polypeptides may have been translated in vitro from two or more operably linked polynucleotide coding sequences.

As used herein, two or more polypeptides are “operably fused” if each linked polypeptide is able to function in its intended manner.

In certain embodiments, a first polypeptide that contains two or more distinct polypeptide units is considered to be linked to a second polypeptide so long as at least one of the distinct polypeptide units of the first polypeptide is linked to the second polypeptide. As a non-limiting example, in certain embodiments, an antibody is considered linked to a second polypeptide in all of the following instances: (a) the second polypeptide is linked to one of the heavy chain polypeptides of the antibody; (b) the second polypeptide is linked to one of the light chain polypeptides of the antibody; (c) a first molecule of the second polypeptide is linked to one of the heavy chain polypeptides of the antibody and a second molecule of the second polypeptide is linked to one of the light chain polypeptides of the antibody; and (d) first and second molecules of the second polypeptide are linked to the first and second heavy chain polypeptides of the antibody and third and fourth molecules of the second polypeptide are linked to first and second light chain polypeptides of the antibody.

In certain embodiments, the language “a first polypeptide linked to a second polypeptide” encompasses situations where: (a) only one molecule of a first polypeptide is linked to only one molecule of a second polypeptide; (b) only one molecule of a first polypeptide is linked to more than one molecule of a second polypeptide; (c) more than one molecule of a first polypeptide is linked to only one molecule of a second polypeptide; and (d) more than one molecule of a first polypeptide is linked to more than one molecule of a second polypeptide. In certain embodiments, when a linked molecule comprises more than one molecule of a first polypeptide and only one molecule of a second polypeptide, all or fewer than all of the molecules of the first polypeptide may be covalently or noncovalently linked to the second polypeptide. In certain embodiments, when a linked molecule comprises more than one molecule of a first polypeptide, one or more molecules of the first polypeptide may be covalently or noncovalently linked to other molecules of the first polypeptide.

As used herein, a “flexible linker” refers to any linker that is not predicted, according to its chemical structure, to be fixed in three-dimensional space. One skilled in the art can predict whether a particular linker is flexible in its intended context. In certain embodiments, a peptide linker comprising 3 or more amino acids is a flexible linker.

As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Immunology—A Synthesis (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)). In certain embodiments, one or more unconventional amino acids may be incorporated into a polypeptide. The term “unconventional amino acid” refers to any amino acid that is not one of the twenty conventional amino acids. The term “non-naturally occurring amino acids” refers to amino acids that are not found in nature. Non-naturally occurring amino acids are a subset of unconventional amino acids. Unconventional amino acids include, but are not limited to, stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α,α -disubstituted amino acids, N-alkyl amino acids, lactic acid, homoserine, homocysteine, 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,

N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline) known in the art. In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

In certain embodiments, conservative amino acid substitutions include substitution with one or more unconventional amino acid residues. In certain embodiments, unconventional amino acid residues are incorporated by chemical peptide synthesis rather than by synthesis in biological systems.

The term "acidic residue" refers to an amino acid residue in D- or L-form that comprises at least one acidic group when incorporated into a polypeptide between two other amino acid residues that are the same or different. In certain embodiments, an acidic residue comprises a sidechain that comprises at least one acidic group. Exemplary acidic residues include, but are not limited to, aspartic acid (D) and glutamic acid (E). In certain embodiments, an acidic residue may be an unconventional amino acid.

The term "aromatic residue" refers to an amino acid residue in D- or L-form that comprises at least one aromatic group. In certain embodiments, an aromatic residue comprises a sidechain that comprises at least one aromatic group. Exemplary aromatic residues include, but are not limited to, phenylalanine (F), tyrosine (Y), and tryptophan (W). In certain embodiments, an aromatic residue may be an unconventional amino acid.

The term "basic residue" refers to an amino acid residue in F- or L-form that may comprise at least one basic group when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. In certain embodiments, a basic residue comprises a sidechain that comprises at least one basic group. Exemplary basic residues include, but are not limited to, histidine (H), lysine (K), and arginine (R). In certain embodiments, a basic residue may be an unconventional amino acid.

The term "neutral hydrophilic residue" refers to an amino acid residue in D- or L-form that comprises at least one hydrophilic and/or polar group, but does not comprise an acidic or basic group when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. Exemplary neutral hydrophilic residues include, but are not limited to, alanine (A), cysteine (C), serine (S), threonine (T), asparagine (N), and glutamine (Q). In certain embodiments, a neutral hydrophilic residue may be an unconventional amino acid.

The terms "lipophilic residue" and "Laa" refer to an amino acid residue in D- or L-form having at least one uncharged, aliphatic and/or aromatic group. In certain embodiments, a lipophilic residue comprises a side chain that comprises at least one uncharged, aliphatic, and/or aromatic group. Exemplary lipophilic sidechains include, but are not limited to, alanine (A), phenylalanine (F), isoleucine (I), leucine (L), norleucine (Nle), methionine (M), valine (V), tryptophan (W), and tyrosine (Y). In certain embodiments, a lipophilic residue may be an unconventional amino acid.

The term "amphiphilic residue" refers to an amino acid residue in D- or L-form that is capable of being either a hydrophilic or lipophilic residue. An exemplary amphiphilic residue includes, but is not limited to, alanine (A). In certain embodiments, an amphiphilic residue may be an unconventional amino acid.

The term "nonfunctional residue" refers to an amino acid residue in D- or L-form that lacks acidic, basic, and aromatic

groups when incorporated into a polypeptide next to one or more amino acid residues that are the same or different. Exemplary nonfunctional amino acid residues include, but are not limited to, methionine (M), glycine (G), alanine (A), valine (V), isoleucine (I), leucine (L), and norleucine (Nle). In certain embodiments, a nonfunctional residue may be an unconventional amino acid.

In certain embodiments, glycine (G) and proline (P) are considered amino acid residues that can influence polypeptide chain orientation.

In certain embodiments, a conservative substitution may involve replacing a member of one residue type with a member of the same residue type. As a non-limiting example, in certain embodiments, a conservative substitution may involve replacing an acidic residue, such as D, with a different acidic residue, such as E. In certain embodiments, a non-conservative substitution may involve replacing a member of one residue type with a member of a different residue type. As a non-limiting example, in certain embodiments, a non-conservative substitution may involve replacing an acidic residue, such as D, with a basic residue, such as K. In certain embodiments, a cysteine residue is substituted with another amino acid residue to prevent disulfide bond formation with that position in the polypeptide.

In making conservative or non-conservative substitutions, according to certain embodiments, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. The hydropathic indices of the 20 naturally-occurring amino acids are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte et al., *J. Mol. Biol.*, 157:105-131 (1982). It is known in certain instances that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the polypeptide.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 \pm 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5) and tryptophan (−3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2

is included, in certain embodiments, those which are within ± 1 are included, and in certain embodiments, those within ± 0.5 are included. In certain instances, one may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Exemplary amino acid substitutions are set forth in Table 1.

TABLE 1

Amino Acid Substitutions		
Original Residues	Exemplary Substitutions	More specific exemplary substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

Similarly, as used herein, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to herein as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to herein as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to herein as "downstream sequences."

In certain embodiments, conservative amino acid substitutions encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. Those non-naturally occurring amino acid residues include, but are not limited to, peptidomimetics and other reversed or inverted forms of amino acid moieties.

A skilled artisan will be able to determine suitable substitution variants of a reference polypeptide as set forth herein using well-known techniques. In certain embodiments, one skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. In certain embodiments, one can identify residues and portions of the molecules that are conserved among similar polypeptides. In certain embodiments, even areas that may be important for biological activity, including, but not limited to, the CDRs of an antibody, or that may be important for structure may be

subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, in certain embodiments, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity and/or structure. In view of such a comparison, in certain embodiments, one can predict the importance of amino acid residues in a polypeptide that correspond to amino acid residues which are important for activity or structure in similar polypeptides. In certain embodiments, one skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

In certain embodiments, one skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art may predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. In certain embodiments, one skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, in certain embodiments, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. In certain embodiments, the variants can then be screened using activity assays known to those skilled in the art. For example, in certain embodiments, the variants can be screened for their ability to bind to TR-2. In certain embodiments, such variants could be used to gather information about suitable variants. For example, in certain embodiments, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change may be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided, either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See Moulton J., *Curr. Op. in Biotech.*, 7(4):422-427 (1996); Chou et al., *Biochemistry*, 13(2):222-245 (1974); Chou et al., *Biochemistry*, 113(2):211-222 (1974); Chou et al., *Adv. Enzymol. Relat. Areas Mol. Biol.*, 47:45-148 (1978); Chou et al., *Ann. Rev. Biochem.*, 47:251-276 and Chou et al., *Biophys. J.*, 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See Holm et al., *Nucl. Acid. Res.*, 27(1):244-247 (1999). It has been suggested that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate. See, e.g., Brenner et al., *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997).

Additional exemplary methods of predicting secondary structure include, but are not limited to, "threading" (Jones, D., *Curr. Opin. Struct. Biol.*, 7(3):377-87 (1997); Sippl et al., *Structure*, 4(1):15-19 (1996)), "profile analysis" (Bowie et al., *Science*, 253:164-170 (1991); Gribskov et al., *Meth. Enzym.*, 183:146-159 (1990); Gribskov et al., *Proc. Nat.*

Acad. Sci., 84(13):4355-4358 (1987)), and "evolutionary linkage" (See Holm, *supra* (1999), and Brenner, *supra* (1997)).

In certain embodiments, the identity and similarity of related polypeptides can be readily calculated by known methods. Such methods include, but are not limited to, those described in *Computational Molecular Biology*, Lesk, A. M., ed., Oxford University Press, New York (1988); *Biocomputing: Informatics and Genome Projects*, Smith, D. W., ed., Academic Press, New York (1993); *Computer Analysis of Sequence Data*, Part 1, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey (1994); *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press (1987); *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M. Stockton Press, New York (1991); and Carillo et al., *SIAMJ. Applied Math.*, 48:1073 (1988). In certain embodiments, polypeptides have amino acid sequences that are about 90 percent, or about 95 percent, or about 96 percent, or about 97 percent, or about 98 percent, or about 99 percent identical to amino acid sequences shown in FIGS. 3-19.

In certain embodiments, methods to determine identity are designed to give the largest match between the sequences tested. In certain embodiments, certain methods to determine identity are described in publicly available computer programs. Certain computer program methods to determine identity between two sequences include, but are not limited to, the GCG program package, including GAP (Devereux et al., *Nucl. Acid. Res.*, 12:387 (1984); Genetics Computer Group, University of Wisconsin, Madison, Wis., BLASTP, BLASTN, and FASTA (Altschul et al., *J. Mol. Biol.*, 215:403-410 (1990)). The BLASTX program is publicly available from the National Center for Biotechnology Information (NCBI) and other sources (*BLAST Manual*, Altschul et al. NCB/NLM/NIH Bethesda, Md. 20894; Altschul et al., *supra* (1990)). In certain embodiments, the Smith Waterman algorithm, which is known in the art, may also be used to determine identity.

Certain alignment schemes for aligning two amino acid sequences may result in the matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, in certain embodiments, the selected alignment method (GAP program) will result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

For example, using the computer algorithm GAP (Genetics Computer Group, University of Wisconsin, Madison, Wis.), two polypeptides for which the percent sequence identity is to be determined are aligned for optimal matching of their respective amino acids (the "matched span", as determined by the algorithm). In certain embodiments, a gap opening penalty (which is calculated as 3x the average diagonal; the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix is also used by the algorithm. See, e.g., Dayhoff et al., *Atlas of Protein Sequence and Structure*, 5(3)(1978) for the PAM 250 comparison matrix; Henikoff et al., *Proc. Natl. Acad. Sci. USA*, 89:10915-10919 (1992) for the BLOSUM 62 comparison matrix.

In certain embodiments, the parameters for a polypeptide sequence comparison include the following:

Algorithm: Needleman et al., *J. Mol. Biol.*, 48:443-453 (1970);

Comparison matrix: BLOSUM 62 from Henikoff et al., *supra* (1992);

Gap Penalty: 12

Gap Length Penalty: 4

Threshold of Similarity: 0

In certain embodiments, the GAP program may be useful with the above parameters. In certain embodiments, the aforementioned parameters are the default parameters for polypeptide comparisons (along with no penalty for end gaps) using the GAP algorithm.

According to certain embodiments, amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence (in certain embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts).

In certain embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described, e.g., in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W.H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al. *Nature* 354:105 (1991).

The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion. In certain embodiments, fragments are at least 5 to 500 amino acids long. It will be appreciated that in certain embodiments, fragments are at least 5, 6, 8, 10, 14, 20, 50, 70, 100, 150, 200, 250, 300, 350, 400, 450, or 500 amino acids long.

Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics." Fauchere, *J. Adv. Drug Res.* 15:29 (1986); Veber and Freidinger *TINS* p. 392 (1985); and Evans et al. *J. Med. Chem.* 30:1229 (1987). Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce a similar therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from: —CH₂NH—, —CH₂S—, —CH₂—CH₂—, —CH=CH—(cis and trans), —COCH₂—, —CH(OH)CH₂—, and —CH₂SO—, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used in certain embodiments to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence

variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992)); for example, and not limitation, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

The term "specific binding agent" refers to a natural or non-natural molecule that specifically binds to a target. Examples of specific binding agents include, but are not limited to, proteins, peptides, nucleic acids, carbohydrates, lipids, and small molecule compounds. In certain embodiments, a specific binding agent is an antibody. In certain embodiments, a specific binding agent is an antigen binding region.

The term "specifically binds" refers to the ability of a specific binding agent to bind to a target with greater affinity than it binds to a non-target. In certain embodiments, specific binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity for a non-target. In certain embodiments, affinity is determined by an affinity ELISA assay. In certain embodiments, affinity is determined by a BIAcore assay. In certain embodiments, affinity is determined by a kinetic method. In certain embodiments, affinity is determined by an equilibrium/solution method.

The term "specific binding agent to TR-2" refers to a specific binding agent that specifically binds any portion of TR-2. In certain embodiments, a specific binding agent to TR-2 is an antibody to TR-2. In certain embodiments, a specific binding agent is an antigen binding region.

"Antibody" or "antibody peptide(s)" both refer to an intact antibody, or a fragment thereof. In certain embodiments, the antibody fragment may be a binding fragment that competes with the intact antibody for specific binding. The term "antibody" also encompasses polyclonal antibodies and monoclonal antibodies. In certain embodiments, binding fragments are produced by recombinant DNA techniques. In certain embodiments, binding fragments are produced by enzymatic or chemical cleavage of intact antibodies. In certain embodiments, binding fragments are produced by recombinant DNA techniques. Binding fragments include, but are not limited to, Fab, Fab', F(ab')₂, Fv, and single-chain antibodies. Non-antigen binding fragments include, but are not limited to, Fc fragments. In certain embodiments, an antibody specifically binds to an epitope that is specifically bound by at least one antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q. The term "antibody" also encompasses anti-idiotypic antibodies that specifically bind to the variable region of another antibody. In certain embodiments, an anti-idiotypic antibody specifically binds to the variable region of an anti-TR-2 antibody. In certain embodiments, anti-idiotypic antibodies may be used to detect the presence of a particular anti-TR-2 antibody in a sample or to block the activity of an anti-TR-2 antibody.

The term "anti-TR-2 antibody" as used herein means an antibody that specifically binds to TR-2. In certain embodiments, an anti-TR-2 antibody binds to a TR-2 epitope to which at least one antibody selected from Ab A to Q binds. In various embodiments, TR-2 may be the TR-2 of any species, including, but not limited to, human, cynomolgus monkeys, mice, and rabbits. Certain assays for determining the specificity of an antibody are well known to the skilled artisan and include, but are not limited to, ELISA, ELISPOT, western blots, BIAcore assays, solution affinity binding assays, T cell costimulation assays, and T cell migration assays.

The term "isolated antibody" as used herein means an antibody which (1) is free of at least some proteins with which it would normally be found, (2) is essentially free of other

proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

The term "polyclonal antibody" refers to a heterogeneous mixture of antibodies that bind to different epitopes of the same antigen.

The term "monoclonal antibodies" refers to a collection of antibodies encoded by the same nucleic acid molecule. In certain embodiments, monoclonal antibodies are produced by a single hybridoma or other cell line, or by a transgenic mammal. Monoclonal antibodies typically recognize the same epitope. The term "monoclonal" is not limited to any particular method for making an antibody.

The term "CDR grafted antibody" refers to an antibody in which the CDR from one antibody is inserted into the framework of another antibody. In certain embodiments, the antibody from which the CDR is derived and the antibody from which the framework is derived are of different species. In certain embodiments, the antibody from which the CDR is derived and the antibody from which the framework is derived are of different isotypes.

The term "multi-specific antibody" refers to an antibody wherein two or more variable regions bind to different epitopes. The epitopes may be on the same or different targets. In certain embodiments, a multi-specific antibody is a "bi-specific antibody," which recognizes two different epitopes on the same or different antigens.

The term "catalytic antibody" refers to an antibody in which one or more catalytic moieties is attached. In certain embodiments, a catalytic antibody is a cytotoxic antibody, which comprises a cytotoxic moiety.

The term "humanized antibody" refers to an antibody in which all or part of an antibody framework region is derived from a human, but all or part of one or more CDR regions is derived from another species, for example a mouse.

The terms "human antibody" and "fully human antibody" are used interchangeably and refer to an antibody in which both the CDR and the framework comprise substantially human sequences. In certain embodiments, fully human antibodies are produced in non-human mammals, including, but not limited to, mice, rats, and lagomorphs. In certain embodiments, fully human antibodies are produced in hybridoma cells. In certain embodiments, fully human antibodies are produced recombinantly.

In certain embodiments, an anti-TR-2 antibody comprises: (i) a first polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a

wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present;

wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is

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selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present;

wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and

wherein the first polypeptide, in association with an antibody light chain, binds TR-2; and

- (ii) a second polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b

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wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present;

wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine;

wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and wherein the second polypeptide, in association with an antibody heavy chain, binds TR-2.

In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 2 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 36. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 4 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 38. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 6 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 40. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 8 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 42.

In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 10 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 44. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 12 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 46. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 14 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 48. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 16 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 50. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 18 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 52. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 20 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 54. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 22 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 56. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 24 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 58. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 26 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 60. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 28 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 62. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 30 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 64. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 32 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 66. In certain embodiments, an anti-TR-2 antibody comprises: a first polypeptide comprising complementarity determining regions (CDRs) as set forth in SEQ ID NO: 34 and a second polypeptide comprising CDRs as set forth in SEQ ID NO: 68. In certain embodiments, an anti-TR-2 antibody comprises a first polypeptide as set forth in paragraph [079] above and a second polypeptide as set forth in paragraph [084] above. In certain embodiments, an anti-TR-2 antibody comprises a first polypeptide as set forth in paragraph [080] above and a second polypeptide as set forth in paragraph [085] above. In certain embodiments, an anti-TR-2 antibody is a human antibody. In certain embodiments, an anti-TR-2 antibody comprises a detectable label. In certain embodiments, an anti-TR-2 antibody is a chimeric antibody.

“Chimeric antibody” refers to an antibody that has an antibody variable region of a first species fused to another molecule, for example, an antibody constant region of another second species. See, e.g., U.S. Pat. No. 4,816,567 and Morrison et al., *Proc Natl Acad Sci (USA)*, 81:6851-6855 (1985).

In certain embodiments, the first species may be different from the second species. In certain embodiments, the first species may be the same as the second species. In certain embodiments, chimeric antibodies may be made through mutagenesis or CDR grafting to match a portion of the known sequence of anti-TR-2 antibody variable regions. CDR grafting typically involves grafting the CDRs from an antibody with desired specificity onto the framework regions (FRs) of another antibody.

A bivalent antibody other than a “multispecific” or “multifunctional” antibody, in certain embodiments, typically is understood to have each of its binding sites be identical.

An antibody substantially inhibits adhesion of a ligand to a receptor when an excess of antibody reduces the quantity of receptor bound to the ligand by at least about 20%, 40%, 60%, 80%, 85%, or more (as measured in an in vitro competitive binding assay).

The term “epitope” refers to a portion of a molecule capable of being bound by a specific binding agent. Exemplary epitopes may comprise any polypeptide determinant capable of specific binding to an immunoglobulin and/or T-cell receptor. Exemplary epitope determinants include, but are not limited to, chemically active surface groupings of molecules, for example, but not limited to, amino acids, sugar side chains, phosphoryl groups, and sulfonyl groups. In certain embodiments, epitope determinants may have specific three dimensional structural characteristics, and/or specific charge characteristics. In certain embodiments, an epitope is a region of an antigen that is bound by an antibody. Epitopes may be contiguous or non-contiguous. In certain embodiments, epitopes may be mimetic in that they comprise a three dimensional structure that is similar to an epitope used to generate the antibody, yet comprise none or only some of the amino acid residues found in that epitope used to generate the antibody.

The term “inhibiting and/or neutralizing epitope” refers to an epitope, which when bound by a specific binding agent results in a decrease in a biological activity in vivo, in vitro, and/or in situ. In certain embodiments, a neutralizing epitope is located on or is associated with a biologically active region of a target.

The term “activating epitope” refers to an epitope, which when bound by a specific binding agent results in activation or maintenance of a biological activity in vivo, in vitro, and/or in situ. In certain embodiments, an activating epitope is located on or is associated with a biologically active region of a target.

In certain embodiments, an epitope is specifically bound by at least one antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q. In certain such embodiments, the epitope is substantially pure. In certain such embodiments, the epitope is at a concentration of at least 1 nM. In certain such embodiments, the epitope is at a concentration of between 1 nM and 5 nM. In certain such embodiments, the epitope is at a concentration of between 5 nM and 10 nM. In certain such embodiments, the epitope is at a concentration of between 10 nM and 15 nM.

In certain embodiments, an antibody specifically binds to an epitope that is specifically bound by at least one antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q, and is substantially pure. In certain such embodiments, the antibody is at a concentration of at least 1 nM. In certain such embodiments, the antibody is at a concentration of between 1 nM and 5 nM. In certain such embodiments, the antibody is at

a concentration of between 5 nM and 10 nM. In certain such embodiments, the antibody is at a concentration of between 10 nM and 15 nM.

In certain embodiments, an antibody specifically binds to amino acids 1 to 85 of mature human TR-2, and is substantially pure. In certain such embodiments, the antibody is at a concentration of at least 1 nM. In certain such embodiments, the antibody is at a concentration of between 1 nM and 5 nM. In certain such embodiments, the antibody is at a concentration of between 5 nM and 10 nM. In certain such embodiments, the antibody is at a concentration of between 10 nM and 15 nM.

In certain embodiments, an antibody competes for binding to an epitope with at least one antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q. In certain such embodiments, the antibody is substantially pure. In certain such embodiments, the antibody is at a concentration of at least 1 nM. In certain such embodiments, the antibody is at a concentration of between 1 nM and 5 nM. In certain such embodiments, the antibody is at a concentration of between 5 nM and 10 nM. In certain such embodiments, the antibody is at a concentration of between 10 nM and 15 nM.

In certain embodiments, an antibody competes for binding to amino acids 1 to 85 of mature human TR-2 with at least one antibody selected from Ab A, Ab B, Ab C, Ab D, Ab E, Ab F, Ab G, Ab H, Ab I, Ab J, Ab K, Ab L, Ab M, Ab N, Ab O, Ab P, and Ab Q. In certain such embodiments, the antibody is substantially pure. In certain such embodiments, the antibody is at a concentration of at least 1 nM. In certain such embodiments, the antibody is at a concentration of between 1 nM and 5 nM. In certain such embodiments, the antibody is at a concentration of between 5 nM and 10 nM. In certain such embodiments, the antibody is at a concentration of between 10 nM and 15 nM.

The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

As used herein, the term "label" refers to any molecule that can be detected. In a certain embodiment, an antibody may be labeled by incorporation of a radiolabeled amino acid. In a certain embodiment, biotin moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods) may be attached to the antibody. In certain embodiments, a label may be incorporated into or attached to another reagent which in turn binds to the antibody of interest. In certain embodiments, a label may be incorporated into or attached to an antibody that in turn specifically binds the antibody of interest. In certain embodiments, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Certain general classes of labels include, but are not limited to, enzymatic, fluorescent, chemiluminescent, and radioactive labels. Certain examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^3H , ^{14}C , ^{15}N , ^{35}S , ^{90}Y , ^{99}Tc , ^{111}In , ^{125}I , ^{131}I), fluorescent labels (e.g., fluorescein isothiocyanate (FITC), rhodamine, lanthanide phosphors, phycoerythrin (PE)), enzymatic labels (e.g., horseradish peroxidase, β -galactosidase, luciferase, alkaline phosphatase, glucose oxidase, glucose-6-phosphate dehydrogenase, alcohol dehydrogenase, malate dehydrogenase, penicillinase, luciferase), chemiluminescent labels, biotinyl groups, and predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding

domains, epitope tags). In certain embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

The term "sample", as used herein, includes, but is not limited to, any quantity of a substance from a living thing or formerly living thing. Such living things include, but are not limited to, humans, mice, monkeys, rats, rabbits, and other animals. Such substances include, but are not limited to, blood, serum, urine, cells, organs, tissues, bone, bone marrow, lymph nodes, and skin.

The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

The term "modulator," as used herein, is a compound that changes or alters the activity or function of a molecule. For example, a modulator may cause an increase or decrease in the magnitude of a certain activity or function of a molecule compared to the magnitude of the activity or function observed in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of at least one activity or function of a molecule. Certain exemplary activities and functions of a molecule include, but are not limited to, binding affinity, enzymatic activity, and signal transduction. Certain exemplary inhibitors include, but are not limited to, proteins, peptides, antibodies, peptibodies, carbohydrates, and small organic molecules. Exemplary peptibodies are described, e.g., in WO 01/83525.

As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present. In certain embodiments, a substantially pure composition will comprise more than about 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In certain embodiments, the object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

The term "patient" includes human and animal subjects.

According to certain embodiments, a cell line expressing anti-TR-2 antibodies is provided.

In certain embodiments, chimeric antibodies that comprise at least a portion of a human sequence and another species' sequence are provided. In certain embodiments, such a chimeric antibody may result in a reduced immune response in a host than an antibody without that host's antibody sequences. For example, in certain instances, an animal of interest may be used as a model for a particular human disease. To study the effect of an antibody on that disease in the animal host, one could use an antibody from a different species. But, in certain instances, such antibodies from another species, may elicit an immune response to the antibodies themselves in the host animal, thus impeding evaluation of these antibodies. In certain embodiments, replacing part of the amino acid sequence of an anti-TR-2 antibody with antibody amino acid sequence from the host animal may decrease the magnitude of the host animal's anti-antibody response.

In certain embodiments, a chimeric antibody comprises a heavy chain and a light chain, wherein the variable regions of the light chain and the heavy chain are from a first species and the constant regions of the light chain and the heavy chain are from a second species. In certain embodiments, the antibody

heavy chain constant region is an antibody heavy chain constant region of a species other than human. In certain embodiments, the antibody light chain constant region is an antibody light chain constant region of a species other than human. In certain embodiments, the antibody heavy chain constant region is a human antibody heavy chain constant region, and the antibody heavy chain variable region is an antibody heavy chain variable region of a species other than human. In certain embodiments, the antibody light chain constant region is a human antibody light chain constant region, and the antibody light chain variable region is an antibody light chain variable region of a species other than human. Exemplary antibody constant regions include, but are not limited to, a human antibody constant region, a cynomolgus monkey antibody constant region, a mouse antibody constant region, and a rabbit antibody constant region. Exemplary antibody variable regions include, but are not limited to, a human antibody variable region, a mouse antibody variable region, a pig antibody variable region, a guinea pig antibody variable region, a cynomolgus monkey antibody variable region, and a rabbit antibody variable region. In certain embodiments, the framework regions of the variable region in the heavy chain and light chain may be replaced with framework regions derived from other antibody sequences.

Certain exemplary chimeric antibodies may be produced by methods well known to those of ordinary skill in the art. In certain embodiments, the polynucleotide of the first species encoding the heavy chain variable region and the polynucleotide of the second species encoding the heavy chain constant region can be fused. In certain embodiments, the polynucleotide of the first species encoding the light chain variable region and the nucleotide sequence of the second species encoding the light chain constant region can be fused. In certain embodiments, these fused nucleotide sequences can be introduced into a cell either in a single expression vector (e.g., a plasmid) or in multiple expression vectors. In certain embodiments, a cell comprising at least one expression vector may be used to make polypeptide. In certain embodiments, these fused nucleotide sequences can be introduced into a cell either in separate expression vectors or in a single expression vector. In certain embodiments, the host cell expresses both the heavy chain and the light chain, which combine to produce an antibody. In certain embodiments, a cell comprising at least one expression vector may be used to make an antibody. Exemplary methods for producing and expressing antibodies are discussed below.

In certain embodiments, conservative modifications to the heavy and light chains of an anti-TR-2 antibody (and corresponding modifications to the encoding nucleotides) will produce antibodies having functional and chemical characteristics similar to those of the original antibody. In contrast, in certain embodiments, substantial modifications in the functional and/or chemical characteristics of an anti-TR-2 antibody may be accomplished by selecting substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain.

Certain desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In certain embodiments, amino acid substitutions can be used to identify important residues of the anti-TR-2 antibodies, such as those which may increase or decrease the affinity of the antibodies to TR-2 or the effector function of the antibodies.

In certain embodiments, the effects of an anti-TR-2 antibody may be evaluated by measuring a reduction in the amount of symptoms of the disease. In certain embodiments, the disease of interest may be caused by a pathogen. In certain embodiments, a disease may be established in an animal host by other methods including introduction of a substance (such as a carcinogen) and genetic manipulation. In certain embodiments, effects may be evaluated by detecting one or more adverse events in the animal host. The term "adverse event" includes, but is not limited to, an adverse reaction in an animal host that receives an antibody that is not present in an animal host that does not receive the antibody. In certain embodiments, adverse events include, but are not limited to, a fever, an immune response to an antibody, inflammation, and/or death of the animal host.

Various antibodies specific to an antigen may be produced in a number of ways. In certain embodiments, an antigen containing an epitope of interest may be introduced into an animal host (e.g., a mouse), thus producing antibodies specific to that epitope. In certain instances, antibodies specific to an epitope of interest may be obtained from biological samples taken from hosts that were naturally exposed to the epitope. In certain instances, introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated offers the opportunity to obtain human monoclonal antibodies (MAbs).

Naturally Occurring Antibody Structure

Naturally occurring antibody structural units typically comprise a tetramer. Each such tetramer typically is composed of two identical pairs of polypeptide chains, each pair having one full-length "light" chain (in certain embodiments, about 25 kDa) and one full-length "heavy" chain (in certain embodiments, about 50-70 kDa). The term "heavy chain" includes any polypeptide having sufficient variable region sequence to confer specificity for a particular antigen. A full-length heavy chain includes a variable region domain, V_H , and three constant region domains, C_{H1} , C_{H2} , and C_{H3} . The V_H domain is at the amino-terminus of the polypeptide, and the C_{H3} domain is at the carboxy-terminus. The term "heavy chain", as used herein, encompasses a full-length antibody heavy chain and fragments thereof.

The term "light chain" includes any polypeptide having sufficient variable region sequence to confer specificity for a particular antigen. A full-length light chain includes a variable region domain, V_L , and a constant region domain, C_L . Like the heavy chain, the variable region domain of the light chain is at the amino-terminus of the polypeptide. The term "light chain", as used herein, encompasses a full-length light chain and fragments thereof.

The amino-terminal portion of each chain typically includes a variable region (V_H in the heavy chain and V_L in the light chain) of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxy-terminal portion of each chain typically defines a constant region (C_H domains in the heavy chain and C_L in the light chain) that may be responsible for effector function. Antibody effector functions include activation of complement and stimulation of opsonophagocytosis. Human light chains are typically classified as kappa and lambda light chains. Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subclasses, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM has subclasses including, but not limited to, IgM1 and IgM2. IgA is similarly subdivided into subclasses including, but not limited to, IgA1 and IgA2. Within full-length light and

heavy chains, typically, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See, e.g., *Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)). The variable regions of each light/heavy chain pair typically form the antigen binding site.

The variable regions typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the heavy and light chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From N-terminal to C-terminal, both light and heavy chain variable regions typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The assignment of amino acids to each domain is typically in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk *J. Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

As discussed above, there are several types of antibody fragments. A Fab fragment is comprised of one light chain and the C_H1 and variable regions of one heavy chain. The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A Fab' fragment contains one light chain and one heavy chain that contains more of the constant region, between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between two heavy chains to form a F(ab')₂ molecule. A Fab fragment is similar to a F(ab')₂ molecule, except the constant region in the heavy chains of the molecule extends to the end of the C_H2 domain. The Fv region comprises the variable regions from both the heavy and light chains, but lacks the constant regions. Single-chain antibodies are Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain which forms an antigen-binding region. Exemplary single chain antibodies are discussed in detail, e.g., in WO 88/01649 and U.S. Pat. Nos. 4,946,778 and 5,260,203. A Fc fragment contains the C_H2 and C_H3 domains of the heavy chain and contains more of the constant region, between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between two heavy chains.

In certain embodiments, functional domains, C_H1 , C_H2 , C_H3 , and intervening sequences can be shuffled to create a different antibody constant region. For example, in certain embodiments, such hybrid constant regions can be optimized for half-life in serum, for assembly and folding of the antibody tetramer, and/or for improved effector function. In certain embodiments, modified antibody constant regions may be produced by introducing single point mutations into the amino acid sequence of the constant region and testing the resulting antibody for improved qualities, e.g., one or more of those listed above.

In certain embodiments, an antibody of one isotype is converted to a different isotype by isotype switching without losing its specificity for a particular target molecule. Methods of isotype switching include, but are not limited to, direct recombinant techniques (see e.g., U.S. Pat. No. 4,816,397) and cell-cell fusion techniques (see e.g., U.S. Pat. No. 5,916,771), among others. In certain embodiments, an antibody can be converted from one subclass to another subclass using techniques described above or otherwise known in the art without losing its specificity for a particular target molecule, including, but not limited to, conversion from an IgG2 subclass to an IgG1, IgG3, or IgG4 subclass.

Bispecific or Bifunctional Antibodies

A bispecific or bifunctional antibody typically is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Bispecific antibodies may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann *Clin. Exp. Immunol.* 79: 315-321 (1990), Kostelny et al. *J. Immunol.* 148:1547-1553 (1992).

Certain Preparation of Antibodies

In certain embodiments, antibodies can be expressed in cell lines other than hybridoma cell lines. In certain embodiments, sequences encoding particular antibodies, including chimeric antibodies, can be used for transformation of a suitable mammalian host cell. According to certain embodiments, transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus or by transfecting a vector using procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461; and 4,959,455.

In certain embodiments, an expression vector comprises any of the polynucleotide sequences discussed herein. In certain embodiments, a method of making a polypeptide comprising producing the polypeptide in a cell comprising any of the above expression vectors in conditions suitable to express the polynucleotide contained therein to produce the polypeptide is provided.

In certain embodiments, an expression vector comprises a polynucleotide comprising a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1a, CDR2a, and CDR3a, wherein CDR1a comprises the amino acid sequence a b c d e f g h i j k l, wherein amino acid a is glycine, amino acid b is selected from glycine, tyrosine, or phenylalanine; amino acid c is selected from serine or threonine; amino acid d is selected from isoleucine or phenylalanine; amino acid e is selected from serine, threonine, or asparagine; amino acid f is selected from serine, aspartic acid, tyrosine, asparagine, threonine, or glycine; amino acid g is selected from glycine, aspartic acid, or tyrosine; amino acid h is selected from glycine, aspartic acid, tyrosine, asparagine, or serine; amino acid i is selected from tyrosine, isoleucine, histidine, methionine, or tryptophan; amino acid j is selected from asparagine, tyrosine, histidine, serine, or phenylalanine; amino acid k is tryptophan or is not present; and amino acid l is serine or is not present; wherein CDR2a comprises the amino acid sequence m n o p q r s t u v w x y z a' b' c', wherein amino acid m is selected from tryptophan, tyrosine, histidine, valine, glutamic acid, or serine; amino acid n is selected from methionine or isoleucine; amino acid o is selected from asparagine, tyrosine, serine, tryptophan, or histidine; amino acid p is selected from proline, tyrosine, serine, arginine, histidine, or asparagine; amino acid q is selected from asparagine, serine, or aspartic acid; amino acid r is selected from serine or glycine; amino acid s is selected from aspartic acid, serine, threonine, or arginine; amino acid t is selected from asparagine, threonine, alanine, isoleucine, or tyrosine; amino acid u is selected from threonine, tyrosine, leucine, lysine, asparagine, or isoleucine; amino acid v is selected from glycine, tyrosine, aspartic acid, or cysteine; amino acid w is selected from tyrosine or asparagine; amino acid x is selected from alanine or proline; amino acid y is selected from glutamine, serine, or aspartic acid; amino acid z is selected from lysine, leucine, or serine; amino acid a' is selected from phenylalanine, lysine, or valine; amino

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acid b' is selected from glutamine, serine, or lysine; and amino acid c' is glycine or is not present; wherein CDR3a comprises the amino acid sequence d' e' f' g' h' i' j' k' l' m' n' o' p' q' r' s' t' u' v' w', wherein amino acid d' is selected from tryptophan, aspartic acid, glycine, serine, or glutamic acid; amino acid e' is selected from asparagine, aspartic acid, glycine, arginine, serine, valine, or leucine; amino acid f' is selected from histidine, serine, alanine, tyrosine, proline, asparagine, glycine or threonine; amino acid g' is selected from tyrosine, serine, alanine, arginine, tryptophan, glycine or valine; amino acid h' is selected from glycine, alanine, serine, asparagine, methionine, tyrosine, tryptophan, cysteine, or aspartic acid; amino acid i' is selected from serine, tryptophan, glycine, phenylalanine, aspartic acid, tyrosine, or threonine; amino acid j' is selected from glycine, threonine, serine, leucine, valine, asparagine, tryptophan, or tyrosine; amino acid k' is selected from serine, phenylalanine, aspartic acid, tryptophan, glycine, or tyrosine, or is not present; amino acid l' is selected from histidine, aspartic acid, alanine, tryptophan, tyrosine, serine, phenylalanine, valine, or glycine, or is not present; amino acid m' is selected from phenylalanine, tyrosine, glutamic acid, proline, aspartic acid, cysteine, isoleucine, or methionine, or is not present; amino acid n' is selected from aspartic acid, phenylalanine, alanine, leucine, or serine, or is not present; amino acid o' is selected from tyrosine, leucine, aspartic acid, phenylalanine, proline, or valine, or is not present; amino acid p' is selected from leucine, aspartic acid, or tyrosine, or is not present; amino acid q' is selected from serine or tyrosine, or is not present; amino acid r' is tyrosine or is not present; amino acid s' is selected from glycine or tyrosine, or is not present; amino acid t' is selected from glycine or methionine, or is not present; amino acid u' is selected from methionine or aspartic acid, or is not present; amino acid v' is selected from aspartic acid or valine, or is not present; and amino acid w' is valine or is not present; and wherein the polypeptide, in association with an antibody light chain, binds TR-2. In certain embodiments, a method of making a polypeptide comprising producing the polypeptide in a cell comprising the above expression vector in conditions suitable to express the polynucleotide contained therein to produce the polypeptide is provided.

In certain embodiments, an expression vector comprises a polynucleotide comprising a sequence encoding a polypeptide comprising at least one complementarity determining region (CDR) selected from CDR1b, CDR2b, and CDR3b, wherein CDR1b comprises the amino acid sequence a1 b1 c1 d1 e1 f1 g1 h1 i1 j1 k1 l1 m1 n1 o1 p1 q1, wherein amino acid a1 is selected from arginine or lysine; amino acid b1 is selected from threonine, alanine, or serine; amino acid c1 is serine; amino acid d1 is glutamine; amino acid e1 is selected from serine or glycine; amino acid f1 is selected from isoleucine, leucine, or valine; amino acid g1 is selected from serine, leucine, or arginine; amino acid h1 is selected from threonine, serine, isoleucine, asparagine, arginine, histidine, or tyrosine; amino acid i1 is selected from tyrosine, arginine, tryptophan, aspartic acid, or serine; j1 is selected from leucine, isoleucine, asparagine, tyrosine, or serine; amino acid k1 is selected from asparagine, glycine, valine, alanine, or leucine; amino acid l1 is selected from tyrosine, alanine, or asparagine, or is not present; amino acid m1 is selected from asparagine or lysine, or is not present; amino acid n1 is selected from tyrosine, asparagine, or isoleucine, or is not present; amino acid o1 is selected from leucine or tyrosine, or is not present; amino acid p1 is selected from aspartic acid or leucine, or is not present; and amino acid q1 is selected from valine, alanine, or threonine, or is not present; wherein CDR2b comprises the amino acid sequence r1 s1 t1 u1 v1 w1 x1, wherein amino acid r1 is

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selected from alanine, aspartic acid, leucine, tryptophan, glycine, or valine; amino acid s1 is selected from threonine, valine, glycine, or alanine; amino acid t1 is serine; amino acid u1 is selected from serine, asparagine, or threonine; amino acid v1 is selected from leucine, phenylalanine, or arginine; amino acid w1 is selected from glutamine, alanine, or glutamic acid; and amino acid x1 is selected from serine, arginine, or threonine; wherein CDR3b comprises the amino acid sequence y1 z1 a1' b1' c1' d1' e1' f1' g1', wherein amino acid y1 is selected from glutamine, methionine, leucine, or histidine; amino acid z1 is selected from glutamine or lysine; amino acid a1' is selected from serine, threonine, alanine, histidine, tyrosine, or phenylalanine; amino acid b1' is selected from tyrosine, leucine, asparagine, or glycine; amino acid c1' is selected from serine, glutamine, isoleucine, or lysine; amino acid d1' is selected from threonine, phenylalanine, tyrosine, alanine, or serine; amino acid e1' is proline; amino acid f1' is selected from leucine, phenylalanine, tryptophan, serine, or arginine; and amino acid g1' is selected from threonine or serine; and wherein the polypeptide, in association with an antibody heavy chain, binds TR-2. In certain embodiments, a method of making a polypeptide comprising producing the polypeptide in a cell comprising the above expression vector in conditions suitable to express the polynucleotide contained therein to produce the polypeptide is provided. In certain embodiments, a cell comprising at least one of the above expression vectors is provided. In certain embodiments, a method of making a polypeptide comprising producing the polypeptide in a cell comprising the above expression vector in conditions suitable to express the polynucleotide contained therein to produce the polypeptide is provided.

In certain embodiments, an expression vector expresses an anti-TR-2 antibody heavy chain. In certain embodiments, an expression vector expresses an anti-TR-2 antibody light chain. In certain embodiments, an expression vector expresses both an anti-TR-2 antibody heavy chain and an anti-TR-2 antibody light chain. In certain embodiments, a method of making an anti-TR-2 antibody comprising producing the antibody in a cell comprising at least one of the expression vectors described herein in conditions suitable to express the polynucleotides contained therein to produce the antibody is provided.

In certain embodiments, the transfection procedure used may depend upon the host to be transformed. Certain methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

Certain mammalian cell lines available as hosts for expression are known in the art and include, but are not limited to, many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, E5 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), NSO cells, SP20 cells, Per C6 cells, 293 cells, and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and produce antibodies with constitutive antigen binding properties.

In certain embodiments, the vectors that may be transfected into a host cell comprise control sequences that are operably linked to a polynucleotide encoding an anti-TR-2

antibody. In certain embodiments, control sequences facilitate expression of the linked polynucleotide, thus resulting in the production of the polypeptide encoded by the linked polynucleotide. In certain embodiments, the vector also comprises polynucleotide sequences that allow chromosome-independent replication in the host cell. Exemplary vectors include, but are not limited to, plasmids (e.g., BlueScript, puc, etc.), cosmids, and YACS.

Certain Antibody Uses

According to certain embodiments, antibodies are useful for detecting a particular antigen in a sample. In certain embodiments, this allows the identification of cells or tissues which produce the protein. For example, in certain embodiments, anti-TR-2 antibodies may be used to detect the presence of TR-2 in a sample. In certain embodiments, a method for detecting the presence or absence of TR-2 in a sample comprises (a) combining an anti-TR-2 antibody and the sample; (b) separating antibodies bound to an antigen from unbound antibodies; and (c) detecting the presence or absence of antibodies bound to the antigen.

Assays in which an antibody may be used to detect the presence or absence of an antigen include, but are not limited to, an ELISA and a western blot. In certain embodiments, an anti-TR-2 antibody may be labeled. In certain embodiments, an anti-TR-2 antibody may be detected by a labeled antibody that binds to the anti-TR-2 antibody. In certain embodiments, a kit for detecting the presence or absence of TR-2 in a sample is provided. In certain embodiments, the kit comprises an anti-TR-2 antibody and reagents for detecting the antibody.

In certain embodiments, antibodies may be used to substantially isolate a chemical moiety such as, but not limited to, a protein. In certain embodiments, the antibody is attached to a "substrate," which is a supporting material used for immobilizing the antibody. Substrates include, but are not limited to, tubes, plates (i.e., multi-well plates), beads such as microbeads, filters, balls, and membranes. In certain embodiments, a substrate can be made of water-insoluble materials such as, but not limited to, polycarbonate resin, silicone resin, or nylon resin. Exemplary substrates for use in affinity chromatography include, but are not limited to, cellulose, agarose, polyacrylamide, dextran, polystyrene, polyvinyl alcohol, and porous silica. There are many commercially available chromatography substrates that include, but are not limited to, Sepharose 2B, Sepharose 4B, Sepharose 6B and other forms of Sepharose (Pharmacia); Bio-Gel (and various forms of Bio-Gel such as Biogel A, P, or CM), Cellex (and various forms of Cellex such as Cellex AE or Cellex-CM), Chromagel A, Chromagel P and Enzafix (Wako Chemical Indus.). The use of antibody affinity columns is known to a person of ordinary skill in the art. In certain embodiments, a method for isolating TR-2 comprises (a) attaching a TR-2 antibody to a substrate; (b) exposing a sample containing TR-2 to the antibody of part (a); and (c) isolating TR-2. In certain embodiments, a kit for isolating TR-2 is provided. In certain embodiments, the kit comprises an anti-TR-2 antibody attached to a substrate and reagents for isolating TR-2.

The term "affinity chromatography" as used herein means a method of separating or purifying the materials of interest in a sample by utilizing the interaction (e.g., the affinity) between a pair of materials, such as an antigen and an antibody, an enzyme and a substrate, or a receptor and a ligand.

In certain embodiments, antibodies which bind to a particular protein and block interaction with other binding compounds may have therapeutic use. In this application, when discussing the use of anti-TR-2 antibodies to treat diseases or conditions, such use may include use of the anti-TR-2 anti-

bodies themselves; compositions comprising anti-TR-2 antibodies; and/or combination therapies comprising anti-TR-2 antibodies and one or more additional active ingredients. When anti-TR-2 antibodies are used to "treat" a disease or condition, such treatment may or may not include prevention of the disease or condition. In certain embodiments, anti-TR-2 antibodies can block the interaction of the TR-2 receptor with its ligand, TRAIL. In certain embodiments, anti-TR-2 antibodies can activate the TR-2 receptor. In certain embodiments, anti-TR-2 antibodies can constitutively activate the TR-2 receptor. Because TR-2 is associated with apoptosis, in certain embodiments, anti-TR-2 antibodies may have therapeutic use in treating diseases in which cell death or prevention of cell death is desired. Such diseases include, but are not limited to, cancer associated with any tissue expressing TR-2, inflammation, and viral infections.

In certain embodiments, an anti-TR-2 antibody is administered alone. In certain embodiments, an anti-TR-2 antibody is administered prior to the administration of at least one other therapeutic agent. In certain embodiments, an anti-TR-2 antibody is administered concurrent with the administration of at least one other therapeutic agent. In certain embodiments, an anti-TR-2 antibody is administered subsequent to the administration of at least one other therapeutic agent. Exemplary therapeutic agents, include, but are not limited to, at least one other cancer therapy agent. Exemplary cancer therapy agents include, but are not limited to, radiation therapy and chemotherapy.

In certain embodiments, anti-TR-2 antibody pharmaceutical compositions can be administered in combination therapy, i.e., combined with other agents. In certain embodiments, the combination therapy comprises an anti-TR-2 antibody, in combination with at least one anti-angiogenic agent. Exemplary agents include, but are not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, radionuclides, and combinations and conjugates thereof. In certain embodiments, an agent may act as an agonist, antagonist, allosteric modulator, or toxin. In certain embodiments, an agent may act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote cell death or arrest cell growth.

Exemplary chemotherapy treatments include, but are not limited to anti-neoplastic agents including, but not limited to, alkylating agents including, but not limited to: nitrogen mustards, including, but not limited to, mechlorethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas, including, but not limited to, carmustine BCNU, lomustine, CCNU, and semustine, methyl-CCNU; TEMODAL™, temozolomide; ethylenimines/methylmelamine, including, but not limited to, triethylenemelamine (TEM), triethylene, thiophosphoramide, thiotepa, hexamethylmelamine (HMM), and altretamine; alkyl sulfonates, including, but not limited to, busulfan; triazines, including, but not limited to, dacarbazine (DTIC); antimitabolites, including, but not limited to, folic acid analogs such as methotrexate and trimetrexate; pyrimidine analogs, including, but not limited to, 5-fluorouracil (5FU), fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, and 2,2'-difluorodeoxycytidine; purine analogs, including, but not limited to, 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, cladribine, and 2-chlorodeoxyadenosine (2-CdA); natural products, including, but not limited to, antimetotic drugs such as paclitaxel; ymca alkaloids, including, but not limited to, vinblastine (VLB), vincristine, and vinorelbine; taxotere; estramustine and estramustine phosphate; ppi-

podophylotoxins, including, but not limited to, etoposide and teniposide; antibiotics, including, but not limited to, actinomycin D, daunomycin, rubidomycin, doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin, mithramycin, mitomycin C, and actinomycin; enzymes, including, but not limited to, L-asparaginase; biological response modifiers, including, but not limited to, interferon-alpha, IL-2, G-CSF, and GM-CSF; doxycycline; irinotecan hydrochloride; miscellaneous agents, including, but not limited to, platinum coordination complexes such as cisplatin and carboplatin; anthracenediones, including, but not limited to, mitoxantrone; substituted urea, including, but not limited to, hydroxyurea; methylhydrazine derivatives, including, but not limited to, N-methylhydrazine (MIH) and procarbazine; ad renocortical suppressants, including, but not limited to, mitotane (o,p'-DDD) and aminoglutethimide; hormones and antagonists, including, but not limited to, adrenocorticosteroid antagonists such as prednisone and equivalents, dexamethasone and aminoglutethimide; GEMZAR™, gemcitabine; progestin, including, but not limited to, hydroxyprogesterone caproate, medroxyprogesterone acetate and megestrol acetate; estrogen, including, but not limited to, diethylstilbestrol and ethinyl estradiol equivalents; antiestrogen, including, but not limited to, tamoxifen; androgens, including, but not limited to, testosterone propionate and fluoxymesterone/equivalents; antiandrogens, including, but not limited to, flutamide, gonadotropin-releasing hormone analogs and leuprolide; and non-steroidal antiandrogens, including, but not limited to, flutamide.

Exemplary cancer therapies, which may be administered with an anti-TR-2 antibody, include, but are not limited to, targeted therapies. Examples of targeted therapies include, but are not limited to, use of therapeutic antibodies. Exemplary therapeutic antibodies, including, but are not limited to, mouse, mouse-human chimeric, CDR-grafted, humanized, and human antibodies, and synthetic antibodies, including, but not limited to, those selected by screening antibody libraries. Exemplary antibodies include, but are not limited to, those which bind to cell surface proteins Her2CDC20, CD33, mucin-like glycoprotein, and epidermal growth factor receptor (EGFR) present on tumor cells, and optionally induce a cytostatic and/or cytotoxic effect on tumor cells displaying these proteins. Exemplary antibodies also include, but are not limited to, HERCEPTIN™, trastuzumab, which may be used to treat breast cancer and other forms of cancer; RITUXAN™, rituximab, ZEVALIN™, ibritumomab tixetan, and LYMPHOCIDE™, epratuzumab, which may be used to treat non-Hodgkin's lymphoma and other forms of cancer; GLEEVEC™, imatinib mesylate, which may be used to treat chronic myeloid leukemia and gastrointestinal stromal tumors; and BEXXAR™, tositumomab and iodine 131 tositumomab, which may be used for treatment of non-Hodgkin's lymphoma. Certain exemplary antibodies also include ERBITUX™, cetuximab, IMC-C225; Iressa™; gefitinib; TARCEVA™, erlotinib; KDR (kinase domain receptor) inhibitors; anti VEGF antibodies and antagonists (e.g., AVASTIN™, bevacizumab; and VEGF-TRAP™, aflibercept); anti VEGF receptor antibodies and antigen binding regions; anti-Ang-1 and Ang-2 antibodies and antigen binding regions; antibodies to Tie-2 and other Ang-1 and Ang-2 receptors; Tie-2 ligands; antibodies against Tie-2 kinase inhibitors; and CAMPATH®, alemtuzumab. In certain embodiments, cancer therapy agents are other polypeptides which selectively induce apoptosis in tumor cells, including, but not limited to, TNF-related polypeptides such as TRAIL.

In certain embodiments, specific binding agents (including, but not limited to, anti-IGF-R1 antibodies) that antago-

nize the binding of the ligands IGF-1 and/or IGF-2 to insulin-like growth factor-1 receptor ("IGF-1R") and promote apoptosis of cells expressing IGF-1R are formulated or administered in combination with specific binding agents (including, but not limited to, TRAIL and anti-TR2 antibodies) that agonize and thereby promote apoptosis of cells expressing TRAIL-R2. Exemplary anti-IGF-1 R antibodies are known in the art and are disclosed, for example, in WO 2006/069202, filed Dec. 20, 2005, which is incorporated by reference herein for any purpose.

In certain embodiments, cancer therapy agents are anti-angiogenic agents which decrease angiogenesis. Certain such agents include, but are not limited to, ERBITUX™, cetuximab, IMC-C225; KDR (kinase domain receptor) inhibitory agents (e.g., antibodies and antigen binding regions that specifically bind to the kinase domain receptor); anti-VEGF agents (e.g., antibodies or antigen binding regions that specifically bind VEGF, or soluble VEGF receptors or a ligand binding region thereof) such as AVASTIN™, bevacizumab, or VEGF-TRAP™, aflibercept; anti-VEGF receptor agents (e.g., antibodies or antigen binding regions that specifically bind thereto); EGFR inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto) such as ABX-EGF, panitumumab, IRESSA™, gefitinib, TARCEVA™, erlotinib, anti-Ang1 and anti-Ang2 agents (e.g., antibodies or antigen binding regions specifically binding thereto or to their receptors, e.g., Tie2/Tek); and anti-Tie-2 kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto). In certain embodiments, the pharmaceutical compositions may also include one or more agents (e.g., antibodies, antigen binding regions, or soluble receptors) that specifically bind and inhibit the activity of growth factors, such as antagonists of hepatocyte growth factor (HGF, also known as Scatter Factor), and antibodies or antigen binding regions that specifically bind its receptor "c-met."

Exemplary anti-angiogenic agents include, but are not limited to, Campath, IL-8, B-FGF, Tek antagonists (Ceretti et al., U.S. Patent Application Publication No. 2003/0162712; U.S. Pat. No. 6,413,932); anti-TWEAK agents (e.g., specifically binding antibodies or antigen binding regions, or soluble TWEAK receptor antagonists; see, e.g., Wiley, U.S. Pat. No. 6,727,225); ADAM disintegrin domain to antagonize the binding of integrin to its ligands (Fanslow et al., U.S. Patent Application Publication No. 2002/0042368); specifically binding anti-eph receptor and/or anti-ephrin antibodies or antigen binding regions (U.S. Pat. Nos. 5,981,245; 5,728,813; 5,969,110; 6,596,852; 6,232,447; 6,057,124; and patent family members thereof); anti-PDGF-BB antagonists (e.g., specifically binding antibodies or antigen binding regions) as well as antibodies or antigen binding regions specifically binding to PDGF-BB ligands, and PDGFR kinase inhibitory agents (e.g., antibodies or antigen binding regions that specifically bind thereto).

Exemplary anti-angiogenic/anti-tumor agents include, but are not limited to, SF-7784 (Pfizer, USA); cilengitide (Merck KGaA, Germany, EPO 770622); pegaptanib octasodium (Gilead Sciences, USA); Alphastatin (BioActa, UK); M-PGA (Celgene, USA, U.S. Pat. No. 5,712,291); ilomastat (Arriva, USA, U.S. Pat. No. 5,892,112); emaxanib (Pfizer, USA, U.S. Pat. No. 5,792,783); vatalanib (Novartis, Switzerland); 2-methoxyestradiol (EntreMed, USA); TLC ELL-12 (Elan, Ireland); anecortave acetate (Alcon, USA); alpha-D148 Mab (Amgen, USA); CEP-7055 (Cephalon, USA); anti-Vn Mab (Crucell, Netherlands); DAC:antiangiogenic (ConjuChem, Canada); Angiocidin (InKine Pharmaceutical, USA); KM-2550 (Kyowa Hakko, Japan); SU-0879 (Pfizer,

USA); CGP-79787 (Novartis, Switzerland, EP 970070); ARGENT technology (Ariad, USA); YIGSR-Strealth (Johnson & Johnson, USA); fibrinogen-E fragment (Bio-Acta, UK); angiogenesis inhibitor (Trigen, UK); TBC-1635 (Encysive Pharmaceuticals, USA); SC-236 (Pfizer, USA); ABT-567 (Abbott, USA); Metastatin (EntreMed, USA); angiogenesis inhibitor (Tripep, Sweden); maspin (Sosei, Japan); 2-methoxyestradiol (Oncology Sciences Corporation, USA); ER-68203-00 (IVAX, USA); Benefin (Lane Labs, USA); Tz-93 (Tsumura, Japan); TAN-1120 (Takeda, Japan); FR-111142 (Fujisawa, Japan, JP 02233610); platelet factor 4 (RepliGen, USA, EP 407122); vascular endothelial growth factor antagonist (Boreau, Denmark); temsirolimus (CCI-779) (University of South Carolina, USA); bevacizumab (pINN) (Genentech, USA); angiogenesis inhibitors (SUGEN, USA); XL 784 (Exelixis, USA); XL 647 (Exelixis, USA); Mab, alpha5beta3 integrin, Vitaxin and second generation Vitaxin (Applied Molecular Evolution, USA and MedImmune USA); Retinostat® gene therapy (Oxford Biomedica, UK); enzastaurin hydrochloride (USAN) (Lilly, USA); CEP 7055 (Cephalon, USA and Sanofi-Synthelabo, France); BC 1 (Genoa Institute of Cancer Research, Italy); angiogenesis inhibitor (Alchemia, Australia); VEGF antagonist (Regeneron, USA); rBPI 21 and BPI-derived antiangiogenic (XOMA, USA); PI 88 (Progen, Australia); cilengitide (pINN) (Merck KGaA, Germany; Munich Technical University, Germany; Scripps Clinic and Research Foundation, USA); cetuximab (INN) (Aventis, France); AVE 8062 (Ajinomoto, Japan); AS 1404 (Cancer Research Laboratory, New Zealand); SG 292 (Telios, USA); Endostatin (Boston Children's Hospital, USA); 2-methoxyestradiol (Boston Children's Hospital, USA); ZD 6474 (AstraZeneca, UK); ZD 6126 (Angiogene Pharmaceuticals, UK); PPI 2458 (Praecis, USA); AZD 9935 (AstraZeneca, UK); AZD 2171 (AstraZeneca, UK); vatalanib (pINN) (Novartis, Switzerland and Schering AG, Germany); tissue factor pathway inhibitors (EntraMed, USA); pegaptanib (Pinn) (Gilead Sciences, USA); xanthorhizol (Yonsei University, South Korea); vaccine, gene-based, VEGF-2 (Scripps Clinic and Research Foundation, USA); SPV5.2 (Supratek, Canada); SDX 103 (University of California at San Diego, USA); PX 478 (ProIX, USA); Metastatin (EntreMed, USA); troponin I (Harvard University, USA); SU 6668 (SUGEN, USA); OXI 4503 (OXIGENE, USA); o-guanidines (Dimensional Pharmaceuticals, USA); motuporamine C (British Columbia University, Canada); CDP 791 (Celltech Group, UK); atiprimod (pINN) (Glaxo-SmithKline, UK); E 7820 (Eisai, Japan); CYC 381 (Harvard University, USA); AE 941 (Aeterna, Canada); FGF2 cancer vaccine (EntreMed, USA); urokinase plasminogen activator inhibitor (Dendreon, USA); oglufanide (pINN) (Melmotte, USA); HIF-1alpha inhibitors (Xenova, UK); CEP 5214 (Cephalon, USA); BAY RES 2622 (Bayer, Germany); Angiocidin (InKine, USA); A6 (Angstrom, USA); KR 31372 (Korean Research Institute of Chemical Technology, South Korea); GW 2286 (GlaxoSmithKline, UK); EHT 0101 (ExonHit, France); CP 868596 (Pfizer, USA); CP 564959 (OSI, USA); CP 547632 (Pfizer, USA); 786034 (GlaxoSmithKline, UK); KRN 633 (Kirin Brewery, Japan); drug delivery system, intraocular, 2-methoxyestradiol (EntreMed, USA); anginex (Maastricht University, Netherlands, and Minnesota University, USA); ABT 510 (Abbott, USA); AAL 993 (Novartis, Switzerland); VEGI (ProteomTech, USA); tumor necrosis factor-alpha inhibitors (National Institute on Aging, USA); SU 11248 (Pfizer, USA and SUGEN USA); ABT 518 (Abbott, USA); YH16 (Yantai Rongchang, China); S-3APG (Boston Children's Hospital, USA and EntreMed, USA); Mab, KDR (ImClone Systems, USA); Mab, alpha5 beta1

(Protein Design, USA); KDR kinase inhibitor (Celltech Group, UK, and Johnson & Johnson, USA); GFB 116 (South Florida University, USA and Yale University, USA); CS 706 (Sankyo, Japan); combretastatin A4 prodrug (Arizona State University, USA); chondroitinase AC (IBEX, Canada); BAY RES 2690 (Bayer, Germany); AGM 1470 (Harvard University, USA, Takeda, Japan, and TAP, USA); AG 13925 (Agoron, USA); Tetrathiomolybdate (University of Michigan, USA); GCS 100 (Wayne State University, USA); CV 247 (Ivy Medical, UK); CKD 732 (Chong Kun Dang, South Korea); Mab, vascular endothelium growth factor (Xenova, UK); irsogladine (INN) (Nippon Shinyaku, Japan); RG 13577 (Aventis, France); WX 360 (Willex, Germany); squalamine (pINN) (Genaera, USA); RPI 4610 (Sirna, USA); galacto fucan sulphate (Marinova, Australia); heparanase inhibitors (InSight, Israel); KL 3106 (Kolon, South Korea); Honokiol (Emory University, USA); ZK CDK (Schering AG, Germany); ZK Angio (Schering AG, Germany); ZK 229561 (Novartis, Switzerland, and Schering AG, Germany); XMP 300 (XOMA, USA); VGA 1102 (Taisho, Japan); VEGF receptor modulators (Pharmacopeia, USA); VE-cadherin-2 antagonists (ImClone Systems, USA); Vasostatin (National Institutes of Health, USA); vaccine, Flk-1 (ImClone Systems, USA); TZ 93 (Tsumura, Japan); TumStatIn (Beth Israel Hospital, USA); truncated soluble FLT 1 (vascular endothelial growth factor receptor 1) (Merck & Co, USA); Tie-2 ligands (Regeneron, USA); and thrombospondin 1 inhibitor (Allegheny Health, Education and Research Foundation, USA).

Certain cancer therapy agents include, but are not limited to: thalidomide and thalidomide analogues (N-(2,6-dioxo-3-piperidyl)phthalimide); tecogalan sodium (sulfated polysaccharide peptidoglycan); VELCADE®, bortezomib; rapamycin; TAN 1120 (8-acetyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-10-[[octahydro-5-hydroxy-2-(2-hydroxypropyl)-4,10-dimethylpyrano[3,4-d]-1,3,6-dioxazocin-8-yl]oxy]-5,12-naphthacenedione); suradista (7,7'-[carbonylbis[imino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino]]bis-1,3-naphthalenedisulfonic acid tetrasodium salt); SU 302; SU 301; SU 1498 ((E)-2-cyano-3-[4-hydroxy-3,5-bis(1-methylethyl)phenyl]-N-(3-phenylpropyl)-2-pro penamide); SU 1433 (4-(6,7-dimethyl-2-quinolalanyl)-1,2-benzenediol); ST 1514; SR 25989; soluble Tie-2; SERM derivatives; Pharmos; semaxanib (pINN)(3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-2H-indol-2-one); S 836; RG 8803; RESTIN; R 440 (3-(1-methyl-1H-indol-3-yl)-4-(1-methyl-6-nitro-1H-indol-3-yl)-1H-pyrrole-2,5-dione); R 123942 (1-[6-(1,2,4-thiadiazol-5-yl)-3-pyridazinyl]-N-[3-(trifluoromethyl)phenyl]-4-piperidinamine); prolyl hydroxylase inhibitor; progression elevated genes; prinomastat (INN) ((S)-2,2-dimethyl-4-[[p-(4-pyridyloxy)phenyl]sulfonyl]-3-thiomorpholinecarboxylic acid); NV 1030; NM 3 (8-hydroxy-6-methoxy-alpha-methyl-1-oxo-1H-2-benzopyran-3-acetic acid); NE 681; NF 050; MIG; METH2; METH1; manassantin B (alpha-[1-[4-[5-[4-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methylethoxy]-3-methoxyphenyl]tetrahydro-3,4-dimethyl-2-furanyl]-2-methoxyphenoxy]ethyl]-1,3-benzodioxole-5-methanol); KDR monoclonal antibody; alpha5beta3 integrin monoclonal antibody; LY 290293 (2-amino-4-(3-pyridinyl)-4H-naphtho[1,2-b]pyran-3-carbonitrile); KP 0201448; KM 2550; integrin-specific peptides; INGN 401; GYKI 66475; GYKI 66462; greenstatin (101-354-plasminogen (human)); gene therapy for rheumatoid arthritis, prostate cancer, ovarian cancer, glioma, endostatin, colorectal cancer, ATF BTPI, antiangiogenesis genes, angiogenesis inhibitor, or angiogenesis; gelatinase inhibitor, FR 111142 (4,5-dihydroxy-2-hexenoic acid

5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester); forfenimex (pINN)(S)-alpha-amino-3-hydroxy-4-(hydroxymethyl)benzeneacetic acid; fibronectin antagonist (1-acetyl-L-prolyl-L-histidyl-L-seryl-L-cysteinyl-L-aspartamide); fibroblast growth factor receptor inhibitor; fibroblast growth factor antagonist; FCE 27164 (7,7'-[carbonylbis(imino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino)]bis-1,3,5-naphthalenetrisulfonic acid hexasodium salt); FCE 26752 (8,8'-[carbonylbis(imino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)carbonylimino)]bis-1,3,6-naphthalenetrisulfonic acid); endothelial monocyte activating polypeptide II; VEGFR antisense oligonucleotide; anti-angiogenic and trophic factors; ANCHOR angiostatic agent; endostatin; Del-1 angiogenic protein; CT 3577; contortrostatin; CM 101; chondroitinase AC; CDP 845; CanStatin; BST 2002; BST 2001; BLS 0597; BIBF 1000; ARRESTIN; apomigren (1304-1388-type XV collagen (human gene COL15A1 alpha1-chain precursor)); angioinhibin; aaATIII; A 36; 9alpha-fluoromedroxyprogesterone acetate ((6-alpha)-17-(acetyloxy)-9-fluoro-6-methyl-pregn-4-ene-3,20-dione); 2-methyl-2-phthalimidino-glutaric acid (2-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-2-methylpentanedioic acid); Yttrium 90 labelled monoclonal antibody BC-1; Semaxanib (3-(4,5-Dimethylpyrrol-2-ylmethylene)indolin-2-one)(C15 H14 N2 O); PI 88 (phosphomannopentaose sulfate); Alvocidib (4H-1-Benzopyran-4-one, 2-(2-chlorophenyl)-5,7-dihydroxy-8-(3-hydroxy-1-methyl-4-piperidinyl)-cis(-)-)(C21 H20 Cl N O5); E 7820; SU 11248 (5-[3-Fluoro-2-oxo-1,2-dihydroindol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylaminoethyl)amide) (C22 H27 F N4 O2); Squalamine (Cholestane-7,24-diol, 3-[[3-[(4-aminobutyl)aminopropyl]amino]-, 24-(hydrogen sulfate), (3.beta.,5.alpha.,7.alpha.)-(C34 H65 N3 O5 S); Eriochrome Black T; AGM 1470 (Carbamic acid, (chloroacetyl)-, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2.5]oct-6-yl ester, [3R-[3alpha, 4alpha (2R, 3R),5beta, 6beta]]) (C19 H28 Cl N O6); AZD 9935; BIBF 1000; AZD 2171; ABT 828; KS-interleukin-2; Uteroglobin; A 6; NSC 639366 (1-[3-(Diethylamino)-2-hydroxypropylamino]-4-(oxyran-2-ylmethylamino)anthraquinone fumerate)(C24 H29 N3 O4. C4 H4 O4); ISV 616; anti-ED-B fusion proteins; HUI 77; Troponin I; BC-1 monoclonal antibody; SPV 5.2; ER 68203; CKD 731 (3-(3,4,5-Trimethoxyphenyl)-2(E)-propenoic acid (3R,4S,5S,6R)-4-[2(R)-methyl-3(R)-3(R)-(3-methyl-2-butenyl)oxiran-2-yl]-5-methoxy-1-oxaspiro[2.5]oct-6-yl ester) (C28 H38 O8); IMC-1C11; aaATIII; SC 7; CM 101; Angiocol; Kringle 5; CKD 732 (3-[4-[2-(Dimethylamino)ethoxy]phenyl]-2(E)-propenoic acid)(C29 H41 N O6); U 995; Canstatin; SQ 885; CT 2584 (1-[11-(Dodecylamino)-10-hydroxyundecyl]-3,7-dimethylxanthine)(C30 H55 N5 O3); Salmosin; EMAP II; TX 1920 (1-(4-Methylpiperazino)-2-(2-nitro-1H-1-imidazolyl)-1-ethanone) (C10 H15 N5 O3); Alpha-v Beta-x inhibitor; CHIR 11509 (N-(1-Propynyl)glycyl-[N-(2-naphthyl)glycyl-[N-(carbamoylmethyl)glycine bis(4-methoxyphenyl)methylamide) (C36 H37 N5 O6); BST 2002; BST 2001; B 0829; FR 111142; 4,5-Dihydroxy-2(E)-hexenoic acid (3R, 4S,5S,6R)-4-[1(R),2(R)-epoxy-1,5-dimethyl-4-hexenyl]-5-methoxy-1-oxaspiro[2.5]octan-6-yl ester (C22 H34 O7); and kinase inhibitors including, but not limited to, N-(4-chlorophenyl)-4-(4-pyridinylmethyl)-1-phthalazinamine; 4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methyl-2-pyridinecarboxamide; N-[2-(diethylamino)ethyl]-5-[5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide; 3-[4-(bromo-2,6-difluorophenyl)methoxy]-5-

[[[4-(1-pyrrolidinyl)butyl]amino]carbonyl]amino]-4-isothiazolecarboxamide; N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-4-quinazolinamine; 3-[5,6,7,13-tetrahydro-9-[(1-methylethoxy)methyl]-5-oxo-12H-indeno[2,1-a]pyrrolo[3,4-c]carbazol-12-yl]propyl ester N,N-dimethyl-glycine; N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide; N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6-[5-[[[2-(methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine; 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide;N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine; N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine; N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-((3-(1,3-oxazol-5-yl)phenyl)amino)-3-pyridinecarboxamide; 2-(((4-fluorophenyl)methyl)amino)-N-(3-(((2R)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide; N-[3-(Azetidin-3-ylmethoxy)-5-trifluoromethyl-phenyl]-2-(4-fluoro-benzylamino)-nicotinamide; 6-fluoro-N-(4-(1-methylethyl)phenyl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; 2-(((4-pyridinylmethyl)amino)-N-(3-(((2S)-2-pyrrolidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-3-pyridinecarboxamide; N-(3-(1,1-dimethylethyl)-1H-pyrazol-5-yl)-2-(((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; N-(3,3-dimethyl-2,3-dihydro-1-benzofuran-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-2-(((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; 2-(((4-pyridinylmethyl)amino)-N-(3-(((2-1-pyrrolidinyl)ethyl)oxy)-4-(trifluoromethyl)phenyl)-3-pyridinecarboxamide; N-(3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; N-(4-(pentafluoroethyl)-3-(((2S)-2-pyrrolidinylmethyl)oxy)phenyl)-2-(((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; N-(3-((3-azetidinylmethyl)oxy)-5-(trifluoromethyl)phenyl)-2-(((4-pyridinylmethyl)amino)-3-pyridinecarboxamide; N-(3-(4-piperidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-(((2-(3-pyridinyl)ethyl)amino)-3-pyridinecarboxamide; N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-(1H-indazol-6-ylamino)-nicotinamide; 2-(1H-indazol-6-ylamino)-N-[3-(1-methylpyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide; N-[1-(2-dimethylamino-acetyl)-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl]-2-(1H-indazol-6-ylamino)-nicotinamide; 2-(1H-indazol-6-ylamino)-N-[3-(pyrrolidin-2-ylmethoxy)-5-trifluoromethyl-phenyl]-nicotinamide; N-(1-acetyl-3,3-dimethyl-2,3-dihydro-1H-indol-6-yl)-2-(1H-indazol-6-ylamino)-nicotinamide; and N-[4-(tert-butyl)-3-(3-piperidylpropyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; N-[5-(tert-butyl)isoxazol-3-yl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide; and N-[4-(tert-butyl)phenyl][2-(1H-indazol-6-ylamino)(3-pyridyl)]carboxamide, and kinase inhibitors disclosed in U.S. Pat. Nos. 6,258,812; 6,235,764; 6,630,500; 6,515,004; 6,713,485; 5,521,184; 5,770,599; 5,747,498; 5,990,141; U.S. Patent Application Publication No. US2003/0105091; and Patent Cooperation Treaty publication nos. WO01/37820; WO01/32651; WO02/68406; WO02/66470; WO02/55501; WO04/05279; WO04/07481; WO04/07458; WO04/09784; WO02/59110; WO99/45009; WO98/35958; WO00/59509; WO99/

61422; WO00/12089; and WO00/02871, each of which publications are hereby incorporated by reference for any purpose.

TR-2 is expressed in a variety of cells, including liver, brain, kidney, colon, breast, lung, spleen, thymus, peripheral blood lymphocytes, pancreas, prostate, testis, ovary, uterus, and various tissues along the gastro-intestinal tract. Exemplary TR-2 related cancers include, but are not limited to, liver cancer, brain cancer, renal cancer, breast cancer, pancreatic cancer, colorectal cancer, lung cancer (small cell lung cancer and non-small-cell lung cancer), spleen cancer, cancer of the thymus or blood cells (i.e., leukemia), prostate cancer, testicular cancer, ovarian cancer, uterine cancer, gastric carcinoma, head and neck squamous cell carcinoma, melanoma, and lymphoma.

In certain embodiments, an anti-TR-2 antibody may be used alone or with at least one additional therapeutic agent for the treatment of cancer. In certain embodiments, an anti-TR-2 antibody is used in conjunction with a therapeutically effective amount of an additional therapeutic agent. Exemplary therapeutic agents that may be administered with an anti-TR-2 antibody include, but are not limited to, a member of the geldanamycin family of anisamycin antibiotics; a Pro-HGF; NK2; a c-Met peptide inhibitor; an antagonist of Grb2 Src homology 2; a Gab1 modulator; dominant-negative Src; a von-Hippel-Landau inhibitor, including, but not limited to, wortmannin; P13 kinase inhibitors, other anti-receptor therapies, anti EGFR, a COX-2 inhibitor, CELEBREX™, celecoxib, VIOXX™, rofecoxib; a vascular endothelial growth factor (VEGF), a VEGF modulator, a fibroblast growth factor (FGF), an FGF modulator, an epidermal growth factor (EGF); an EGF modulator; a keratinocyte growth factor (KGF), a KGF-related molecule, a KGF modulator; and a matrix metalloproteinase (MMP) modulator.

In certain embodiments, anti-TR-2 antibody is used with particular therapeutic agents to treat various cancers. In certain embodiments, in view of the condition and the desired level of treatment, two, three, or more agents may be administered. Where the compounds are used together with one or more other components, the compound and the one or more other components may be administered together, separately, or sequentially (e.g., in a pharmaceutical format). In certain embodiments, such agents may be provided together by inclusion in the same formulation. In certain embodiments, such agents and an anti-TR-2 antibody may be provided together by inclusion in the same formulation. In certain embodiments, such agents may be formulated separately and provided together by inclusion in a treatment kit. In certain embodiments, such agents and an anti-TR-2 antibody may be formulated separately and provided together by inclusion in a treatment kit. In certain embodiments, such agents may be provided separately.

In certain embodiments, when administered by gene therapy, the genes encoding protein agents and/or an anti-TR-2 antibody may be included in the same vector. In certain embodiments, the genes encoding protein agents and/or an anti-TR-2 antibody may be under the control of the same promoter region. In certain embodiments, the genes encoding protein agents and/or an anti-TR-2 antibody may be in separate vectors.

In certain embodiments, anti-TR-2 antibodies may be used to treat non-human animals, such as pets (dogs, cats, birds, primates, etc.), and domestic farm animals (horses, cattle, sheep, pigs, birds, etc.). In certain such instances, an appropriate dose may be determined according to the animal's body weight. For example, in certain embodiments, a dose of 0.2-1 mg/kg may be used. In certain embodiments, the dose

may be determined according to the animal's surface area, an exemplary dose ranging from 0.1 to 20 mg/in², or from 5 to 12 mg/m². For small animals, such as dogs or cats, in certain embodiments, a suitable dose is 0.4 mg/kg. In certain embodiments, anti-TR-2 antibodies are administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

It is understood that the response by individual patients to the aforementioned medications or combination therapies may vary, and an appropriate efficacious combination of drugs for each patient may be determined by his or her physician.

The cynomolgus monkey provides a useful model for certain diseases. Exemplary diseases include, but are not limited to, transplantation rejection syndrome and inflammatory bowel disease-like disease. When testing the efficacy of a human MAb in cynomolgus monkey human disease model, in certain embodiments, it is useful to determine whether the anti-TR-2 MAb binds to TR-2 in humans and cynomolgus monkeys at a comparable level.

In certain embodiments, an anti-TR-2 antibody may be part of a conjugate molecule comprising all or part of the anti-TR-2 antibody and a cytotoxic agent. The term "cytotoxic agent" refers to a substance that inhibits or prevents the function of cells and/or causes the death or destruction of cells. The term includes, but is not limited to, radioactive isotopes (e.g., I¹³¹, I¹²⁵, Y⁹⁰ and Re¹⁸⁶), chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof. Exemplary cytotoxic agents include, but are not limited to, Adriamycin, Doxorubicin, 5-Fluorouracil, Cytosine arabinoside ("Ara-C"), Cyclophosphamide, Thiotepe, Taxotere (docetaxel), Busulfan, Cytosine, Taxol, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincristine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Carminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins, Melphalan and other related nitrogen mustards.

In certain embodiments, an anti-TR-2 antibody may be part of a conjugate molecule comprising all or part of the anti-TR-2 antibody and a prodrug. In certain embodiments, the term "prodrug" refers to a precursor or derivative form of a pharmaceutically active substance. In certain embodiments, a prodrug is less cytotoxic to cells compared to the parent drug and is capable of being enzymatically activated or converted into the more active cytotoxic parent form. Exemplary prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, beta-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs and optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into a more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form include, but are not limited to, those cytotoxic agents described above. See, e.g., U.S. Pat. No. 6,702,705.

In certain embodiments, antibody conjugates function by having the antibody portion of the molecule target the cytotoxic portion or prodrug portion of the molecule to a specific population of cells in the patient. In the case of anti-TR-2 antibodies, such conjugate molecules may be used, for example, in certain embodiments, to destroy abnormally proliferating cells, such as cancer cells.

In certain embodiments, methods of treating a patient comprising administering a therapeutically effective amount of an anti-TR-2 antibody are provided. In certain embodiments, methods of treating a patient comprising administering a therapeutically effective amount of an antibody conjugate are provided. In certain embodiments, an antibody is used in conjunction with a therapeutically effective amount of at least one additional therapeutic agent, as discussed above.

As discussed above, in certain embodiments, anti-TR-2 antibodies may be administered concurrently with one or more other drugs that are administered to the same patient, each drug being administered according to a regimen suitable for that medicament. Such treatment encompasses pre-treatment, simultaneous treatment, sequential treatment, and alternating regimens. Additional examples of such drugs include, but are not limited to, antivirals, antibiotics, analgesics, corticosteroids, antagonists of inflammatory cytokines, DMARDs, nonsteroidal anti-inflammatories, chemotherapeutics, inhibitors of angiogenesis, and stimulators of angiogenesis.

In certain embodiments, various medical disorders are treated with anti-TR-2 antibodies in combination with another stimulator of apoptosis. For example, in certain embodiments, anti-TR-2 antibodies may be administered in a composition that also contains a compound that stimulates apoptosis of one or more cells. In certain embodiments, the anti-TR-2 antibody and stimulators of apoptosis may be administered as separate compositions, and these may be administered by the same or different routes.

In certain embodiments, pharmaceutical compositions are provided comprising a therapeutically effective amount of an antibody together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

In certain embodiments, pharmaceutical compositions are provided comprising a therapeutically effective amount of an antibody and a therapeutically effective amount of at least one additional therapeutic agent, together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

In certain embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, antibodies of the present invention are provided in a bufferless formulation as disclosed in PCT/US06/22599 filed Jun. 8, 2006, which is incorporated by reference herein for any purpose.

In certain embodiments, the pharmaceutical composition may contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolality, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In certain embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as

sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerol, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (*Remington's Pharmaceutical Sciences*, 18th Edition, A. R. Gennaro, ed., Mack Publishing Company (1990).

In certain embodiments, an antibody and/or an additional therapeutic molecule is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, the Fc domain, polyethylene glycol, and dextran. Such vehicles are described, e.g., in U.S. Pat. No. 6,660,843 and published PCT Application No. WO 99/25044.

In certain embodiments, the optimal pharmaceutical composition will be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, *Remington's Pharmaceutical Sciences*, supra. In certain embodiments, such compositions may influence the physical state, stability, rate of in vivo release and rate of in vivo clearance of the antibodies.

In certain embodiments, the primary vehicle or carrier in a pharmaceutical composition may be either aqueous or non-aqueous in nature. For example, in certain embodiments, a suitable vehicle or carrier may be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In certain embodiments, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In certain embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which may further include sorbitol or a suitable substitute therefor. In certain embodiments, a pharmaceutical composition is an aqueous or liquid formulation comprising an acetate buffer of about pH 4.0-5.5, a polyol (polyalcohol), and optionally, a surfactant, wherein the composition does not comprise a salt, e.g., sodium chloride, and wherein the composition is isotonic for the patient. Exemplary polyols include, but are not limited to, sucrose, glucose, sorbitol, and mannitol. An exemplary surfactant includes, but is not limited to, polysorbate. In certain embodiments, a pharmaceutical composition is an aqueous or liquid formulation comprising an acetate buffer of about pH 5.0, sorbitol, and a polysorbate, wherein the composition does not comprise a salt, e.g., sodium chloride, and wherein the composition is isotonic for the patient. Certain exemplary compositions are found, for example, in U.S. Pat. No. 6,171,586. Additional pharmaceutical carriers include, but are not limited to, oils, including petroleum oil, animal oil, vegetable oil, peanut oil, soybean oil, mineral oil, sesame oil, and the like. In certain embodiments, aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. In certain embodiments, a composition comprising an antibody, with or without at least one additional therapeutic agent, may be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (*Remington's Pharmaceutical Sciences*, supra) in the form of a lyophilized cake or an aqueous solution. Further, in certain

embodiments, a composition comprising an antibody, with or without at least one additional therapeutic agent, may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents.

In certain embodiments, anti-TR-2 antibodies are administered in the form of a physiologically acceptable composition comprising purified recombinant protein in conjunction with physiologically acceptable carriers, excipients or diluents. In certain embodiments, such carriers are nontoxic to recipients at the dosages and concentrations employed. In certain embodiments, preparing such compositions may involve combining the anti-TR-2 antibodies with buffers, antioxidants such as ascorbic acid, low molecular weight polypeptides (such as those having fewer than 10 amino acids), proteins, amino acids, carbohydrates such as glucose, sucrose or dextrans, chelating agents such as EDTA, glutathione and/or other stabilizers, and excipients. In certain embodiments, appropriate dosages are determined in standard dosing trials, and may vary according to the chosen route of administration. In certain embodiments, in accordance with appropriate industry standards, preservatives may also be added, which include, but are not limited to, benzyl alcohol. In certain embodiments, the amount and frequency of administration may be determined based on such factors as the nature and severity of the disease being treated, the desired response, the age and condition of the patient, and so forth.

In certain embodiments, pharmaceutical compositions can be selected for parenteral delivery. The preparation of certain such pharmaceutically acceptable compositions is within the skill of the art.

In certain embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. In certain embodiments, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

In certain embodiments, when parenteral administration is contemplated, a therapeutic composition may be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising the desired antibody, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In certain embodiments, a vehicle for parenteral injection is sterile distilled water in which the antibody, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In certain embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that may provide for the controlled or sustained release of the product which may then be delivered via a depot injection. In certain embodiments, hyaluronic acid may also be used, and may have the effect of promoting sustained duration in the circulation. In certain embodiments, implantable drug delivery devices may be used to introduce the desired molecule.

In certain embodiments, a pharmaceutical composition may be formulated for inhalation. In certain embodiments, an antibody, with or without at least one additional therapeutic agent, may be formulated as a dry powder for inhalation. In certain embodiments, an inhalation solution comprising an antibody, with or without at least one additional therapeutic agent, may be formulated with a propellant for aerosol delivery. In certain embodiments, solutions may be nebulized. Pulmonary administration is further described in PCT publication no. WO94/20069, which describes pulmonary delivery of chemically modified proteins.

In certain embodiments, it is contemplated that formulations may be administered orally. In certain embodiments, an antibody, with or without at least one additional therapeutic agent, that is administered in this fashion may be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In certain embodiments, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In certain embodiments, at least one additional agent can be included to facilitate absorption of the antibody and/or any additional therapeutic agents. In certain embodiments, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and/or binders may also be employed.

In certain embodiments, a pharmaceutical composition may involve an effective quantity of antibodies, with or without at least one additional therapeutic agent, in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In certain embodiments, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions may be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; and binding agents, such as starch, gelatin, and acacia; and lubricating agents such as magnesium stearate, stearic acid, and talc.

Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving antibodies, with or without at least one additional therapeutic agent, in sustained- or controlled-delivery formulations. In certain exemplary sustained- or controlled-delivery formulations include, but are not limited to, liposome carriers, bio-erodible microparticles, porous beads, and depot injections. Certain exemplary techniques for preparing certain formulations are known to those skilled in the art. See for example, PCT publication no. WO93/15722, which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In certain embodiments, sustained-release preparations may include semipermeable polymer matrices in the form of shaped articles, e.g. films, or microcapsules. Sustained release matrices include, but are not limited to, polyesters, hydrogels, polylactides (U.S. Pat. No. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman et al., *Biopolymers*, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer et al., *J. Biomed. Mater. Res.*, 15:167-277 (1981) and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *supra*), and poly-D(-)-3-hydroxybutyric acid (EP 133,988). In certain embodiments, sustained release compositions may also include liposomes, which can be prepared, in certain embodiments, by any of several methods known in the art. See e.g., Eppstein et al., *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

In certain embodiments, the pharmaceutical composition to be used for in vivo administration is sterile. In certain embodiments, the pharmaceutical composition to be used for in vivo administration is made sterile by filtration through sterile filtration membranes. In certain embodiments, where the composition is lyophilized, sterilization using sterile filtration membranes may be conducted either prior to or following lyophilization and reconstitution. In certain embodiments, the composition for parenteral administration may be stored in lyophilized form or in a solution. In certain embodiments, parenteral compositions generally are placed into a

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container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

In certain embodiments, after the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In certain embodiments, such formulations may be stored either in a ready-to-use form or in a form (e.g., a lyophilized form) that is reconstituted prior to administration.

In certain embodiments, kits for producing a single-dose administration unit are provided. In certain embodiments, the kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. In certain embodiments, kits containing single and/or multi-chambered pre-filled syringes (e.g., liquid syringes and lysyringes) are included.

In certain embodiments, the effective amount of a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which the antibody, with or without at least one additional therapeutic agent, is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In certain embodiments, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. In certain embodiments, a typical dosage may range from about 0.1 $\mu\text{g/kg}$ to up to about 100 mg/kg or more, depending on the factors mentioned above. In certain embodiments, the dosage may range from 0.1 $\mu\text{g/kg}$ up to about 100 mg/kg ; or 1 $\mu\text{g/kg}$ up to about 100 mg/kg ; or 5 $\mu\text{g/kg}$ up to about 100 mg/kg ; or 0.1 mg/kg up to about 100 mg/kg .

In certain embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of the antibody and/or any additional therapeutic agents in the formulation used. In certain embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In certain embodiments, the composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Certain methods of further refining the appropriate dosage are within the skill in the art. In certain embodiments, appropriate dosages may be ascertained through use of appropriate dose-response data.

In certain embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, e.g. orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In certain embodiments, the compositions may be administered by bolus injection or continuously by infusion, or by implantation device.

As discussed above, in various embodiments, any efficacious route of administration may be used to administer anti-TR-2 antibodies. If injected, in certain embodiments, anti-TR-2 antibodies may be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal, intracranial, intranasal, inhalation or subcutaneous routes by bolus injection or by continuous infusion. Exemplary methods of administration include, but are not

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limited to, sustained release from implants, aerosol inhalation, eyedrops, oral preparations, including pills, syrups, lozenges, and chewing gum, and topical preparations such as lotions, gels, sprays, ointments, and other suitable techniques.

In certain embodiments, administration by inhalation is beneficial when treating diseases associated with pulmonary disorders. In certain embodiments, anti-TR-2 antibodies may be administered by implanting cultured cells that express the antibodies. In certain embodiments, the patient's own cells are induced to produce by transfection *in vivo* or *ex vivo* with one or more vectors that encode an anti-TR-2 antibody. In certain embodiments, this vector can be introduced into the patient's cells, for example, by injecting naked DNA or liposome-encapsulated DNA that encodes an anti-TR-2 antibody, or by other methods of transfection. When anti-TR-2 antibodies are administered in combination with one or more other biologically active compounds, in certain embodiments, these may be administered by the same or by different routes, and may be administered together, separately, or sequentially.

In certain embodiments, the composition may be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In certain embodiments, where an implantation device is used, the device may be implanted into any suitable tissue or organ, and delivery of the desired molecule may be via diffusion, timed-release bolus, or continuous administration.

In certain embodiments, it may be desirable to use a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, in an *ex vivo* manner. In such embodiments, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising an antibody, with or without at least one additional therapeutic agent, after which the cells, tissues and/or organs are subsequently implanted back into the patient.

In certain embodiments, an antibody and any additional therapeutic agents can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides. In certain embodiments, such cells may be animal or human cells, and may be autologous, heterologous, or xenogeneic. In certain embodiments, the cells may be immortalized. In certain embodiments, in order to decrease the chance of an immunological response, the cells may be encapsulated to avoid infiltration of surrounding tissues. In certain embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

EXAMPLES

Example 1

Production of Certain Human Monoclonal Antibodies

Human anti-TR-2 antibodies were produced in one of two ways. Transgenic mice expressing human immunoglobulin genes (Xenomouse®) were exposed to human TR-2. Certain human anti-TR-2 monoclonal antibodies were produced from those mice using hybridoma-techniques. Certain other human anti-TR-2 monoclonal antibodies were produced

from those mice using XenoMax technology, which incorporates the selected lymphocyte antibody method ("SLAM") technique (see, e.g., U.S. Pat. No. 5,627,052; and Babcock et al., *Proc. Natl. Acad. Sci. USA* 93:7843-7848 (1996)).

The methodology used to produce human anti-TR-2 monoclonal antibodies in transgenic mice expressing human immunoglobulin genes was as follows. Five groups of mice were immunized with recombinant human TR-2 with a C-terminal hexahistidine tag (TR-2-His) (mature amino acid sequence

ALITQQDLAPQQRAAPQQKRSSPSEG-
LCPGHHISEDGRDCISKY GQDYSTHWNDLFLC-
RCTRCDSGEVELSPCTTTRNTVCQCEEGTFREEDS
PEMCRKCRTGCPRGMVKVGDCPTWS-

DIECVHKESGTHKSGEAPAVEETVT

SSPGT-
PASRSGSSHHHHHHH (SEQ ID NO: 140)) (Genbank Refer-

ence Number NM-003842), as shown in FIG. 1. The mice in group one, group three, group four, and group five were engineered to produce antibodies of the IgG2 isotype (FIG. 2). The mice in group two were engineered to produce antibodies of the IgG4 isotype (FIG. 2). Group one included 7 mice, group two included 8 mice, group three included 8 mice, group four included 10 mice, and group five included 5 mice. The mice in group one, group two, and group three were immunized by injection of TR-2-His into the footpad (10 µg per injection), while the mice in group four and group five were immunized intraperitoneally (10 µg per injection) with TR-2-His. On day 0, 10 µg antigen was administered by the described route. At specified intervals, booster injections were administered to the mice. Group one mice had nine booster injections, at days 5, 11, 14, 18, 24, 28, 34, 42, and 46. Group two and group three mice had 7 booster injections; those for group 2 were at days 3, 7, 10, 14, 17, 24, and 27, and those for group three were at days 5, 8, 15, 21, 26, 30, and 33. Group four and group five mice had 5 booster injections, at days 14, 28, 42, 56, and 72. Each first injection and each booster injection contained 10 µg TR-2-His with an adjuvant, either Titermax Gold (Groups one, two, and three), alum gel (groups one, two, and three), Complete Freund's Adjuvant (CFA) (groups four and five), Incomplete Freund's Adjuvant (IFA) (groups four and five), or Dulbecco's phosphate-buffered saline (D-PBS) (groups one, two, three, four, and five) (see FIG. 1). Mice were bled after three injections (groups four and five), after four injections (groups one, two, and three), after six injections (groups one and two), and after ten injections (group one). The reactivity of each bleed to TR-2-His was assessed by ELISA, as shown in FIG. 2.

The ELISA assay was performed as follows. Multiwell plates were coated with soluble TR-2-His (0.5 µg/mL) by passive adsorption overnight at 4° C. The coated wells were washed and blocked for 30 minutes with milk. Ten µL of each mouse serum was combined with 40 µL milk and incubated in the wells of different plates for 1 hour, 1.25 hours, or 2 hours. The plates were washed five times with water. The plates were then incubated with a goat anti-human IgG Fc-specific horseradish peroxidase-conjugated antibody (Pierce) at a final concentration of 1 µg/mL for 1 hour at room temperature. The plates were washed five times with water. The plates were incubated with K blue substrate (Neogen) for 30 minutes. Negative controls included blank wells lacking TR-2-His and wells including TR-2-His but incubated with naive G2 sera expected to lack anti-TR-2 antibodies.

The methodologies used to produce human anti-TR-2 monoclonal antibodies were as follows. For XenoMax technology, CD19 + B cells were isolated from the hyperimmune transgenic mice that were harvested on day 37 (mouse M712-7 from group three), or day 76 (mouse M564-1 from group four, and mice M564-3, M564-5, and M563-5 from group five after the initiation of immunization. The B cells were cultured for 1 week to allow their expansion and conse-

quent differentiation into plasma cells. The supernatants containing the secreted antibody was saved for further analysis and the plasma cells in each well were frozen at -80 degrees celcius in media containing 10 % DMSO and 90 % FCS. For hybridoma technology, the cells from the remaining hyperimmune transgenic mice were harvested on day 31, 37 or 46 for further analysis as shown in FIG. 1.

For XenoMax technology, supernates from the B cell cultures were screened by ELISA for the presence of antibodies to TR-2. Anti-TR-2 antibodies were detected by assessing binding to immobilized TR-2-His using an anti-human IgG antibody detection reagent as follows. Plates were coated with soluble TR-2-His (0.5 µg/mL) by passive adsorption overnight at 4° C. After washing the plates five times with water and blocking the wells in the plates with milk for 30 minutes, 10 µL cell culture supernate from each individual hybridoma was combined with 40 µL milk and incubated in the wells of different plates for 1 hour, 1.25 hours, or 2 hours. The plates were washed five times with water, and incubated with a goat anti-human IgG Fc-specific horseradish peroxidase (Pierce)-conjugated antibody at a final concentration of 1 µg/mL for 1 hour at room temperature. After washing the plates five times with water, the plates were incubated with K blue substrate (Neogen) for 30 minutes. Negative controls included blank wells lacking TR-2-His and wells using naive G2 sera expected to lack anti-TR-2 antibodies. Positive samples were screened by ELISA a second time against TR-2-His to confirm the identity of cells producing antibodies specific for TR-2.

The antibodies reactive with TR-2, identified above, were screened for their ability to induce apoptosis of WM-266 melanoma cells (ATCC Cat. No. CRL-1676) using an apoptosis assay. WM-266 cells were cultured in a microtiter plate at a density of 4500 cells/well in normal culture medium as recommended by ATCC overnight. For B cell cultures, 20 µL of antigen-specific B cell culture supernatant or control B cell culture supernatant was added to 180 µL of apoptosis medium mixture (cell culture medium containing 1 µg/mL cycloheximide (CHX) and 0.5 % fetal calf serum ("FCS")). The culture media from the WM-266 cells was removed and the antibody-apoptosis medium mixture was added to the cells one row at a time. The cells were incubated with the antibody-apoptosis medium for 20 hours to allow apoptosis to occur. The DNA-binding fluorescent dyes propidium iodide (Sigma) and Hoechst 33342 (Molecular Probes) were added to each well at a final concentration of 0.5 µg/mL and 2.5 µg/mL, respectively. Hoechst 33342 is membrane-permeable, and thus labels both live and dead cells; propidium iodide is not membrane-permeable, and thus labels only dead cells. After one hour at 37° C., images of each well were captured and analyzed for total number of cells (by assessing the amount of Hoechst label) and total number of dead cells (by assessing the amount of propidium iodide label). The percent apoptosis was determined as (propidium iodide-positive cells/Hoechst-positive cells)×100.

For XenoMax technology, the antibodies from several wells that displayed the best induction of apoptosis were selected for rescue using the haemolytic plaque assay. TR-2-His was biotinylated and coated onto streptavidin-coated sheep red blood cells. Plasma cells corresponding to antigen-specific wells were thawed and incubated with the antigen-coated red blood cells in the presence of complement and guinea pig anti-human IgG enhancing serum. Plasma cells producing antibodies against TR-2-His caused the sheep red blood cells around them to lyse and thus allowed the identification of antigen-specific plasma cells in the mixture. Those

plasma cells were isolated by micromanipulation of single cells from the mixture.

After isolation of the desired single plasma cells, mRNA was extracted from those cells. The mRNAs encoding the heavy and light chain variable sequences were converted to

cDNA and amplified by reverse transcriptase PCR using degenerate antisense primers specific for the leader sequences and the constant regions of human IgG2 and human kappa mRNA. The primer sequences are provided in Table 2 below:

TABLE 2

Primer Name	Primer seq
AS-Ck RT	5' GTA GGT GCT GTC CT 3' (SEQ ID NO: 97)
AS-γCH1 RT	5' TGA GTT CCA CGA CA 3' (SEQ ID NO: 98)
AS-C Lambda RT	5' CTT CCA AGC CAC T 3' (SEQ ID NO: 99)
AS-C Lambda RT	5' CA (GA) GC ACT GTC A 3' (SEQ ID NO: 100)
AS-Ck outer	5' GTA GGT GCT GTC CTT GCT 3' (SEQ ID NO: 101)
AS-Ck middle	5' CTC TGT GAC ACT CTC CTG GGA 3' (SEQ ID NO: 102)
AS-Ck inner with Xba I	5' GCT CTA GAT TGG AGG GCG TTA TCC ACC TTC CAC T 3' (SEQ ID NO: 103)
AS-Ck inner with Nhe I	5' AAC TAG CTA GCA GTT CCA GAT TTC AAC TGC TCA TCA GAT 3' (SEQ ID NO: 104)
AS-CL outer	5' GCT CCC GGG TAG AAG TCA 3' (SEQ ID NO: 105)
AS-CL middle	5' AC(CT) AGT GTG GCC TTG TTG GCT T 3' (SEQ ID NO: 106)
AS-CL inner	5' GCT CTA GAG GG(CT) GGG AAC AGA GTG AC 3' (SEQ ID NO: 107)
ASγ-CH1 outer	5' ACG ACA CCG TCA CCG GTT 3' (SEQ ID NO: 108)
ASγ-CH1 middle	5' AAG TAG TCC TTG ACC AGG CAG CCC A 3' (SEQ ID NO: 109)
ASγ-CH1 inner with Xba I (G1 specific)	5' GCT CTA GAG GGT GCC AGG GGG AAG ACC GAT 3' (SEQ ID NO: 110)
ASγ-CH1 inner with Xba I (G2, G3 & G4 specific)	5' GCT CTA GAG CAG GGC GCC AGG GGG AAG A 3' (SEQ ID NO: 111)
S-Vk1&2 Leader outer	5' ATG AGG (CG)TC CC(CT) GCT CAG CT 3' (SEQ ID NO: 112)
S-Vk3 Leader outer	5' ATG GAA (AG)CC CCA GC(GT) CAG CTT 3' (SEQ ID NO: 113)
S-Vk4 Leader outer	5' ATG GTG TTG CAG ACC CAG GTC T 3' (SEQ ID NO: 114)
S-Vk1&2 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG AGG (CG)TC CC(CT) GCT CAG CT(CT) CT 3' (SEQ ID NO: 115)
S-Vk3 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GAA (AG)CC CCA GC(GT) CAG CTT CTC TT 3' (SEQ ID NO: 116)
S-Vk4 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GTG TTG CAG ACC CAG GTC TTC AT 3' (SEQ ID NO: 117)
S-VL1-4 Leader outer	5' C(GA)T C(AT)C CAC CAT G(GA)C (CA)(TA)G 3' (SEQ ID NO: 118)
S-VL1 Leader outer	5' CAC CAT G(GA)C C(TA)G (GC)T(CT) CCC T 3' (SEQ ID NO: 119)

TABLE 2-continued

Primer Name	Primer seq
S-VL2 Leader outer	5' ACC ATG GCC TGG (GA)CT C(TC)(GT) CT 3' (SEQ ID NO: 120)
S-VL3 Leader outer	5' CAC CAT GGC (CA)TG G(GA)(TC) C(CGA)(CT) T 3' (SEQ ID NO: 121)
S-VL4 Leader outer	5' CAC CAT GGC (CT)TG G(GA)(TC) CC(CA) A(CT)T 3' (SEQ ID NO: 122)
S-VL1 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG (GA)CC (TA)G(GC) T(CT)C CCT CT 3' (SEQ ID NO: 123)
S-VL2 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GCC TGG (GA)CT C(TC) (GT) CT(CG) (TC)T 3' (SEQ ID NO: 124)
(Also amplifies VL5-7, 9, 10)	
S-VL3 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GC(CA) TGG (GA)(TC)C (CGA)(CT)T CTC 3' (SEQ ID NO: 125)
S-VL4 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GC(CT) TGG (GA)(TC)C C(CA)A (CT)TC 3' (SEQ ID NO: 126)
S-VH1 Leader outer	5' CAC CAT GGA (GC)TG GAC CTG GAG (GCA) (AGTC)T C 3' (SEQ ID NO: 127)
S-VH2 Leader outer	5' CAC CAT GGA CAT ACT TTG (CT)TC CAC GCT C 3' (SEQ ID NO: 128)
S-VH3 Leader outer	5' CAC CAT GGA [AG]TT [TG]GG [AG]CT [GCT][ACT]G CT 3' (SEQ ID NO: 129)
S-VH4 Leader outer	5' CAC CAT GAA [AG]CA [TC]CT GTG GTT CTT CCT [TC]CT 3' (SEQ ID NO: 130)
S-VH5 Leader outer	5' CAC CAT GGG GTC AAC CG[CT] CAT CCT 3' (SEQ ID NO: 131)
S-VH6 Leader outer	5' CAC CAT GTC TGT CTC CTT CCT CAT CTT C 3' (SEQ ID NO: 132)
S-VH1 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GA[GC] TGG ACC TGG AG[GCA] [AGTC]TC C 3' (SEQ ID NO: 133)
S-VH2 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GAC ATA CTT TG[CT] TCC ACG CTC C 3' (SEQ ID NO: 134)
S-VH3 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GA[AG] TT[TG] GG[AG] CT[GCT] [ACT]GC TGG (GAC)TT TT(TC) CT 3' (SEQ ID NO: 135)
S-VH4 Leader inner with Bgl II	5' GAA GAT CT C ACC ATG AA[AG] CA[TC] CTG TGG TTC TTC CT[TC] CTC 3' (SEQ ID NO: 136)
S-VH5 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GGG TCA ACC G[CT]C ATC CT 3' (SEQ ID NO: 137)
S-VH6 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG TCT GTC TCC TTC CTC ATC TTC T 3' (SEQ ID NO: 138)
S-VH7 Leader inner with Bgl II	5' GAA GAT CTC ACC ATG GAC TGG ACC TGG AGG ATC CTC TTC TTG GT 3' (SEQ ID NO: 139)

The primers introduced the following restriction sites at the 5' end (BglII) and the 3' end (XbaI) of the heavy chain cDNA. Similarly, the primers introduced the following restriction sites at the 5' end (BglII) and the 3' end (NheI) of the kappa chain cDNA.

The variable heavy chain cDNA amplicon was digested with appropriate restriction enzymes for the restriction enzyme sites that were added during the PCR reaction. The

60 products of that digestion were cloned into each of an IgG1, IgG2, and IgG4 expression vector with compatible overhangs for cloning. The IgG2 and IgG4 expression vectors were digested with BamHI and XbaI to generate compatible overhangs for sub-cloning. The IgG1 expression construct was digested with BamHI and NheI to generate compatible overhangs for sub-cloning. These vectors were generated by cloning the constant domain of human IgG1, IgG2 or IgG4 into

the multiple cloning site of the vector pcDNA3.1+/Hygro (Invitrogen).

The variable light chain cDNA amplicon was also digested with appropriate restriction enzymes for the restriction enzyme sites that were added during the PCR reaction. The products of that digestion were cloned into an IgK expression vector that had been digested with BamHI and NheI to provide compatible overhangs for sub-cloning. That vector was generated by cloning the constant domain of the human IgK gene into the multiple cloning site of the vector pcDNA4.1+/Neo (Invitrogen).

The heavy chain and the light chain expression vectors were then co-lipofected into a 60 mm dish of 70 % confluent human embryonal kidney 293 cells (ATCC, Cat. No. CRL-1573). For 24 hours, the transfected cells were allowed to secrete a recombinant antibody with the identical specificity as the original plasma cell. The supernatant (3 mL) was harvested from the HEK 293 cells and the secretion of an intact antibody was demonstrated with a sandwich ELISA to specifically detect human IgG. Control plates were coated with 2 mg/mL Goat anti-human IgG H+L O/N as for binding plates. The plates were washed five times with water. Recombinant antibodies were titrated 1:2 for 7 wells from the undiluted lipofection supernatant. The plates were washed five times with dH₂O. A goat anti-human IgG Fc-specific HRP-conjugated antibody was added at a final concentration of 1 µg/mL for 1 hour at room temperature for the secretion and the two binding assays. The plates were washed five times with dH₂O. The plates were developed with the addition of tetramethylbenzidine (TMB) for 30 minutes and the ELISA was stopped by the addition of 1 M phosphoric acid.

In addition to the XenoMax methodology described above, certain antibodies were obtained using hybridoma technology. Immunized mice were sacrificed by cervical dislocation, and the draining lymph nodes were harvested and pooled from each cohort. The lymphoid cells were dissociated by grinding in Dulbecco's Modified Eagle's Medium ("DMEM") to release the cells from the tissues. Recovered cells were suspended in DMEM. The cells were counted, and 0.9 mL DMEM per 100 million lymphocytes was added to the cell pellet to resuspend the cells gently but completely. The resuspended cells were incubated with 100 µL of CD90⁺ magnetic beads per 100 million cells at 4° C. for 15 minutes. The magnetically-labeled cell suspension (containing up to 10⁸ positive cells (or up to 2×10⁹ total cells)) was loaded onto an LS⁺ column. The column was washed with DMEM. The total effluent was collected as the CD90⁻ negative fraction, which was expected to contain mostly B cells.

The fusion was performed by mixing washed enriched B cells from above and nonsecretory myeloma P3X63Ag*.653 cells (ATCC (CRL 1580, see, e.g., Kearney et al., J. Immunol. 123, 1979, 1548-1550)) at a ratio of 1:1. The cell mixture was gently pelleted by centrifugation at 800 ×g. After complete removal of the supernatant from the cells, the cells were treated with 2 to 4 mL of Pronase solution (CalBiochem; 0.5 mg/mL in phosphate-buffered saline ("PBS")) for no more than 2 minutes. Three to five mL of fetal bovine serum ("FBS") was added to stop the enzyme activity and the suspension was adjusted to a 40 mL total volume using electro cell fusion solution ("ECFS") (0.3 M sucrose, 0.1 mM magnesium acetate, 0.1 mM calcium acetate). The supernatant was removed after centrifugation and the cells were resuspended in 40 mL ECFS. This wash step was repeated and the cells again were resuspended in 40 mL ECFS to a concentration of 2×10⁶ cells/mL.

Electro-cell fusion was performed using a fusion generator (model ECM2001, Genetronic, Inc.). The fusion chamber size used was 2.0 mL, using the following instrument settings: alignment condition: 50 V, 50 seconds; membrane breaking at 3000 V, 30 microseconds; post-fusion holding time: 3 seconds.

After electro-cell fusion took place, the cell suspensions were carefully removed from the fusion chamber under sterile conditions and transferred into a sterile tube containing the same volume of hybridoma culture medium, containing DMEM, (JRH Biosciences), 15 % FBS (Hyclone), supplemented with L-glutamine, penicillin/streptomycin, OPI (oxaloacetate, pyruvate, bovine insulin), and IL-6 (Boehringer Mannheim). The cells were incubated for 15 to 30 minutes at 37° C., and then centrifuged at 400 ×g (1000 rpm) for 5 minutes. The cells were gently resuspended in a small volume of hybridoma selection medium (hybridoma culture medium supplemented with 0.5 × hyaluronic acid (Sigma)). The total volume was adjusted appropriately with more hybridoma selection medium based on a final plating volume of 5×10⁶ B cells total per 96-well plate and 200 µL per well. The cells were mixed gently, pipetted into 96-well plates, and allowed to grow. On day 7 or 10, one-half the medium was removed, and the cells were re-fed with fresh hybridoma selection medium.

After 14 days of culture, hybridoma supernatants were screened for TR2-specific monoclonal antibodies by ELISA. In the Primary screen, the ELISA plates (Fisher, Cat. No. 12-565-136) were coated with 50 µL/well of TR2 protein (2 µg/mL) in Coating Buffer (0.1 M Carbonate Buffer, pH 9.6, NaHCO₃ 8.4 g/L), then incubated at 4° C. overnight. After incubation, the plates were washed with Washing Buffer (0.05 % Tween 20 in PBS) one time. 200 µL/well Blocking Buffer (0.5 % BSA, 0.1 % Tween 20, 0.01 % Thimerosal in 1 × PBS) were added and the plates were incubated at room temperature for 1 hour. After incubation, the plates were washed with Washing Buffer one time. Aliquots (50 µL/well) of hybridoma supernatants and positive and negative controls were added, and the plates were incubated at room temperature for 2 hours. The positive control used throughout was serum from a hyperimmune XenoMouse animal and the negative control was serum from the KLH-immunized XenoMouse animal. After incubation, the plates were washed three times with Washing Buffer. 100 µL/well of detection antibody goat anti-huIgGFC-HRP (Caltag Inc., Cat. No. H10507, using concentration was 1:2000 dilution) was added and the plates were incubated at room temperature for 1 hour. After incubation, the plates were washed three times with Washing Buffer. 100 µL/well of TMB (BioFX Lab. Cat. No. TMSK-0100-01) was added, and the plates were allowed to develop for about 10 minutes (until negative control wells barely started to show color). 50 µL/well stop solution (TMB Stop Solution (BioFX Lab. Cat. No. STPR-0100-01) was then added and the plates were read on an ELISA plate reader at a wavelength of 450 nm.

The antibodies produced by the hybridomas were analyzed using the same apoptosis assay described above. WM-266 cells were cultured at a density of 4500 cells/well in normal culture medium overnight in a microtiter plate. A 2× apoptosis medium mixture was prepared using cell culture medium without FCS and additionally including 1.8 µg/mL cycloheximide and 0.9 % FCS. Separate microtiter plates were used to titrate hybridoma supernatant 1:2 (in the 2× apoptosis medium mixture) in parallel with an isotype-matched negative control anti-KLH antibody. The culture media was removed from the WM-266 cells and 100 µL of the antibody-apoptosis medium mixture was added to each cell-containing

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well, one row at a time. The microtiter plates were incubated for 20 hours to allow apoptosis to occur. The DNA-binding fluorescent dyes propidium iodide (Sigma) and Hoechst 33342 (Molecular Probes) were added to each well at a final concentration of 0.5 $\mu\text{g}/\text{mL}$ and 2.5 $\mu\text{g}/\text{mL}$ respectively. After 1 hour at 37° C., fluorescent images of each well were captured and analyzed for total number of dead cells (PI) and total number of cells (Hoechst). The percent apoptosis was determined as (PI-positive cells/Hoechst-positive cells)×100.

Seventeen different anti-TR-2 antibodies were obtained (Antibodies A-Q) using either the XenoMax or hybridoma methodologies. All of the antibodies were sequenced, and the sequences of the heavy and light chain variable regions identified (see FIGS. 3-19). Alignments of the heavy chains and the light chains of the seventeen antibodies are shown in FIGS. 20 and 21.

Certain antibodies were examined for their ability to induce apoptosis in cells, using a similar apoptosis assay to the one described above. WM-266 melanoma cells were cultured in a microtiter plate at a density of 4500 cells/well in normal culture medium overnight. In a separate microtiter plate, the recombinant antibodies to be tested, an appropriate positive control (M413, a mouse IgG1 anti-TR-2 antibody having a heavy chain variable sequence: MEVQLVESGGGLVQPGGSLKLSAASG-FTFTYGMWVRQTPDKRLELVA LINSQGGSTYNS-DSVKGRFTISRDNARNLTLYLQMSSLK-SEDTAMYYCARRD YESLDSWGQGTSTVTSSG (SEQ ID NO: 141) and a light chain variable sequence: DIVLTQSPASLPVSLGQRATISCRASESVEY-SGTSLIQWYRQKPGQPPKLLIY AASNVDSEVPARFSGSGSGTDFSLYIHPVEEDDIAMFYCQQRKVPWTFGG GTKLEIKRTDAAPGLEAA (SEQ ID NO: 142)), and isotype-matched negative control antibodies (a potential anti-TR2 antibody that failed to show activity) were titrated such that the final concentration of antibody would cover a range of 0.0001 $\mu\text{g}/\text{mL}$ to 5 $\mu\text{g}/\text{mL}$. The antibodies were mixed in apoptosis medium containing a final concentration of 0.9 $\mu\text{g}/\text{mL}$ CHX and 0.45 % FCS. The culture media was removed from the WM-266 cells and the antibody-apoptosis medium mixture was added to the cells. After 20 hours of culture, the cells were stained with propidium iodide (Sigma) and Hoechst 33342 (Molecular Probes). After 1 hour at 37° C., an image of each well was captured and analyzed for total number of dead cells (PI) and total number of cells (Hoechst). The percent apoptosis was determined as (PI-positive cells/Hoechst-positive cells)×100. Significant cell death was observed in cells treated with M413 or with certain anti-TR-2 antibodies described above.

Example 2

Kinetic Analyses of Anti-TR-2 Antibody Binding to TR-2

The kinetics of the binding of anti-TR-2 antibodies A to Q to TR-2 was analyzed using a Biacore® 2000 instrument. High-density goat anti-human antibody surfaces were prepared on CM-5 Biacore® chips using routine amine coupling. Each purified anti-TR-2 antibody was diluted to approximately 1 $\mu\text{g}/\text{mL}$ in HBS-P running buffer containing 100 $\mu\text{g}/\text{mL}$ BSA. Each anti-TR-2 antibody was captured on a separate surface using a two minute contact time and a five minute wash to stabilize the anti-TR-2 antibody surface on the chip.

To analyze the kinetics of TR-2 binding to each individual anti-TR-2 antibody, 226 nM recombinant human TR-2-His (described in Example 1) was kinetically injected over each

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anti-TR-2 surface for one minute (using kinject) at 25° C., followed by a five minute dissociation period. The baseline drift resulting from a buffer injection lacking TR-2 over the anti-TR-2 antibody surface was subtracted from the observed binding on each of the other surfaces. Additionally, the data for TR-2 binding to anti-TR-2 antibody were normalized for the amount of monoclonal antibody captured on each surface. Each data set was fit globally to a 1:1 interaction model to determine binding kinetics. The k_a , k_d , and K_d values obtained for each antibody are shown in Table 3.

TABLE 3

Kinetics of TR-2 binding to anti-TR-2 antibody at 25° C.			
Antibody	k_a ($\text{M}^{-1}\text{s}^{-1}$)	k_d (s^{-1})	K_d (nM)
A	5.3×10^5	3.7×10^{-3}	6.9
B	5.7×10^5	1.1×10^{-2}	19
C	6.8×10^5	2.6×10^{-3}	3.9
D	6.2×10^5	2.7×10^{-3}	4.5
E	8.7×10^5	1.8×10^{-3}	2.1
F	3.8×10^5	5.0×10^{-3}	13
G	6.0×10^5	1.9×10^{-2}	31
H	8.6×10^5	8.4×10^{-3}	9.8
I	2.9×10^5	1.3×10^{-3}	4.4
J	5.7×10^5	7.1×10^{-3}	12
K	6.8×10^5	1.2×10^{-2}	18
L	6.0×10^5	1.1×10^{-2}	18
M	3.4×10^5	1.2×10^{-2}	37
N	8.1×10^5	5.5×10^{-2}	68*
O	4.4×10^5	8.4×10^{-3}	19
P	8.1×10^5	2.7×10^{-2}	33*
Q	1.2×10^6	1.6×10^{-2}	13*

*Data for that sample exhibited heterogeneity and fit poorly to a 1:1 model.

Example 3

Cell Killing Assays

Cell killing assays were performed with certain human anti-TR-2 antibodies described in Example 2 to determine the degree to which each antibody triggered apoptosis and cell death. Certain human anti-TR-2 antibodies, as well as mouse anti-TR-2 antibodies M412 and M413, were immobilized in separate wells of 96-well Protein G-coated plates (reactinbind Protein G coated plates, Pierce Cat. No. 15131). M412 is a mouse IgG1 anti-TR-2 antibody having a heavy chain variable sequence: KVQLQQSGTGLVKGASVKLSCKASGYTFTEYIIHWVKQRSGQGLEWIGWF YPGSGYIKYNEKFKDKATMTADKSSSTVYMELSRLTSEDSAV YFCTRHEED GYAAAYWGQGTLLTVSA (SEQ ID NO: 143) and a light chain variable sequence: DIVMTQSHK-FMSTSVGDRVSITCKASQDVSSAVAW-YQQKPGQSPKLLIYWA STRHTGVDPDRFTGSGSGT-DYTLTISSVQAEDLALYYCQQHYSTPYTFGGGT KLEIKR (SEQ ID NO: 144). M413 is a mouse IgG1 anti-TR-2 antibody as described above in Example 1. Each antibody was added at a concentration of 50 $\mu\text{g}/\text{mL}$ to a first well, and serially diluted 1:3× in each of seven additional wells. Each antibody dilution was performed in triplicate. Plates were incubated for 24 hours at 4° C. prior to use. Following the washing of each well with culture media (RPMI plus 10 % FBS), one of four different cell lines was plated onto each immobilized antibody, at a density of 50,000 cells per well in a total volume of 200 μL . The cell lines tested were COLO 205 cells (human colon adenocarcinoma), MDA-231 cells (human breast cancer), WM35 cells (human melanoma), and WM793 cells (human melanoma). Cells were incubated at 37° C./6 % CO_2 for 24 hours, followed by a 6 hour incubation

with ^3H -thymidine. The percentage of viable cells was assessed by determining the level of ^3H -thymidine incorporation into the treated cells relative to the level of ^3H -thymidine incorporation into the untreated cells. The ED_{50} of each antibody was derived from the cell viability titration curve by determining the concentration of antibody that reduced the viability of treated cells by 50 % relative to untreated cells. The ED_{50} of the human antibodies for COLO 205 cells ranged from 0 $\mu\text{g}/\text{ml}$ to 3.25 $\mu\text{g}/\text{ml}$. The mouse antibodies M412 and M413 had ED_{50} s of 1.85 $\mu\text{g}/\text{ml}$ and 0.07 $\mu\text{g}/\text{ml}$, respectively, for those cells. The ED_{50} of the human antibodies for MDA-231 cells ranged from 0.05 $\mu\text{g}/\text{ml}$ to 0.5 $\mu\text{g}/\text{ml}$. The mouse antibodies M412 and M413 had ED_{50} s of 0.6 $\mu\text{g}/\text{ml}$ and 0.07 $\mu\text{g}/\text{ml}$, respectively, for those cells. The ED_{50} of the human antibodies for WM35 cells ranged from 0.1 $\mu\text{g}/\text{ml}$ to 0.6 $\mu\text{g}/\text{ml}$. The mouse antibodies M412 and M413 had ED_{50} s of 1.85 $\mu\text{g}/\text{ml}$ and 0.07 $\mu\text{g}/\text{ml}$, respectively, for those cells. The ED_{50} of the human antibodies for WM793 cells ranged from 0.02 $\mu\text{g}/\text{ml}$ to 0.2 $\mu\text{g}/\text{ml}$. The mouse antibodies M412 and M413 had ED_{50} s of 1.85 $\mu\text{g}/\text{ml}$ and 0.05 $\mu\text{g}/\text{ml}$, respectively, for those cells.

Example 4

Human TR-2 Expression in Tumor Cell Lines

Human tumor cell lines were screened for expression of TR-2. Cell lines used included those from breast, central nervous system, colon, liver, lung, cervix, uterine, ovarian, pancreatic, prostate, and renal cancers, as well as leukemia and melanoma.

The expression of TR-2 on human tumor cells was determined using a cell-based array. Briefly, 4×10^5 cells in 100 MI CBA buffer (PBS, 3 % FBS, 0.02 % Azide) were distributed into each of the wells of 20 V-bottom 96-well plates. CBA buffer (150 μL) was added to each well and the plates were centrifuged to spin down the cells. The medium was discarded and 100 μL of antibody solution (one of the antibodies A to Q) at 10 $\mu\text{g}/\text{ml}$ was added to the cell pellet resuspended in PBS containing 2 % PBS ("assay buffer"). After a 25 minute incubation on ice, the cells were washed once in assay buffer. 100 μL of a secondary goat anti-human IgG Fc-specific horseradish peroxidase (HRP, Pierce) was added to the wells, and the plates were incubated on ice for 20 minutes. The plates were washed twice with assay buffer, and 100 μL of the TMB substrate (ZYMED) was added for 10 minutes at room temperature. The plates were centrifuged and 50 μL of each supernate was transferred into a clean plate containing 50 μL stop solution (BioFX Laboratories). Optical density readings were performed at 450 nm using the SpectraMax/plus reader (Molecular Devices). The data were normalized by subtracting the optical density values obtained from an isotype control antibody.

Several cell lines had an OD_{450} greater than 0.1 in the assay, including breast cancer cell lines HS 578.T (OD of 0.122) and T-47 D (OD of 0.112), colon cancer cell lines TE 671 (u) (OD of 0.109), HT-29 (OD of 0.193), SW-948 (OD of 0.122), KM-12 (OD of 0.354), and HCC-2998 (OD of 0.133), liver cancer cell lines NCI-N87 (OD of 0.154) and NCI-SNU-5 (OD of 0.137), leukemia cell lines HL-60 (OD of 0.233) and hPBMC (OD of 0.131), non-small-cell lung cancer cell line JY (OD of 0.118), CCRF-CEM (OD of 0.106), NCI-H2126 (OD of 0.108) and NCI-H460 (OD of 0.122), melanoma cell lines SK-mel-5 (OD of 0.131), LOX IMVI (OD of 0.102), RPMI 7951 (OD of 0.101), and UACC-62 (OD of 0.127), pancreas cancer cell lines HPAF II (OD of 0.117) and CAPAN-1 (OD of 0.101), prostate cancer cell line LNCaP

(OD of 0.174), and renal carcinoma cell lines Caki-1 (OD of 0.148) and UO-31 (OD of 0.104). The greatest expression of TR-2 among the tumor cell lines studied was found in colon cancer cell lines KM-12 and HT-29, and in leukemia cell line HL-60. None of the central nervous system, small-cell liver, cervical, uterine, or ovarian cancer cell lines studied had an OD_{450} greater than background.

To determine TR-2 expression profile on human tumor cell lines, the above human tumor cell lines were assayed with the mouse anti-TR-2 antibody M412. The expression of TR-2 on human tumor cells was determined using a cell-based array. Briefly, 4×10^5 cells in 100 MI CBA buffer (PBS, 3 % FBS, 0.02 % Azide) were distributed into each of the wells of 20 V-bottom 96-well plates. CBA buffer (150 μL) was added to each well and the plates were centrifuged to spin down the cells. The medium was discarded and 100 μL of mouse anti-TR-2 monoclonal antibody M412 at 10 $\mu\text{g}/\text{ml}$ was added to the cell pellet resuspended in PBS containing 2 % PBS ("assay buffer"). After a 25 minute incubation on ice, the cells were washed once in assay buffer. 100 μL of a secondary goat anti-mouse IgG Fc-specific horseradish peroxidase (HRP, Pierce) was added to the wells, and the plates were incubated on ice for 20 minutes. The plates were washed twice with assay buffer, and 100 μL of the TMB substrate (ZYMED) was added for 10 minutes at room temperature. The plates were centrifuged and 50 μL of each supernate was transferred into a clean plate containing 50 μL stop solution (BioFX Laboratories). Optical density readings were performed at 450 nm using the SpectraMax/plus reader (Molecular Devices). The data were normalized by subtracting the optical density values obtained from an isotype control antibody.

Many of the cell lines had TR-2 expression. The highest expressors (those with an OD_{450} nm greater than 0.3) included breast cancer cell lines HS 578.T (OD of 0.403), MDA-MB-231 (OD of 0.408), and T-47 D (OD of 0.366), CNS cancer cell lines SF-295 (OD of 0.354) and U251 (OD of 0.323), colon cancer cell lines HCT-116 (OD of 0.41), HT-29 (OD of 0.869), SW-707 (OD of 0.323), SW-948 (OD of 0.423), KM-12 (OD of 0.77), and HCC-2998 (OD of 0.635), liver cancer cell line NCI-SNU-1 (OD of 0.354), leukemia cell line A 673 (OD of 0.347), non-small-cell lung cancer cell lines HOP-62 (OD of 0.313), HOP-62 (OD of 0.47), NCI-H2126 (OD of 0.501), NCI-H460 (OD of 0.326), small cell lung cancer line A549 (OD of 0.381), melanoma cell lines LOX IMVI (OD of 0.573), RPMI 7951 (OD of 0.322), and UACC-62 (OD of 0.319), ovarian cancer cell line IGROV1 (OD of 0.312), prostate cancer cell lines DU 145 (OD of 0.372), 22 Rv1 (OD of 0.301), and LNCaP (OD of 0.63), and renal carcinoma cell lines Caki-1 (OD of 0.93), Caki-2 (OD of 0.443), SN12 C (OD of 0.313), and UO-31 (OD of 0.331). The greatest expression of TR-2 among the tumor cell lines treated with mouse anti-TR-2 antibody was found in renal carcinoma cell line Caki-1, and in colon cancer cell lines HT-29 and KM-12.

Example 5

Antibody Cross-Reactivity

The ability of certain of the human anti-TR-2 antibodies to block the binding of the others to TR-2 was assessed, as described in Jia et al., J. Immunol. Methods 288: 91-98 (2004). The beads were conjugated with anti-human IgG antibodies using the coupling procedure taken directly from the Luminex 100 User's Manual, Version 1.7. After the beads were activated, they were coupled to a Pharmingen mouse anti-hIgG mAb, following the manufacturer's instructions.

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Two experiments were performed. In a first experiment, the coated beads were incubated for two hours at room temperature. In a second experiment, the coated beads were incubated overnight at 4° C. At the end of the incubation, the coated beads were blocked and then counted using a Coulter cell counter. Conjugated beads were either used immediately or were stored at 4° C. in the dark for future use.

The categorization of the anti-TR-2 antibodies based on epitope cross-reactivity was performed by the following steps. First, each set of bead-mouse anti-hlgG complexes from above were separately incubated with a reference antibody ("reference antibody") on a rotator overnight at 4° C. The reference antibody was selected from anti-TR-2 antibodies A-Q, described above. After antibody capture, 2000 of each bead-mouse anti-hlgG-reference Ab complexes were pooled together in one tube, and then immediately added to each well of a 96-well plate and aspirated. TR-2 (50 ng) was added to each well and incubated for 1 hour at room temperature. After washing the wells, 100-500 ng/mL of another of the human anti-TR-2 antibodies (the "probe antibody") was added to each well and incubated for 2 hours at room temperature. After washing the wells, bound probe antibody was detected using 1 µg/ml of a biotinylated version of the same monoclonal mouse anti-hlgG used for capturing the reference antibody. Following incubation and washing of the wells, 0.5 µg/ml streptavidin-phycoerythrin was added. The mixture was incubated for 30 minutes at room temperature and then the phycoerythrin signal was detected using the Luminex 100. An additional set of wells lacking antigen was used as a negative control to aid in data analysis.

The data was analyzed in a two-step process. First, the data was normalized using the negative control values. Second, the anti-TR-2 antibodies were clustered according to their ability to impede binding of one or more other anti-TR-2 antibodies. For the clustering analysis, a dissimilarity matrix was generated from the normalized intensity matrix. Antibodies were clustered based on the values in the average dissimilarity matrix using the SPLUS 2000 agglomerative nesting hierarchical clustering subroutine with the Manhattan metric, using an input dissimilarity matrix of the actual average dissimilarity matrix.

Based on the findings, the antibodies were placed into four different epitope groups. Within any one group, the binding of one of the group members to TR-2 blocks the binding of another member of the same group to TR-2. However, the binding of one of the members of group 1 to TR-2, for example, does not block the binding of one of the members of groups 2, 3, or 4 to TR-2. Those groups are shown in FIG. 22.

Example 6

Epitope Mapping

To identify the specific region of TR-2 important for binding to certain described anti-TR-2 antibodies, an epitope mapping study was performed. An N-avidin-TR-2 construct was made by PCR-amplifying the coding sequence for mature TR-2 (MacFarlane, 1997) from a template source and cloning it into a pCEP4 vector (Invitrogen) containing the chicken avidin sequence in an orientation such that upon insertion at a HindIII site, the TR-2 sequence was joined at the C-terminus of the avidin sequence. The forward primer for the mature TR-2 coding sequence was GTAAGCAAGCTTGGCTCTGATCACCAACAAGA (SEQ ID NO: 145), and the reverse primer was GATTAGGGATCCAGAGGCAGGAGTCCCTGG (SEQ ID NO: 146). The amino acid sequence of the resulting avidin-TR-2 fusion protein was

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MVHATSPLLLLLL LSLALVAPGLSARKCSLTGKWT-
NDLGSNMTIGAVNSKGFTGTYTTAVTATS
NEIKESPLHGTQNTINKRTQPTFGFTVN-
WKFSESTTVFTGQCFIDRNGKEVL KTMWLLRSSVN-
DIGDDWKATRVGINIFTRLRTQKEQL-
LASLALITQQDLAPQ
QRAAPQQKRSSPSEGLCPPGH-
HISEDGRDCISCKYGGDYSTHWNDDLLFCL RCTRCDS-
GEVELSPCTTTRNTVCQCEEGTFREED-
SPEMCRKCRGTGCPRG
MVKVGDCPTWSDIECVHKESGTHKS-
GEAPAVEETVTSSPGTPAS (SEQ ID NO: 69).

Twelve molecules comprising N-avidin and truncations of human TR-2 were synthesized as described below. Three molecules had only C-terminal truncations of human TR-2 (TR-2-1 through TR-2-3), and nine molecules had truncations at both the N- and the C-terminus of human TR-2 (TR-2-4 through TR-2-13) (shown schematically in FIG. 23). Polynucleotides encoding human TR-2 truncations were prepared by PCR amplification using the primers described below. To form each of the twelve molecules, the truncated human TR-2 resulting from the amplification was inserted into the pCEP4 vector (Invitrogen) containing the chicken avidin sequence that is described above. The polynucleotide encoding amino acids 1-43 of mature TR-2 was amplified using the forward primer GTAAGCAAGCTTGGCTCTGATCACCAACAAGA (SEQ ID NO: 145) and the reverse primer TAGTTGGGATCCTCAGGAGATGCAATCTCTACCGT (SEQ ID NO: 147). The amino acid sequence of TR-2-1 was MVHATSPLLLLLLLLLSLALVAPGLSARKCSLTGKWTNDLGSNMTIGAVNS KGEFTGTYTTAVTATSNEIKESPLHGTQNTINKRTQPTFGFTVNWKFSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLASLALITQQDLAPQQRAAPQQKRSSPSEGLCPPGHHISEDGRDCIS (SEQ ID NO: 70).

The polynucleotide encoding amino acids 1-85 of mature TR-2 was amplified using the forward primer GTAAGCAAGCTTGGCTCTGATCACCAACAAGA (SEQ ID NO: 145) and the reverse primer GGTAAGTGGATCCTCACTGACACACTGTGTTTCTGG (SEQ ID NO: 148). The amino acid sequence of TR-2-2 was MVHATSPLLLLLLLLLSLALVAPGLSARKCSLTGKWTNDLGSNMTIGAVNSKG EFTGTYTTAVTATSNEIKESPLHGTQNTINKRTQPTFGFTVNWKFSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLASLALITQQDLAPQQRAAPQQKRSSPSEGLCPPGH- HISEDGRDCISCKYGGDYSTHWNDDLLFCLRCTRCDSGEVELSPCTTTRNTVCQ (SEQ ID NO: 71).

The polynucleotide encoding amino acids 1-126 of mature TR-2 was amplified using the forward primer GTAAGCAAGCTTGGCTCTGATCACCAACAAGA (SEQ ID NO: 145) and the reverse primer GTAATGGGATCCTCAGACACATTCGATGTCACCTCC (SEQ ID NO: 149). The amino acid sequence of TR-2-3 was MVHATSPLLLLLLLLLSLALVAPGLSARKCSLTGKWTNDLGSNMTIGAVNSKGFTGTYTTAVTATSNEIKESPLHGTQNTINKRTQPTFGFTVNWKFSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQ KEQLLASLALITQQDLAPQQRAAPQQKRSSPSEGLCPPGHHISEDGRDCIS

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KYGDYSTHWNDLLFCLRCTRCDSEGEV-
ELSPCTTTRNTVCQCEEGTFREE DSPEMCRKCR-
GCPRGMVKVGDCTPWSDIECV (SEQ ID NO: 72).

The polynucleotide encoding amino acids 16-43 of mature TR-2 was amplified using the forward primer GTAATGAAGCTTGCCACAACA AAAGAGGTCCAG (SEQ ID NO: 150) and the reverse primer TAGTTGGGAT CCTCAGGAGATGCAATCTCTACCGT (SEQ ID NO: 147). The amino acid sequence of TR-2-4 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTIGAVNSKGE FTGTYT-TAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLA SLPQQRSSPSEG-LCPPGHHISEDGRDCIS (SEQ ID NO: 73).

The polynucleotide encoding amino acids 16-85 of mature TR-2 was amplified using the forward primer GTAATGAAGCTTGCCACAACAAA AGAGGTCCAG (SEQ ID NO: 150) and the reverse primer GGTAGTGGA TCCTCACTGACACACTGTGTTTCTGG (SEQ ID NO: 148). The amino acid sequence of TR-2-5 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDL GSNMTIGAVNSKGEFTGTYT-TAVTATSNEIKESPLHGTQNTINKRTQPTFGF TVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQL-LASLPQQRSSPSEGLCPPGH-HISEDGRDCISCKYGDYSTHWNDLLFCLRCTRCDSEGEVELSPCTTTRNTVCQ (SEQ ID NO: 74).

The polynucleotide encoding amino acids 16-126 of mature TR-2 was amplified using the forward primer GTAATGAAGCTTGCCACAACAAA AGAGGTCCAG (SEQ ID NO: 150) and the reverse primer GTAATGGGATCCTCA GACACATTCGATGTCCTCC (SEQ ID NO: 149). The amino acid sequence of TR-2-6 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTIGA VNSKGEFTGTYT-TAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQL-LASLPQQRSSPSEGLCPPGH-HISEDGRDCISCKYGDYSTHWNDLLFCLRCTRCDSEGEVELSPCTTTRNTVCQ-CEEFTFREEDSPEMCRKCRITGCP RGMVKVGDCTPWSDIECV (SEQ ID NO: 75).

The polynucleotide encoding amino acids 42-85 of mature TR-2 was amplified using the forward primer GAT-TGAAAGCTTGATCTCCTGCAAATATGGACAG (SEQ ID NO: 151) and the reverse primer GGTAGTGGATCCTCACTGACACACTGTGTTTCTGG (SEQ ID NO: 148). The amino acid sequence of TR-2-7 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTIGAVNS KGEFTGTYT-TAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLASLISCKYGDYSTHWNDLLFCLRCTRCDSEGEVELSPCTTTRNTVCQ (SEQ ID NO: 76).

The polynucleotide encoding amino acids 42-126 of mature TR-2 was amplified using the forward primer GAT-TGAAAGCTTGATCTCCTGCAAATATGGACAG (SEQ ID NO: 151) and the reverse primer GTAATGGGATCCTCAGACACATTCGATGTCCTCC (SEQ ID NO: 149). The amino acid sequence of TR-2-9 was

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MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTIGA VNSKGEFTGTYT-TAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQ KEQLLASLISCKYGDYSTHWNDLLFCLRCTRCDSEGEVELSPCTTTRNTVCQCEEGTFREEDSPEMCRKCRITGCPRGM-VKVGDCPTPWSDIECV (SEQ ID NO: 77).

The polynucleotide encoding amino acids 85-154 of mature TR-2 was amplified using the forward primer GTAATGAAGCTTGCAAGTGCAGGAAGAAGGCACCT (SEQ ID NO: 152) and the reverse primer GATTAGGGATCCAGAGGCAGGAGTCCCTGG (SEQ ID NO: 146). The amino acid sequence of TR-2-10 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTIGAVNSKG EFTGTYT-TAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLA SLQCEEGTFREEDSPEMCRKCRITGCPRGMVKVGDCTPWSDIECVHKESGT KHSGEAPAVEETVTSSPGTPAS (SEQ ID NO: 78).

The polynucleotide encoding amino acids 42-154 of mature TR-2 was amplified using the forward primer GAT-TGAAAGCTTGATCTCCTGC AAATATGGACAG (SEQ ID NO: 151) and the reverse primer GATTAGGGATCCAGAGGCAGGAGTCCCTGG (SEQ ID NO: 146). The amino acid sequence of TR-2-11 was MVHATSPLLLLLLLSLALVAPGLSARKCSLTGKWTNDLGSNMTIGAVNSKGEFTGTYTTAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSEST TVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQLLASLISCKYGDYSTHWNDLLFCLRCTRCDSEGEVELSPCTTTRNTVCQC EEGTFREEDSPEMCRKCRITGCPRGMVKVGDCTPWSDIECVHKESGT KHS GEAPAVEETVTSSPGTPAS (SEQ ID NO: 79).

The polynucleotide encoding amino acids 16-66 of mature TR-2 was amplified using the forward primer TGAT-TGAAGCTTGCCACAACA AAGAGGTCCAG (SEQ ID NO: 150) and the reverse primer GATGGAGGATCCTCAACACCTGGTGCAGCGCAAG (SEQ ID NO: 153). The amino acid sequence of TR-2-12 was MVHATSPLLLLLLLSLALVAPGLSARKC-SLTGKWTNDLGSNMTI GAVNSKGEFTGTYT-TAVTATSNEIKESPLHGTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRLRTQKEQL-LASLPQQRSSPSEGLCPPGH-HISEDGRDCISYKYGDYSTHWND LLFCLRCTRC (SEQ ID NO: 80).

The polynucleotide encoding amino acids 16-74 of mature TR-2 was amplified using the forward primer TGAT-TGAAGCTTGCCACAACA AAAGAGGTCCAG (SEQ ID NO: 150) and the reverse primer GTAAGTGGATCC TCAGCAGGGACTTAGCTCCACT (SEQ ID NO: 154). The amino acid sequence of TR-2-13 was MVHATSPLLLLLLLSLALVAPGLSARKCSLTGKWTNDLGSNMT IGAVNSKGEFTGTYTTAVTATSNEIKESPLH-GTQNTINKRTQPTFGFTVNWKFSSESTTVFTGQCFIDRNGKEVLKTMWLLRSSVNDIGDDWKATRVGINIFTRL RTQKEQL-LASLPQQRSSPSEGLCPPGH-

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HI SEDGRDCISCKYGDYSTHW
NDLLFCLRCTRCDSGEVELS (SEQ ID NO: 81). Four
molecules comprising N-avidin and truncations of TR-2 from
cynomolgus monkey were synthesized as described below.
The polynucleotide encoding amino acids 1 to 132 of mature
cyno TR-2 was amplified using the forward primer GTTAG-
TAAGCTTGGCTCCAATCACCCGAC (SEQ ID NO: 155)
and the reverse primer GTTGATGGATCCTTCTTTGTG-
GACACTCGAT (SEQ ID NO: 156). The amino acid
sequence of cyno TR-2 (short) was MVHATS
PLLLLLLSLALVAPGLSARKCSLTGK-
WTNDLGSNMTIGAVNSKGFTGTYT TAVTATS-
NEIKESPLHGTQNTINKRTQPTFGFTVN-
WKFSESTTVFTGQCFFIDR
NGKEVLKTMWLLRSSVNDIGDDWKATRV-
GINIFTRLRTQKEQLLASLAPITR QSLDPQR-
RAAPQQRSSPTEGLCPPGHHISEDSRD-
CISCKYGDYSTHW
DFLFCRLCTKCDSEGEVSSCTIIRN-
TVQCCEEGTFREEDSPEICRKCRTG CPRGM-
VKVKDCTPWSIDIECPQRRIT (SEQ ID NO: 82).

The polynucleotide encoding amino acids 1 to 154 of
mature cyno TR-2 was amplified using the forward primer
GTTAGTAAGCTTGGCTCCA ATCACCCGAC (SEQ ID
NO: 155) and the reverse primer GTAGTTGGATCCTC
AAGAAGCAGGAGTCCCAGGG (SEQ ID NO: 157). The
amino acid sequence of cyno TR-2 (long) was
MVHATSPLLLLLSLALVAPGLSARKC-
SLTGKWTNDLG SNMTIGAVNSKGFTGTYT-
TAVTATSNEIKESPLHGTQNTINKRTQPTFGFTV
NWKFSESTTVFTGQCFFIDRNGKEVLKTM-
WLLRSSVNDIGDDWKATRVGINIF TRLRTQKEQL-
LASLAPITRQSLDPQRRM-
PQQRSSPTEGLCPPGHHISEDS
RDCISCKYGDYSTHWNDLFLCLRCT-
KCDSGEVEVSSCTTTRNTVCQCEE GTFREEDSPE-
ICRKCRTGCPRGMVKVKDCTPWS-
DIECVHKEGSKHTGEV PAVEKTVTTSPGTPAS (SEQ
ID NO: 83).

The polynucleotide encoding amino acids 1 to 85 of mature
cyno TR-2 was amplified using the forward primer GTTAG-
TAAGCTTGGCTCCA ATCACCCGAC (SEQ ID NO: 155)
and the reverse primer GTATGAGGGATCCTC ACTGACA-
CACCGTGTCTTCTGG (SEQ ID NO: 158). The amino acid
sequence of cyno 1-85 was MVHATSPLLLLLSLAL-
VAPGLSARKCSLTGKWTNDLGSNMT IGAVN-
SKGFTGTYTTAVTATSNEIKESPLH-
GTQNTINKRTQPTFGFTVNWK
FSESTTVFTGQCFFIDRNGKEVLKTMWLL-
RSSVNDIGDDWKATRVGINIFTRL RTQKEQL-
LASLAPITRQSLDPQR-
RAAPQQRSSPTEGLCPPGHHISEDSRD
CISCKYGDYSTHWNDLFLCLRCTKCD-
SEGEVSSCTTTRNTVCQ (SEQ ID NO: 84).

The polynucleotide encoding amino acids 16 to 85 of
mature cyno TR-2 was amplified using the forward primer
GTATGGAAGCTTGCCACAA CAAAAGAGATCCAGC
(SEQ ID NO: 159) and the reverse primer GTATGAGGG
ATCCTCACTGACACACCGTGTCTTCTGG (SEQ ID NO:
158). The amino acid sequence of cyno 16-85 was
MVHATSPLLLLLSLALVAPGLSARKCSLTGK
TNDLGSNMTIGAVNSKGFTGTYT-
TAVTATSNEIKESPLHGTQNTINKRTQPT TFGFTVN-
WKFSESTTVFTGQCFFIDRNGKEVLKTM-
WLLRSSVNDIGDDWKAT
RVGINIFTRLRTQKEQL-
LASLPQQRSSPIEGLCPPGHHISEDSRDCISCKY

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QDYSTHWNDLFLCLRCTKCDSEGEVSS-
CTTTRNTVCQ (SEQ ID NO: 85).

Four N-avidin-fused chimeras were also made using dif-
ferent portions of human TR-2 and cyno TR-2, as shown in
FIG. 25. Each chimera was constructed by preparing two
PCR products with overlapping ends that were then amplified
together using the same 5' and 3' primers. To form each of the
chimeras, the amplified polynucleotide was then subcloned
into the pCEP4 vector (Invitrogen) containing the chicken
avidin sequence that is described above. An alignment of the
human, cyno (short), and mouse TR-2 sequences is shown in
FIG. 26.

Cyno/human chimera #1 was prepared by amplifying a
region of mature cyno TR-2 corresponding to amino acids
1-16 using the forward primer GTTAGTAAGCTTGGCTC-
CAATCACCCGAC (SEQ ID NO: 155) and the reverse
primer GGACCTCTTTTGTGTTGGAGCCGCTCT-
TCGCTGG (SEQ ID NO: 159) and amplifying a region of
mature human TR-2 corresponding to amino acids 17-85
using the forward primer CAGCGAAGAGCGGCTCCA-
CAACAAAAG AGGTCCAG (SEQ ID NO: 160) and the
reverse primer GGTAGTGGATCCTCACT GACACACT-
GTGTTTCTGG (SEQ ID NO: 148). Overlapping PCR of the
cyno and human TR-2 fragments was performed using the
forward primer for the cyno TR-2 amino acids 1-16 fragment,
above (SEQ ID NO: 155) and the reverse primer for the
human TR-2 amino acids 17-85 fragment, above (SEQ ID
NO: 148). The amino acid sequence for cyno/human chimera
#1 was MVHATSPLLLLLSLALVAPGLSARKC-
SLTGKWT NDLGSNMTIGAVNSKGFTGTYT-
TAVTATSNEIKESPLHGTQNTINKRTQPT FGFTVN-
WKFSESTTVFTGQCFFIDRNGKEVLKTMWLLRSSV
DIGDDWKATR VGINIFTRLRTQKEQL-
LASLAPITRQSLDPQRRRAAPQQRSSPEGLCPPGH
HI SEDGRDCISCKYGDYSTHWNDLFL-
CLRCTRCDSGEVELSPCTTTRNTV CQ (SEQ ID NO:
86).

Cyno/human chimera #2 was prepared by amplifying a
region of mature cyno TR-2 corresponding to amino acids
1-16 using the forward primer GTTAGTAAGCTTGGCTC-
CAATCACCCGAC (SEQ ID NO: 155) and the reverse
primer GGACCTCTTIGTTGTGTTGGAGCCGCTCT-
TCGCTGG (SEQ ID NO: 159) and amplifying a region of
mature human TR-2 corresponding to amino acids 17-154
using the forward primer CAGCGAAGAGCGGCTCCA-
CAACAAAAG AGGTCCAG (SEQ ID NO: 160) and the
reverse primer GATTAGGGATCCTCAA GAGGCAG-
GAGTCCCTGG (SEQ ID NO: 146). Overlapping PCR of the
cyno and human TR-2 fragments was performed using the
forward primer for the cyno TR-2 amino acids 1-16 fragment,
above (SEQ ID NO: 155) and the reverse primer for the
human TR-2 amino acids 17-154 fragment, above (SEQ ID
NO: 146). The amino acid sequence for cyno/human chimera
#2 was MVHATSPLLLLLSLALVAPGLSARKC-
SLTGKW TNDLGSNMTIGAVNSKGFTGTYT-
TAVTATSNEIKESPLHGTQNTINKRTQPT TFGFTVN-
WKFSESTTVFTGQCFFIDRNGKEVLKTMWLLRSSV
NDIGDDWKAT RVGINIFTRLRTQKEQL-
LASLAPITRQSLDPQRRRAAPQQRSSPEGLCPPG
HHISEDRDYISCKYGDYSTHWNDLFL-
CLRCTRCDSGEVELSPCTTTRNT VCQCEEGTFREED-
SPEMCRKCRGCPRGMVKVGDCTPWS-
DIECVHKEG TKHSGEAPAVEETVTTSSPGTPAS (SEQ
ID NO: 87).

Cyno/human chimera #3 was prepared by amplifying a
region of mature human TR-2 corresponding to amino acids
1-16 using the forward primer GTAAGCAAGCTTG-

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GCTCTGATCACCCAACAAGA (SEQ ID NO: 145) and the reverse primer GGATCTCTTTTGTGTGGGGC-CGCTCTCTGCTGG G (SEQ ID NO: 161) and amplifying a region of mature cynoTR-2 corresponding to amino acids 17-85 using the forward primer CAGCAGAGAGCGGC-CCCACA ACAAAGAGATCCAGC (SEQ ID NO: 162) and the reverse primer GTATGAGG GATCCTCACTGACACACCGTGTCTTCTGG (SEQ ID NO: 158). Overlapping PCR of the cyno and human TR-2 fragments was performed using the forward primer for the human TR-2 amino acids 1-16 fragment, above (SEQ ID NO: 145) and the reverse primer for the cyno TR-2 amino acids 17-85 fragment, above (SEQ ID NO: 158). The amino acid sequence for cyno/human chimera #3 was MVHATSPLLLLLLSLALVAPGLSAR KCSLTGKWTNDLGSNMTIGAVNSKGEFT-GTYTTAVTATSNEIKESPLHGTQN TINKRTQPTFGFTVNWKFSESTTVFTGQCFIDRNGKEV-LKTMWLLRSSVNDI GDDWKATRVGINIFTRLRTQKEQL-LASLALITQDDLAPQQRAPQQRSSPT EGLCPPGH-HISEDSDCISCKYGGDYSTHWNDLF-CLRCTKCDSEGEVSS CTTTRNTVCQ (SEQ ID NO: 88).

Cyno/human chimera #4 was prepared by amplifying a region of mature human TR-2 corresponding to amino acids 1-16 using the forward primer GTAAGCAAGCTTG-GCTCTGATCACCCAACAAGA (SEQ ID NO: 145) and the reverse primer GGATCTCTTTTGTGTGGGGC-CGCTCTCTGCTGG G (SEQ ID NO: 161) and amplifying a region of mature cyno TR-2 corresponding to amino acids 17-154 using the forward primer CAGCAGAGAGCGGC-CCCACA ACAAAGAGATCCAGC (SEQ ID NO: 162) and the reverse primer GTAGTTGGA TCCTCAAGAAG-CAGGAGTCCAGGG (SEQ ID NO: 157). Overlapping PCR of the cyno and human TR-2 fragments was performed using the forward primer for the human TR-2 amino acids 1-16 fragment, above (SEQ ID NO: 145) and the reverse primer for the cyno TR-2 amino acids 17-154 fragment, above (SEQ ID NO: 157). The amino acid sequence for cyno/human chimera #4 was MVHATSPLLLLLLSLALVAPGLSAR KCSLTGKWTNDLGSNMTIGAVNSKGEFTGTYTTAVTATSNEIKESPLHGTQN TINKRTQPTFGFTVNWKFSESTTVFT-GQCFIDRNGKEVLKTMWLLRSSVNDI GDDWKATRVGINIFTRLRTQKEQL-LASLALITQDDLAPQQRAPQQRSSPT EGLCPPGH-HISEDSDCISCKYGGDYSTHWNDLF-CLRCTKCDSEGEVSS CTTTRNTVCQEEGTFREEDSPE-ICRKCRTGCPRGMVKVKDCTPWSDIECV HKESGTHKHTGEVPAVEKTVTTPGTPAS (SEQ ID NO: 89). Four additional modified TR-2 proteins were constructed by replacing short regions of human TR-2 with the corresponding mouse TR-2 sequence, in the context of an N-avidin fusion. Human/mouse TR-2 #1 comprised the mouse TR-2 sequence from amino acids 1-22 and the human TR-2 sequence from amino acids 23-150. Human/mouse TR-2 #2 comprised the human TR-2 sequence from amino acids 1-28 and 35-150 and the mouse TR-2 sequence from amino acids 29-34. Human/mouse TR-2 #3 comprised the human TR-2 sequence from amino acids 1-53 and 60-150 and the mouse TR-2 sequence from amino acids 54-59. Human/mouse TR-2 #4 comprised the human TR-2 sequence from amino acids 1-66 and 76-150 and the mouse TR-2 sequence from amino acids 67-75. To form each of the modified proteins, the ampli-

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fied polynucleotide was then subcloned into the pCEP4 vector (Invitrogen) containing the chicken avidin sequence that is described above.

Human/mouse TR-2 #1 was prepared by amplifying a region of mature human TR-2 corresponding to amino acids 23-150 using the forward primer CAGCGGCCGGAG-GAGAGCCCCCTCAGAGGGATTGT (SEQ ID NO: 163) and the reverse primer GATTGAGGATCCCTAAGAGGCAG-GAGTCCCCTGG (SEQ ID NO: 164) and amplifying a region of mature mouse TR-2 corresponding to amino acids 1-22 using the forward primer TGAATGAAGCTTGGTTC-CAGTA ACAGCTAACCCA (SEQ ID NO: 165) and the reverse primer TCCCTCTGAGGG GCTCTCCTCCGGC-CGCTGTAG (SEQ ID NO: 166). Overlapping PCR of the human and mouse TR-2 fragments was performed using the forward primer for the mouse TR-2 amino acids 1-22 fragment, above (SEQ ID NO: 165) and the reverse primer for the human TR-2 amino acids 23-150 fragment, above (SEQ ID NO: 164). The amino acid sequence for human/mouse TR-2 #1 was MVHATSPLLLLLLSLALV APGLSARKCSLTGKWTNDLGSNMTIGAVNSKGEFTGTYT-TAVTATSNEIKES PLHGTQNTINKRTQPTFGFTVN-WKFSESTTVFTGQCFIDRNGKEVLKTMWL LRSSVNDIGDDWKATRVGINIFTRL-RTQKEQLLASLVPVTANPAHNRPAQLQ RPEESPSEG-LCPPGHISEDGRDCISCKYGGDYSTH-WNDLLFCLRCTRCDS GEVELSPCTTTRNTVCQEEGTFREED-SPEMCRKCRTGCPRGMVKVGDC T PWSDIECVHKES-GTKHSGEAPAVEETVTSSPGTPAS (SEQ ID NO: 90).

Human/mouse TR-2 #2 was prepared by amplifying a region of mature human TR-2 corresponding to amino acids 1-28 using the forward primer GTAAGCAAGCTTG-GCTCTGATCACCCAACAAGA (SEQ ID NO: 145) and the reverse primer CAGGTACTGGCCTGCTAGACACAATC-CCTCTGAGGGG (SEQ ID NO: 167), amplifying a region of mature human TR-2 corresponding to amino acids 35-150 using the forward primer CTAGCAGGCCAGTACCTGT-CAG AAGACGGTAGAGATTGC (SEQ ID NO: 168), and the reverse primer GATTGAG GATCCCTAAGAGGCAG-GAGTCCCCTGG (SEQ ID NO: 164) and amplifying a region of mature mouse TR-2 corresponding to amino acids 29-34 using the forward primer CAGGTACTGGCCTGCTAGACACAATCCCTCTGAGGGG (SEQ ID NO: 169) and the reverse primer CTAGCAGGCCAGTACCTGTCTAGAA-GACGG TAGAGATTGC (SEQ ID NO: 170). Overlapping PCR of the human and mouse TR-2 fragments was performed using the forward primer for the human TR-2 amino acids 1-28 fragment, above (SEQ ID NO: 145) and the reverse primer for the human TR-2 amino acids 35-150 fragment, above (SEQ ID NO: 170). The amino acid sequence for human/mouse TR-2 #2 was MVHATSPLLLLLLSLALVAPGLSARKCSLTGKW TNDLGSNMTIGAVNSKGEFTGTYTTAVTATSNEIKESPLHGTQNTINKRTQP TF GFTVNWKFSESTTVFTGQCFIDRNGKEV-LKTMWLLRSSVNDIGDDWKATRV GINIFTRL-RTQKEQLLASLALITQDD-LAPQQRAPQQRSSPSEGLCLAGQY LSEDGRDCISCKYGGDYSTHWNDLLFCL-RCTRCDSGEVELSPCTTTRNTVC QEEGTFREED-SPEMCRKCRTGCPRGMVKVGDC T PWS-DIECVHKESGTK HSGEAPAVEETVTSSPGTPAS (SEQ ID NO: 91).

Human/mouse TR-2 #3 was prepared by amplifying a region of mature human TR-2 corresponding to amino acids 1-53 using the forward primer GTAAGCAAGCTTG-GCTCTGATCACCCAACAAGA (SEQ ID NO: 145) and the

reverse primer TGAATCCAGAGAAATGGTTGGAGT-GAGTGTATAGTCCTG TC (SEQ ID NO: 171), and amplifying a region of mature human TR-2 corresponding to amino acids 60-154 using the forward primer TCCAACCAT-TCTCTGGATTCA TGCTTGCGCTGCACCAGG (SEQ ID NO: 172) and the reverse primer GATTG AGGATCCCTAA-GAGGCAGGAGTCCCTGG (SEQ ID NO: 173). The above primers include nucleotides encoding mouse TR-2 corresponding to amino acids 54-59. Overlapping PCR of the human and mouse TR-2 fragments was performed using the forward primer for the human TR-2 amino acids 1-53 fragment, above (SEQ ID NO: 145) and the reverse primer for the human TR-2 amino acids 60-154 fragment, above (SEQ ID NO: 173). The amino acid sequence for human/mouse TR-2 #3 was MVHATSPLLLLLLSLALVAPGLSARKCSLTGKWT NDLSNMTIGAVNSKGEFTGTYT-TAVTATSNEIKESPLHGTQNTINKRTQPT FGFTVN-WKFSESTTVFTGQCIFDRNGKEVLKTMWLLRSSVN DIGDDWKATRVGINIFTRLRTQKEQLLASLALITQQD-LAPQQRAPQQRSSPSEGLCPPGH HISEDGRD-CISCKYQGQDYSTHWNDDLLFCLRCTRCD-GEVELSPCTTTRNTV CQCEEGTFREEDSPEMCRKCRGTGCPGRM-VKVGDCPTWSDIECVHKESGT KHS-GEAPAVEETVTSSPGTPAS (SEQ ID NO: 92).

Human/mouse chimera #4 was prepared by amplifying a region of mature human TR-2 corresponding to amino acids 1-66 using the forward primer GTAAGCAAGCTTG-GCTCTGATCACCAACAAGA (SEQ ID NO: 145) and the reverse primer TCGGGTTTCTACGACTTTATCTTCCT-TACACCTGG TGCAGCGCAAG (SEQ ID NO: 174), and amplifying a region of mature human TR-2 corresponding to amino acids 76-154 using the forward primer AAGGAAGATAAAGTCGTAGAAACCCGATGCACCAC-GACCAGAAAC AC (SEQ ID NO: 175) and the reverse primer GATTGAGGATCCCTAAGAGGCA GGAGTC-CCTGG (SEQ ID NO: 176). The above primers include nucleotides encoding mouse TR-2 corresponding to amino acids 67-75. Overlapping PCR of the human and mouse TR-2 fragments was performed using the forward primer for the human TR-2 amino acids 1-66 fragment, above (SEQ ID NO: 145) and the reverse primer for the human TR-2 amino acids 76-154 fragment, above (SEQ ID NO: 176). The amino acid sequence for human/mouse TR-2 #4 was MVHATSPLLLLLLSLALVAPGL SARKCSLTGKWT-NDLSNMTIGAVNSKGEFTGTYT-TAVTATSNEIKESPLHG TQNTINKRTQPTFGFTVN-WKFSESTTVFTGQCIFDRNGKEVLKTMWLLRSS VNDIGDDWKATRVGINIFTRLRTQKEQL-LASLALITQQDLAPQQRMPQQR SSPSEGLCPPGH-HISEDGRDCISCKYQGQDYSTHSNHS-LCLRCTRCD-SGEVELSPCTTTRNTVCQCEEGTFREED-SPEMCRKCRGTGCPGRMVKVGDCPT WSDIECVHKES-GTKHSGEAPAVEETVTSSPGTPAS (SEQ ID NO: 93).

Expression of avidin fusion proteins was performed by transient transfection of human 293 T adherent cells in vented T75 tissue culture flasks. Cells were grown and maintained in DMEM with 10 % dialyzed FBS and 1 × pen-step-glutamine at 37° C. with 5 % CO₂. To prepare for transfection, approximately 3×10⁶ 293 T cells were inoculated into each of a series of clean T75 flasks containing 15 ml growth medium, and all of the flasks were grown overnight for approximately 20 hours. Each of the pCEP4 -Avidin(N)-TR-2 constructs were transfected into different cells as follows. 15 µg DNA was mixed with 75 µL Lipofectamine 2000 (Invitrogen) in the presence of Opti-MEM medium (Invitrogen) to form a DNA-

Lipofectamine complex. The complex was incubated for 20 minutes. During that incubation period, the growth medium was aspirated from the T75 flasks and replaced with 15 mL Opti-MEM. Following incubation, each transfection complex was inoculated into a different flask and incubated at 37° C. for 4 to 5 hours. At the end of the incubation period, the Opti-MEM medium in each flask was replaced with fresh growth medium. Approximately 48 hours post-transfection, the conditioned media was harvested and transferred to 50 ml tubes (Falcon). The tubes were centrifuged at 2000 ×g for 10 minutes at 4° C. to remove cells and debris, and subsequently transferred to a clean 50 mL tube. A control flask lacking transfected DNA was also made following the same protocol, yielding negative control conditioned media for binding experiments.

The concentration of each N-avidin-TR-2 fusion protein was determined using a quantitative FACS-based assay. The avidin fusion proteins were captured on 6.7 µm biotin polystyrene beads (Spherotech, Inc.). Two samples were prepared for each fusion protein: 5 µL (approximately 3.5×10⁵) bead suspension plus 20 µL of 1× conditioned media, and 5 µL bead suspension plus 200 µL of 1× conditioned media. All samples were incubated for 1 hour at room temperature with rotation. Conditioned media was removed from each sample by centrifugation and washing with PBS containing 0.5 % BSA (BPBS). The avidin beads were stained with 200 µL of a 0.5 µg/mL solution of a goat FITC-labeled anti-avidin antibody (Vector Labs, Burlingame, Calif.) in BPBS. The reaction was allowed to proceed at room temperature for 45 minutes with the reaction tubes covered by foil. Following incubation, the beads were collected again by centrifugation and washing with BPBS, and resuspended for analysis in 0.5 ml BPBS. The FITC fluorescence was detected using a FAC-Scan (Becton Dickinson Bioscience). The signal was converted to protein mass using a standard curve derived with recombinant avidin.

The binding of two human anti-TR-2 antibodies to each of the human TR-2 truncations, to human TR-2, and to TR-2 from cynomolgus monkey was assessed. The binding assay was performed as follows. Biotin beads, described above, were loaded with approximately 100 ng of one of the N-Avidin TR-2 fusion proteins per 3.5×10⁵ beads and brought to volume with growth medium. The beads were mixed with 1 µg of FITC-conjugated human anti-TR-2 monoclonal antibody in 0.2 mL BPBS. After incubation for 1 hour at room temperature, 3 mL BPBS was added and the antibody-bead complexes were collected by centrifugation for 5 minutes at 750 ×g. The pellet was washed in 3 mL BPBS. The antibody bound to the avidin-bead complexes was detected by FACS analysis. The mean fluorescent intensity was recorded for each sample. Binding of those antibodies to conditioned media lacking TR-2 was used as a negative control ("Neg CM"). The results are shown in FIG. 24.

The observed binding patterns of the two antibodies were similar. The strongest observed binding was to the positive control, human TR-2, with an average fluorescent intensity of 7349. Observed binding of the antibodies (as measured in fluorescent intensity) to truncation TR-2-2 was 6561-6693, to truncations TR-2-3 and TR-2-5 was 3158-3866, to truncation TR-2-6 was 1959-2202, and to truncation TR-2-1 was 662-759. Binding of the antibodies to full-length TR-2 from cynomolgus monkey (as measured in fluorescent intensity) was 666-764. The antibodies did not bind to mouse or rat TR-2, or to truncations TR-2-4, TR-2-7, TR-2-9, TR-2-10, TR-2-11, TR-2-12, or TR-2-13, as determined by the fact that the binding was similar to the background for the experiment.

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TR-2-1 is a C-terminal truncation of TR-2 after amino acid 43, and TR-2-2, -3, -5, and -6 all include at least amino acids 16 to 85. Binding occurred when the entire region from amino acids 1 to 85 was present (see results for TR-2-2). The addition of amino acids 86 to 126 decreased binding by approximately two-fold (compare results for TR-2-2 to TR-2-3). The absence of amino acids 1 to 15 from the N-terminus of TR-2 in TR-2-2 decreased binding by approximately two-fold (compare results for TR-2-2 to TR-2-5). The simultaneous absence of amino acids 1 to 15 and the addition of amino acids 86 to 126 decreased binding by approximately three-fold (compare results for TR-2-2 to TR-2-6). Elimination of residues 44 to 85 (TR-2-1) reduced binding to about 11 % of that observed to TR-2-2. Those results indicate that one or more residues in the regions of amino acids 1 to 15 (SEQ ID NO: 94; ALITQQDLAPQQRAA) and 44 to 85 (SEQ ID NO: 95; CKYGGDYSTHWNDLL FCLRCTRCDSGEVE LSPCTTTRNTVCQ) are important for binding of those two human anti-TR-2 antibodies and human TR-2.

The binding of a human anti-TR-2 antibody to each of the cyno TR-2 truncations, to human/cyno chimeras, and to human TR-2 comprising certain mouse TR-2 domains was also assessed. The anti-TR-2 antibody bound strongly to full-length human TR-2 (fluorescent intensity ("FI") of 5681). The binding of the anti-TR-2 antibody to the full-length long version of cyno TR-2 was about five-fold reduced (FI of 1573) from that to full-length human TR-2. Only background levels of binding were observed to the full-length short version of cyno TR-2 (FI of 209) and to cyno TR-2 truncations 17-154 (FI of 51), cyno 1-85 (FI of 11), and cyno 17-85 (FI of 8).

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The binding of certain human anti-TR-2 antibodies to cyno/human TR-2 chimeras was also assessed (see FIG. 27). Observed binding (FI) of the antibodies to the four chimeras was as follows: cyno/human chimera #1; FI of 5977; cyno/human chimera #2; FI of 47; cyno/human chimera #3; FI of 12; cyno/human chimera #4; FI of 1507. As above, observed binding of the antibodies to full-length human TR-2 was 5681, while binding of the antibodies to full-length cyno TR-2 was 1573 (long form) and 209 (short form).

Because the antibody binding to cyno/human chimera #1 was similar to that to the truncation TR-2-5, replacement of amino acids 1-16 with the corresponding cyno sequence apparently did not affect antibody binding in the context of human amino acids 17-85. However, replacement of amino acids 1-16 with the corresponding cyno sequence in the context of the full-length human TR-2 (cyno/human #2) significantly abrogated binding, confirming that at least one amino acid in the region from 1-16 forms part of the epitope. Binding to cyno/human chimeras #3, and #4 was significantly attenuated from that to full-length human TR-2, suggesting that amino acids 17-85 of the human sequence are important for binding. Overall, one or more of the amino acids in the region of 1-85 of the human sequence (SEQ ID NO: 96; ALITQQDLAPQQRAAPQQ KRSSPSEGLCPPGHHISEDGRDCISCKYGGDYSTHWNDLLFCLRCTRCDSG EVELSPCTTTRNTVCQ) are involved in epitope binding. Similarly, replacement of various human sequences in the region of amino acids 1-85 with the corresponding mouse sequence significantly attenuates antibody binding (see FIG. 27), further confirming that one or more amino acids in that region are involved in epitope binding.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 204

<210> SEQ ID NO 1

<211> LENGTH: 363

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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tcctgcaagg cttctggata caccttcacc agttatgata tcaactgggt gcgacaggcc      120
actggacaag ggcttgagtg gatgggatgg atgaacccta acagtgataa cacaggctat      180
gcacagaagt tccagggcag agtcaccatg accaggaaca cctccataag cacagcctac      240
atggagttga gcagcctgag atctgaggac acggccgtgt attactgtgc gagatggaat      300
cactatgggt cggggagtc ttttgactac tggggccagg gaacctgtgt caccgtctcc      360
tca
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<210> SEQ ID NO 2

<211> LENGTH: 121

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
          20             25             30
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Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
 35 40 45

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

Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80

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

Ala Arg Trp Asn His Tyr Gly Ser Gly Ser His Phe Asp Tyr Trp Gly
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 3

<211> LENGTH: 360

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 3

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acctgcactg tctctggtgg ctccatcagc agtgggtggc actactggag ctggatccgc    120
cagcaccacg ggaagggcct ggagtggatt gggatcatct attacagtgg gagcacctac    180
tacaacccgt cctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc    240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattattg tgcgagagat    300
gacagcagtg gctggggttt tgactactgg ggccagggaa tcctgggtcac cgtctcctca    360

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<210> SEQ ID NO 4

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

Gly His Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
 65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
 85 90 95

Cys Ala Arg Asp Asp Ser Ser Gly Trp Gly Phe Asp Tyr Trp Gly Gln
 100 105 110

Gly Ile Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 5

<211> LENGTH: 360

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 5

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caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtggtggtc actactggag ctggatccgc	120
cagcaccag ggaagggcct ggagtggatt gggtagatct attacagtgg gagcgccctac	180
tacaaccgct cctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat	300
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<210> SEQ ID NO 6
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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

<210> SEQ ID NO 7
 <211> LENGTH: 360
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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cagcaccag ggaagggcct ggagtggatt gggtagatct attacagtgg gagcgccctac	180
tacaaccgct cctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc	240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat	300
gacagcagtg gctgggggtt tgactactgg ggccagggaa tcctgggtcac cgtctcctca	360

<210> SEQ ID NO 8
 <211> LENGTH: 120
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln	
1 5 10 15	
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly	
20 25 30	
Gly His Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu	

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35	40	45	
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Ala Tyr Tyr Asn Pro Ser			
50	55	60	
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe			
65	70	75	80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr			
85	90	95	
Cys Ala Arg Asp Asp Ser Ser Gly Trp Gly Phe Asp Tyr Trp Gly Gln			
100	105	110	
Gly Ile Leu Val Thr Val Ser Ser			
115	120		
<210> SEQ ID NO 9			
<211> LENGTH: 363			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 9			
caggtgcagc tgggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc			60
tcctgtgcag cctctggatt caccttcagt gactactaca tgaactggat ccgccaggct			120
ccaggaagg gactggagtg ggtttcacac attagtagta gtggtagtat cttagactac			180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcaactgtat			240
ctgcaaatga acagcctgag agtcgaggac acggccgtgt attactgtgc gagagatggg			300
gctgcagctg gtacggatgc ttttgatctc tggggccaag ggacaatggc caccgtctct			360
tca			363

<210> SEQ ID NO 10
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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

<210> SEQ ID NO 11
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagggagg	300
tatagcagct cgtctgggtg gtacttcgat ctctggggcc gtggcaccct ggtcactgtc	360
tcctca	366

<210> SEQ ID NO 12
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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

<210> SEQ ID NO 13
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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acctgcactg tctctggtgg ctccatcagt aattactact ggagctggat ccggcagccc	120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caagtacaac	180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctaacct ctgtgaccac tgcggacacg gccgtgtatt actgtgcgag agactcccct	300
cgtggattta gtggctacga ggccttttgac tcttggggcc agggaacct ggtcaccgtc	360
tcctca	366

<210> SEQ ID NO 14
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

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

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

<210> SEQ ID NO 15

<211> LENGTH: 360

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

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acctgcactg tctctggtgg ctccatcagc agtgataatt actactggag ctggatccgc      120
cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac      180
tacaaccctt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc      240
tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagga      300
gttaactgga actttctttt tgatatctgg ggccaaggga caatggtcac cgtctcttca      360
  
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<210> SEQ ID NO 16

<211> LENGTH: 120

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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

<210> SEQ ID NO 17

<211> LENGTH: 348

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 17

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ccagggaagg ggctggagtg ggtttcatatc attagtagaa gtggtagtac catatactac    180
gcagactctg tgaagggccg attcaccatc tccagggaca acgccaagaa ctcactgtat    240
ctgcaaatga acagcctgag agccgaggac acggccgtgt attactgtgc gagatcttta    300
ggcgggtatgg acgtctgggg ccaagggacc acggtcaccg tctcctca    348

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<210> SEQ ID NO 18

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
      20           25           30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35           40           45
Ser Tyr Ile Ser Arg Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val
      50           55           60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
      65           70           75           80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
      85           90           95
Ala Arg Ser Leu Gly Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val
      100          105          110
Thr Val Ser Ser
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<210> SEQ ID NO 19

<211> LENGTH: 387

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat    180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatagg    300
accgtatata gcaactcgtc acccttttac tactactact acggtatgga cgtctggggc    360
caagggaacca cggtcaccgt ctcctca    387

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<210> SEQ ID NO 20

<211> LENGTH: 129

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

```

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

```


-continued

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

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

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

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

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

Ala Arg Asp Arg Thr Val Tyr Ser Asn Ser Ser Pro Phe Tyr Tyr Tyr
 100 105 110

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

Ser

<210> SEQ ID NO 21
 <211> LENGTH: 387
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```

caggtgcagc tggtaggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc      60
tcctgtgcag cgtctggatt caccttcagt acctatggca tgcactgggt ccgccaggct      120
ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatga acagcctgag agccgaggac acggtctgtg attattgtgc gagagatagg      300
accgtatata gcagctcgtc acccttttac tactactact acggtatgga cgtctggggc      360
caagggacca cggtcaccgt ctctctca                                         387

```

<210> SEQ ID NO 22
 <211> LENGTH: 129
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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

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

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

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

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

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

Ala Arg Asp Arg Thr Val Tyr Ser Ser Ser Ser Pro Phe Tyr Tyr Tyr
 100 105 110

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

Ser

-continued

<210> SEQ ID NO 23
 <211> LENGTH: 357
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

```
cagggtgcagc tacagcagtg gggcgcacga ctgttgaagc ctcggagac cctgtccctc    60
acctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc    120
ccagggaagg ggctggagtg gattggggaa atcaatcata gtggaagcac caactacaac    180
ccgtccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg    240
aagctgaggt ctgtgaccgc cgcggacacg gctgtgtatt actgtgagag agggggaagc    300
agtggctact ggtacttcga tctctggggc cgtggcaccc tggctactgt ctctca      357
```

<210> SEQ ID NO 24
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

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

<210> SEQ ID NO 25
 <211> LENGTH: 363
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

```
gagggtgcagg tggtggagtc tgggggaggc ctggtcaagc ctggggggtc cctgagactc    60
tcctgtgcag cctctggatt caccttcagt agctatagca tgaactgggt ccgccaggct    120
ccagggaagg ggctggagtg ggtctcatcc attagtagta gtagtagtta catatactac    180
gcagactcag tgaagggccg attcaccatc tccagagaca acgccaagaa ctactgtat    240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagggggggc    300
agcagctggt acggggactg gttcgacccc tggggccagg gaacctggt caccgtctcc    360
tca                                              363
```

<210> SEQ ID NO 26
 <211> LENGTH: 121
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 26

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

<210> SEQ ID NO 27

<211> LENGTH: 378

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

cagctgggtgg agtctggggg aggcgtgggc cagcctggga ggccctgag actctcctgt 60
 gcagcgtctg gattcacctt cagtagctat ggcatgcact gggtccgcca ggctccaggc 120
 aaggggctgg agtgggtggc agttatatgg tatgatggaa gaaataaata ctatgcagac 180
 tccgtgaagg gccgattcac catctccaga gacaattcca agaacacgct gtatctgcaa 240
 atgaacagcc tgagagccga ggacacggct gtgtattact gtgcgagaga agtgggatat 300
 tgtactaatg gtgtatgctc ctactactac tacggtatgg acgtctgggg ccaagggacc 360
 acggtcaccg tctcctca 378

<210> SEQ ID NO 28

<211> LENGTH: 126

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

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

-continued

115	120	125	
<210> SEQ ID NO 29			
<211> LENGTH: 366			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 29			
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc			60
acctgcactg tctctggtgg ctccatcagc agtgggtgatt acttctggag ctggatccgc			120
cagctcccag ggaagggcct ggagtgcatt gggcacatcc ataacagtgg gaccacctac			180
tacaatccgt cctcaagag tcgagttacc atatcagtag acacgtctaa gaagcagttc			240
tccttgaggc tgagttctgt gactgccgcg gacacggccg tatattactg tgcgagagat			300
cgagggggtg actactacta tggatatggac gtctggggcc aagggaccac ggtcaccgtc			360
tcctca			366

<210> SEQ ID NO 30
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 30

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

<210> SEQ ID NO 31
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 31

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagc agtgggtggtt actactggag ctggatccgc	120
cagcaccag ggaagggcct ggagtggatt gggtagatct attacagtgg gagcacctac	180
tgcaaccctg cctcaagag tcgagttacc atatcagtcg acacgtctaa gaaccagttc	240
tcctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagac	300
aatggttcgg ggagttatga ctggttcgac cctgggggcc agggaatcct ggtcaccgtc	360
tcctca	366

-continued

<210> SEQ ID NO 32
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

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

<210> SEQ ID NO 33
 <211> LENGTH: 366
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

```
caggtgcaga tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc      60
acctgcactg tctctggtgg ctccatcagc agtgggtgatt actactggag ctggatccgc      120
cagcaccagc ggaagaacct ggagtggtatt gggtagatct attacagtgg gagcacctac      180
tacaaccctg ccctcaagag tctgagttacc atatcagtag acacgtctaa gaaccagttc      240
tccttgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagac      300
aatggttcgg ggagttatga ctgggttcgac ccttggggcc agggaacctt ggtaaccgtc      360
tcctca                                           366
```

<210> SEQ ID NO 34
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

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

-continued

Cys Ala Arg Asp Asn Gly Ser Gly Ser Tyr Asp Trp Phe Asp Pro Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
 115 120

<210> SEQ ID NO 35

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggcaagtca gagcattagc atttatttaa attggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctatgct gcattccagtt tgcaaagtgg ggtcccatta      180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct      240
gaagatattg caacttacta ctgtcaacag agttacaaaa ccccgctcac ttctggcgga      300
gggaccaagg tggagatcaa a                                              321
```

<210> SEQ ID NO 36

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

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

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

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

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

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

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

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 37

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

```
gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgttgaga cagagtcacc      60
atcacttgcc gggcaagtca gggccttaga aatgatttag gctgggttca gcagaaacca      120
gggaaagtca ctaagcgctt gatctatgct gcattccagtt tgcaaagagg ggtcccatta      180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct      240
gaagattttg caacttatta ctgtctacag cattatagtt tcccgtaggac gttcgcccaa      300
gggaccaagg tggagatcaa a                                              321
```

<210> SEQ ID NO 38

<211> LENGTH: 107

<212> TYPE: PRT

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

```

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

```

<210> SEQ ID NO 39

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

```

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgttgagaga cagagtcacc      60
atcacttgcc gggcaagtca gggccttaga aatgatttag gctgggttca gcagaaacca      120
gggaaagccc ctaagcgct gatctatgct gcatccagtt tgcaaagagg ggtcccatca      180
aggttcagcg gcagtgatc tgggacagaa ttcactctca caatcagcag cctgcagcct      240
gaagatttta caacttattt ctgtctacag cataatagtt tcccgaggac gttcggccaa      300
gggaccaagg tggaaatcaa a                                     321

```

<210> SEQ ID NO 40

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

```

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

```

<210> SEQ ID NO 41

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

-continued

<400> SEQUENCE: 41

```

gacatccaga tgaccacgac tccatcctcc ctgtctgcat ctgttgagaga cagagtcacc      60
atcacttgcc gggcaagtca gggccttaga aatgatttag gctgggttca gcagaaacca      120
gggaaagccc ctaagcgccct gatctatgct gcatccagtt tgcaaagagg ggtcccatca      180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct      240
gaagatttta caacttattt ctgtctacag cataaatagtt tcccgtggac gttcggccaa      300
gggaccaagg tggaatcaa a                                                    321

```

<210> SEQ ID NO 42

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

```

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

```

<210> SEQ ID NO 43

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

```

gacatccaga tgaccacgac tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc ggtcaagtca gacatttagt aactatataa attggtatca acagagacca      120
gggaaagccc cgaacctcct gatccatgat gtatccagtt tccaaagtgc ggtcccatca      180
aggttcagtc gcagtggatc tgggacagtt ttcactctca ccacagcag tctgcaacct      240
gaagattttg caacttactt ctgtcaacag acttacatta cccattcac tttcggccct      300
gggaccaaag tggatatcaa a                                                    321

```

<210> SEQ ID NO 44

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
  1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Gln Ser Ile Ser Asn Tyr
             20             25             30
Ile Asn Trp Tyr Gln Gln Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile

```


-continued

35	40	45	
His Asp Val Ser Ser Phe Gln Ser Ala Val Pro Ser Arg Phe Ser Arg			
50	55	60	
Ser Gly Ser Gly Thr Val Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro			
65	70	75	80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Thr Tyr Ile Thr Pro Phe			
	85	90	95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys			
100	105		
<210> SEQ ID NO 45			
<211> LENGTH: 321			
<212> TYPE: DNA			
<213> ORGANISM: Homo sapiens			
<400> SEQUENCE: 45			
gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc			60
atcacttgcc gggcgagtc gggcattagc aattatttag cctgggtatca gcagaaacca			120
gggaaagttc ctaagctcct gatctatgct gcatccactt tgcaatcagg ggtcccatct			180
cgggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct			240
gaagatgttg caacttatta ctgtcaaaag tataacagtg ccccgctcac ttctggcgga			300
gggaccaagg tggagatcaa a			321

<210> SEQ ID NO 46
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 46

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

<210> SEQ ID NO 47
 <211> LENGTH: 339
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 47

gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc			60
atcaactgca agtccagcca gagtgtttta tacaggtcca acaataagat ctacttagct			120
tggtaccagc agaaaccagg acagctcctc aagctgctca ttactgggc atcgaccgg			180
gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc			240

-continued

```
atcagcagcc tgctggctga agatgtggca gtttattact gtcagcaata ttatagtact 300
ccattcactt tcggccctgg gaccaaagtg gatatcaaa 339
```

```
<210> SEQ ID NO 48
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

```
<400> SEQUENCE: 48
```

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

```
Lys
```

```
<210> SEQ ID NO 49
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
```

```
<400> SEQUENCE: 49
```

```
gatattgtga tgactcagtc tccactctcc ctgcccgtea cccctggaga gccggcctcc 60
atctcctgca ggtctagtca gagectcctg cgtcgtaatg gatacaacta tttggattgg 120
tacctgcaga agccagggca gtctccacaa ctctgatctt atttgggttc taatcggggc 180
tccgggggtcc cagacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaagctct acaaactccg 300
ctcactttcg gcggaggggac cgagggtggag atcaaaa 336
```

```
<210> SEQ ID NO 50
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
```

```
<400> SEQUENCE: 50
```

```
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
  1             5             10             15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Arg Arg
          20             25             30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35             40             45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
          50             55             60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
          65             70             75             80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
```


-continued

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

```

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

```

<210> SEQ ID NO 55

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

```

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc      60
atcacttgcc gggcaagtc gagcattagc agctatttaa attggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctctgct acatccagtt ttcaaagtgg ggtcccatca      180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct      240
gaagattttg cagcttacta ctgtcaacag agttacagta ccccgctcac ttcggcgga      300
gggaccaagg tggagatcaa a                                     321

```

<210> SEQ ID NO 56

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

```

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

```

<210> SEQ ID NO 57

<211> LENGTH: 339

<212> TYPE: DNA

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

```

gacatcgtga tgaccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc      60
atcaactgca agtccagcca gagtgtttta cacagctcca acaataagaa ttatttagtt      120
tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccggt      180
gaatccgggg tccctgaccg attcagtggtc agcgggtctg ggacagattt cactctcacc      240
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtact      300
cctctcactt tcggcggagg gaccaaggtg gagatcaaa                               339

```

<210> SEQ ID NO 58

<211> LENGTH: 113

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

```

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

```

Lys

<210> SEQ ID NO 59

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

```

gacatccaga tgaccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc      60
atcacttgtc gggcgagtc ggggtattagc agctgggttag tctgggtatca gcagaaacca      120
gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca      180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct      240
gaagattttg caacttacta ttgtcagcag gctaacagtt tccctttcac ttctggcgga      300
gggaccaagg tggagatcaa a                               321

```

<210> SEQ ID NO 60

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
  1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp

```

-continued

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

<210> SEQ ID NO 61
 <211> LENGTH: 321
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 61

gacatccaga tgaccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgtc gggcgagtc gggcattagc aattatttag cctgggttca gcagaaacca	120
gggaaagccc ctaagtcct gatctatgct gcaccagtt tgcaaagtgg ggtcccatca	180
aaattcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct	240
gaagattttg caacttatta ctgccaacag tataatagtt accctctcac ttctggcgga	300
gggaccaagg tggagatcaa a	321

<210> SEQ ID NO 62
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	
1	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Asn Tyr	
20	30
Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile	
35	45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly	
50	60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	
65	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu	
85	95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys	
100	105

<210> SEQ ID NO 63
 <211> LENGTH: 324
 <212> TYPE: DNA
 <213> ORGANISM: Homo sapiens
 <400> SEQUENCE: 63

gaaattgtgt tgacgcagtc tccaggcacc ctgtcttgt ctccaggga aagagccacc	60
ctctcctgca gggccagtc gggattagt agaagctact tagcctggta ccagcagaaa	120
cctggccagg ctcccagcct cctcatctat ggtgcatcca gcagggccac tggcatccca	180

-continued

```

gacagggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
cctgaagatt ttgcagtgtta ttactgtcaa caatttggtta gttcacctgtg gacgttcggc 300
caagggacca aggtggaaat caaa 324

```

```

<210> SEQ ID NO 64
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 64

```

```

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

```

```

<210> SEQ ID NO 65
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 65

```

```

gacattcaga tgacccagtc tccatcctcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtc ggggtattagc agctggtagg cctgggtatca gcagaaacca 120
gggaaagccc caaagttcct gatctttggt gcatccagtt tccaaagtgg ggtcccatca 180
aggttcacgc gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacag gctaacagtt tccctcggac gttcggccaa 300
gggaccaagg tggaaatcaa a 321

```

```

<210> SEQ ID NO 66
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

```

```

<400> SEQUENCE: 66

```

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
 20             25             30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
 35             40             45
Phe Val Ala Ser Ser Phe Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65             70             75             80

```

-continued

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

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

<210> SEQ ID NO 67

<211> LENGTH: 321

<212> TYPE: DNA

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgttgaga cagagtcacc 60
 atcacttgtc gggcgagtc ggggtattagc agctggtagc cctggtagc gcagaaacca 120
 gggaaagccc ctaagttcct gatctttgtt gcacccagtt tgcaaagtgg ggtcccatca 180
 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
 gaagattttg caacttacta ttgtcaacag gctaacagtt tccctcggac gttcggccaa 300
 gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 68

<211> LENGTH: 107

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

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

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

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

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

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

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

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

<210> SEQ ID NO 69

<211> LENGTH: 312

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 69

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile

-continued

65	70	75	80
Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe	85	90	95
Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn	100	105	110
Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn	115	120	125
Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe	130	135	140
Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu	145	150	155
Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln	165	170	175
Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile	180	185	190
Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr	195	200	205
Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys	210	215	220
Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr	225	230	235
Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu	245	250	255
Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val	260	265	270
Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser	275	280	285
Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val Thr	290	295	300
Ser Ser Pro Gly Thr Pro Ala Ser	305	310	

<210> SEQ ID NO 70

<211> LENGTH: 201

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 70

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

-continued

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
 145 150 155 160

Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
 165 170 175

Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
 180 185 190

Ser Glu Asp Gly Arg Asp Cys Ile Ser
 195 200

<210> SEQ ID NO 71
 <211> LENGTH: 243
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 71

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65 70 75 80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85 90 95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
 145 150 155 160

Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
 165 170 175

Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
 180 185 190

Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
 195 200 205

Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys
 210 215 220

Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr
 225 230 235 240

Val Cys Gln

<210> SEQ ID NO 72
 <211> LENGTH: 284

-continued

<212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 72

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
  35             40             45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
  50             55             60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
  65             70             75             80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
      85             90             95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
  100            105            110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
  115            120            125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
  130            135            140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
  145            150            155            160

Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
  165            170            175

Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
  180            185            190

Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
  195            200            205

Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys
  210            215            220

Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr
  225            230            235            240

Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu
  245            250            255

Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val
  260            265            270

Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val
  275            280

```

<210> SEQ ID NO 73
 <211> LENGTH: 186
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 73

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

```

-continued

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

<210> SEQ ID NO 74
 <211> LENGTH: 228
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 74

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

-continued

Cys Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn
 210 215 220

Thr Val Cys Gln
 225

<210> SEQ ID NO 75
 <211> LENGTH: 269
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 75

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65 70 75 80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85 90 95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Pro Gln
 145 150 155 160

Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His
 165 170 175

Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp
 180 185 190

Tyr Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg
 195 200 205

Cys Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn
 210 215 220

Thr Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro
 225 230 235 240

Glu Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys
 245 250 255

Val Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val
 260 265

<210> SEQ ID NO 76
 <211> LENGTH: 202
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 76

-continued

```

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

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<210> SEQ ID NO 77
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide sequence

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<400> SEQUENCE: 77

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Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1           5           10           15
Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
  20           25           30
Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
  35           40           45
Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
  50           55           60
Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
  65           70           75           80
Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
  85           90           95
Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
  100          105          110
Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
  115          120          125
Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
  130          135          140
Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ile Ser

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145	150	155	160
Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe	165	170	175
Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro	180	185	190
Cys Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe	195	200	205
Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys	210	215	220
Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile	225	230	235
			240

Glu Cys Val

<210> SEQ ID NO 78
 <211> LENGTH: 228
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 78

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu	1	5	10	15
Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly	20	25	30	
Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn	35	40	45	
Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr	50	55	60	
Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile	65	70	75	80
Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe	85	90	95	
Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn	100	105	110	
Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn	115	120	125	
Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe	130	135	140	
Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Gln Cys	145	150	155	160
Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys	165	170	175	
Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr	180	185	190	
Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser Gly Thr Lys His	195	200	205	
Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val Thr Ser Ser Pro Gly	210	215	220	
Thr Pro Ala Ser	225			

<210> SEQ ID NO 79
 <211> LENGTH: 271
 <212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 79

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1           5           10           15
Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
 20           25           30
Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35           40           45
Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50           55           60
Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65           70           75           80
Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85           90           95
Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
100          105          110
Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
115          120          125
Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
130          135          140
Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ile Ser
145          150          155          160
Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe
165          170          175
Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro
180          185          190
Cys Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe
195          200          205
Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys
210          215          220
Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile
225          230          235          240
Glu Cys Val His Lys Glu Ser Gly Thr Lys His Ser Gly Glu Ala Pro
245          250          255
Ala Val Glu Glu Thr Val Thr Ser Ser Pro Gly Thr Pro Ala Ser
260          265          270

```

<210> SEQ ID NO 80

<211> LENGTH: 209

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 80

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1           5           10           15
Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
 20           25           30
Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35           40           45
Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr

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

Cys

<210> SEQ ID NO 81
 <211> LENGTH: 217
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 81

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

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195	200	205
Cys Asp Ser Gly Glu Val	Glu Leu Ser	
210	215	
<210> SEQ ID NO 82		
<211> LENGTH: 290		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence		
<400> SEQUENCE: 82		
Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Ser Leu		
1 5 10 15		
Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly		
20 25 30		
Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn		
35 40 45		
Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr		
50 55 60		
Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile		
65 70 75 80		
Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe		
85 90 95		
Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn		
100 105 110		
Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn		
115 120 125		
Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe		
130 135 140		
Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Pro		
145 150 155 160		
Ile Thr Arg Gln Ser Leu Asp Pro Gln Arg Arg Ala Ala Pro Gln Gln		
165 170 175		
Lys Arg Ser Ser Pro Thr Glu Gly Leu Cys Pro Pro Gly His His Ile		
180 185 190		
Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr		
195 200 205		
Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr Lys Cys		
210 215 220		
Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Arg Asn Thr		
225 230 235 240		
Val Cys Gln Cys Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu		
245 250 255		
Ile Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val		
260 265 270		
Lys Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Pro Gln Arg Arg Ile		
275 280 285		
Gln Thr		
290		
<210> SEQ ID NO 83		
<211> LENGTH: 312		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 83

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
  35             40             45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
  50             55             60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
  65             70             75             80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
      85             90             95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
  100            105            110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
  115            120            125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
  130            135            140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Pro
  145            150            155            160

Ile Thr Arg Gln Ser Leu Asp Pro Gln Arg Arg Ala Ala Pro Gln Gln
      165            170            175

Lys Arg Ser Ser Pro Thr Glu Gly Leu Cys Pro Pro Gly His His Ile
  180            185            190

Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
  195            200            205

Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr Lys Cys
  210            215            220

Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Thr Arg Asn Thr
  225            230            235            240

Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu
      245            250            255

Ile Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val
  260            265            270

Lys Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser
  275            280            285

Gly Thr Lys His Thr Gly Glu Val Pro Ala Val Glu Lys Thr Val Thr
  290            295            300

Thr Ser Pro Gly Thr Pro Ala Ser
  305            310

```

<210> SEQ ID NO 84

<211> LENGTH: 243

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 84

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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Ala	Leu	Val	Ala	Pro	Gly	Leu	Ser	Ala	Arg	Lys	Cys	Ser	Leu	Thr	Gly
			20					25					30		
Lys	Trp	Thr	Asn	Asp	Leu	Gly	Ser	Asn	Met	Thr	Ile	Gly	Ala	Val	Asn
		35					40					45			
Ser	Lys	Gly	Glu	Phe	Thr	Gly	Thr	Tyr	Thr	Thr	Ala	Val	Thr	Ala	Thr
		50				55					60				
Ser	Asn	Glu	Ile	Lys	Glu	Ser	Pro	Leu	His	Gly	Thr	Gln	Asn	Thr	Ile
		65			70					75					80
Asn	Lys	Arg	Thr	Gln	Pro	Thr	Phe	Gly	Phe	Thr	Val	Asn	Trp	Lys	Phe
				85					90					95	
Ser	Glu	Ser	Thr	Thr	Val	Phe	Thr	Gly	Gln	Cys	Phe	Ile	Asp	Arg	Asn
			100					105					110		
Gly	Lys	Glu	Val	Leu	Lys	Thr	Met	Trp	Leu	Leu	Arg	Ser	Ser	Val	Asn
		115					120					125			
Asp	Ile	Gly	Asp	Asp	Trp	Lys	Ala	Thr	Arg	Val	Gly	Ile	Asn	Ile	Phe
		130				135					140				
Thr	Arg	Leu	Arg	Thr	Gln	Lys	Glu	Gln	Leu	Leu	Ala	Ser	Leu	Ala	Pro
		145			150						155				160
Ile	Thr	Arg	Gln	Ser	Leu	Asp	Pro	Gln	Arg	Arg	Ala	Ala	Pro	Gln	Gln
			165					170						175	
Lys	Arg	Ser	Ser	Pro	Thr	Glu	Gly	Leu	Cys	Pro	Pro	Gly	His	His	Ile
			180					185					190		
Ser	Glu	Asp	Ser	Arg	Asp	Cys	Ile	Ser	Cys	Lys	Tyr	Gly	Gln	Asp	Tyr
		195				200						205			
Ser	Thr	His	Trp	Asn	Asp	Phe	Leu	Phe	Cys	Leu	Arg	Cys	Thr	Lys	Cys
		210				215					220				
Asp	Ser	Gly	Glu	Val	Glu	Val	Ser	Ser	Cys	Thr	Thr	Thr	Arg	Asn	Thr
		225			230					235				240	

Val Cys Gln

<210> SEQ ID NO 85
 <211> LENGTH: 228
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 85

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

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Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140
 Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Pro Gln
 145 150 155 160
 Gln Lys Arg Ser Ser Pro Ile Glu Gly Leu Cys Pro Pro Gly His His
 165 170 175
 Ile Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp
 180 185 190
 Tyr Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr Lys
 195 200 205
 Cys Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Thr Arg Asn
 210 215 220
 Thr Val Cys Gln
 225

<210> SEQ ID NO 86
 <211> LENGTH: 243
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 86

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15
 Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
 20 25 30
 Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45
 Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60
 Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65 70 75 80
 Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85 90 95
 Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110
 Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125
 Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140
 Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Pro
 145 150 155 160
 Ile Thr Arg Gln Ser Leu Asp Pro Gln Arg Arg Ala Ala Pro Gln Gln
 165 170 175
 Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
 180 185 190
 Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
 195 200 205
 Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys
 210 215 220
 Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr
 225 230 235 240
 Val Cys Gln

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<210> SEQ ID NO 87
<211> LENGTH: 312
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide sequence

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<400> SEQUENCE: 87

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```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
      35             40             45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
      50             55             60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
      65             70             75             80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
      85             90             95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
      100            105            110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
      115            120            125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
      130            135            140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Pro
      145            150            155            160

Ile Thr Arg Gln Ser Leu Asp Pro Gln Arg Arg Ala Ala Pro Gln Gln
      165            170            175

Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
      180            185            190

Ser Glu Asp Gly Arg Asp Tyr Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
      195            200            205

Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys
      210            215            220

Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr
      225            230            235            240

Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu
      245            250            255

Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val
      260            265            270

Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser
      275            280            285

Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val Thr
      290            295            300

Ser Ser Pro Gly Thr Pro Ala Ser
      305            310

```

```

<210> SEQ ID NO 88
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide sequence

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<400> SEQUENCE: 88

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
  35             40             45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
  50             55             60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
  65             70             75             80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
  85             90             95

Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100             105             110

Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115             120             125

Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130             135             140

Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
 145             150             155             160

Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
 165             170             175

Lys Arg Ser Ser Pro Thr Glu Gly Leu Cys Pro Pro Gly His His Ile
 180             185             190

Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
 195             200             205

Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr Lys Cys
 210             215             220

Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Thr Arg Asn Thr
 225             230             235             240

Val Cys Gln

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<210> SEQ ID NO 89

<211> LENGTH: 312

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 89

```

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
  1             5             10             15

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

Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
  35             40             45

Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
  50             55             60

Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
  65             70             75             80

Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
  85             90             95

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Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110
 Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125
 Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140
 Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
 145 150 155 160
 Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
 165 170 175
 Lys Arg Ser Ser Pro Thr Glu Gly Leu Cys Pro Pro Gly His His Ile
 180 185 190
 Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
 195 200 205
 Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr Lys Cys
 210 215 220
 Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Thr Arg Asn Thr
 225 230 235 240
 Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu
 245 250 255
 Ile Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val
 260 265 270
 Lys Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser
 275 280 285
 Gly Thr Lys His Thr Gly Glu Val Pro Ala Val Glu Lys Thr Val Thr
 290 295 300
 Thr Ser Pro Gly Thr Pro Ala Ser
 305 310

<210> SEQ ID NO 90
 <211> LENGTH: 311
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 90

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15
 Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
 20 25 30
 Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45
 Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60
 Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65 70 75 80
 Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85 90 95
 Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110
 Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125
 Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140

-continued

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

<210> SEQ ID NO 91
 <211> LENGTH: 312
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 91

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

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180	185	190
Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr		
195	200	205
Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr Arg Cys		
210	215	220
Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr		
225	230	235
Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu		
245	250	255
Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val		
260	265	270
Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser		
275	280	285
Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val Thr		
290	295	300
Ser Ser Pro Gly Thr Pro Ala Ser		
305	310	

<210> SEQ ID NO 92

<211> LENGTH: 312

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide sequence

<400> SEQUENCE: 92

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

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Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn Thr
 225 230 235 240
 Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro Glu
 245 250 255
 Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys Val
 260 265 270
 Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu Ser
 275 280 285
 Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val Thr
 290 295 300
 Ser Ser Pro Gly Thr Pro Ala Ser
 305 310

<210> SEQ ID NO 93
 <211> LENGTH: 313
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide sequence

<400> SEQUENCE: 93

Met Val His Ala Thr Ser Pro Leu Leu Leu Leu Leu Leu Ser Leu
 1 5 10 15
 Ala Leu Val Ala Pro Gly Leu Ser Ala Arg Lys Cys Ser Leu Thr Gly
 20 25 30
 Lys Trp Thr Asn Asp Leu Gly Ser Asn Met Thr Ile Gly Ala Val Asn
 35 40 45
 Ser Lys Gly Glu Phe Thr Gly Thr Tyr Thr Thr Ala Val Thr Ala Thr
 50 55 60
 Ser Asn Glu Ile Lys Glu Ser Pro Leu His Gly Thr Gln Asn Thr Ile
 65 70 75 80
 Asn Lys Arg Thr Gln Pro Thr Phe Gly Phe Thr Val Asn Trp Lys Phe
 85 90 95
 Ser Glu Ser Thr Thr Val Phe Thr Gly Gln Cys Phe Ile Asp Arg Asn
 100 105 110
 Gly Lys Glu Val Leu Lys Thr Met Trp Leu Leu Arg Ser Ser Val Asn
 115 120 125
 Asp Ile Gly Asp Asp Trp Lys Ala Thr Arg Val Gly Ile Asn Ile Phe
 130 135 140
 Thr Arg Leu Arg Thr Gln Lys Glu Gln Leu Leu Ala Ser Leu Ala Leu
 145 150 155 160
 Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro Gln Gln
 165 170 175
 Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His His Ile
 180 185 190
 Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln Asp Tyr
 195 200 205
 Ser Thr His Ser Asn His Ser Leu Asp Ser Cys Leu Arg Cys Thr Arg
 210 215 220
 Cys Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg Asn
 225 230 235 240
 Thr Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser Pro
 245 250 255
 Glu Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val Lys
 260 265 270

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Val Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys Glu
275 280 285

Ser Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr Val
290 295 300

Thr Ser Ser Pro Gly Thr Pro Ala Ser
305 310

<210> SEQ ID NO 94
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala
1 5 10 15

<210> SEQ ID NO 95
<211> LENGTH: 42
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe
1 5 10 15

Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro
20 25 30

Cys Thr Thr Thr Arg Asn Thr Val Cys Gln
35 40

<210> SEQ ID NO 96
<211> LENGTH: 85
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro
1 5 10 15

Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His
20 25 30

His Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln
35 40 45

Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr
50 55 60

Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg
65 70 75 80

Asn Thr Val Cys Gln
85

<210> SEQ ID NO 97
<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 97

gtaggtgctg tcct

14

<210> SEQ ID NO 98

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<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 98

tgagttccac gaca 14

<210> SEQ ID NO 99
<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 99

cttccaagcc act 13

<210> SEQ ID NO 100
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 100

cargcactgt ca 12

<210> SEQ ID NO 101
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 101

gtaggtgctg tccttgct 18

<210> SEQ ID NO 102
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 102

ctctgtgaca ctctctggg a 21

<210> SEQ ID NO 103
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 103

gctctagatt ggagggcgtt atccaccttc cact 34

<210> SEQ ID NO 104
<211> LENGTH: 39

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 104

aactagctag cagttccaga ttccaactgc tcatcagat 39

<210> SEQ ID NO 105
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 105

gctcccggtt agaagtca 18

<210> SEQ ID NO 106
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 106

acyagtgtgg ccttgttggc tt 22

<210> SEQ ID NO 107
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 107

gctctagagg gygggaacag agtgac 26

<210> SEQ ID NO 108
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 108

acgacaccgt caccggtt 18

<210> SEQ ID NO 109
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 109

aagtagtcct tgaccaggca gccca 25

<210> SEQ ID NO 110
<211> LENGTH: 30
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 110

gctctagagg gtgccagggg gaagaccgat                               30

<210> SEQ ID NO 111
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 111

gctctagagc agggcgccag ggggaaga                               28

<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 112

atgaggstcc cygctcagct                                       20

<210> SEQ ID NO 113
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 113

atggaarccc cagckcagct t                                   21

<210> SEQ ID NO 114
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 114

atggtgttgc agaccaggt ct                                   22

<210> SEQ ID NO 115
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 115

gaagatctca ccatgaggst ccygctcag ctyct                     35

<210> SEQ ID NO 116
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 116
gaagatctca ccatggaarc cccagckcag cttctctt 38

<210> SEQ ID NO 117
<211> LENGTH: 38
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 117
gaagatctca ccatggtgtt gcagaccag gtcttcat 38

<210> SEQ ID NO 118
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 118
crtcwccacc atgrcmwg 18

<210> SEQ ID NO 119
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 119
caccatgrcc wgstyccct 19

<210> SEQ ID NO 120
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 120
accatggcct ggretcykct 20

<210> SEQ ID NO 121
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 121
caccatggcm tggrycvyt 19

<210> SEQ ID NO 122
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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

<400> SEQUENCE: 122

caccatggcy tggryccmay t                               21

<210> SEQ ID NO 123
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 123

gaagatctca ccatgrccwg styccctct                       29

<210> SEQ ID NO 124
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 124

gaagatctca ccatggcctg grtcykcts yt                     32

<210> SEQ ID NO 125
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 125

gaagatctca ccatggcmtg grycvytc                         30

<210> SEQ ID NO 126
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer

<400> SEQUENCE: 126

gaagatctca ccatggcyyt gryccmaytc                       30

<210> SEQ ID NO 127
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      primer
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (23)
<223> OTHER INFORMATION: a, c, g or t

<400> SEQUENCE: 127

caccatggas tggacctgga gvnctc                           25

<210> SEQ ID NO 128
<211> LENGTH: 28

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 128

caccatggac atactttggt ccacgctc                28

<210> SEQ ID NO 129
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 129

caccatggar ttkggretbh gct                      23

<210> SEQ ID NO 130
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 130

caccatgaar cayctgtggt tcttctctct             30

<210> SEQ ID NO 131
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 131

caccatgggg tcaaccgyca tcct                    24

<210> SEQ ID NO 132
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer

<400> SEQUENCE: 132

caccatgtct gtctccttcc tcatcttc                28

<210> SEQ ID NO 133
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        primer
<220> FEATURE:
<221> NAME/KEY: modified_base
<222> LOCATION: (30)
<223> OTHER INFORMATION: a, c, g or t

<400> SEQUENCE: 133

gaagatctca ccatggastg gacctggagv ntcc        34

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<210> SEQ ID NO 134
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 134

gaagatctca ccatggacat actttggtcc acgctcc 37

<210> SEQ ID NO 135
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 135

gaagatctca ccatggartt kggrrctbhgc tggvtttttc t 41

<210> SEQ ID NO 136
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 136

gaagatctca ccatgaarca yctgtgggtc ttcttyctc 39

<210> SEQ ID NO 137
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 137

gaagatctca ccatgggggtc aaccgycatc ct 32

<210> SEQ ID NO 138
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 138

gaagatctca ccatgtctgt ctcttctctc atcttct 37

<210> SEQ ID NO 139
<211> LENGTH: 44
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 139

gaagatctca ccatggactg gacctggagg atctctttct tggt 44

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<210> SEQ ID NO 140
 <211> LENGTH: 165
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 140

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

<210> SEQ ID NO 141
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Mus sp.

<400> SEQUENCE: 141

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

<210> SEQ ID NO 142
 <211> LENGTH: 122
 <212> TYPE: PRT
 <213> ORGANISM: Mus sp.

<400> SEQUENCE: 142

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

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<210> SEQ ID NO 143
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Mus sp.

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<400> SEQUENCE: 143

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

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<210> SEQ ID NO 144
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Mus sp.

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<400> SEQUENCE: 144

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Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val Gly
 1           5           10           15
Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Ser Ser Ala
      20           25           30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile
      35           40           45
Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Thr Gly
      50           55           60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Val Gln Ala
      65           70           75           80

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-continued

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

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

<210> SEQ ID NO 145

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 145

gtaagcaagc ttggctctga tcaccaaca aga 33

<210> SEQ ID NO 146

<211> LENGTH: 30

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 146

gattagggat ccagaggcag gagtccttg 30

<210> SEQ ID NO 147

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 147

tagttgggat cctcaggaga tgcaatctct accgt 35

<210> SEQ ID NO 148

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 148

ggtagtggat cctcactgac aactgtgtt tctgg 35

<210> SEQ ID NO 149

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 149

gtaatgggat cctcagacac attcgatgtc actcc 35

<210> SEQ ID NO 150

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

primer

<400> SEQUENCE: 150

gtaatgaagc ttgccacaac aaaagaggtc cag

33

<210> SEQ ID NO 151

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 151

gattgaaagc ttgatctcct gcaaatatgg acag

34

<210> SEQ ID NO 152

<211> LENGTH: 32

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 152

gtaatgaagc ttgcagtgcg aagaaggcac ct

32

<210> SEQ ID NO 153

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 153

gatggaggat cctcaacacc tggcgcagcg caag

34

<210> SEQ ID NO 154

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 154

gtaagtggat cctcagcagg gacttagctc cact

34

<210> SEQ ID NO 155

<211> LENGTH: 29

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 155

gttagtaagc ttggctccaa tcacccgac

29

<210> SEQ ID NO 156

<211> LENGTH: 31

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

<400> SEQUENCE: 156

gttgatggat ccttctttgt ggacactcga t

31

<210> SEQ ID NO 157

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 157

gtagttggat cctcaagaag caggagtccc aggg

34

<210> SEQ ID NO 158

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 158

gtatgagggga tcctcactga cacaccgtgt ttctgg

36

<210> SEQ ID NO 159

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 159

gtatggaagc tgccacaac aaaagagatc cagc

34

<210> SEQ ID NO 160

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 160

cagcgaagag cggctccaca aaaaaagagg tccag

35

<210> SEQ ID NO 161

<211> LENGTH: 35

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 161

ggatctcttt tgttgtgggg ccgctctctg ctggg

35

<210> SEQ ID NO 162

<211> LENGTH: 36

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

<400> SEQUENCE: 162

cagcagagag cggccccaca acaaaagaga tccagc

36

<210> SEQ ID NO 163

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 163

cagcggccgg aggagagccc ctgagaggga ttgt

34

<210> SEQ ID NO 164

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 164

gattgaggat ccctaagagg caggagtccc tgg

33

<210> SEQ ID NO 165

<211> LENGTH: 34

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 165

tgaatgaagc ttggttccag taacagctaa ccca

34

<210> SEQ ID NO 166

<211> LENGTH: 33

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 166

tccctctgag gggctctcct ccggccgctg tag

33

<210> SEQ ID NO 167

<211> LENGTH: 37

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 167

cagggtactgg cctgctagac acaatccctc tgagggg

37

<210> SEQ ID NO 168

<211> LENGTH: 39

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 168

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ctagcaggcc agtacctgtc agaagacggt agagattgc 39

<210> SEQ ID NO 169
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 169

cagggtactgg cctgctagac acaatccctc tgagggg 37

<210> SEQ ID NO 170
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 170

ctagcaggcc agtacctgtc agaagacggt agagattgc 39

<210> SEQ ID NO 171
<211> LENGTH: 41
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 171

tgaatccaga gaatgggttg agtgagtgc atagtcctgt c 41

<210> SEQ ID NO 172
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 172

tccaaccatt ctctggattc atgcttgcgc tgcaccagg 39

<210> SEQ ID NO 173
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 173

gattgaggat ccctaagagg caggagtccc tgg 33

<210> SEQ ID NO 174
<211> LENGTH: 46
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 174

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 tcgggtttct acgactttat cttccttaca cctggtgcag cgcaag 46

<210> SEQ ID NO 175
 <211> LENGTH: 47
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 primer

<400> SEQUENCE: 175

aaggaagata aagtcgtaga aacccgatgc accacgacca gaaacac 47

<210> SEQ ID NO 176
 <211> LENGTH: 33
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 primer

<400> SEQUENCE: 176

gattgaggat ccctaagagg caggagtccc tgg 33

<210> SEQ ID NO 177
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 177

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

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

 Asp Ile Asn Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
 35 40 45

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

 Gln Gly Arg Val Thr Met Thr Arg Asn Thr Ser Ile Ser Thr Ala Tyr
 65 70 75 80

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

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

 Val Thr Val Ser Ser Ala
 115

<210> SEQ ID NO 178
 <211> LENGTH: 118
 <212> TYPE: PRT
 <213> ORGANISM: Homo sapiens

<400> SEQUENCE: 178

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

 Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20 25 30

 Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35 40 45

 Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
 50 55 60

-continued

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Ser Ser Gly Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser Ala
115

<210> SEQ ID NO 179
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 179

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

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

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

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

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

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

Ala Arg Ala Ala Gly Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
100 105 110

Thr Val Ser Ser Ala
115

<210> SEQ ID NO 180
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 180

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

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

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

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

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

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

Ala Arg Tyr Ser Ser Ser Trp Tyr Phe Asp Leu Trp Gly Arg Gly Thr
100 105 110

Leu Val Thr Val Ser Ser Ala
115

<210> SEQ ID NO 181

-continued

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<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 181
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
 1             5             10             15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
      20             25             30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
      35             40             45
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
      50             55             60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
      65             70             75             80
Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
      85             90             95
Arg Gly Tyr Ser Gly Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
      100            105            110

Thr Val Ser Ser Ala
      115

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<210> SEQ ID NO 182
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 182
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1             5             10             15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
      20             25             30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
      35             40             45
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
      50             55             60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
      65             70             75             80
Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
      85             90             95
Cys Ala Arg Asn Trp Asn Phe Asp Ile Trp Gly Gln Gly Thr Met Val
      100            105            110

Thr Val Ser Ser Ala
      115

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<210> SEQ ID NO 183
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 183
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
      20             25             30
Tyr Met Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
      35             40             45

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

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

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

Ala Arg Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser
  100          105          110

Ser Ala

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<210> SEQ ID NO 184
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 184

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

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

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

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

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

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

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

Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
  115          120

```

```

<210> SEQ ID NO 185
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 185

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

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

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
          35          40          45

Gly Glu Ile Asn His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
  50          55          60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
  65          70          75          80

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

Arg Ser Ser Gly Tyr Trp Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu
  100          105          110

Val Thr Val Ser Ser Ala
  115

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-continued

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<210> SEQ ID NO 186
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 186
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20             25             30
Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35             40             45
Ser Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
 50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
 65             70             75             80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85             90             95
Ala Ser Ser Trp Tyr Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val
 100            105            110
Thr Val Ser Ser Ala
 115

```

```

<210> SEQ ID NO 187
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 187
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1             5             10             15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20             25             30
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35             40             45
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
 50             55             60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65             70             75             80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85             90             95
Ala Arg Gly Tyr Cys Thr Asn Gly Val Cys Tyr Tyr Tyr Tyr Gly Met
 100            105            110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
 115            120            125

```

```

<210> SEQ ID NO 188
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 188
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
 1             5             10             15
Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
 20             25             30
Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
 35             40             45

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Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Ala
115

<210> SEQ ID NO 189
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 189

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

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

Thr Leu Val Thr Val Ser Ser Ala
115 120

<210> SEQ ID NO 190
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 190

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

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

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

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

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

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

Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 191

-continued

```

<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 191
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
          20             25             30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
          65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Phe
          85             90             95
Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg
          100             105

```

```

<210> SEQ ID NO 192
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 192
Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
 1             5             10             15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
          20             25             30
Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
          35             40             45
Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
          50             55             60
Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
          65             70             75             80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
          85             90             95
Leu Gln Thr Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
          100             105             110

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<210> SEQ ID NO 193
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
          20             25             30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
          35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
          50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
          65             70             75             80

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

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
 100 105

<210> SEQ ID NO 194

<211> LENGTH: 106

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194

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

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

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

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

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

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Trp Thr Phe
 85 90 95

Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 195

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

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

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

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Ser Leu Ile
 35 40 45

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

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

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

Thr Phe Gly Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 196

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 196

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
 20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln

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35					40					45					
Pro	Pro	Lys	Leu	Leu	Ile	Tyr	Trp	Ala	Ser	Thr	Arg	Glu	Ser	Gly	Val
	50					55					60				
Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr
	65				70					75				80	
Ile	Ser	Ser	Leu	Gln	Ala	Glu	Asp	Val	Ala	Val	Tyr	Tyr	Cys	Gln	Gln
				85					90					95	
Tyr	Tyr	Ser	Thr	Pro	Leu	Thr	Phe	Gly	Gly	Gly	Thr	Lys	Val	Glu	Ile
			100					105					110		

Lys Arg

<210> SEQ ID NO 197

<211> LENGTH: 114

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 197

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

Lys Arg

<210> SEQ ID NO 198

<211> LENGTH: 106

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 198

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

<210> SEQ ID NO 199

<211> LENGTH: 111

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 199
Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
 1             5             10             15
Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
          20             25             30
Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
      35             40             45
Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
      50             55             60
Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
      65             70             75             80
Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
          85             90             95
Tyr Tyr Ser Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
      100             105             110

<210> SEQ ID NO 200
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 200
Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1             5             10             15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
      20             25             30
Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
      35             40             45
Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
      50             55             60
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
      65             70             75             80
Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
      85             90             95
Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100             105

<210> SEQ ID NO 201
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 201
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1             5             10             15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
      20             25             30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
      35             40             45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
      50             55             60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
      65             70             75             80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Arg

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      85              90              95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
      100              105

<210> SEQ ID NO 202
<211> LENGTH: 129
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 202
Ala Pro Ile Thr Arg Gln Ser Leu Asp Pro Gln Arg Arg Ala Ala Pro
  1              5              10              15
Gln Gln Lys Arg Ser Ser Pro Thr Glu Gly Leu Cys Pro Pro Gly His
      20              25              30
His Ile Ser Glu Asp Ser Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln
      35              40              45
Asp Tyr Ser Thr His Trp Asn Asp Phe Leu Phe Cys Leu Arg Cys Thr
      50              55              60
Lys Cys Asp Ser Gly Glu Val Glu Val Ser Ser Cys Thr Thr Thr Arg
      65              70              75              80
Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser
      85              90              95
Pro Glu Ile Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val
      100              105              110
Lys Val Lys Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys
      115              120              125

Glu

<210> SEQ ID NO 203
<211> LENGTH: 154
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 203
Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln Gln Arg Ala Ala Pro
  1              5              10              15
Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu Cys Pro Pro Gly His
      20              25              30
His Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser Cys Lys Tyr Gly Gln
      35              40              45
Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe Cys Leu Arg Cys Thr
      50              55              60
Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro Cys Thr Thr Thr Arg
      65              70              75              80
Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe Arg Glu Glu Asp Ser
      85              90              95
Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys Pro Arg Gly Met Val
      100              105              110
Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile Glu Cys Val His Lys
      115              120              125

Glu Ser Gly Thr Lys His Ser Gly Glu Ala Pro Ala Val Glu Glu Thr
      130              135              140
Val Thr Ser Ser Pro Gly Thr Pro Ala Ser
      145              150

<210> SEQ ID NO 204

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<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Mus sp.

<400> SEQUENCE: 204

Pro Val Thr Ala Asn Pro Ala His Asn Arg Pro Ala Gly Leu Gln Arg
 1             5             10             15

Pro Glu Glu Ser Pro Ser Arg Gly Pro Cys Leu Ala Gly Gln Tyr Leu
                20             25             30

Ser Glu Gly Asn Cys Lys Pro Cys Arg Glu Gly Ile Asp Tyr Thr Ser
                35             40             45

His Ser Asn His Ser Leu Asp Ser Cys Ile Leu Cys Thr Val Cys Lys
 50             55             60

Glu Asp Lys Val Val Glu Thr Arg Cys Asn Ile Thr Thr Asn Thr Val
 65             70             75             80

Cys Arg Cys Lys Pro Gly Thr Phe Glu Asp Lys Asp Ser Pro Glu Ile
                85             90             95

Cys Gln Ser Cys Ser Asn Cys Thr Asp Gly Glu Glu Glu Leu Thr Ser
 100            105            110

Cys Thr Pro Arg Glu Asn Arg Lys Cys Val Ser Lys Thr Ala Trp Ala
 115            120            125

Ser Trp His Lys Leu
 130

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We claim:

1. An isolated antibody comprising a heavy chain and a light chain that binds TRAIL Receptor-2 (TR-2), wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 2, and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 36.
2. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 4 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 38.
3. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 6 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 40.
4. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 8 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 42.
5. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 10 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 44.
6. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 12 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 46.
7. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 14 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 48.
8. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 16 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 50.
9. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 18 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 52.
10. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 20 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 54.
11. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 22 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 56.
12. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 24 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 58.
13. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 26 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 60.
14. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 28 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 62.

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15. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 30 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 64.

16. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 32 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 66.

17. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 34 and the light chain comprises CDR1, CDR2, and CDR3 of SEQ ID NO: 68.

18. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 2, and the light chain comprises the amino acid sequence of SEQ ID NO: 36.

19. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 4 and the light chain comprises the amino acid sequence of SEQ ID NO: 38.

20. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 6 and the light chain comprises the amino acid sequence of SEQ ID NO: 40.

21. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 8 and the light chain comprises the amino acid sequence of SEQ ID NO: 42.

22. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 10 and the light chain comprises the amino acid sequence of SEQ ID NO: 44.

23. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 12 and the light chain comprises the amino acid sequence of SEQ ID NO: 46.

24. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 14 and the light chain comprises the amino acid sequence of SEQ ID NO: 48.

25. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 16 and the light chain comprises the amino acid sequence of SEQ ID NO: 50.

26. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain com-

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prises the amino acid sequence of SEQ ID NO: 18 and the light chain comprises the amino acid sequence of SEQ ID NO: 52.

27. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 20 and the light chain comprises the amino acid sequence of SEQ ID NO: 54.

28. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 22 and the light chain comprises the amino acid sequence of SEQ ID NO: 56.

29. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 24 and the light chain comprises the amino acid sequence of SEQ ID NO: 58.

30. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 26 and the light chain comprises the amino acid sequence of SEQ ID NO: 60.

31. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 28 and the light chain comprises the amino acid sequence of SEQ ID NO: 62.

32. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises amino acid sequence of SEQ ID NO: 30 and the light chain comprises amino acid sequence of SEQ ID NO: 64.

33. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 32 and the light chain comprises the amino acid sequence of SEQ ID NO: 66.

34. An isolated antibody comprising a heavy chain and a light chain that binds TR-2, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 34 and the light chain comprises the amino acid sequence of SEQ ID NO: 68.

35. The isolated antibody of any of claims 1, 2, 9, 10, 15, 16, 17, 18, 19, 26, 27, 32, 33, and 34, wherein the antibody is a fully human antibody.

36. The isolated antibody of any of claims 1, 2, 9, 10, 15, 16, 17, 18, 19, 26, 27, 32, 33, and 34, wherein the antibody is a Fab, a Fab', a F(ab')₂, an Fv, or a single-chain Fv.

37. A pharmaceutical composition comprising the isolated antibody of any of claims 1, 2, 9, 10, 15, 16, 17, 18, 19, 26, 27, 32, 33, and 34 a pharmaceutically acceptable carrier.

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