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Fanslow, III et al.(10) **Pub. No.: US 2014/0004121 A1**(43) **Pub. Date: Jan. 2, 2014**(54) **ANTI-MESOTHELIN BINDING PROTEINS****Publication Classification**(71) Applicant: **AMGEN INC.**, Thousand Oaks, CA
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435/252.33; 435/254.2; 435/254.11; 435/419;
435/331(21) Appl. No.: **13/926,847**(22) Filed: **Jun. 25, 2013****Related U.S. Application Data**(60) Provisional application No. 61/789,678, filed on Mar.
15, 2013, provisional application No. 61/665,139,
filed on Jun. 27, 2012.(57) **ABSTRACT**

The present disclosure provides compositions and methods relating to antigen binding proteins, in particular, antibodies and bispecific antibodies which specifically bind to mesothelin. The disclosure provides nucleic acids encoding such antigen binding proteins and antibodies and methods of making and using such antibodies, including methods of treating and preventing cancer or other hypoproliferative disorders and related disorders by administering such antigen binding proteins and antibodies to a subject in need of such treatment.

FIG. 1

MSLN mRNA is Abundantly Expressed in Ovarian Serous and Pancreatic Cancer but not Normal Ovary or Pancreas

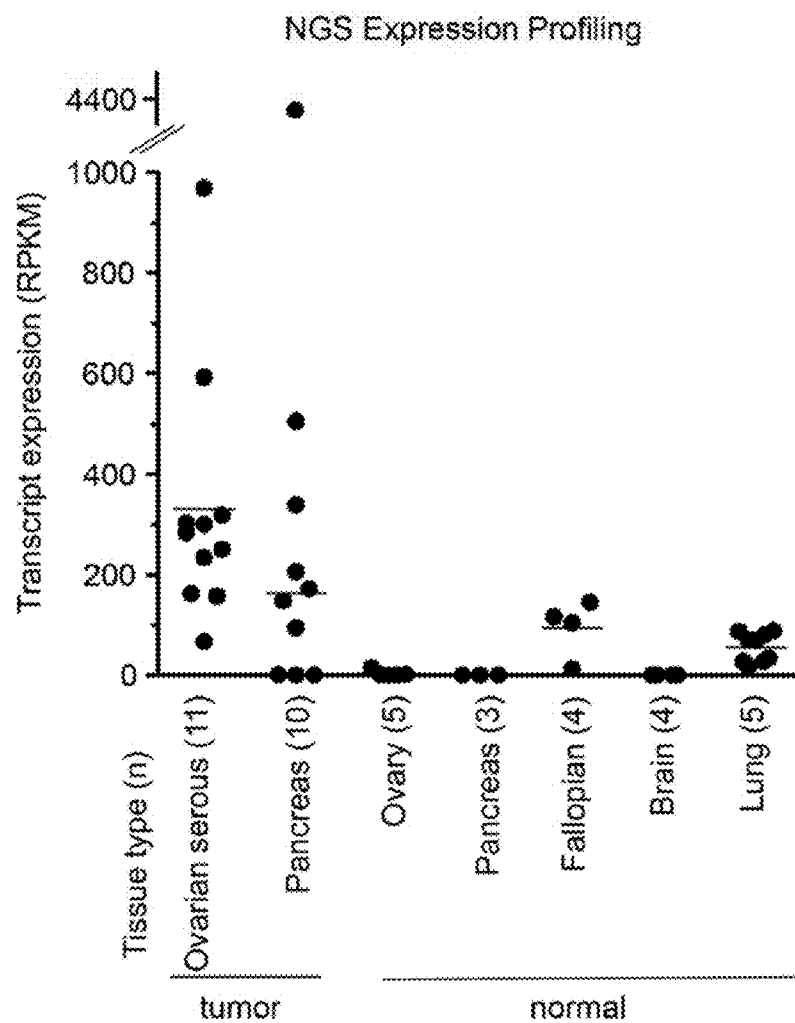


FIG. 2

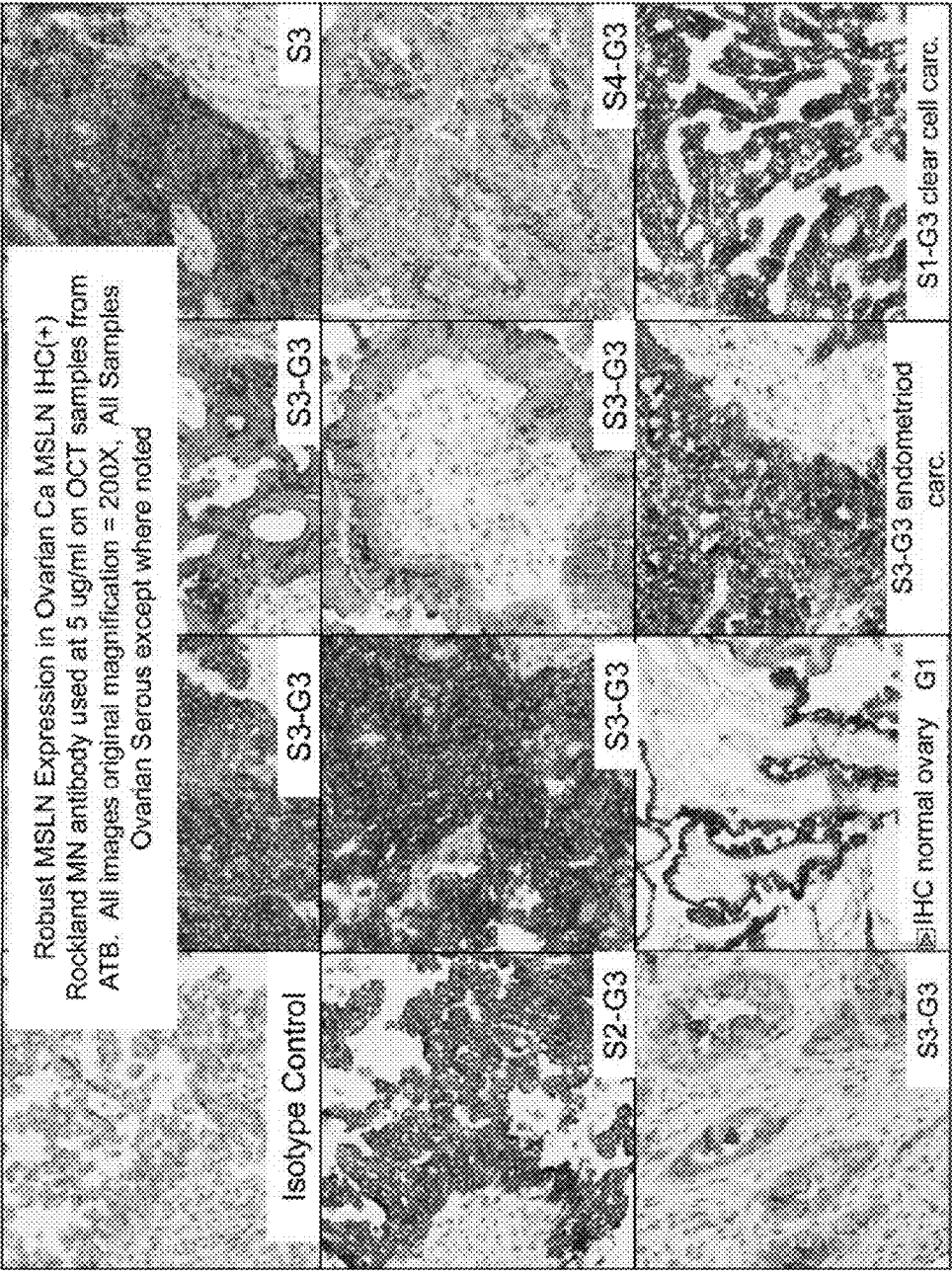


FIG. 3

MSLN Expressing Tumors

Cancer Type	Estimated New Cases (US)	Estimated Deaths (US)	MSLN Expression (mRNA) % Incidence	MSLN Expression (protein) % Incidence
Ovarian Serous Carcinoma	21,900	13,900	33/35 (94%)	76/77 (99%)
Pancreatic carcinoma	43,100	36,800	8/9 (89%)	39/42 (93%)
Mesothelioma	2-3,000	2,700	123/131 (94%)	44/44 (100%)
Lung Adenocarcinoma	156,000	82,000	6/10 (60%)	78/148 (53%)
Squamous	56,000	28,000	3/10 (30%)	29/124 (23%)
Gastric	37,000	25,000	19/41 (46%)	156/621 (25%)

FIG. 4

Comparison of Xenomouse Derived anti MSLN antibodies to Morab-009

mAb	Kd (Biacore, pM) Soluble human MSLN	Kd(Kinexa, pM) Native hu MSLN (cells)	Cyno MSLN Reactivity	Rat MSLN Reactivity	Mouse MSLN Reactivity
237	120	3.5	+++	++	++
158.3	2400	12.2	no	not done	no
151	17400	30	+	not done	no
1.12	282	not done	yes	not done	not done
1.33	965	not done	yes	not done	not done
1.68	9737	not done	yes	not done	not done
1.78	1277	not done	yes	not done	not done
1.119	112	not done	yes	not done	not done
2.69 LC2	228	not done	yes	not done	not done
Morab- 009 (ssl CDRs)	160 (1500 published#)	2.2	+++	No (Hassan 2007)	++

FIG. 5

Antibody Binning Data

Antibody used for detection														
1.5.1	1.5.2	1.58.3 g1	1.58.3 g2	1.1.2	1.33.1	1.68.1	1.78.1	1.119.1	1.80.3	2.37.1	2.69.2	2.85.3	2.26.1	Bin Number
1.51	940	842	1101	1032	3699	3379	4927	4140	3057	2992	7644	6060	7041	731
1.5.2	983	810	1201	1070	3590	3619	4726	4252	2961	2877	7353	6033	6227	801
1.58.3 g1	919	956	849	918	4449	5168	7909	4933	4892	4846	11989	9754	10229	701
1.58.3 g2	982	1001	1168	1074	3914	4677	6065	4836	3964	3665	9982	8061	8215	849
1.1.2	4004	3735	6393	4149	838	603	936	827	737	4514	8901	7161	6445	825
1.33.1	5839	5575	8489	5762	768	709	914	788	730	5605	5976	7144	5291	746
1.68.1	7424	7586	12054	7665	828	857	970	789	731	6147	8611	8713	5368	664
1.78.1	4655	4539	6848	4733	960	914	1244	976	901	5898	10190	8084	7531	1116
1.119.1	4323	4097	6645	4569	632	521	792	642	471	4071	4444	5349	3943	581
1.80.3	2385	2384	6956	2310	6063	4281	3822	6205	3829	301	10454	9733	8792	494
2.37.1	6365	6175	11865	6271	7734	832	6364	8035	752	6865	3693	3902	1020	746
2.69.2	3672	3400	6428	3860	3507	2700	3599	3887	2187	4704	2936	685	3474	612
2.85.3	6039	5573	9382	5818	4527	3577	3797	5093	3038	5425	5107	4894	656	394
2.26.1	62	92	170	87	51	74	73	111	62	37	158	160	133	94
N/A														

Ab binned against itself
Binning observed
No Binning observed

Ab binned against itself
Binning observed
No Binning observed

FIG. 6

Antibody Binning Data

	Morab-009	237	158	151	MN	MB	CA125	OV569	4H3
Morab-009	(-)	(+)	(+)	(nd)	(-)	(+)	(-)	(nd)	(nd)
237	(+)	(-)	(+)	(nd)	(+)	(+)	(+)	(+)	(+)
158	(+)	(+)	(-)	(nd)	(+)	(+/-)	(nd)	(nd)	(nd)
151	(nd)	(nd)	(nd)	(-)					
MN	(-)	(+)	(+)						
MB	(+)	(+)	(+/-)						
CA125	(-)	(+)	(nd)						
OV569		(+)							
4H3		(+)							

(-) = cross competition for binding to human MSLN observed

(+) = little to no cross competition for binding to human MSLN observed

(nd) = not done

FIG. 7

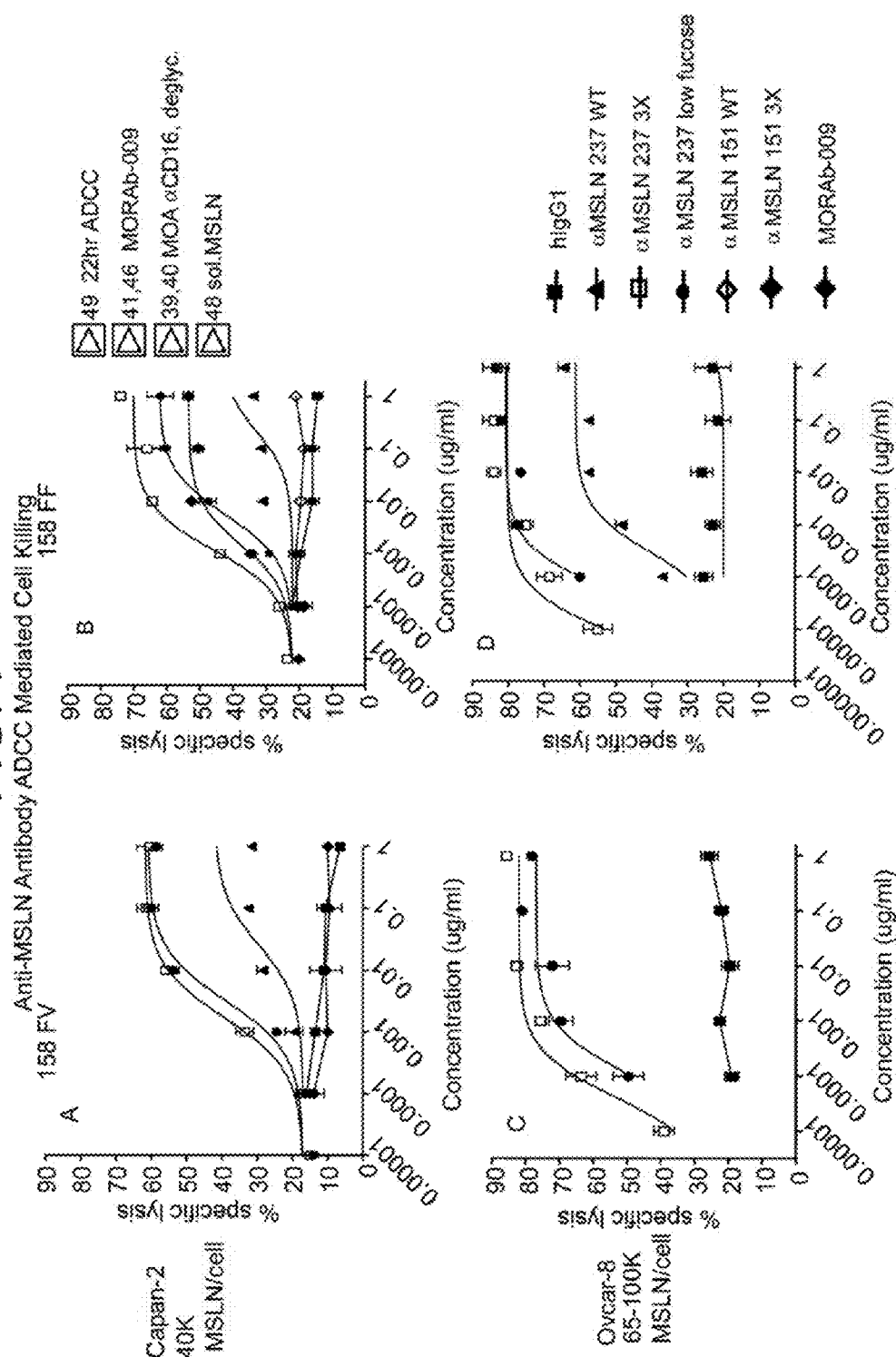
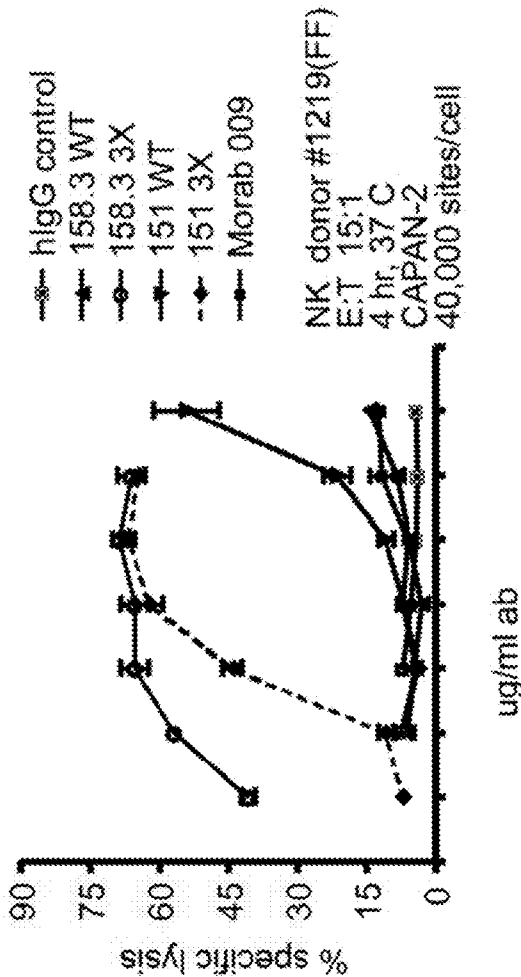


FIG. 8

Anti-MSLN Antibody ADCC Mediated Cell Killing



Cell line	MSLN level (sites/cell)	ADCC(3x)
A2780	<LLOQ	(-)
Caki-1	13 K	(-)
ASPC-1	20 K	(+)
CAPAN-2	40 K	(++)
Ovcar-8	65 K	(++)

sample	EC50 (nM)
158.3 WT	>67
158.3 3x	0.00031
151 WT	21
151 3x	0.0042
Morab 009	>67

FIG. 9

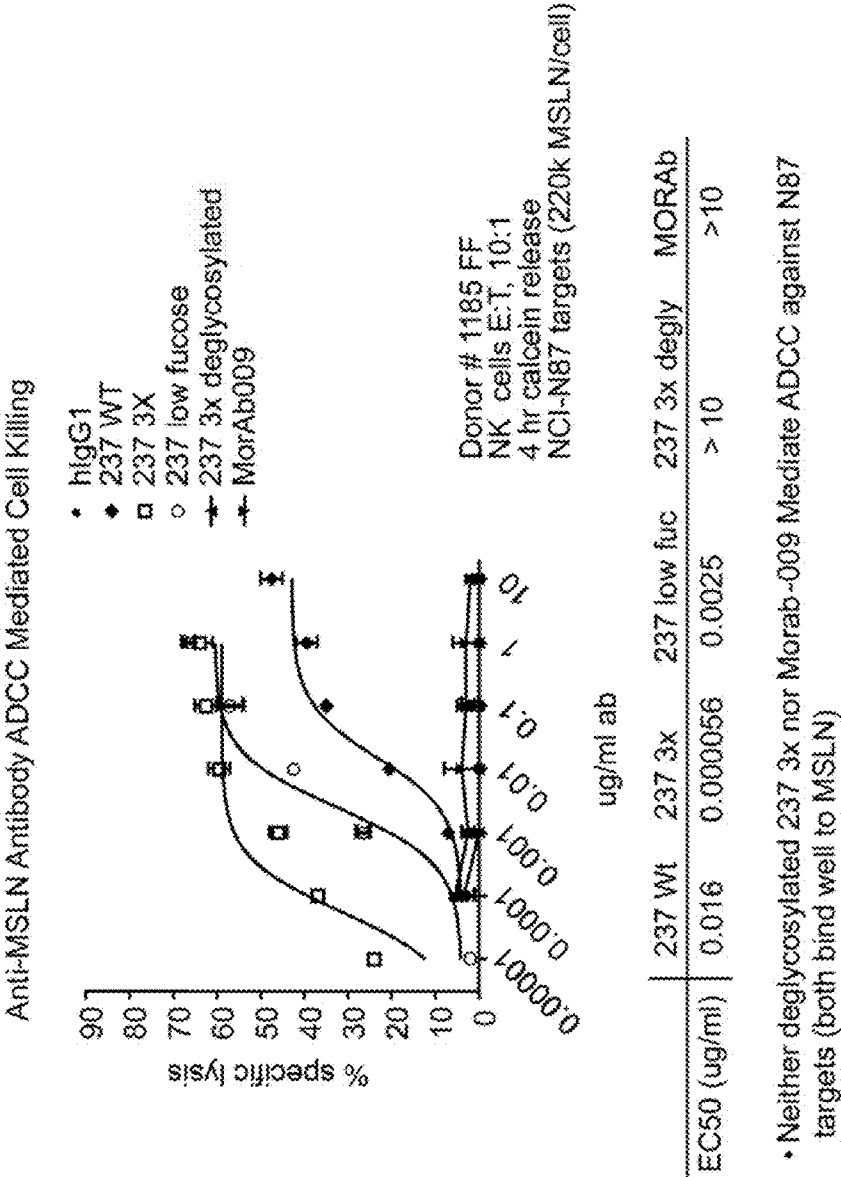


FIG. 10

Anti-MSLN Antibody CDC Mediated Cell Killing

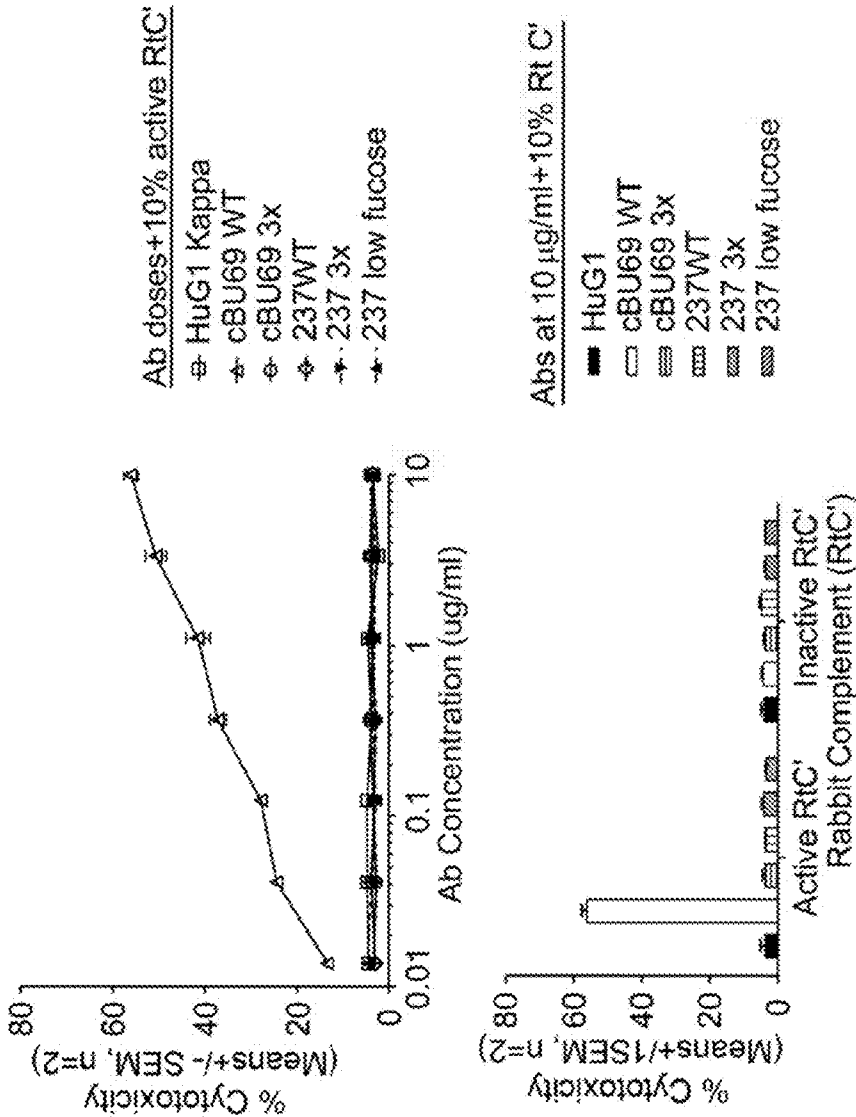


FIG. 11

Anti-MSLN Antibody CDC Mediated Cell Killing

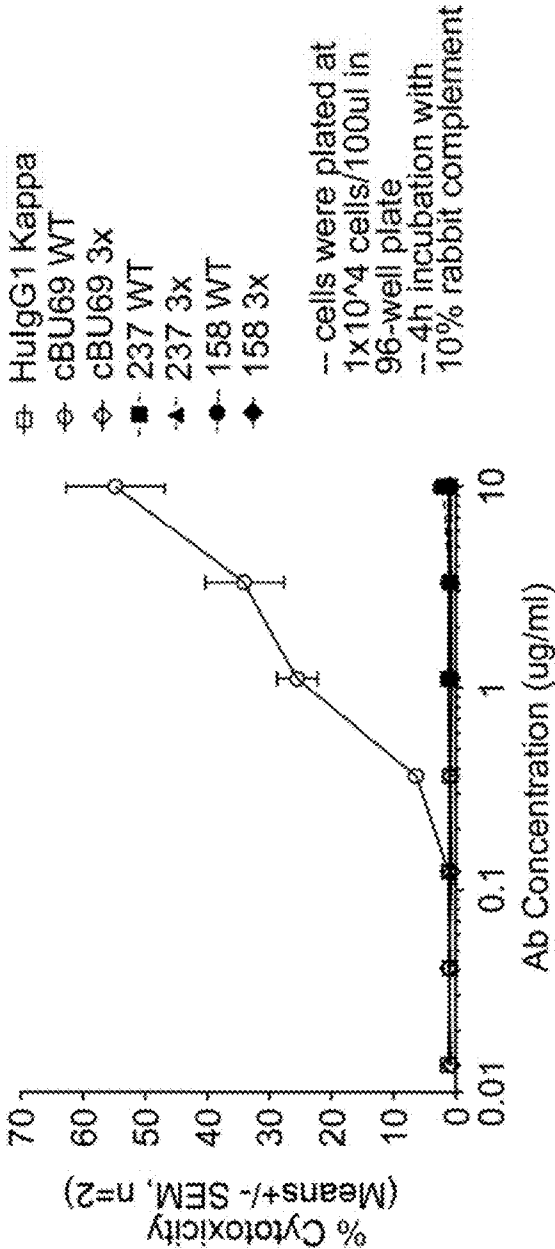


FIG. 12
Anti-MSLN Antibody CDC Mediated Cell Killing

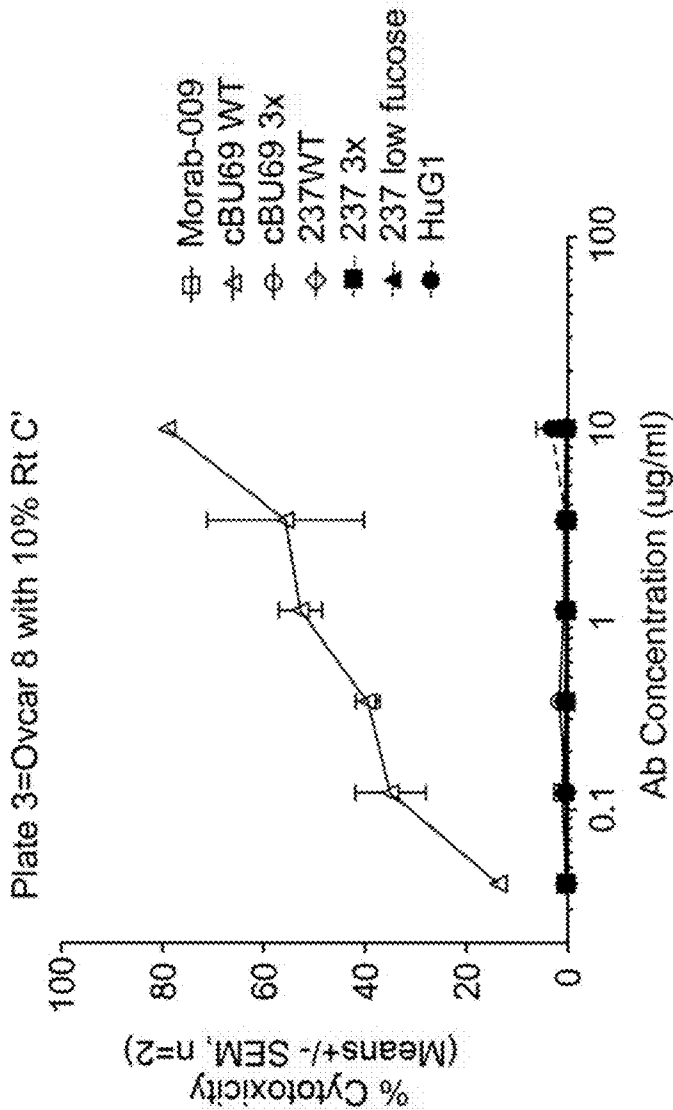
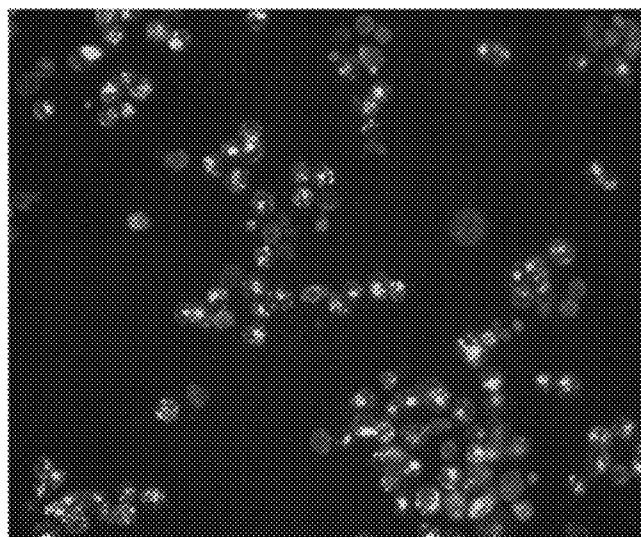
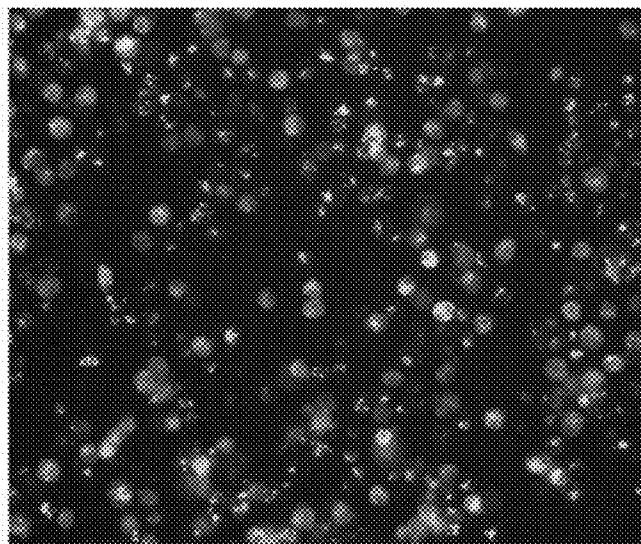


FIG. 13

Anti-MSLN Antibodies Induce Human Macrophages to Phagocytose Ovarian 8 Cells



30 ng/ml hulgG1 Kappa



30 ng/ml 237 Low Fucose MSLN

FIG. 14

Anti-MSLN Antibody ADCP Mediated Cell Killing

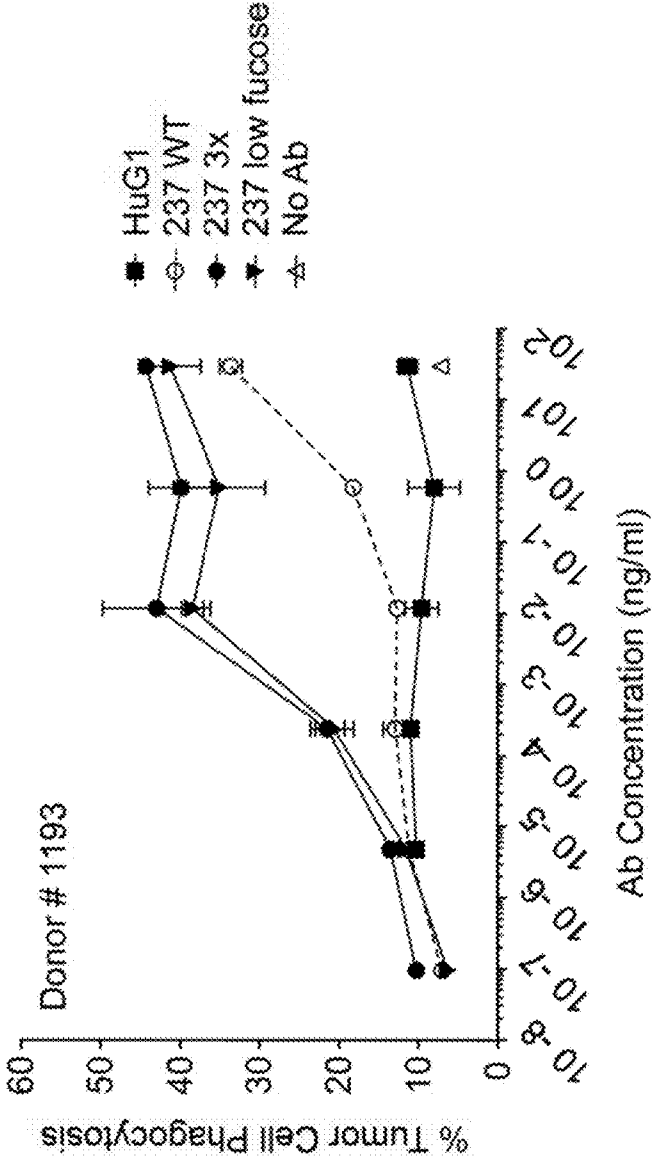
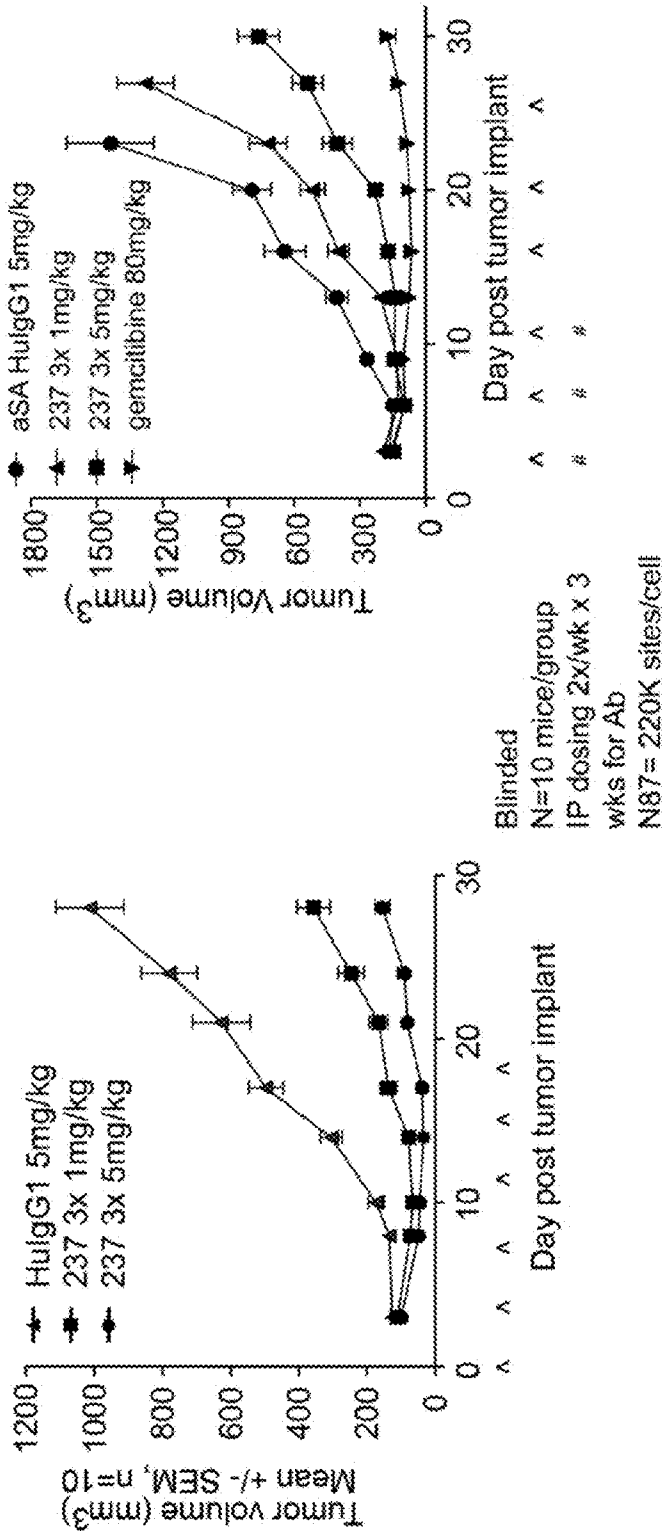


FIG. 15

Fc-Enhanced 237 3x anti MSLN hulG1 Induces Dose-Dependent Anti-Tumor Activity in a MSLN+ve N87 Xenograft Model (CB-17/SCID mice)



- Increased response observed in MRD setting as compared to established tumor setting
- Able to evince robust anti tumor activity in standard mouse xenograft model

FIG. 16

Fc-Enhanced 237(3x) anti MSLN Mediates Superior Anti-Tumor Activity
Compared to Competitor in an NCI-N87 Xenograft Model

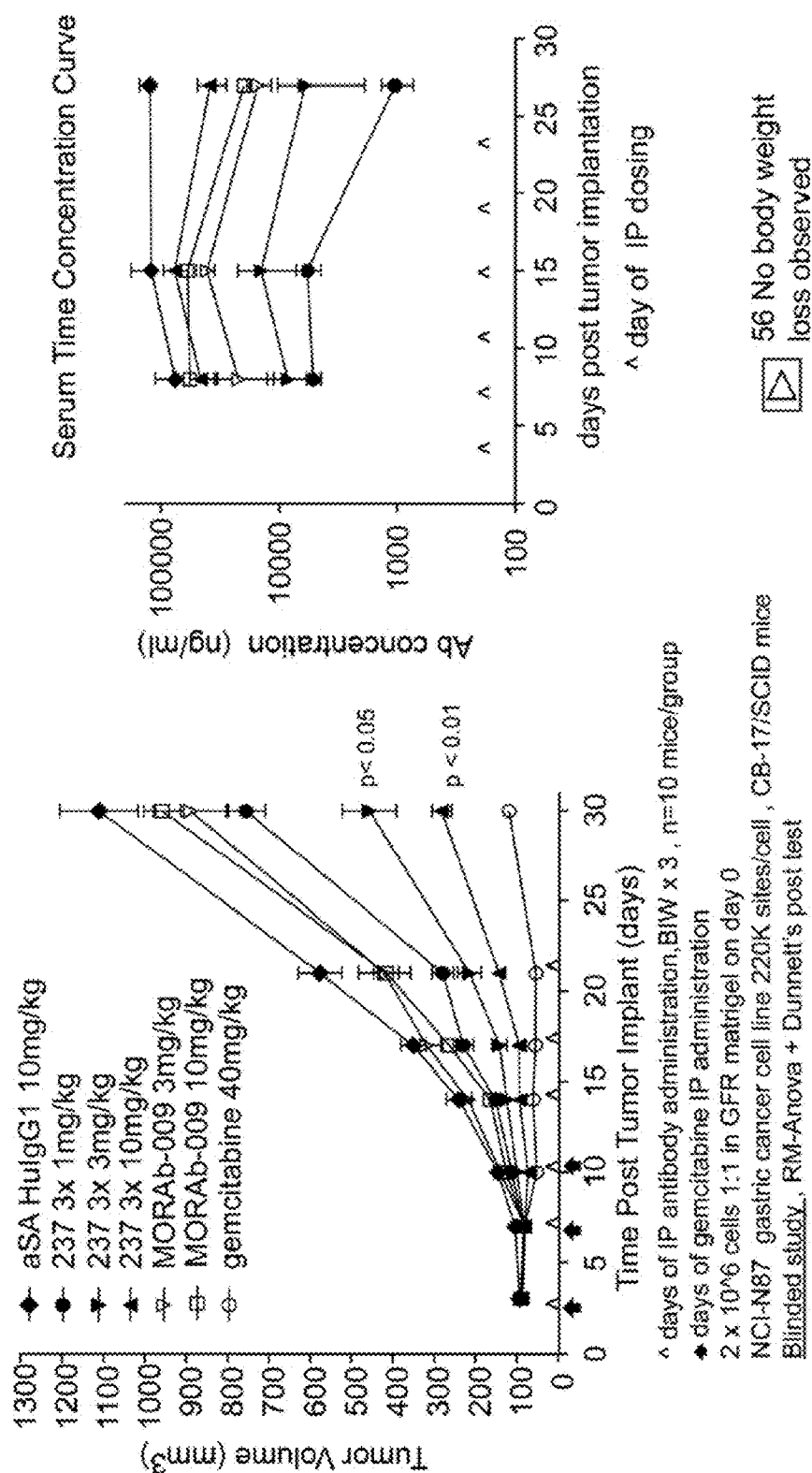


FIG. 17
Combining 237 3x anti Human MSLN and Gemcitabine Mediate Greater than Additive Anti-Tumor Activity in the N87 Xenograft Model

FIG. 19

Antibody binning

Antibody bins were determined by competitive binding of an anti-mesothelin antibody to a labeled anti-mesothelin antibody with known epitope. Sequence comparison was used to generate the dendrogram.

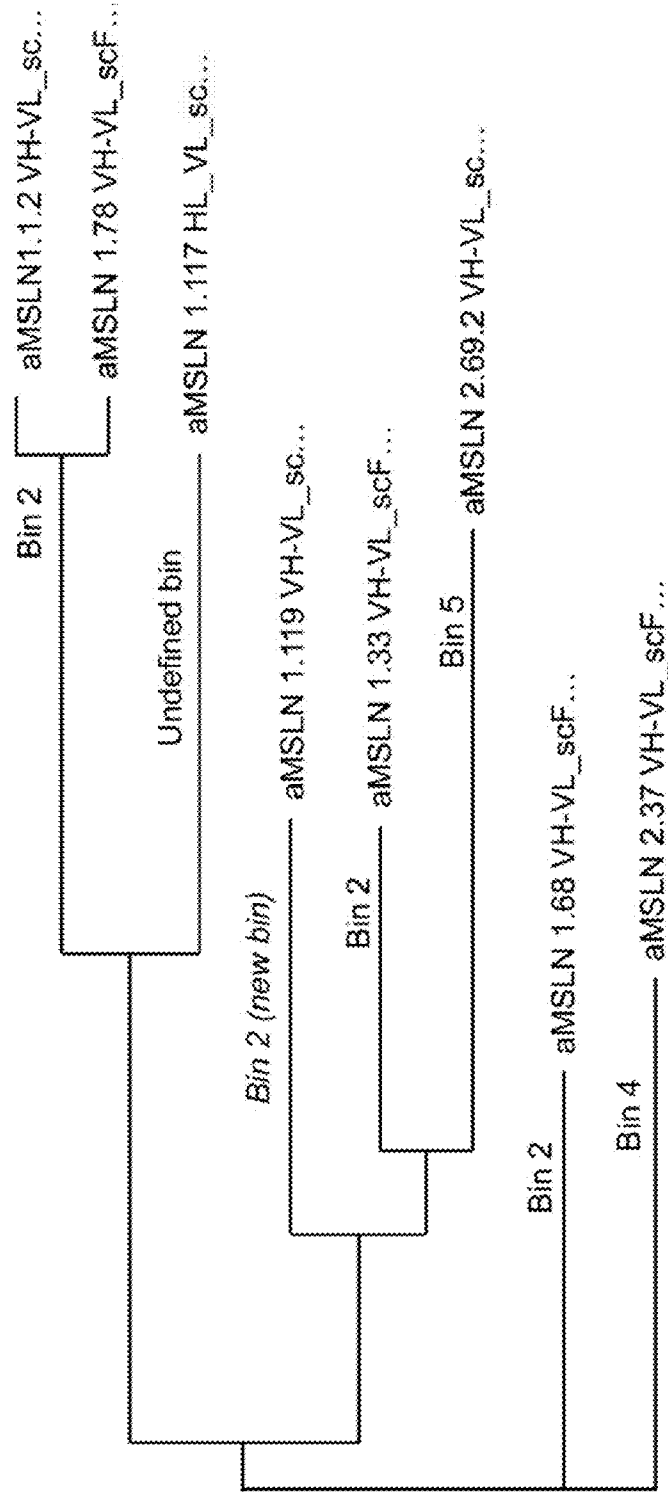


FIG. 20
MSLN-BITE molecules bind human MSLN and CD3

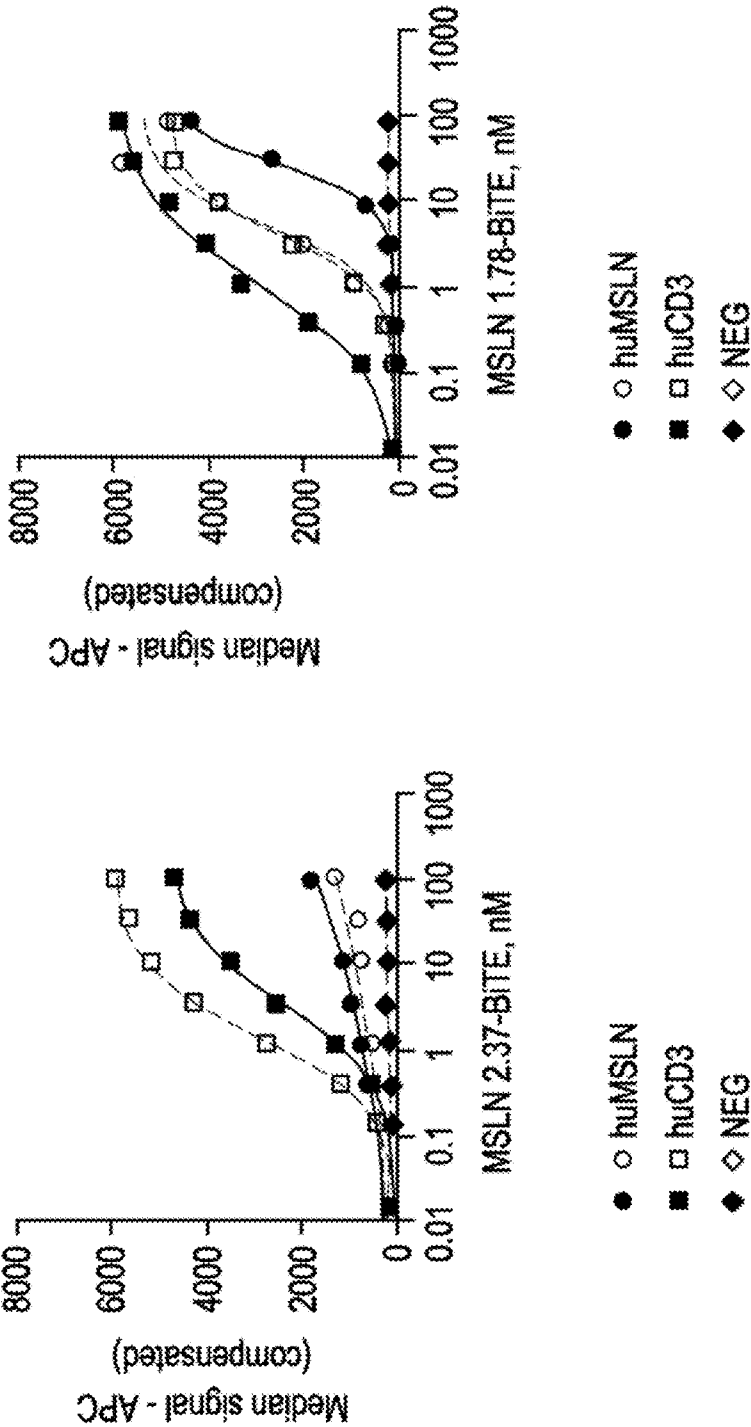


FIG. 21

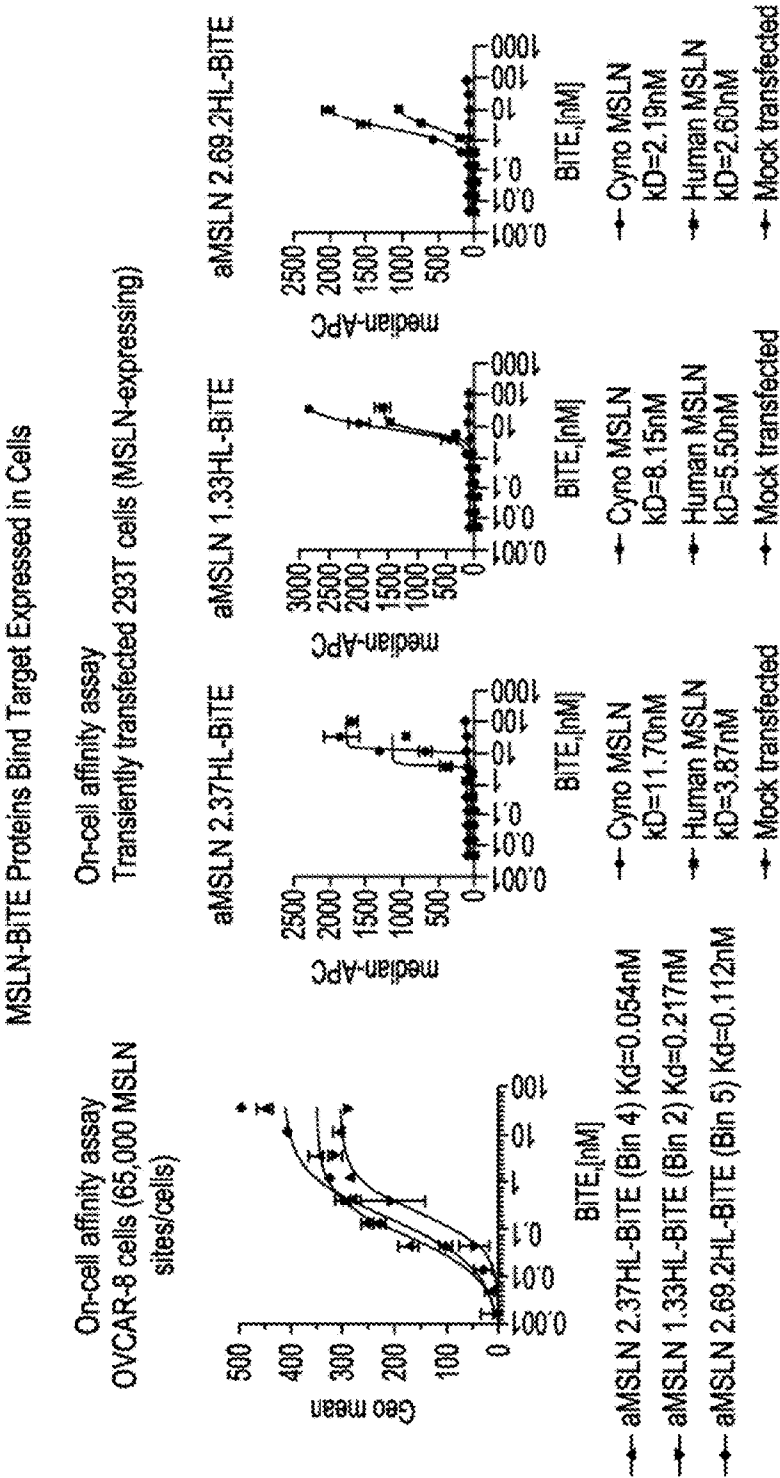


FIG. 22

MSLN-BITE molecules activate T cells and cause cytokine release.

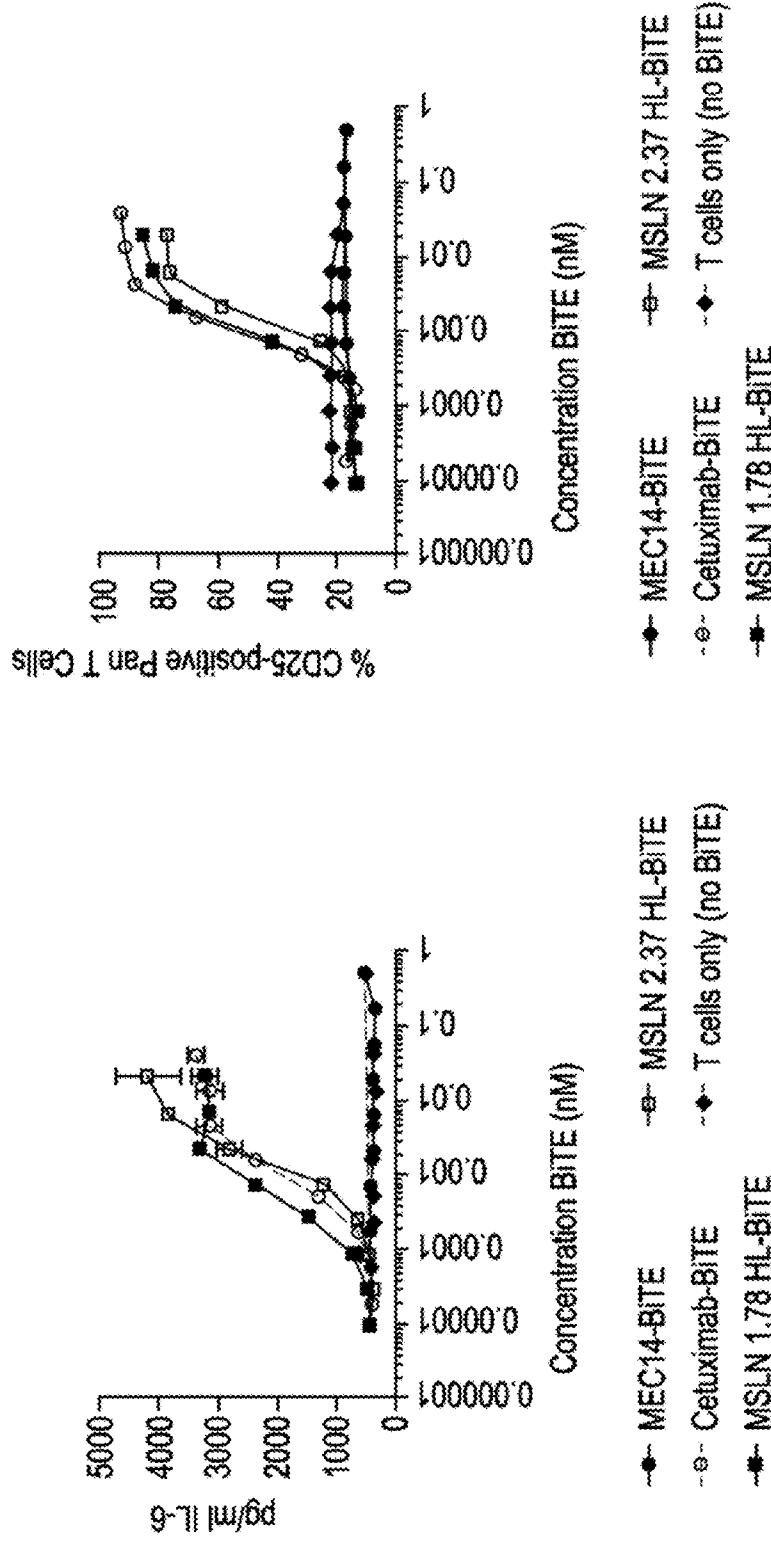


FIG. 23

MSLN-BiTE molecules cause cytokine release.

	Th1 type cytokines					Th2 type cytokines				
	INF γ EC50 pM	TNF α EC50 pM	IL-1B EC50 pM	IL-2 EC50 pM	IL-6 EC50 pM	IL-4 EC50 pM	IL-5 EC50 pM	IL-10 EC50 pM	IL-12 EC50 pM	IL-13 EC50 pM
Cetuximab-BiTE	10	40	9	10	0.8	2	2	6	4	4
MSLN 2.37-BiTE	20	30	4	9	0.4	3	1	2	3	1
MSLN 1.78-BiTE	50	70	5	10	0.3	4	1	4	3	2

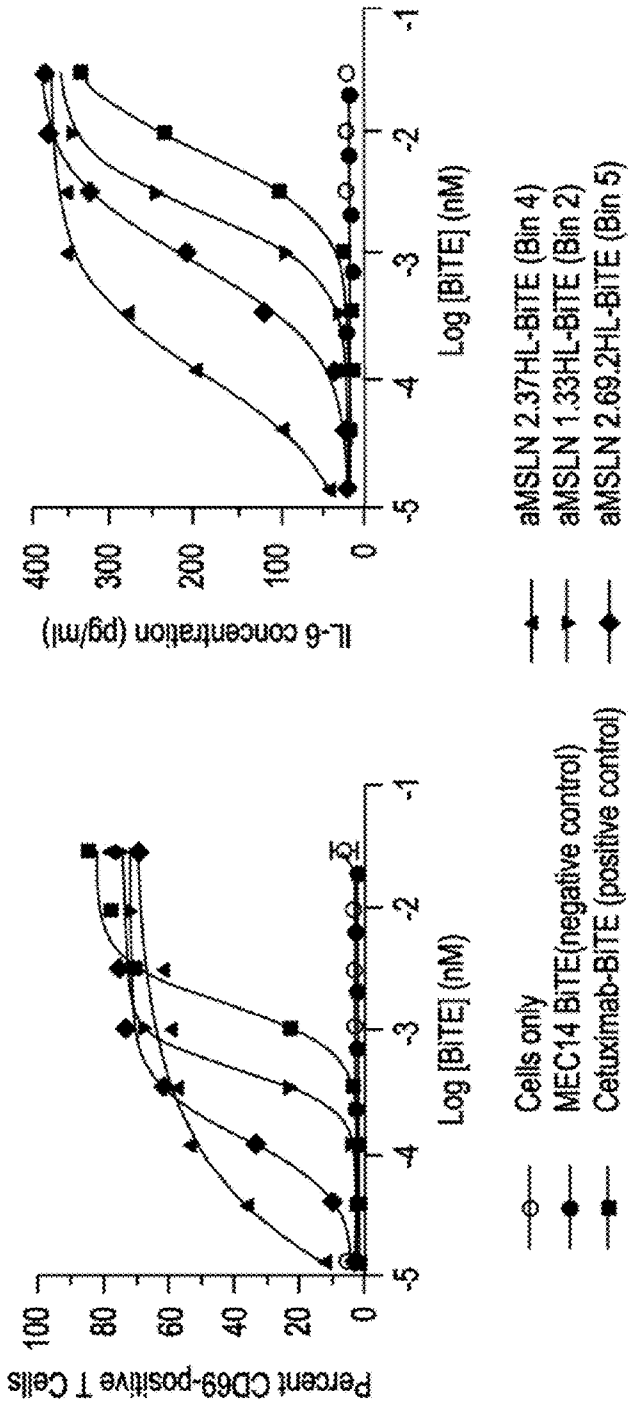
FIG. 24

MSLN-BiTE Proteins Activate T Cells and Cause Cytokine Production

OVCAR-8 cells (65,000 site/cell) and human pan-T cells 10:1

24h T cell activation assay

48h Cytokine release assay

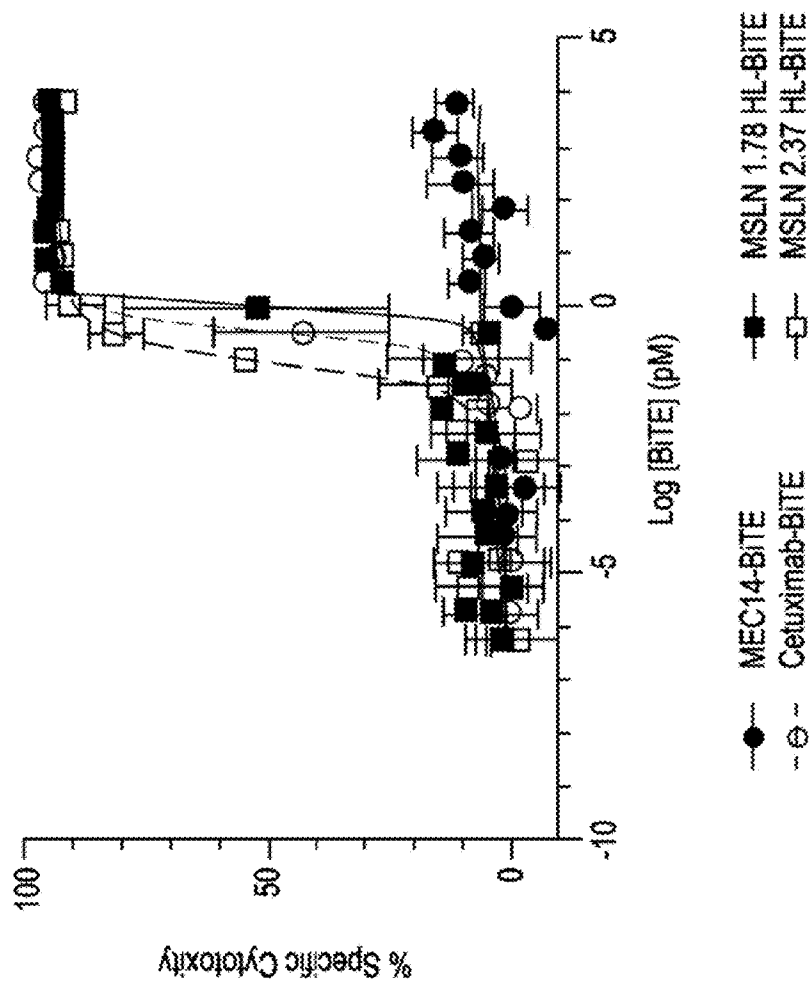


• Similar rank order of molecules as for the cytotoxicity assay

• BiTE proteins also increase CD25+ T cells and release additional cytokines including IFN γ and TNF α

FIG. 25

MSLN-BiTE induces cytotoxicity in tumor cells.



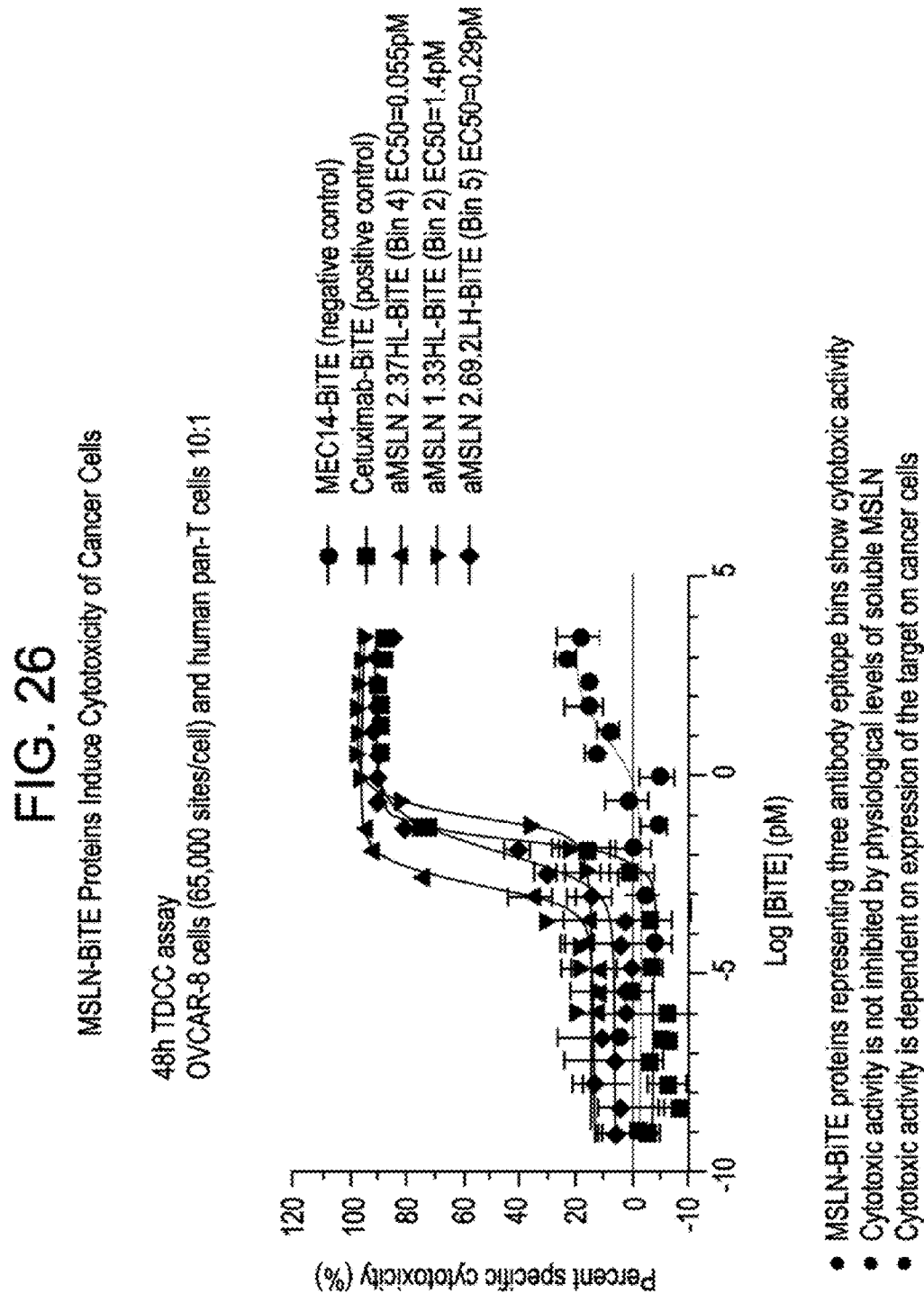
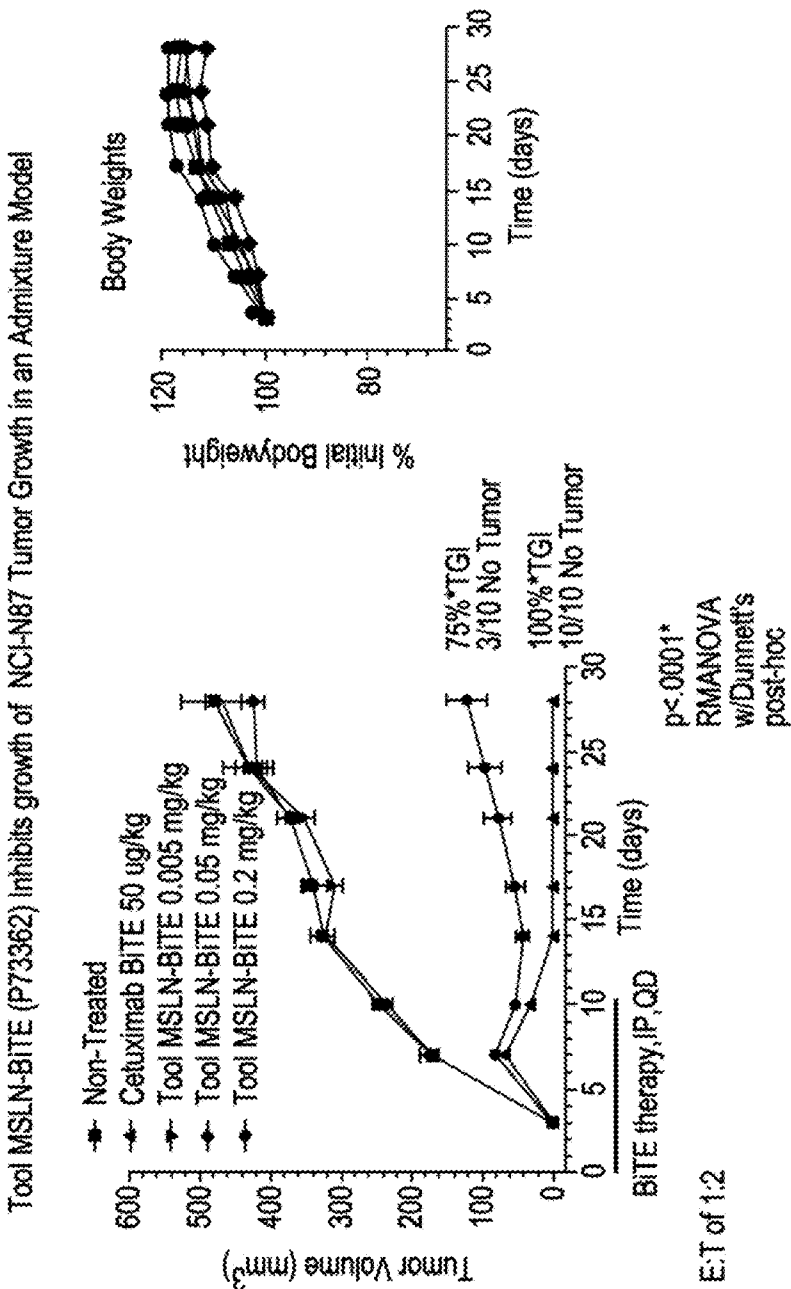


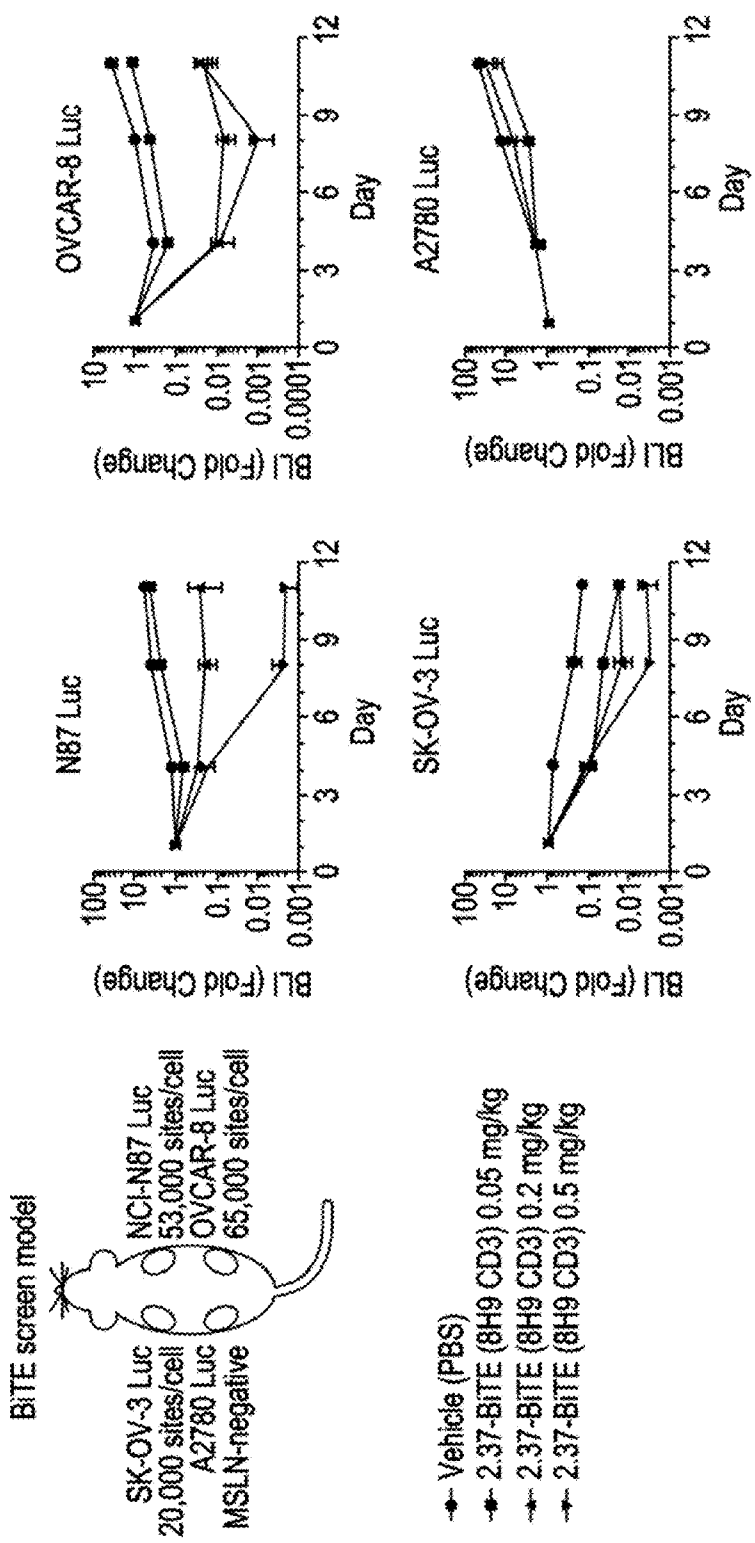
FIG. 27



• Tool MSLN-BITE is 2.37 scFv with 8H9 CD3

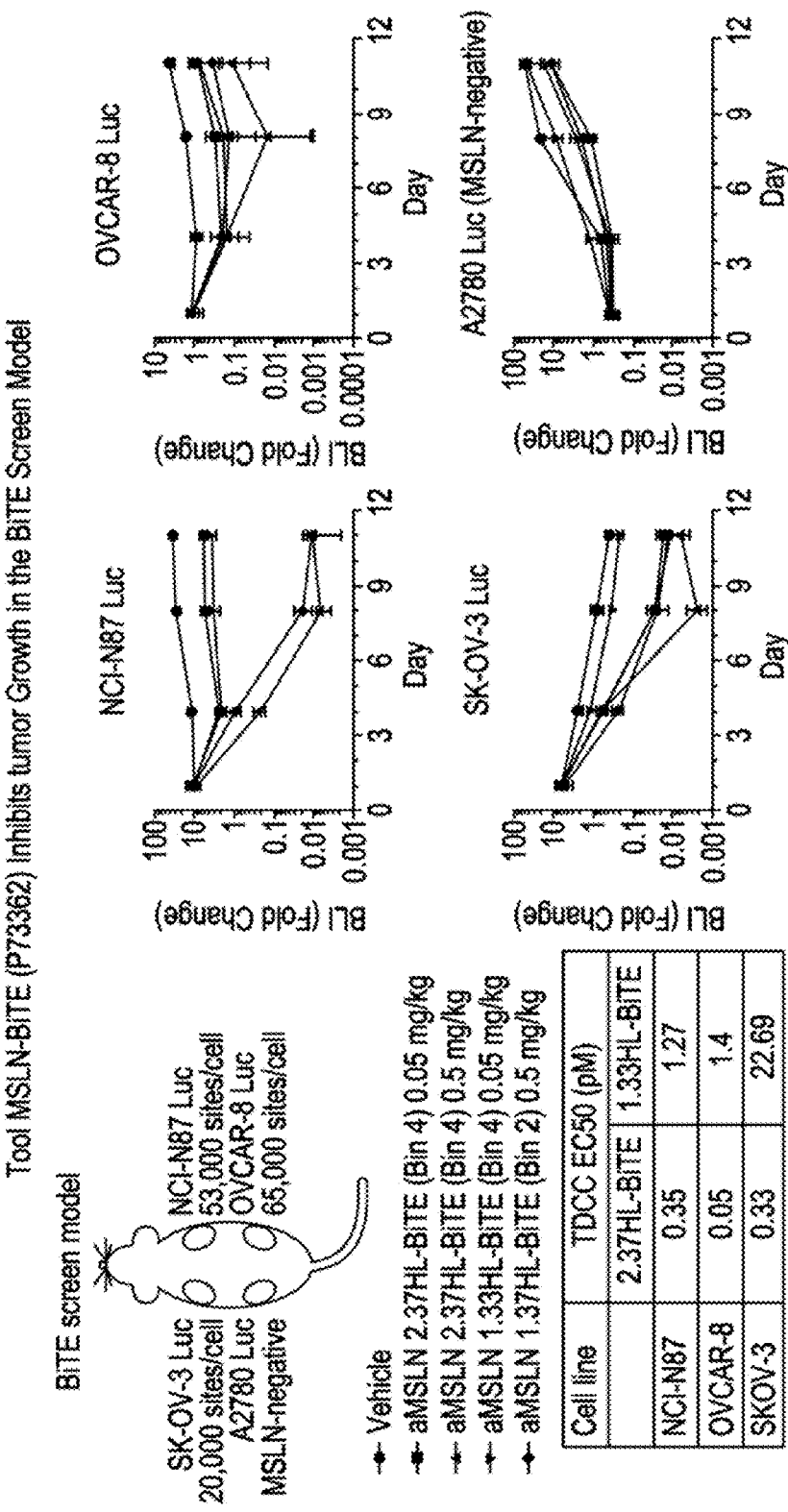
FIG. 28

Tool MSLN-BiTE (P73362) Inhibits Tumor Growth in the BiTE Screen Model



- Athymic nude mice implanted with 4 different luciferase labeled tumor cell lines and human pan T cells in 1:1 ratio
- Mice dosed IP once a day from Day 1 to Day 11
- Data graphed as fold change from Day 1 bioluminescence

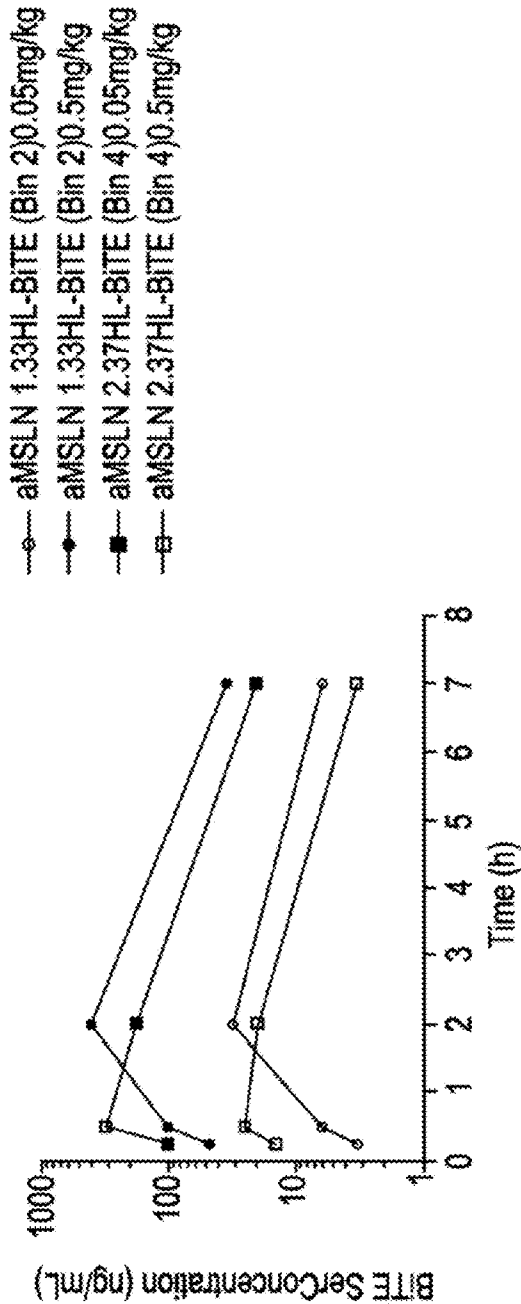
FIG. 29



- Athymic nude mice implanted with 4 different luciferase labeled tumor cell lines and human pan T cells in 1:1 ratio
- Mice dosed IP once a day from Day 1 to Day 11
- Data graphed as fold change from Day 1 bioluminescence

FIG. 30

Pharmacokinetics of MSLN-BiTE is Consistent with Dose-Dependent Inhibition of Tumor Growth



IP Dose (μg/kg)	t _{1/2,z} (h)	CL/F (mL/h/kg)	C _{max} (ng/mL)	AUC _{inf} (ng·h/mL)
1.33 50	2.1	397	31.3	126
1.33 500	1.4	407	402	1230
2.37 50	2.0	522	25.3	95.8
2.37 500	1.6	598	317	837

ANTI-MESOTHELIN BINDING PROTEINS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/789,678 filed Mar. 15, 2013 and U.S. Provisional Application No. 61/665,139 filed Jun. 27, 2012, both of which are incorporated by reference in their entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled A-1719-US-NP_SL.txt created Jun. 25, 2013, which is 258 KB in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

[0003] The field of this invention relates to compositions and methods related to anti-mesothelin binding proteins.

BACKGROUND OF THE INVENTION

[0004] Mesothelin is a glycoprotein present on the surface of cells of the mesothelial lining of the peritoneal, pleural and pericardial body cavities. Mesothelin (MSLN) was identified in 1992 with the mAb K1 that was generated by the immunization of mice with human ovarian carcinoma (OVCAR-3) cells (Chang, et al., *Int J. Cancer* (1992) 50:373-81). It was purified from the human pancreatic cancer cell line HPC-Y5 and was shown to have megakaryocyte potentiating ability and hence named megakaryocyte potentiating factor (MPF) (Yamaguchi et al. (1994) *J. Biol. Chem.* 269:805-808). The mesothelin gene (MSLN) encodes a 71-kilodalton (kDa) precursor protein that is processed to a 40-kDa protein termed mesothelin, which is a glycosyl-phosphatidylinositol-anchored glycoprotein present on the cell surface (Chang, et al, *Proc Natl Acad Sci USA* (1996) 93:136-40). The mesothelin cDNA was cloned from a library prepared from the HPC-Y5 cell line (Kojima et al. (1995) *J. Biol. Chem.* 270:21984-21990). The cDNA also was cloned using the monoclonal antibody K1, which recognizes mesotheliomas (Chang and Pastan (1996) *Proc. Natl. Acad. Sci. USA* 93:136-40).

[0005] Mesothelin is a differentiation antigen whose expression in normal human tissues is limited to mesothelial cells lining the body cavity, such as the pleura, pericardium and peritoneum. Mesothelin is also highly expressed in several different human cancers, including mesotheliomas, pancreatic adenocarcinomas, ovarian cancers, stomach and lung adenocarcinomas. (Hassan, et al., *Eur J Cancer* (2008) 44:46-53) (Ordonez, *Am J Surg Pathol* (2003) 27:1418-28; Ho, et al., *Clin Cancer Res* (2007) 13:1571-5).

[0006] Mesothelin is also shed from tumor cells as a soluble form of the protein, as compared to the native membrane bound version (Hellstrom, et al, *Cancer Epidemiol Biomarkers Prev* (2006) 15:1014-20.; Ho, et al., *Cancer Epidemiol Biomarkers Prev* (2006) 15:1751). Structurally, mesothelin is expressed on the cell surface as a 60 kDa precursor polypeptide, which is proteolytically processed into a 31 kDa shed component (corresponding to MPF) and a 40 kDa membrane bound component (Hassan et al. (2004) *Clin. Cancer. Res.* 10:3937-3942). Shed serum mesothelin has been approved by the US Food and Drug Administration as a diagnostic biomarker in malignant mesothelioma.

[0007] The biological function of mesothelin is still not clear. Knockout mice have been prepared in which the mesothelin gene was disrupted by homologous recombination (B era, T. K. and Pastan, I. (2000) *Mol. Cell. Biol.* 20:2902-2906). No anatomical, hematologic or reproductive abnormalities were detected, indicating that mesothelin function is not essential for growth or reproduction, at least in those mice.

[0008] Mesothelin does specifically interact with CA125 (also known as MUC-16), a mucin-like glycoprotein present on the surface of tumor cells that previously had been identified as an ovarian cancer antigen. Further, binding of CA125 to membrane-bound mesothelin mediates heterotypic cell adhesion and CA125 and mesothelin are co-expressed in advanced grade ovarian adenocarcinoma (Rump, A. et al. (2004) *J. Biol. Chem.* 279:9190-9198). Expression of mesothelin in the lining of the peritoneum correlates with the preferred site of metastasis formation of ovarian cancer and mesothelin-CA125 binding is thought to facilitate peritoneal metastasis of ovarian tumors (Gubbels, J.A. et al. (2006) *Mol. Cancer.* 5:50).

[0009] Mesothelin can also be used a marker for diagnosis and prognosis of certain types of cancer because trace amounts of mesothelin can be detected in the blood of some patients with mesothelin-positive cancers (Cristaudo et al., *Clin. Cancer Res.* 13:5076-5081, 2007). It has been reported that mesothelin may be released into serum through deletion at its carboxyl terminus or by proteolytic cleavage from its membrane bound form (Hassan et al., *Clin. Cancer Res.* 10:3937-3942, 2004). An increase in the soluble form of mesothelin was detectable several years before malignant mesotheliomas occurred among workers exposed to asbestos (Creaney and Robinson, *Hematol. Oncol. Clin. North Am.* 19:1025-1040, 2005). Furthermore, patients with ovarian, pancreatic, and lung cancers also have elevated soluble mesothelin in serum (Cristaudo et al., *Clin. Cancer Res.* 13:5076-5081, 2007; Hassan et al., *Clin. Cancer Res.* 12:447-453, 2006; Croso et al., *Cancer Detect. Prev.* 30:180-187, 2006). Accordingly, mesothelin is an appropriate target for methods of disease prevention or treatment and there is a need for effective antibodies specific for mesothelin.

SUMMARY OF THE INVENTION

[0010] In one embodiment, the invention provides an isolated anti-mesothelin human antibody or fragment thereof, wherein said antibody has at least one of the following properties: binds to a different epitope than the MORAb-009 antibody; competes for binding with Ab237; specifically binds to human, cyno, rat and murine mesothelin; does not internalize upon binding to mesothelin; when bound to mesothelin, does not inhibit CA125 interaction with mesothelin; has a binding affinity KD of at least 5.0 pM against human mesothelin; has enhanced effector function; binds to membrane-bound mesothelin preferentially over soluble mesothelin; reduces the growth of mesothelin expressing tumor cells in vivo.

[0011] In another embodiment, the invention provides a method of inhibiting or reducing the growth of mesothelin expressing tumor cells in an animal, comprising administering to said animal a therapeutically effective dose of the antibodies of the invention.

[0012] In a further embodiment, the invention provides a method of determining if a subject has mesothelin expressing tumor cells, comprising: contacting a tumor sample from the

subject with an antibody of the invention; and detecting binding of the antibody to the sample, wherein an increase in binding of the antibody to the sample as compared to binding of the antibody to a control sample identifies the subject as having mesothelin expressing tumor cells.

[0013] In another embodiment, the invention provides an isolated antibody or antigen binding protein or fragment thereof, wherein the antibody or antigen binding protein or fragment thereof specifically binds to mesothelin and comprises 3 heavy chain CDRs and 3 light chain CDRs with sequences selected from the group consisting of: SEQ ID NOs: 45, 46, 47 of the heavy chain and SEQ ID NOs: 9, 10, 11 of the light chain; SEQ ID NOs: 48, 49, 50 of the heavy chain and SEQ ID NOs: 12, 13, 14 of the light chain; SEQ ID NOs: 51, 52, 53 of the heavy chain and SEQ ID NOs: 15, 16, 17 of the light chain; SEQ ID NOs: 51, 52, 53 of the heavy chain and SEQ ID NOs: 18, 19, 20 of the light chain; SEQ ID NOs: 54, 55, 56 of the heavy chain and SEQ ID NOs: 21, 22, 23 of the light chain; SEQ ID NOs: 57, 58, 59 of the heavy chain and SEQ ID NOs: 24, 25, 26 of the light chain; SEQ ID NOs: 60, 61, 62 of the heavy chain and SEQ ID NOs: 27, 28, 29 of the light chain; SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 30, 31, 32 of the light chain; SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 33, 34, 35 of the light chain; and SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 36, 37, 38 of the light chain, wherein each of said CDRs are identical to or comprise 1, 2, or 3 amino acid residue substitutions relative to their specified sequence.

[0014] In another embodiment, the invention provides an isolated antibody or antigen binding protein or fragment thereof, wherein the antibody or antigen binding protein or fragment thereof specifically binds mesothelin and comprises a heavy chain variable domain and a light chain variable domain selected from the group consisting of: a heavy chain variable domain comprising SEQ ID NO: 86 and a light chain variable domain comprising SEQ ID NO: 72; a heavy chain variable domain comprising SEQ ID NO: 87 and a light chain variable domain comprising SEQ ID NO: 73; a heavy chain variable domain comprising SEQ ID NO: 88 and a light chain variable domain comprising SEQ ID NO: 74; a heavy chain variable domain comprising SEQ ID NO: 88 and a light chain variable domain comprising SEQ ID NO: 75; a heavy chain variable domain comprising SEQ ID NO: 89 and a light chain variable domain comprising SEQ ID NO: 76; a heavy chain variable domain comprising SEQ ID NO: 90 and a light chain variable domain comprising SEQ ID NO: 77; a heavy chain variable domain comprising SEQ ID NO: 91 and a light chain variable domain comprising SEQ ID NO: 78; a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 79; a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 80; a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 81; a heavy chain variable domain comprising SEQ ID NO: 93 and a light chain variable domain comprising SEQ ID NO: 82; a heavy chain variable domain comprising SEQ ID NO: 94 and a light chain variable domain comprising SEQ ID NO: 83, wherein each of said heavy chain variable domain and light chain variable domain have at least 90%, 95% or 100% identity relative to their specified sequence.

[0015] In a further embodiment, the invention provides an antibody or antigen binding protein or fragment thereof is a bispecific antibody and binds an additional target other than

MSLN. In one embodiment, the additional target is CD3. In a further embodiment, the CD3 is human and/or cynomolgus CD3. In yet a further embodiment, the CD3 is human and/or mouse and/or rat and/or cynomolgus CD3.

[0016] In another embodiment, the invention provides a bispecific single chain antibody, said bispecific single chain antibody comprising binding domains specific for CD3 and MSLN, wherein the corresponding variable heavy chain regions (V_H) and the corresponding variable light chain regions (V_L) regions are arranged, from N-terminus to C-terminus, in the order, $V_H(\text{MSLN})-V_L(\text{MSLN})-V_H(\text{CD3})-V_L(\text{CD3})$, or $V_H(\text{CD3})-V_L(\text{CD3})-V_H(\text{MSLN})-V_L(\text{MSLN})$, or $V_L(\text{MSLN})-V_H(\text{MSLN})-V_H(\text{CD3})-V_L(\text{CD3})$, or $V_H(\text{CD3})-V_L(\text{CD3})-V_L(\text{MSLN})-V_H(\text{MSLN})$, or $V_L(\text{MSLN})-V_H(\text{MSLN})-V_L(\text{CD3})-V_H(\text{CD3})$, or $V_L(\text{CD3})-V_H(\text{CD3})-V_L(\text{MSLN})-V_H(\text{MSLN})$, or $V_H(\text{MSLN})-V_L(\text{MSLN})$, or $V_H(\text{MSLN})-V_L(\text{MSLN})-V_L(\text{CD3})-V_H(\text{CD3})$, or $V_L(\text{CD3})-V_H(\text{CD3})-V_H(\text{MSLN})-V_L(\text{MSLN})$.

[0017] In one embodiment, the invention provides a bispecific single chain antibody that comprises a first V_H as set forth in SEQ ID NO: 86, a first V_L as set forth in SEQ ID NO: 72, a second V_H as set forth in SEQ ID NO: 118, and a second V_L as set forth in SEQ ID NO: 120.

[0018] In another embodiment, the invention provides a bispecific single chain antibody that comprises: a first V_H CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 45; a first V_H CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 46; a first V_H CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 47; a first V_L CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 9; a first V_L CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 10; and a first V_L CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 11; a second V_H CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 115; a second V_H CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 116; a second V_H CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 117; a second V_L CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 112; a second V_L CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 113; and a second V_L CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 114.

[0019] In another embodiment, the invention provides a bispecific single chain antibody having the sequence is set forth in SEQ ID NO: 127 or SEQ ID NO: 129. In another embodiment, the invention provides a bispecific single chain antibody comprising any of SEQ ID NOs: 158-185 and further comprising SEQ ID NO: 122.

BRIEF DESCRIPTION OF THE FIGURES

[0020] FIG. 1 provides a summary of MSLN expression data from ovarian and pancreatic tumor and normal cells.

[0021] FIG. 2 provides images of MSLN expression from primary ovarian tumor samples.

[0022] FIG. 3 summarizes the estimated new cases and deaths attributed to cancers expressing MSLN, and the % incidence of MSLN expression.

[0023] FIG. 4 summarizes binding and biochemical characteristics of the anti-MSLN antibodies, including K_d and species (cynomolgus, rat, mouse) cross-reactivity.

[0024] FIGS. 5 and 6 summarize antibody binning data of the anti-MSLN antibodies.

[0025] FIGS. 7-9 summarize anti-MSLN antibody ADCC mediated cell killing data for several different tumor lines.

[0026] FIGS. 10-12 summarize anti-MSLN antibody CDC mediated cell killing data.

[0027] FIG. 13 provides a photographic summary of results of ADCC assays using anti-MSLN antibodies.

[0028] FIG. 14 summarizes anti-MSLN antibody ADCC mediated cell killing data.

[0029] FIGS. 15-17 summarize in vivo results of anti-tumor activity of the anti-MSLN antibodies.

[0030] FIG. 18 provides an alignment of several different scFv anti-MSLN molecules used in the generation of BiTE molecules.

[0031] FIG. 19 summarizes anti-MSLN antibody binning based on competitive binding assays and sequence comparisons.

[0032] FIGS. 20 and 21 summarize in vitro assays performed with several anti-MSLN/anti-CD3 BiTE molecules (different VH/VL orientations of the same BiTE) as compared to control, demonstrating binding to both human MSLN and human CD3 expressed on tumor cells; experiments were also performed that demonstrate binding to both cynomolgus MSLN and cynomolgus CD3 (data not shown).

[0033] FIG. 22 summarizes an in vitro T-cell activation assay performed with several anti-MSLN/anti-CD3 BiTE molecules as compared to control BiTE molecules, demonstrating T-cell activation by the anti-MSLN/anti-CD3 BiTE molecules.

[0034] FIGS. 23-24 summarize in vitro assays performed with several anti-MSLN/anti-CD3 BiTE molecules as compared to control BiTE molecules, demonstrating cytokine release when the anti-MSLN/anti-CD3 BiTE molecules are incubated with MSLN expressing tumor cells in the presence of unstimulated T-cells.

[0035] FIGS. 25 and 26 summarize in vitro cytotoxicity assays performed with several anti-MSLN/anti-CD3 BiTE molecules as compared to control BiTE molecules, demonstrating specific T-cell mediated lysis of MSLN-expressing ovarian tumor cells.

[0036] FIG. 27-29 summarize in vivo tumor growth inhibition assay using several different tumor types (gastric cancer cells, SK-OV-3, NCI-N87, OVCAR-8, A-2780) performed with an anti-MSLN/anti-CD3 BiTE molecule as compared to controls, demonstrating a dramatic reduction in tumor growth by the anti-MSLN/anti-CD3 BiTE molecule against MSLN expression tumor cells.

[0037] FIG. 30 summarizes the results of an in vivo pharmacokinetic assay using MSLN BiTE molecules, indicating the pharmacokinetics are consistent with inhibition of tumor growth.

DETAILED DESCRIPTION OF THE INVENTION

[0038] The present invention relates to antigen binding proteins such as antibodies that specifically bind to mesothelin.

In one embodiment, the mesothelin is human mesothelin. In another embodiment, the mesothelin is cynomolgous mesothelin. In another embodiment, the mesothelin is murine mesothelin. In another embodiment, the mesothelin is rat mesothelin. In one embodiment, the antibodies of the invention specifically bind to human, cynomolgous, murine and rat mesothelin, and as such, the term mesothelin as used herein refers to all of these species of mesothelin. The antigen binding proteins are useful for treating cancer and related diseases.

[0039] The present invention further provides compositions, kits, and methods relating to antigen binding proteins that specifically bind to mesothelin. Also provided are nucleic acid molecules, and derivatives and fragments thereof, comprising a sequence of polynucleotides that encode all or a portion of a polypeptide that binds to mesothelin, such as a nucleic acid encoding all or part of an anti-mesothelin antibody, antibody fragment, or antibody derivative. The present invention further provides vectors and plasmids comprising such nucleic acids, and cells or cell lines comprising such nucleic acids and/or vectors and plasmids. The provided methods include, for example, methods of making, identifying, or isolating antigen binding proteins that bind to human mesothelin, such as anti-mesothelin antibodies, methods of determining whether an antigen binding protein binds to mesothelin, methods of making compositions, such as pharmaceutical compositions, comprising an antigen binding protein that binds to human mesothelin, and methods for administering an antigen binding protein that binds mesothelin to a subject, for example, methods for treating cancer that comprises tumor cells that express mesothelin.

DEFINITIONS

[0040] Polynucleotide and polypeptide sequences are indicated using standard one- or three-letter abbreviations. Unless otherwise indicated, polypeptide sequences have their amino termini at the left and their carboxy termini at the right, and single-stranded nucleic acid sequences, and the top strand of double-stranded nucleic acid sequences, have their 5' termini at the left and their 3' termini at the right. A particular section of a polypeptide can be designated by amino acid residue number such as amino acids 1 to 50, or by the actual residue at that site such as asparagine to proline. A particular polypeptide or polynucleotide sequence also can be described by explaining how it differs from a reference sequence.

[0041] Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are 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 unless otherwise indicated. See, e.g., Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing

Associates (1992), and Harlow and Lane *Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), which are incorporated herein by reference. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used 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 can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0042] The following terms, unless otherwise indicated, shall be understood to have the following meanings: The term "isolated molecule" (where the molecule is, for example, a polypeptide, a polynucleotide, or an antibody) is a molecule that by virtue of its origin or source of derivation (1) is not associated with naturally associated components that accompany it in its native state, (2) is substantially free of other molecules from the same species (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a molecule that is chemically synthesized, or expressed in a cellular system different from the cell from which it naturally originates, will be "isolated" from its naturally associated components. A molecule also may be rendered substantially free of naturally associated components by isolation, using purification techniques well known in the art. Molecule purity or homogeneity may be assayed by a number of means well known in the art. For example, the purity of a polypeptide sample may be assayed using polyacrylamide gel electrophoresis and staining of the gel to visualize the polypeptide using techniques well known in the art. For certain purposes, higher resolution may be provided by using HPLC or other means well known in the art for purification.

[0043] The terms "peptide" "polypeptide" and "protein" each refers to a molecule comprising two or more amino acid residues joined to each other by peptide bonds. These terms encompass, e.g., native and artificial proteins, protein fragments and polypeptide analogs (such as muteins, variants, and fusion proteins) of a protein sequence as well as post-translationally, or otherwise covalently or non-covalently, modified proteins. A peptide, polypeptide, or protein may be monomeric or polymeric.

[0044] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion as compared to a corresponding full-length protein. Fragments can be, for example, at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 50, 70, 80, 90, 100, 150 or 200 amino acids in length. Fragments can also be, for example, at most 1,000, 750, 500, 250, 200, 175, 150, 125, 100, 90, 80, 70, 60, 50, 40, 30, 20, 15, 14, 13, 12, 11, or 10 amino acids in length. A fragment can further comprise, at either or both of its ends, one or more additional amino acids, for example, a sequence of amino acids from a different naturally-occurring protein (e.g., an Fc or leucine zipper domain) or an artificial amino acid sequence (e.g., an artificial linker sequence).

[0045] Polypeptides of the invention include polypeptides that have been modified in any way and for any reason, for example, to: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (4) confer or modify other physicochemical or functional

properties. Analogs include muteins of a polypeptide. For example, single or multiple amino acid substitutions (e.g., conservative amino acid substitutions) may be made in the naturally occurring sequence (e.g., in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). A "conservative amino acid substitution" is one that does 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 characterize the parent sequence or are necessary for its functionality). Examples of art-recognized polypeptide secondary and tertiary structures are described 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), which are each incorporated herein by reference.

[0046] A "variant" of a polypeptide (e.g., an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants of the invention include fusion proteins.

[0047] A "derivative" of a polypeptide is a polypeptide (e.g., an antibody) that has been chemically modified, e.g., via conjugation to another chemical moiety such as, for example, polyethylene glycol, albumin (e.g., human serum albumin), phosphorylation, and glycosylation. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below.

[0048] An "antigen binding protein" is a protein comprising a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (e.g., an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise, for example, an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., 2003, *Proteins: Structure, Function, and Bioinformatics*, Volume 53, Issue 1:121-129 (2003); Roque et al., *Biotechnol. Prog.* 20:639-654 (2004). In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronectin components as a scaffold.

[0049] An antigen binding protein can have, for example, the structure of a naturally occurring immunoglobulin. An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region pri-

marily responsible for effector function. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, 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 generally, *Fundamental Immunology* Ch. 7 (Paul, W., ed., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

[0050] Naturally occurring immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. From N-terminus to C-terminus, both light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991.

[0051] An "antibody" refers to an intact immunoglobulin or to an antigen binding portion thereof that competes with the intact antibody for specific binding, unless otherwise specified. Antigen binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen binding portions include, inter alia, Fab, Fab', F(ab')₂, Fv, domain antibodies (dAbs), fragments including complementarity determining regions (CDRs), single-chain antibodies (scFv), chimeric antibodies, diabodies, triabodies, tetrabodies, bispecific single chain antibodies (e.g., bispecific T-cell engagers or BiTEs), and other bispecific antibodies, and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

[0052] The term "bispecific single chain antibody" relates to a construct comprising a first domain consisting of variable regions (or parts thereof) capable of specifically interacting with or binding to human CD3, and comprising a second domain consisting of variable regions (or parts thereof), capable of specifically interacting with or binding to human mesothelin.

[0053] A Fab fragment is a monovalent fragment having the V_L, V_H, C_L and C_H1 domains; a F(ab')₂ fragment is a bivalent fragment having two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment has the V_H and C_H1 domains; an Fv fragment has the V_L and V_H domains of a single arm of an antibody; and a dAb fragment has a V_H domain, a V_L domain, or an antigen-binding fragment of a V_H or V_L domain (U.S. Pat. No. 6,846,634, U.S. Pat. No. 6,696,245, US App. Pub. Nos. 05/0202512, 04/0202995, 04/0038291, 04/0009507, 03/0039958, Ward et al., *Nature* 341:544-546 (1989)).

[0054] A single-chain antibody (scFv) is an antibody in which a V_L and a V_H region are joined via a linker (e.g., a synthetic sequence of amino acid residues) to form a continuous protein chain wherein the linker is long enough to allow the protein chain to fold back on itself and form a monovalent antigen binding site (see, e.g., Bird et al., *Science* 242:423-26 (1988) and Huston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-83 (1988)). Diabodies are bivalent antibodies com-

prising two polypeptide chains, wherein each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:6444-48 (1993), and Poljak et al., *Structure* 2:1121-23 (1994)). If the two polypeptide chains of a diabody are identical, then a diabody resulting from their pairing will have two identical antigen binding sites. Polypeptide chains having different sequences can be used to make a diabody with two different antigen binding sites. Similarly, triabodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different.

[0055] Complementarity determining regions (CDRs) and framework regions (FR) of a given antibody may be identified using the system described by Kabat et al. in *Sequences of Proteins of Immunological Interest*, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication no. 91-3242, 1991. One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an antigen binding protein. An antigen binding protein may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the antigen binding protein to specifically bind to a particular antigen of interest.

[0056] An antigen binding protein may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For example, a naturally occurring human immunoglobulin typically has two identical binding sites, while a "bispecific" or "bifunctional" antibody has two different binding sites.

[0057] The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences. In one embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies may be prepared in a variety of ways known in the art, nonlimiting examples of which are described herein, including through the immunization with an antigen of interest of a mouse that is genetically modified to express antibodies derived from human heavy and/or light chain-encoding genes.

[0058] A humanized antibody has a sequence that differs from the sequence of an antibody derived from a non-human species by one or more amino acid substitutions, deletions, and/or additions, such that the humanized antibody is less likely to induce an immune response, and/or induces a less severe immune response, as compared to the non-human species antibody, when it is administered to a human subject. In one embodiment, certain amino acids in the framework and constant domains of the heavy and/or light chains of the non-human species antibody are mutated to produce the humanized antibody. In another embodiment, the constant domain(s) from a human antibody are fused to the variable domain(s) of a non-human species. In another embodiment, one or more amino acid residues in one or more CDR sequences of a non-human antibody are changed to reduce the likely immunogenicity of the non-human antibody when it is administered to a human subject, wherein the changed amino acid residues either are not critical for immunospecific bind-

ing of the antibody to its antigen, or the changes to the amino acid sequence that are made are conservative changes, such that the binding of the humanized antibody to the antigen is not significantly worse than the binding of the non-human antibody to the antigen. Examples of how to make humanized antibodies may be found in U.S. Pat. Nos. 6,054,297, 5,886,152 and 5,877,293.

[0059] The term “chimeric antibody” refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In one embodiment, one or more of the CDRs are derived from a human anti-mesothelin antibody. In another embodiment, all of the CDRs are derived from a human anti-mesothelin antibody. In another embodiment, the CDRs from more than one human anti-mesothelin antibodies are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human anti-mesothelin antibody, a CDR2 and a CDR3 from the light chain of a second human anti-mesothelin antibody, and the CDRs from the heavy chain from a third anti-mesothelin antibody. Further, the framework regions may be derived from one of the same anti-mesothelin antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. In one example of a chimeric antibody, a portion of the heavy and/or light chain is identical with, homologous to, or derived from an antibody from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with, homologous to, or derived from an antibody or antibodies from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies that exhibit the desired biological activity (i.e., the ability to specifically bind the human mesothelin).

[0060] A “neutralizing antibody” or “inhibitory antibody” refers to an antibody that inhibits the binding of ligand to the receptor, and/or inhibits or reduces receptor signalling. The inhibition need not be complete and may be, in one embodiment, reduced binding or signalling by at least 20%. In further embodiments, the reduction in binding or signalling is at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 97%, 99% and 99.9%.

[0061] Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification and using techniques well-known in the art. Preferred amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Computerized comparison methods can be used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. See, e.g., Bowie et al., *Science* 253:164 (1991).

[0062] A “CDR grafted antibody” is an antibody comprising one or more CDRs derived from an antibody of a particular species or isotype and the framework of another antibody of the same or different species or isotype.

[0063] A “multi-specific antibody” is an antibody that recognizes more than one epitope on one or more antigens. A subclass of this type of antibody is a “bi-specific antibody” which recognizes two distinct epitopes on the same or different antigens.

[0064] An antigen binding protein including an antibody “specifically binds” to an antigen, such as human mesothelin if it binds to the antigen with a high binding affinity as determined by a dissociation constant (K_d , or corresponding K_b , as defined below) value of 10^{-7} M or less. An antigen binding protein that specifically binds to human mesothelin may be able to bind to mesothelin from other species as well with the same or different affinities.

[0065] An “epitope” is the portion of a molecule that is bound by an antigen binding protein (e.g., by an antibody). An epitope can comprise non-contiguous portions of the molecule (e.g., in a polypeptide, amino acid residues that are not contiguous in the polypeptide’s primary sequence but that, in the context of the polypeptide’s tertiary and quaternary structure, are near enough to each other to be bound by an antigen binding protein).

[0066] The “percent identity” of two polynucleotide or two polypeptide sequences is determined by comparing the sequences using the GAP computer program (a part of the GCG Wisconsin Package, version 10.3 (Accelrys, San Diego, Calif.)) using its default parameters.

[0067] The terms “polynucleotide,” “oligonucleotide” and “nucleic acid” are used interchangeably throughout and include DNA molecules (e.g., cDNA or genomic DNA), RNA molecules (e.g., mRNA), analogs of the DNA or RNA generated using nucleotide analogs (e.g., peptide nucleic acids and non-naturally occurring nucleotide analogs), and hybrids thereof. The nucleic acid molecule can be single-stranded or double-stranded. In one embodiment, the nucleic acid molecules of the invention comprise a contiguous open reading frame encoding an antibody, or a fragment, derivative, mutein, or variant thereof, of the invention.

[0068] Two single-stranded polynucleotides are “the complement” of each other if their sequences can be aligned in an anti-parallel orientation such that every nucleotide in one polynucleotide is opposite its complementary nucleotide in the other polynucleotide, without the introduction of gaps, and without unpaired nucleotides at the 5’ or the 3’ end of either sequence. A polynucleotide is “complementary” to another polynucleotide if the two polynucleotides can hybridize to one another under moderately stringent conditions. Thus, a polynucleotide can be complementary to another polynucleotide without being its complement.

[0069] A “vector” is a nucleic acid that can be used to introduce another nucleic acid linked to it into a cell. One type of vector is a “plasmid,” which refers to a linear or circular double stranded DNA molecule into which additional nucleic acid segments can be ligated. Another type of vector is a viral vector (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), wherein additional DNA segments can be introduced into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors comprising a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. An “expression vector” is a type of vector that can direct the expression of a chosen polynucleotide.

[0070] A nucleotide sequence is “operably linked” to a regulatory sequence if the regulatory sequence affects the expression (e.g., the level, timing, or location of expression) of the nucleotide sequence. A “regulatory sequence” is a

nucleic acid that affects the expression (e.g., the level, timing, or location of expression) of a nucleic acid to which it is operably linked. The regulatory sequence can, for example, exert its effects directly on the regulated nucleic acid, or through the action of one or more other molecules (e.g., polypeptides that bind to the regulatory sequence and/or the nucleic acid). Examples of regulatory sequences include promoters, enhancers and other expression control elements (e.g., polyadenylation signals). Further examples of regulatory sequences are described in, for example, Goeddel, 1990, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, Calif. and Baron et al., 1995, *Nucleic Acids Res.* 23:3605-06.

[0071] A “host cell” is a cell that can be used to express a nucleic acid, e.g., a nucleic acid of the invention. A host cell can be a prokaryote, for example, *E. coli*, or it can be a eukaryote, for example, a single-celled eukaryote (e.g., a yeast or other fungus), a plant cell (e.g., a tobacco or tomato plant cell), an animal cell (e.g., a human cell, a monkey cell, a hamster cell, a rat cell, a mouse cell, or an insect cell) or a hybridoma. Typically, a host cell is a cultured cell that can be transformed or transfected with a polypeptide-encoding nucleic acid, which can then be expressed in the host cell. The phrase “recombinant host cell” can be used to denote a host cell that has been transformed or transfected with a nucleic acid to be expressed. A host cell also can be a cell that comprises the nucleic acid but does not express it at a desired level unless a regulatory sequence is introduced into the host cell such that it becomes operably linked with the nucleic acid. It is understood that the term host cell refers not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to, e.g., mutation or environmental influence, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

[0072] As used herein, a “non-chimpanzee primate” or “non-chimp primate” or grammatical variants thereof refers to any primate other than chimpanzee, i.e. other than an animal of belonging to the genus *Pan*, and including the species *Pan paniscus* and *Pan troglodytes*, also known as *Anthropopithecus troglodytes* or *Simia satyrus*. Most preferred is *Macaca fascicularis* (also known as Cynomolgus monkey and, therefore, throughout the application alternatively referred to as “Cynomolgus”) and *Macaca mulatta* (rhesus monkey, or “rhesus”).

[0073] In one embodiment, the antigen binding proteins of the present invention may be selected to bind to membrane-bound mesothelin as expressed on cells. In certain embodiments, the antigen binding proteins of the present invention preferentially bind membrane-bound mesothelin over soluble mesothelin. In one embodiment, the antigen binding proteins bind membrane-bound mesothelin at least 5 fold, 10 fold, 15 fold, 20 fold, 25 fold, 30 fold, 40 fold, 50 fold, 100 fold, 500 fold, or 1000 fold greater than soluble mesothelin. In one embodiment, the antigen binding proteins of the present invention preferentially bind membrane-bound mesothelin 30 fold greater than soluble mesothelin.

[0074] In one embodiment, the antigen binding proteins of the present invention specifically bind to human mesothelin. In a further embodiment, the antigen binding proteins binding to human mesothelin may also bind to mesothelin of other species. In one embodiment, the antigen binding proteins of the present invention bind to human, cynomolgous and murine mesothelin.

[0075] The polynucleotide and polypeptide sequences for several species of mesothelin are known. Table 1 presents nonlimiting, representative examples of sequences for human, mouse, rat, and nonhuman primate (e.g., cynomolgus). Additional examples are readily found in publicly available databases (e.g., NCBI).

TABLE 1

Mesothelin Sequences	
Human (Homo sapiens) polynucleotides	(SEQ ID NO: 1)
NCBI Reference Sequence: NM_005823.5 (Variant 1)	
TGCCAGGCTCTCCACCCCACTTCCCAATTGAGGAAACCGAGGCAGAGGAGCTCAGCGCCACGCACTCC	
TCTTTCTGCCTGGCGGCCACTCCCGTCTGTGTGACGCGCGGACAGAGACTACCGGTGGACCCACGGT	
GCCTCCCTCCCTGGGATCTACACAGACCATGGCCTTGCCAACGGCTCGACCCCTGTTGGGGTCTCTGTGG	
ACCCCGCCCTCGGCAGCCTCCTGTTCTGTCTTTCAGCCTCGGATGGGTGCAGCCCTCGAGGACCTGG	
CTGGAGAGACAGGGCAGGAGCTGCGCCCTGGACGGAGTCTGGCCAACCCACCTAACATTTCCAGCCT	
CTCCCCCTCGCAACTCCTTGGCTTCCCGTGTGCGGAGGTGTCCGGCCTGAGCACGGAGCGTGTCCGGGAG	
CTGGCTGTGGCCTTGGCAGAGAAGATGTCAAGCTCTCAACAGAGCAGCTGCGCTGTCTGGCTCACCGGC	
TCTCTGAGCCCCCGAGGACCTGGACGCCCTCCCATTTGGACCTGCTGTATTCTCAACCCAGATGCGTT	
CTCGGGGCCCCAGGCCTGCACCCGTTTCTTCTCCCGCATCACGAAGGCCAATGTGGACCTGCTCCCGAGG	
GGGGCTCCCGAGCGACAGCGCTGCTGCCTGCGGCTCTGGCCTGCTGGGGTGTGCGGGGTCTCTGCTGA	
GCGAGGCTGATGTGCGGGCTCTGGGAGCCTGGCTTGCGACCTGCCTGGGCGCTTTGTGGCCGAGTCGGC	
CGAAGTGCTGTACCCCGGCTGGTGTGAGCTGCCCGGGACCCCTGGACAGGACAGAGAGGCGAGCCAGG	
GCGGCTCTGCAGGGCGGGGACCCCCCTACGGCCCCCGTGCACATGGTCTGTCTCCACGATGGACGCTC	

TABLE 1-continued

Mesothelin Sequences	
TGCGGGGCTGCTGCCCCGTGCTGGGCCAGCCCATCATCCGAGCATCCCGCAGGGCATCGTGGCCGCGTG GCGGCAACGCTCCTCTCGGGACCCATCTTGGCGGCAGCCTGAACGGACCATCTCCGGCCGCGGTTCCGG CGGGAAGTGGAGAAGACAGCCTGTCTTCAGGCAAGAAGGCCCGCAGATAGACGAGAGCCTCATCTTCT ACAAGAAGTGGGAGCTGGAAGCCTGCGTGGATGCGGCCCTGCTGGCCACCCAGATGGACCGCGTGAACGC CATCCCCCTTACCTACGAGCAGCTGGACGCTCTAAAGCATAAACTGGATGAGCTCTACCCACAAGGTTAC CCCGAGTCTGTGATCCAGCACCTGGGTACCTCTTCTCAAGATGAGCCCTGAGGACATTCGCAAGTGGA ATGTGACGTCCTGGAGACCTGAAGGCTTTGCTTGAAGTCAACAAAGGGCACGAAATGAGTCCTCAGGT GGCCACCCTGATCGACCGCTTTGTGAAGGAAGGGGCCAGCTAGACAAGACACCCTAGACACCCTGACC GCCTTCTACCTGGGTACCTGTGCTCCCTCAGCCCCGAGGAGCTGAGCTCCGTGCCCCCAGCAGCATCT GGGCGGTGAGGCCCCAGGACCTGGACACGTGTGACCCAAGGCAGCTGGACGTCCTCTATCCAAGGCCCG CCTTGCTTTCCAGAACATGAACGGGTCCGAATACTTCGTGAAGATCCAGTCTTCTTGGGTGGGCCCCC ACGGAGGATTGAAGGCGCTCAGTCAGCAGAATGTGAGCATGGACTTGGCCAGTTTATGAAGTGCAGGA CGGATGCGGTGCTGCCGTTGACTGTGGCTGAGGTGCAGAACTTCTGGGACCCACGTGGAGGGCCTGAA GGCGAGGAGCGGCACCGCCCGGTGCGGGACTGGATCTACGGCAGCGGCAGGACGACCTGGACACGCTG GGGCTGGGGCTACAGGCGGCATCCCCAACGGTACCTGGTCTTAGACCTCAGCATGCAAGAGGCCCTCT CGGGGACGCCCTGCCTCCTAGGACCTGGACCTGTTCTCACCGTCTTGGCACTGCTCTAGCCTCCACCTT GGCCTGAGGGCCCCACTCCCTTGCTGGCCCCAGCCCTGCTGGGATCCCCGCTGGCCAGGAGCAGGCAC GGGTGTTCCCGTTCCACCCCAAGAGAACTCGCGCTCAGTAAACGGGAACATGCCCCCTGCAGACAGTA AAAAAAAAAAAAAAAA	
Human (Homo sapiens) amino acid	(SEQ ID NO: 2)
GenBank: BAA08419.1; GenBank: AAH09272.1 MALPTARPLLGSCTPALGSLFLFLFSLGWVQPSRTLGETGQEAAPLDGVLNPPNISI LSPRQLLGFPCEVSGSLSTERVRELAVALAKNVKLSTEQLRCLAHRLSEPPDLDALPL DLFLFLNPDAFSGPQACTRFFSRITKANVDLLPRGAPERQRLPAALACWGVRSLLSEA DVRALGLACDLPRFVAESAIEVLLPRLVSCPGPLDQDQEAARAALQGGGPPYPGPPSTW SVSTMALRGLLPVLGQPIIRSIPQGIWAARQRSSRDPSWRQPRTLPRPRFREVEKT ACPSGKKAREIDESLIFYKKWELEACVDAALLATQMDRVNAIPFTYEQLDVLKHKLDELY PQGYPESVIQHLGYLFLKMPEDIRKWNVTSLETALKALLEVNKGHEMSPQAPRRPLPQVA TLIDRFVKGRQLDKDLDLTAFYPGYLCSLSPEELSSVPPSSIWAVRPQDLDTCDPRQ LDVLYPKARLAFQNMNGSEYFVKIQSFLGGAPTEDLKALSQQNVSMDLATFMKLRTDAVL PLTVAEVQKLLGPHVEGLKAEERHRPVRDWILRQRQDDLDLTGLGLQGGIPNGYLVLDLS MQEALSGTPCLLGPGPVLTVLALLLASTLA	
Mouse (Mus musculus) polynucleotide	(SEQ ID NO: 3)
NCBI Reference Sequence: NM_018857.1 GGACAGCTGCTTTCCAGGCCCAAAGCCCTTCGTTGTCTCCAAACAGTGGTGTGGGTTGAGGGGTGGG ACAAGTGGGACCTCAGAGTCATTGTTATCCACAGACCATGGCCTTGCCAACAGCTCGACCCCTGCTGGG GTCTGTGGAAGTCCCATCTGCAGCCGAAGCTTCTACTGCTTCTCTTAGTCTTGGGTGGATACCAGT CTGCAGACCCAGACTACAAGACAAGCCAGGAGGCCACACTCTCCATGCTGTGAACGGTGCCGCTGACT TTGCCAGTCTCCCCACAGGCCTCTTCTTGGCCTCACATGTGAGGAGGTATCTGACCTGAGCATGGAACA	

TABLE 1-continued

Mesothelin Sequences
AGCCAAGGGGCTGGCTATGGCTGTAAGACAGAAGAACATTACACTCCGGGGACATCAGCTGCGTTGTCTG GCACGTCGCCTTCTAGGCACCTCACCGACGAGGAAGTGAATGCTCTTCCACTGGACCTGCTGCTCTTCC TCAACCCAGCCATGTTTCCAGGGCAACAGGCTTGTGCCACTTCTTCTCCCTCATCTCTAAAGCCAATGT GGATGTACTCCACGGAGGTCTCTGGAGGCCAGAGGCTGCTGATGGAGGCTCTGAAGTGCCAGGGCGTG TATGGATTTCAAGTGAGTGAGGCAGATGTGCGGGCTCTCGGAGGCTGGCCTGTGACCTGCCTGGGAAAT TTGTGGCCAGATCTTCCGAAGTTCTCTCCCTGGCTGGCAGGATGCCAAGGACCCCTGGACCAGAGCCA GGAAAAGGCAGTCAGGGAGGTTCTGAGGAGTGGAAGAACCAATATGGCCCCCATCGAAGTGGTCAGTC TCCACCTGGATGCCCTGCAGAGCTTGGTAGCAGTGTTGGATGAGTCCATCGTCCAGAGCATCCCCAAGG ATGTCAAAGCTGAATGGCTGCAACACATCTCCAGAGACCCCTCCAGGCTGGGGTCTAAGCTGACCGTCAT ACACCCAAGGTTCCGACGGGATGCAGAACAGAAAGCCTGCCCTCCAGGGAAGGAGCCCTACAAGGTGGAT GAAGACCTCATCTTCTACCAGAATTGGGAGCTGGAGGCTTGTGTAGATGGCACCATGCTGGCCAGACAAA TGGACCTTGTGAACGAGATTCCTTCCACCTATGAGCAGCTCAGTATCTTTAAGCACAACTGGACAAGAC CTACCCACAAGGCTATCTGAGTCCCTGATCCAGCAGCTGGGTCACTTCTTCAGATATGTTAGCCCTGAA GACATCCACCAGTGGAATGTGACCTCACCAGACACAGTGAAAACCTCTGCTCAAAGTCAGCAAAGGACAAA AGATGAATGCTCAGGCGATTGCCCTGGTCGCTCTATCTTCGGGGAGGAGGCCAGCTGGACGAGGATAT GGTAAAGCCCTGGGCGACATCCCGTTAAGCTATCTATGTGACTTCAGCCCCCAGGATCTGCACTCGGTA CCCTCCAGTGTCATGTGGCTGGTGGGGCCCAAGACCTGGACAAGTGCAGCCAGAGGCATCTGGGTCTCC TCTACCAGAAGGCTGCTCAGCCTTCCAGAATGTGAGCGGCTAGAACTTTGAGAAAATCAAGACATT CCTGGGTGGGGCTCCGTGAAGGACCTGCGGGCCCTCAGCCAGCACAATGTGAGCATGGACATAGCCACT TTCAAGAGGCTGCAGGTGGATTCCCTGGTGGGGCTGAGTGTGGCTGAGGTACAGAACTTCTGGGGCCAA ACATTGTGGACCTGAAGACCGAGGAGGATAAAAGCCCTGTCCGTGACTGGCTGTTCCGGCAGCATCAGAA AGACCTAGACAGGCTGGGTTTGGGACTTCAGGGTGGCATCCCCAATGGCTACCTGGTCCTGGACTTCAAT GTCCGAGAGGCTTCTCCAGCAGAGCCTCACTCCTTGGGCCAGGATTTGTATTAATATGGATTCCAGCTC TGCTCCAGCTTTAAGGCTGAGCTGAGACCACCCCTGCAAGGCTCCTGGTCCAGCTCTACTGGGGCC CTCTTGACCAGGAGTGGGTACAGGGGTCAATTGCCAAAGTTTGAAGGACTCTTGAACCTCAATAAACAGTGG CATATGCTCCCTTGAAAAAAAAAAAAAAAAAAAAA
Mouse (Mus musculus) amino acid GenBank: EDL22444.1 MALPTARPLLGSCGSPICSRSFLLLLSLGWIPRLQTQTTKTSQEATLLHAVNGAADFASLPTGLFLGLT CEEVSDLSMEQAKGLAMAVRQKNITLRGHQLRCLARRLPRHLTDEELNALPLDLLFLNPFMPGQQA HFFSLISKANVDVLPRLSLERQRLMEALKCQGVYGFQVSEADVRLGGLACDLPKPFVARSEVLLPWL AGCQGPLDQSQEKAVREVLRSRGTQYGPSPKWSVSTLDALQSLVAVLDESIVQSIPKDVKAEWLQHISR PSRLGSKLTVIHPRFRDAEQKACPPGKEPYKVEDLIFYQNWELEACVDGTMLARQMDLVNEIPFTYEQ LSIFKHKLDKTPQGYPELIQQLGHFFRYVSPEDIHQWNVTSPTVKTLLKVSQKQKMAQAIALVACY LRGGQLDEDMVKALGDIPLSYLDCDFSPQDLHSPSSVMWLVPQDLQKCSQRHLGLLYQKACSAFQNV GLEYPEKIKTFLGGASVKDLRALSQHNVSMDIATFKRLQVDSLVLGSLVAEVQKLLGPNIVDLKTEEDKSP VRDWLFRHQKDLDRGLGLQGGIPNGYLVLD FNVREAFSSRASLLGPGFVLIWIPALLPALRLS

TABLE 1-continued

Mesothelin Sequences	
Rat (<i>Rattus norvegicus</i>) polynucleotide	(SEQ ID NO: 5)
GenBank: D87351.1	
TGCCAACAGGCCCTCACTGTGTCCAAACAGTGGTGTGAGTTGAGGGGTGGGACAGTGGGGACCTCAGA	
ACCATTTGTTATCCACAGACCATGGCCCTTGCCAAACAGCCCAACCCCTGCTGGGGTCCTGTGGAAGCCCCAT	
CTGCAGCCGACAGCTTTCTACTGCTTCTCCTTAGTCTTGGGTGGTTGCCACTTCTGCAGACCCAGACTACA	
AGGACAAGCCAGGAGGCCGCACTTCTCCATGCTGTGACCGGCACCGTTGACTTTGCCAGTCTTCCACAG	
GCCTCTTTCTTGGCCTCACGTGTGATGAGGTATCTGGCCTAAGCATGGGACACGCCAAGGAGCTGGCTAT	
GGCTGTGAGACAGAAGAATATCGTGCTCCAAGTACATCAGTGCCTGTCTGGCCCGTCGCCTCCCTAAG	
CACCTCACCAACGAGGAACGTGATGCTCTCCACTGGACCTGCTGCTCTTCTCAATCCAGCCATGTTTC	
CGGGGCAACAGGCTTGTGCCCACTTCTTCTCCCTCATCTCTAAAGCCAATGTAAATGTACTCCACGGAG	
ATCTCTGGAGCGCCAGAGGCTGCTGACCGGGCTCTGAAATGCCAGGTGTGTATGGATTTCAAGTGAGT	
GAGACGGATGCACGGGCTCTCGGAGGCTGGCCTGTGACCTGCCTGGGAATTCTGGCCAAATCTTCGG	
AAGTCCTCTCCCTGGCTGGCAAGATGCGGAGGACCCCTGGACCAAGGCCAGGCAAAGGCTGTCAAGGA	
GGTTCTGAGGAGTGAAGAGCCCCCTATGTTCCCCATCGACGTGGTCAGTCTCCACCCTGGATGCCCTG	
CAGGGTTTGTGTAGTGTGATGAGTCCATTGTCCACAGCATCCCTAAGGATGTTATCACTGAATGGC	
TGCAAGGCATCTCCAGAGAGCCCTCCAGGCTGGGGTCTAAGTGGACTGTCACACACCCAAGTTCCGGCG	
GGACACAGAAACAGAAAGCTGCCCTCCAGGAAGGAGCCTAACGTGGTGGATGAAAACCTCATCTTCTAC	
CAGAATTGGGAGCTGGAGGCTTGTGTCGATGGTACCCTGCTGGCCGGCCAGATGGACCTTGTGAATGAAA	
TTCCCTTTACCTACGAGCAGCTCAGCATCTTCAAGCACAACTGGACAAGACCTACCCACAAGGCTATCC	
CGAGTCCCTGATCAAGCAGCTGGGCCACTTCTTCAGATACGTTAGCCCTGAGGACATCCGGCAGTGGAAT	
GTGACTTCACCAGACAGTGAATACTCTGCTTAAAGTCAGCAAAGGACAAAAGATGGATGCTCAGGTGA	
TTGCCTTGGTCGCCTGCTATCTTCGGGGAGGAGGCAAGCTGGACGAGGACATAGTAAAAGCCCTGGACAA	
CATCCCCCTTAAGTTACCTATGTGACTTCAGCCCCAGGATCTGCACGCTATACCCCTCCAGTGTTATGTGG	
CTGGTTGGGCTCCATGACCTGGACAAGTGCAGCCAGAGGCATCTGGGTATCCTCTATCAGAAGGCCTGCT	
CAGCCTTCCAGAACGTGAGCGGGCTGGAATACTTTGAGAAAATCAGGACATTTCTGGGTGGGGCCTCCAG	
GGAGGACCTGCGGGCCCTCAGCCAGCACAAATGTGAGTATGGACATAGCCACTTTCAAGAAGCTGCAGGTG	
GATGCCCTGGTGGGGCTGAGTGTGGCTGAGGTACAGAACTTCTAGGGCCACACATTGGGGACCTGAAGA	
CTGAGGAGGATAAAAGCCCTGTCCGGGACTGGCTCTTCCGACAGCAGCAGAAAGACCTGGACAGTCTGGG	
TTTGGGACTTCAGGGTGGCATCCCAATGGCTACCTGATCCTAGACTTCAATGTCCGAGAGGCCTTCTCC	
AGTGGAGCCCCACTCCTTGGGCCAGGATTTGTGTTTGCATGGATTCCAGCTCTGCTCTCAGCTTTAAGAC	
TGAGCTGAGACCACCACTCCTAAGGCTCCTGGTCCCAGCTCTATTGTGAGCCCCATCTTGACCAGGAGG	
GGATACCAGGGGTCTATTGCCAAAGTTTGAAGATTCTTGAACCAATAAACAGTGGCATGTGCCCCCTTG	
Rat (<i>Rattus norvegicus</i>) amino acid	(SEQ ID NO: 6)
GenBank: EDM03949.1	
MALPTAQPLLGS CGSPICSRSFLLLLLSLGLWPLLLQTQTRTSQEAALLHAVTGTVDFA SLPTGLFLGLM	
CDEVSGLSM GHAKELAMAVRQKNIVLQVHQLRCLARRLPKHLTNEELDALPLDLLLFLNPAMFPQQQACA	
HFFSLISKANVNVLP RRSLEQRLLTGALKCQGVYGFQVSETDARALGGLACDLPGEFVAKSSEVLLPWL	
ARCGGPLDQ GQAKAVREVLRSGRAPYGPPTSWSVSTLDALQGLLVVLDSEIVHSIPKDVITEWLQGISRE	

TABLE 1-continued

Mesothelin Sequences	
PSRLGSKWTVTTHPRFRDTEQKACPPGKEPNVVDENLIFYQNWLEACVDGTLTAGQMDLVNEIPFTYEQ	
LSIFKHKLDKTYPQGYPESLIKQLGHFFRYVSPEDIRQWNVTSPDTVNTLLKVSQKQMDAQVIALVACY	
LRGGGKLDEDIVKALDNIPLSYLCDFSPQDLHAIPSSVMWLVLGLHDLKCSQRHLGILYQKACSAFQNV	
GLEYPFEKIRTFLLGASREDLRALSQHNVSMDIATFKKLQVDALVGLSVAEVQKLLGPHIGDLKTEEDKSP	
VRDWLFRQQQKDLDSLGLGLQGGIPNGYLILDENVREAFSSGAPLLGPGFVFAWIPALLSALRLS	
Cynomolgus (Macaca mulatta) polynucleotides	(SEQ ID NO: 7)
NCBI Reference Sequence: XM_001087333.2 (predicted)	
ATGGCCTTGCCAATGGCTCGACCCCTGTGCGGGTCTGTGGGACCCCGCCCTCGGCAGCCTCTGTTCC	
TGCTCTTCAGCCTCGGATGGGTGCAGCCCTCGAGGTCCTGGCTGGAGAGACAAGGCAGGCCGCGCCCT	
GGATGGAATCCTGACCAATGCACCTGACATGCGCAGCCTCTCCACGCAACTCCTTGGCTTCACGTGT	
GTGGAGGTGTCCGCGCTGAGCACAGAGCTCGTCCAGGAGCTGGCTGTGGCCTTGGGACAGAAGAATGTCA	
AGCTCTCCGAGAGCAGCTGCGCTGTCTGGCTCACCAGCTCTCTGAGCCCCCGAGGACCTGGACGCCCT	
CCCGCTGGACCTGCTGCTCTTCTCAACCCAGACGCGTTCTCGGGGCCCCAGGCTGCACCCACTTCTTC	
TCCCGCGTCGCGAAGGCCAACGTGGACCTGCTCCCGGGGGGCTCTGAGAGACAGAGGCTGTGCCCCG	
GGGCTCTGACCTGCTGGGGTGTGCGGGGTCTCTGCTGAGCGAGGCTGATGTACGGGCTCTGGGAGGCT	
GGCTTGCAGCTGCTGGGCGCTTGTGGCCGAGTCGCGCAGAGTGGTGCTACCCCGCTGGTCCGCTGC	
TTGGGACCCCTGGACAGGACAGCAGGAAGCAGCCAGGGCGGCTCTGCAGAGAGGAGACCCCTACG	
GCCCCCGTCAACGTGGTCTATCTCCACCCTGGACGATCTGCAGAGCCTGTTGCCTGTGCTGGGCCAGCC	
CGTCATCTCTGCTCGTCTCAGGGCATCCTGGCCGCATGGCGGCAACGCTCCTCTCGGGACCCATCCTGG	
CAGCAGCCGGAACAGACCGTCTCCGGCTGAGGTTCCGGCGGGACGTGGAGAGGACAACCTGTCCCCAG	
AGAAAGAGGTCCACGAGATAGACGAGACCTCATCTTCTACAAGAAGCGGAGCTGGAAGCCTGCGTGGA	
CCCAGCCCTGCTGGCCGCCAGATGGACCGTGTGGACGCCATCCCTTCACCTACGAGCAGCTGGACGTC	
CTAAAGCATAAATGGATGAGCTCTACCCACAAGGCTACCCCGAGTCTGTGATCCGGCACCTGGGCCACC	
TCTTCTCAAGATGAGCCCTGAGGACATTCGAAATGGAACGTGACGTCCCTGGAGACCTGAAGGCTCT	
GCTCAAAGTCAGCAAGGGGATGAAATGAGTGCTCAGGTGGCCACCTGATTGACCGCGTTGTGGTGGGA	
AGGGGCCAGCTAGACAAAGACACCGTAGACACGCTGACTGCCTTCTGCCCGGGTGCCGTGTGCTCCCTCA	
GCCCCGAGAGGCTGAGCTCCGTGCCCCCAGCGTCATCGGGCGGTCAGGCCCCAGGACCTGGACACGTG	
TGGCCCGAGGCGAGCTGGACGTCCTATCCCAAGGCCCGCCTTGCTTCCAGAACATGAGCGGGTCCGAA	
TACTTCGTGAAGATCCGGCCCTTCTGGGTGGGGCCCCACGGAGGATGTGAAGGCTCTCAGTCAGCAGA	
ATGTGAGCATGGAATTGGCCACGTTATGAAGCTGCGGAGGGAAGCGGTGCTGCCGTTGACTGTGGCTGA	
AGTGCAGAACTTCTGGGACCCACGTGGAGGGCTGAAGGTGGAGGAGCAGCACAGCCCCGTGCGGGAC	
TGGATCTTAAGCAGCGGCAGGACGACCTGGACACACTGGGGCTGGGGCTACAGGGCGGCATCCCCAACG	
GCTACCTGATCTTAGACCTCAGTGTGCGAGAGGCCCTCTCGGGACGCCCTGCCTCTAGGACCTGGACC	
TGTACTACCGTCTGGCTTTGCTCTTGGCCTCCACCTGGCCTGAGGACCTACTCCCTGTGTGGCCCC	
AGCCCTGCTGGGGATCCCCGCTGGCCAGGAGCAGGCATAGGTGGTCCCTGTTCCACCCAGGAGAACTT	
GCGCTCAGTAAACGCGAACATGCCCCCT	

TABLE 1-continued

Mesothelin Sequences
Cynomolgus (Macaca fascicularis) amino acid (SEQ ID NO: 8) (partial hypothetical)
GenBank: EHH60027.1
MALPMARPLSGSGTTPALGSLLELLFSLGWVQPSRVLAGETRQEAPLDGILTNAPDIASLSPRQLLGFT
CVEVSGSLSTELVQELAVALLGQKNVKLSAEQLRCLAHRLSEPPEDLDALPLDLLLFLKQASVQGVGRGSLLS
EADVRLGGLACDLPGRFVAESAEEVLPRLVRCCLGPLDQDQQAARALQRGPPYPGPSTWSISTLDDL
QSLLPVLGQPVIHSIPQGILAAWRQRSSRDPSWQQPEQTVLRPRFRDVERTTCPEKEVHEIDENLIFY
KKRELEACVDAALLAAQMDRVDAIPFTYEQLDVLKHKLDLYPQGYVESVIRHLGHLFLKMSPEDIRKWN
VTSLLETALKALKVSKGHEMSAQVATLIDRVVVRGQLDKDTADTLTAFCPGCLCSLSPERLSRVPPSVIG
AVRPQDLDTGPRQLDVLYPKARLAFQNMMSGSEYFVKIRPFLGGAPTEDLKALSQQNVSMDLATFMKLR
EAVLVGRAGGGGSGGDNREGV

Antigen Binding Proteins

[0076] In referring to the different antigen binding proteins of the invention, arbitrary designations have been given to identify the different antigen binding proteins (e.g., “ab237”). In some instances, the designation may have variations for the same antigen binding proteins (e.g., “ab237” “237”, or “2.37” all refer to the same antigen binding protein).

[0077] In one aspect, the present invention provides antigen binding proteins (e.g., antibodies, antibody fragments, antibody derivatives, antibody muteins, and antibody variants), that specifically bind to human mesothelin. In one embodiment the antigen binding protein is a human antibody.

[0078] In one embodiment, the antigen binding protein (e.g., antibody) comprises sequences that each independently differ by 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of those listed in Table 2 below. As used herein, a CDR sequence that differs by no more than a total of, for example, four amino acid additions, substitutions and/or deletions from a CDR sequence shown in Table 2 below refers to a sequence with 4, 3, 2, 1 or 0 single amino acid additions, substitutions, and/or deletions compared with the sequences shown in Table 2.

[0079] The amino acid sequences of light chain CDRs of exemplary antigen binding proteins (antibodies) and the heavy chain CDRs of exemplary antigen binding proteins (antibodies) are shown below in Table 2.

TABLE 2

Ab	CDR 1	CDR 2	CDR 3
LIGHT CHAIN CDR AMINO ACID SEQUENCES			
Ab237	RASQSINNYLN	AASSLQS	QQTYSNPT
AA	(SEQ ID NO: 9)	(SEQ ID NO: 10)	(SEQ ID NO: 11)
Ab1.1.2	RASQYIGSNLH	YASQSFS	HQSSSLPWT
AA	(SEQ ID NO: 12)	(SEQ ID NO: 13)	(SEQ ID NO: 14)
Ab1.33.1	QSSLSLQHSNGKTYLY	EVSNRFS	MQSKQLPCS
AA	(SEQ ID NO: 15)	(SEQ ID NO: 16)	(SEQ ID NO: 17)
Ab1.33.1y	QSSLSLQHSNGKTYLY	EVSNRFS	MQSKQLPYS
AA	(SEQ ID NO: 18)	(SEQ ID NO: 19)	(SEQ ID NO: 20)
Ab1.68.1	RASQTVSSSYLA	GASIRAT	QQYGSSLT
AA	(SEQ ID NO: 21)	(SEQ ID NO: 22)	(SEQ ID NO: 23)
Ab1.78.1	RASQSIGSSLH	YASQSFS	HQSSSLPWT
AA	(SEQ ID NO: 24)	(SEQ ID NO: 25)	(SEQ ID NO: 26)
Ab1.119.1	RSSQSLVHSDRNTYLS	KISNRFS	MQATQFPLT
AA	(SEQ ID NO: 27)	(SEQ ID NO: 28)	(SEQ ID NO: 29)
Ab2.69.2	RSSLSLLHSNGYNYLD	LGSNRAS	MQGLHTPPS
AA	(SEQ ID NO: 30)	(SEQ ID NO: 31)	(SEQ ID NO: 32)
Ab2.69.2-cv	QASQDISNYLN	AASSLET	QQYDNL
AA	(SEQ ID NO: 33)	(SEQ ID NO: 34)	(SEQ ID NO: 35)
Ab2.69.2-s	QASQDISNYLN	AASSLET	QQYDNL
AA	(SEQ ID NO: 36)	(SEQ ID NO: 37)	(SEQ ID NO: 38)
Ab1.58	RASQGIRNALG	AASSLQS	LQHNSYPRT
AA	(SEQ ID NO: 39)	(SEQ ID NO: 40)	(SEQ ID NO: 41)
Ab1.51	RASQGIRNDLH	AASSLQS	LQHYSYPWT
AA	(SEQ ID NO: 42)	(SEQ ID NO: 43)	(SEQ ID NO: 44)
HEAVY CHAINS CDR AMINO ACID SEQUENCES			
Ab237	NNYYWT	YIYYSGSTFYNP	EDTMTGLDV
AA	(SEQ ID NO: 45)	(SEQ ID NO: 46)	(SEQ ID NO: 47)

TABLE 2-continued

Ab	CDR 1	CDR 2	CDR 3
Ab1.1.2	SYGMH	AIWYDGSNKYYADSVKG	DLSIFGVVILSDY
AA	(SEQ ID NO: 48)	(SEQ ID NO: 49)	(SEQ ID NO: 50)
Ab1.33.1	GDGHFWS	YIYSGSTYYNPSLKS	LRGGYKFDY
AA	(SEQ ID NO: 51)	(SEQ ID NO: 52)	(SEQ ID NO: 53)
Ab1.68.1	NYYWS	RIFTSGSTNYNPSLKS	EGGHYGSSGYLYYYYFGMDV
AA	(SEQ ID NO: 54)	(SEQ ID NO: 55)	(SEQ ID NO: 56)
Ab1.78.1	SYGMH	AIWYDGSNKYYADSVKG	DLSIFGVVILSDY
AA	(SEQ ID NO: 57)	(SEQ ID NO: 58)	(SEQ ID NO: 59)
Ab1.119.1	SGGYWVN	YIYSGSTYYNPSLRG	DGGDSYGRMDV
AA	(SEQ ID NO: 60)	(SEQ ID NO: 61)	(SEQ ID NO: 62)
Ab2.69.2	SNSVAWN	RTYRSKWYNDYAVSVKS	GIFVVPVPRFDY
AA	(SEQ ID NO: 63)	(SEQ ID NO: 64)	(SEQ ID NO: 65)
Ab1.58	SHYWS	YIYSGSTNYNPSLKS	DGWSAFDY
	(SEQ ID NO: 66)	(SEQ ID NO: 67)	(SEQ ID NO: 68)
Ab1.51	SYYWS	YIYSGSTNYNPSLKS	VDYKAFDI
	(SEQ ID NO: 69)	(SEQ ID NO: 70)	(SEQ ID NO: 71)

[0080] Table 3 below also provides the amino acid sequences of the variable light and variable heavy domains for exemplary anti-mesothelin antibodies.

TABLE 3

Anti-Mesothelin Variable Region Amino Acid Sequences	
Light Chain Variable Region Polynucleotide and Amino acid sequences	
Ab237	(SEQ ID NO: 72)
DIQMTQSPSSLSASVGRVTITCRASQSINNYLNWYQQKPGKAPTLIIYA	
ASSLQSGVPSRFSRSGSGTDFTLTISLQPEDFAAYFCQQTYSNPTFGQG	
TKVEVK	
Ab1.1.2	(SEQ ID NO: 73)
EIVLTQSPDFQSVTPKEKVTITCRASQYIGSNLHWYQQTPDQSPKLLIKY	
ASQSFSGVPSRFSRSGSGTDFTLTINSLEAEDAATYYCHQSSSLPWTFGQ	
GTKVEIK	
Ab1.33.1	(SEQ ID NO: 74)
DIVMTQTPLSLSVAPGQPASISCSLQHSNKGKTYLYWYLQKPGQPPQ	
LLIYEVSNNRFSRSGVDRFSGSGTDFTLKISRVEAEDVGIYYCMQSKQLP	
CSFGQGTKLEIK	
Ab1.33.1-y	(SEQ ID NO: 75)
DIVMTQTPLSLSVAPGQPASISCSLQHSNKGKTYLYWYLQKPGQPPQ	
LLIYEVSNNRFSRSGVDRFSGSGTDFTLKISRVEAEDVGIYYCMQSKQLP	
YSFGQGTKLEIK	
Ab1.68.1	(SEQ ID NO: 76)
EIVLTQSPGTLSSLSPGERATLSCRASQTVSSSYLAWYQQKPGQAPRLIIY	
GASIRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSTLTFGG	
GTKVEIK	

TABLE 3-continued

Anti-Mesothelin Variable Region Amino Acid Sequences	
Ab1.78.1	(SEQ ID NO: 77)
EIVLTQSPDFQSVTPKEKVTITCRASQSIGSSSLHWYRQKPDQSPKLLIKY	
ASQSFSGVPSRFSGGSGTDFTLTINSLEAEDAATYYCHQSSSLPWTFGQ	
GTKVEIK	
Ab1.119.1	(SEQ ID NO: 78)
DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDRNTYLSWLQQRPGQPPR	
LLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFP	
LTFGGGTKVEIK	
Ab2.69.2	(SEQ ID NO: 79)
DIVMTQSPLSLSVTPGEPASISCRSSSLHNSNGYNLDWFLQKPGQSPQ	
LLIYLGSNRASGVPDRFSGSGSDTDFTLKISRVEAEDVGVYYCMQGLHTP	
PSFGQGTKLEIK	
Ab2.69.2-s	(SEQ ID NO: 80)
DIQMTQSPSSLSASVGDRTTITCQASQDISNYLNWYQQKPGKAPNLLIYA	
ASSLETGVPSRFSGGSGTDFAPTISSLQPEDIAPIYYCQQYDNLFPFGPGT	
KVDIK	
Ab2.69.2-cv	(SEQ ID NO: 81)
DIQMTQSPSSLSASVGDRTTITCQASQDISNYLNWYQQKPGKAPKLLIYA	
ASSLETGVPSRFSGGSGTDFTLTISSLQPEDFATYYCQQYDNLFPFGQGT	
KVDIK	
Ab1.58	(SEQ ID NO: 82)
DIQMTQSPSSLSASVGDRTTITCRASQGIRNALGWYQQKPGKAPKRLIYA	
ASSLQSGVPSRFSGGSGTEFTLTISLQPEDFATYYCLQHNSYPRTFGQ	
GTKVEIRR	
Ab1.51	(SEQ ID NO: 83)
DIQMTQSPSSLSASVGDRTTITCRASQGIRNDLHWYQQKPGKAPKRLIYA	
ASSLQSGVPSRFSGGSGTEFTLTISLQPEDFATYYCLQHYSYPWTFGQ	
GTKVEIK	
Light Chain Constant Domain	
Optionally, a light chain constant domain is provided. An	
exemplary sequence is:	
	(SEQ ID NO: 84)
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD	
NALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGL	
SSPVTKSFNRGEC	

TABLE 3-continued

Anti-Mesothelin Variable Region Amino Acid Sequences	
Leader Sequence	
Optionally, a leader sequence is included to facilitate expression of the light chains in cell culture. An exemplary sequence is:	
MDMRVPAQLLGLLLLWLRGARC	(SEQ ID NO: 85)
Heavy Chain Variable Region Amino acid Sequences	
Ab237	(SEQ ID NO: 86)
QVQLQESGPGLVKPSQTLSTCTVSGGSINNNYYWTWIRQHPGKGLEWI	
GYIYYSGSTFYNP SLKSRVTISVDTSKQFSLKLSSVTAADTAVYYCARE	
DTMTGLDVWGQGT TTVSS	
Ab1.1.2	(SEQ ID NO: 87)
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAA	
IWYDGSNKYYADSVKGRFTISRDN SKNMLYLQMNSLRAEDTAVYYCARDL	
SIFGVVILSDYWGGQGT LVTVSS	
Ab1.33.1	(SEQ ID NO: 88)
QVQLQESGPGLVKPSQTLSTCTVSGGSISGDGHFWSWIRQHPGKGLEWI	
GYIYYSGSTYYPNPSL KSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARL	
RGGYKFDYWGGQGT LVTVSS	
Ab1.68.1	(SEQ ID NO: 89)
QVQLQESGPGLVKPSQTLSTCTVSGDSINNNYWSWIRQAPGKGLEWIGR	
IFTSGSTNYPNPSL KSRVTMSIDTSKNQFSLKLSSVTAADTAVYYCAREGG	
HYGSSGYLYYYYFGMDVWGQGT TTVSS	
Ab1.78.1	(SEQ ID NO: 90)
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAA	
IWYDGSNKYYADSVKGRFTISRDN SKNMLYLQMNSLRAEDTAVYYCARDL	
SIFGVVILSDYWGGQGT LVTVSS	
Ab1.119.1	(SEQ ID NO: 91)
QVQLQESGPGLVKPSQTLSTCTVSGGSISGGYYWNWIRQHPGKGLEWI	
GYIYYSGSTYYPNPSL RGLIISVDTSKNQFSLRLSSVTAADTAVYYCARD	
GGDSYGRMDVWGQGT TTVSA	
Ab2.69.2	(SEQ ID NO: 92)
QVQLQQSGPGLVKPSQTLSTLCAISGDSVSSNSVAWNWIRQSPSRGLEWL	
GRTTYRSKWYNDYAVSVKSRITINPDT SKNQFSLQLNSVTPEDTAVYYCA	
RGIFVVPVAVPRFDYWGGQGT LVTVSS	
Ab1.58	(SEQ ID NO: 93)
QVQLQESGPGLVKPSQTLSTCTVSGGSIISHYWSWIRQPPGKGLEWIGY	
IYYSGSTNYPNPSL KSRVTISVDTSKNQFSLKLTSVTAADTAVYYCARDGW	
SAPFDYWGGQGT LVTVSS	

TABLE 3-continued

Anti-Mesothelin Variable Region Amino Acid Sequences	
Ab1.51	(SEQ ID NO: 94)
QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGY	
IYYSGSTNYNPSLKSRTISVDTSKNQFSLKLSVTAADTAVVYCARVDY	
KAFDIWGQGTMTVSS	
Leader Sequence	
Optionally, a leader sequence is included to facilitate expression of the heavy chains in cell culture. An exemplary sequence is:	
(SEQ ID NO: 95)	
MKHLWFFLLLVAAPRWVLS	
Heavy Chain Constant Domain	
Optionally, a heavy chain constant domain is provided. In certain embodiment, this sequence consists of the heavy chain constant domain sequence from an IgG1, IgG2, IgG3, IgG4 or IgM. An exemplary sequence is:	
(SEQ ID NO: 96)	
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGL	
YSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELGGPSVF	
LPFPKPKDITLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV	
SVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSL	
TCLVKGFPYSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSV	
MHEALHNHYTQKSLSLSPGK	

[0081] Particular embodiments of antigen binding proteins of the present invention comprise one or more amino acid sequences that are identical to the amino acid sequences of one or more of the CDRs and/or FRs (framework regions) illustrated above. In one embodiment, the antigen binding protein comprises a light chain CDR1 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain CDR2 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain CDR3 sequence illustrated in above. In another embodiment, the antigen binding protein comprises a heavy chain CDR1 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain CDR2 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain CDR3 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain FR1 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain FR2 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain FR3 sequence illustrated above. In another embodiment, the antigen binding protein comprises a light chain FR4 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain FR1 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain FR2 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain FR3 sequence illustrated above. In another embodiment, the antigen binding protein comprises a heavy chain FR4 sequence illustrated above.

[0082] In another embodiment, at least one of the antigen binding protein's CDR3 sequences differs by no more than 6, 5, 4, 3, 2, 1 or 0 single amino acid addition, substitution, and/or deletion from a CDR3 sequence from the sequences as shown in Tables 2 and 3 above. In another embodiment, the antigen binding protein's light chain CDR3 sequence differs by no more than 6, 5, 4, 3, 2, 1 or 0 single amino acid addition, substitution, and/or deletion from a light chain CDR3 sequence from the sequences as shown above and the antigen binding protein's heavy chain CDR3 sequence differs by no more than 6, 5, 4, 3, 2, 1 or 0 single amino acid addition, substitution, and/or deletion from a heavy chain CDR3 sequence from the sequences as shown above. In another embodiment, the antigen binding protein further comprises 1, 2, 3, 4, or 5 CDR sequences that each independently differs by 6, 5, 4, 3, 2, 1, or 0 single amino acid additions, substitutions, and/or deletions from a CDR sequence of the sequences shown above. In another embodiment, the antigen binding protein comprises the CDRs of the light chain variable region and the CDRs of the heavy chain variable region set forth above. In a further embodiment, the antigen binding protein comprises the CDRs of any one of the antibodies listed above. In one embodiment, the antigen binding protein is a human antibody. In another embodiment, the antigen binding protein is a humanized antibody.

[0083] In one embodiment, the antigen binding protein (such as an antibody or antibody fragment) comprises a light chain variable domain comprising a sequence of amino acids that differs from the sequence of a light chain variable domain listed above only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0 residues, wherein each such sequence difference is independently either a deletion, insertion, or substitution of

one amino acid residue. In another embodiment, the light-chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a light chain variable domain listed above. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the polynucleotide sequence listed above. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the sequences listed above. In another embodiment, the light chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide that encodes a light chain variable domain selected from the group consisting of the sequences listed above.

[0084] In another embodiment, the present invention provides an antigen binding protein comprising a heavy chain variable domain comprising a sequence of amino acids that differs from the sequence of a heavy chain variable domain selected from the sequences listed above only at 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or 0 residue(s), wherein each such sequence difference is independently either a deletion, insertion, or substitution of one amino acid residue. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to the sequence of a heavy chain variable domain selected from the sequences listed above. In another embodiment, the heavy chain vari-

able domain comprises a sequence of amino acids that is encoded by a nucleotide sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identical to a nucleotide sequence that encodes a heavy chain variable domain selected from the sequences listed above. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under moderately stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the sequences listed above. In another embodiment, the heavy chain variable domain comprises a sequence of amino acids that is encoded by a polynucleotide that hybridizes under stringent conditions to the complement of a polynucleotide that encodes a heavy chain variable domain selected from the sequences listed above.

[0085] Antigen binding proteins (e.g., antibodies, antibody fragments, and antibody derivatives) of the invention can comprise any constant region known in the art. The light chain constant region can be, for example, a kappa- or lambda-type light chain constant region, e.g., a human kappa- or lambda-type light chain constant region. The heavy chain constant region can be, for example, an alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant regions, e.g., a human alpha-, delta-, epsilon-, gamma-, or mu-type heavy chain constant region. In one embodiment, the light or heavy chain constant region is a fragment, derivative, variant, or mutein of a naturally occurring constant region.

[0086] The nucleic acid (DNA) encoding constant heavy and constant light chain domains, and the amino acids sequences of heavy and light chain domains are provided herein below. Lambda variable domains can be fused to lambda constant domains and kappa variable domains can be fused to kappa constant domains.

IgG2 Heavy Constant domain DNA (SEQ ID NO: 186):

```
gctagcaccaagggcccatcggtcttccccctggcgccctgctccaggagcacctccgagagcacagcgccctgggctgcctggt
caaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgctctgaccagcggcggtgcacaccttcccagctgtcctacag
tctcaggactctactccctcagcagcggtgacgctgcctccagcaacttcggcaccagacctacacctgcaacgtagatcaca
agcccagcaacaccaagggtggacaagacagttgagcgcaaatgttgtgtcgagtgccaccgtgccagcaccacctgtggcagga
ccgtcagtccttcttccccccaaaaccaaggacaccctcatgatctcccgaccctgaggtcacgtgcgtggtggtggacgtgag
ccacgaagaccgccgaggtccagttcaactggtacgtggcggcggtggaggtgcataatgccaagacaaagccacgggaggagcag
ttcaacagcagcttccgtgtggtcagcgtcctcaccgttgtgcaccaggactggctgaacggcaaggagtacaagtgaaggtctcca
acaaaggcctcccagcccccatcgagaaaaccatctccaaaacaaaaggcagccccgagaaccacaggtgtacaccttgcctcc
atccccggaggagatgaccaagaaccaggtcagcctgacctgctggtcaaaggcttctaccccagcgacatcgcggtggagtggtg
agagcaatgggcagcgggagaacaactacaagaccacacctcccatgctggactccgacggctccttcttctctacagcaagctcac
cgtggacaagagcaggtggcagcaggggaacgtcttctcatgctccgtgatgcattgaggtctctgcacaaccactacacgcagaaga
gcctctccctgtctccgggtaaatga
```

IgG2 Heavy Constant domain Protein (SEQ ID NO: 187):

```
ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQ
SSGLYSLSVVTPSSNFGTQTYTCNVDHKPSNTKVDKTKVERKCCVECPPCPAPPVA
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPRE
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- continued

EQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYT

LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGGSFFLYS

KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Kappa Light Constant domain DNA (SEQ ID NO: 188):

cgtacgggtggctgcaccatctgtct-

tcattctcccgccatctgatgagcagttgaaatctggaactgcctctgtgtgtgcctgctgaataa

cttctatcccagagagggccaaagtacagtggaggtggataaacgccctccaatcgggtaactcccaggagagtgtcacagagcagga

cagcaaggacagcacctacagcctcagcagcacctcagcgtgagcaaacgagactacgagaaacacaaagtctacgctgcgaa

gtcaccatcagggcctgagctcgcccgctcacaagagcttcaacaggggagagtgttag

Kappa Light Constant domain Protein (SEQ ID NO: 189):

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT

EQSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Lambda Light Constant domain DNA (SEQ ID NO: 190):

ggccaaccgaaagcggcgccctcggtcactctgttcccgccctcctctgaggagcttcaagccaacaagggcacactgggtgtgtctca

taagtgacttctaccgggagccgtgacagtggcctggaaggcagatagcagcccgctcaaggcgggagtgagaccaccacacc

ctccaaacaagcaacaacaagtacgcgccagcagctatctgagcctgacgctgagcagtggaagtcccacagaagctacagct

gccaggtcacgcatgaaggagcaccgtggagaagacagtgggccctacagaatgttcataag

Lambda Light Constant domain Protein (SEQ ID NO: 191):

GQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTP

SKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

[0087] The specific binding agents of the present invention, such as the antibodies, antibody fragments, and antibody derivatives of the invention include those comprising, for example, the variable domain combinations provided herein having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgM, IgE, and IgD) as well as Fab or F(ab')₂ fragments thereof. Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation in the hinge region as described in Bloom et al., 1997, Protein Science

6:407 (incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

[0088] Additional Useful Sequence Information

[0089] The following sequences of the IgG1, IgG2, IgG3, and IgG4 isotypes are used in combination with the variable heavy chain sequences of the antibodies of the present invention to make a specific desired isotype of said antibody:

Human IgG1

(SEQ ID NO: 192)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ

SSGLYSLSVVTVPSLSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPE

LLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK

PREBQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ

VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFF

LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Human IgG2

(SEQ ID NO: 193)

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQ

SSGLYSLSVVTVPSNFGTQTYTCNVDHKPSNTKVDKTVKCCVECPPCPAPPVA

GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPRE

EQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYT

LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGGSFFLYS

KLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

-continued

Human IgG3

(SEQ ID NO: 194)

ASTKGPSVFPLAPCSRSTSGGTAAAGCLVKDYFPEPTVSWNSGALTSGVHTFPAVL
 QSSGLYSLSSVTVPSSSLGTQTYTCNVNHKPSNTKVDKRVELKTPLGDTTHTCPRCP
 EPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPPEPKSCDTPPPCPRCPAPELLGGPSVFLFPPK
 PKDTLMISRTEPTCVVDVSHEDPEVQFKWYVDGVEVHNAKTKPREEQYNSTFRV
 VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKTKGQPREPQVYTLPPSREEMT
 KNQVSLTCLVKGFYPSDIAVEWESSGQPENNYNTTPMLDSGDSFFLYSKLTVDKSR
 WQQGNIFSCSVMHLEALHNRFTQKSLSLSPGK

Human IgG4

(SEQ ID NO: 195)

ASTKGPSVFPLAPCSRSTSESTAAGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQ
 SSGLYSLSSVTVPSSSLGTQTYTCNVNHHKPSNTKVDKRVESKYGPPCPCPAPEFEG
 GPSVFLFPPKPKDTLMISRTEPTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPRE
 EQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKISKAKGQPREPQVYT
 LPQSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYS
 RLTVDKSRWQEGNVFSCSVMHLEALHNYTQKSLSLSLGK

[0090] Techniques are known for deriving an antibody of a different subclass or isotype from an antibody of interest, i.e., subclass switching. Thus, IgG antibodies may be derived from an IgM antibody, for example, and vice versa. Such techniques allow the preparation of new antibodies that possess the antigen-binding properties of a given antibody (the parent antibody), but also exhibit biological properties associated with an antibody isotype or subclass different from that of the parent antibody. Recombinant DNA techniques may be employed. Cloned DNA encoding particular antibody polypeptides may be employed in such procedures, e.g., DNA encoding the constant domain of an antibody of the desired isotype. See also Lanitto et al., *Methods Mol. Biol.* 178:303-16 (2002).

[0091] In one embodiment, an antigen binding protein of the invention further comprises the constant light chain kappa or lambda domains or a fragment of these. Sequences of the light chain constant regions and polynucleotides encoding them are well known in the art. In another embodiment, an antigen binding protein of the invention further comprises a heavy chain constant domain, or a fragment thereof, such as the IgG1 or IgG2 heavy chain constant region, the sequences of which are well known in the art.

[0092] The antigen binding proteins (for example, antibodies) of the present invention include those having a desired isotype (for example, IgA, IgG1, IgG2, IgG3, IgG4, IgM, IgE, and IgD) as well as Fab or F(ab')₂ fragments thereof. Moreover, if an IgG4 is desired, it may also be desired to introduce a point mutation in the hinge region as described in Bloom et al., 1997, *Protein Science* 6:407, (incorporated by reference herein) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies.

Antibodies and Antibody Fragments

[0093] In one embodiment the antigen binding proteins are antibodies. The term "antibody" refers to an intact antibody, or an antigen binding fragment thereof, as described exten-

sively in the definition section. An antibody may comprise a complete antibody molecule (including polyclonal, monoclonal, chimeric, humanized, or human versions having full length heavy and/or light chains), or comprise an antigen binding fragment thereof. Antibody fragments include F(ab')₂, Fab, Fab', Fv, Fc, and Fd fragments, and can be incorporated into single domain antibodies, single-chain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see e.g., Hollinger and Hudson, 2005, *Nature Biotechnology*, 23, 9, 1126-1136). Also included are antibody polypeptides such as those disclosed in U.S. Pat. No. 6,703,199, including fibronectin polypeptide monobodies. Other antibody polypeptides are disclosed in U.S. Patent Publication 2005/0238646, which are single-chain polypeptides. In one embodiment, the antibodies of the present invention comprise at least one CDR set forth in Table 2 above. In another aspect, the present invention provides hybridomas capable of producing the antibodies of the invention, and methods of producing antibodies from hybridomas, as described further below.

[0094] Chimeric antibodies and humanized antibodies are defined in the definition section and may be prepared by known techniques. In one embodiment, a humanized monoclonal antibody comprises the variable domain of a murine antibody (or all or part of the antigen binding site thereof) and a constant domain derived from a human antibody. Alternatively, a humanized antibody fragment may comprise the antigen binding site of a murine monoclonal antibody and a variable domain fragment (lacking the antigen-binding site) derived from a human antibody. Procedures for the production of engineered monoclonal antibodies include those described in Riechmann et al., 1988, *Nature* 332:323, Liu et al., 1987, *Proc. Nat. Acad. Sci. USA* 84:3439, Larrick et al., 1989, *Bio/Technology* 7:934, and Winter et al., 1993, *TIPS* 14:139. In one embodiment, the chimeric antibody is a CDR grafted antibody. Techniques for humanizing antibodies are discussed in, e.g., U.S. Pat. Nos. 5,869,619; 5,225,539; 5,821,337; 5,859,205; 6,881,557, Padlan et al., 1995, *FASEB J.*

9:133-39, Tamura et al., 2000, *J. Immunol.* 164:1432-41, Zhang, W., et al., *Molecular Immunology*, 42(12):1445-1451, 2005; Hwang W. et al., *Methods*, 36(1):35-42, 2005; Dall'Acqua W F, et al., *Methods* 36(1):43-60, 2005; and Clark, M., *Immunology Today*, 21(8):397-402, 2000.

[0095] An antibody of the present invention may also be a fully human monoclonal antibody. Fully human monoclonal antibodies may be generated by any number of techniques with which those having ordinary skill in the art will be familiar. Such methods include, but are not limited to, Epstein Barr Virus (EBV) transformation of human peripheral blood cells (e.g., containing B lymphocytes), in vitro immunization of human B-cells, fusion of spleen cells from immunized transgenic mice carrying inserted human immunoglobulin genes, isolation from human immunoglobulin V region phage libraries, or other procedures as known in the art and based on the disclosure herein.

[0096] Procedures have been developed for generating human monoclonal antibodies in non-human animals. For example, mice in which one or more endogenous immunoglobulin genes have been inactivated by various means have been prepared. Human immunoglobulin genes have been introduced into the mice to replace the inactivated mouse genes. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci (see also Bruggemann et al., *Curr. Opin. Biotechnol.* 8:455-58 (1997)). For example, human immunoglobulin transgenes may be mini-gene constructs, or transloci on yeast artificial chromosomes, which undergo B-cell-specific DNA rearrangement and hypermutation in the mouse lymphoid tissue.

[0097] Antibodies produced in the animal incorporate human immunoglobulin polypeptide chains encoded by the human genetic material introduced into the animal. In one embodiment, a non-human animal, such as a transgenic mouse, is immunized with a suitable mesothelin immunogen.

[0098] Examples of techniques for production and use of transgenic animals for the production of human or partially human antibodies are described in U.S. Pat. Nos. 5,814,318, 5,569,825, and 5,545,806, Davis et al., *Production of human antibodies from transgenic mice* in Lo, ed. *Antibody Engineering: Methods and Protocols*, Humana Press, NJ:191-200 (2003), Kellermann et al., 2002, *Curr Opin Biotechnol.* 13:593-97, Russel et al., 2000, *Infect Immun.* 68:1820-26, Gallo et al., 2000, *Eur J. Immun.* 30:534-40, Davis et al., 1999, *Cancer Metastasis Rev.* 18:421-25, Green, 1999, *J Immunol Methods*, 231:11-23, Jakobovits, 1998, *Advanced Drug Delivery Reviews* 31:33-42, Green et al., 1998, *J Exp Med.* 188:483-95, Jakobovits A, 1998, *Exp. Opin. Invest. Drugs*, 7:607-14, Tsuda et al., 1997, *Genomics*, 42:413-21, Mendez et al., 1997, *Nat. Genet.* 15:146-56, Jakobovits, 1994, *Curr Biol.* 4:761-63, Arbones et al., 1994, *Immunity*, 1:247-60, Green et al., 1994, *Nat. Genet.* 7:13-21, Jakobovits et al., 1993, *Nature*, 362:255-58, Jakobovits et al., 1993, *Proc Natl Acad Sci USA*, 90:2551-55. Chen, J., M. Trounstein, F. W. Alt, F. Young, C. Kurahara, J. Loring, D. Huszar "Immunoglobulin gene rearrangement in B-cell deficient mice generated by targeted deletion of the JH locus." *International Immunology* 5 (1993): 647-656, Choi et al., 1993, *Nature Genetics* 4: 117-23, Fishwild et al., 1996, *Nature Biotechnology* 14: 845-51, Harding et al., 1995, *Annals of the New York Academy of Sciences*, Lonberg et al., 1994, *Nature* 368: 856-59, Lonberg, 1994, *Transgenic Approaches to Human*

Monoclonal Antibodies in Handbook of Experimental Pharmacology 113: 49-101, Lonberg et al., 1995, *Internal Review of Immunology* 13: 65-93, Neuberger, 1996, *Nature Biotechnology* 14: 826, Taylor et al., 1992, *Nucleic Acids Research* 20: 6287-95, Taylor et al., 1994, *International Immunology* 6: 579-91, Tomizuka et al., 1997, *Nature Genetics* 16: 133-43, Tomizuka et al., 2000, *Proceedings of the National Academy of Sciences USA* 97: 722-27, Tuailon et al., 1993, *Proceedings of the National Academy of Sciences USA* 90: 3720-24, and Tuailon et al., 1994, *Journal of Immunology* 152: 2912-20.; Lonberg et al., *Nature* 368:856, 1994; Taylor et al., *Int. Immun* 6:579, 1994; U.S. Pat. No. 5,877,397; Bruggemann et al., 1997 *Curr. Opin. Biotechnol.* 8:455-58; Jakobovits et al., 1995 *Ann. N.Y. Acad. Sci.* 764:525-35. In addition, protocols involving the XenoMouse® (Abgenix, now Amgen, Inc.) are described, for example in U.S. 05/0118643 and WO 05/694879, WO 98/24838, WO 00/76310, and U.S. Pat. No. 7,064,244.

[0099] Lymphoid cells from the immunized transgenic mice are fused with myeloma cells for example to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in such fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0 Bu1; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

[0100] The lymphoid (e.g., spleen) cells and the myeloma cells may be combined for a few minutes with a membrane fusion-promoting agent, such as polyethylene glycol or a nonionic detergent, and then plated at low density on a selective medium that supports the growth of hybridoma cells but not unfused myeloma cells. One selection media is HAT (hypoxanthine, aminopterin, thymidine). After a sufficient time, usually about one to two weeks, colonies of cells are observed. Single colonies are isolated, and antibodies produced by the cells may be tested for binding activity to mesothelin using any one of a variety of immunoassays known in the art and described herein. The hybridomas are cloned (e.g., by limited dilution cloning or by soft agar plaque isolation) and positive clones that produce an antibody specific to mesothelin are selected and cultured. The monoclonal antibodies from the hybridoma cultures may be isolated from the supernatants of hybridoma cultures. Thus the present invention provides hybridomas that comprise polynucleotides encoding the antigen binding proteins of the invention in the chromosomes of the cell. These hybridomas can be cultured according to methods described herein and known in the art.

[0101] Another method for generating human antibodies of the invention includes immortalizing human peripheral blood cells by EBV transformation. See, e.g., U.S. Pat. No. 4,464, 456. Such an immortalized B-cell line (or lymphoblastoid cell line) producing a monoclonal antibody that specifically binds to mesothelin can be identified by immunodetection methods as provided herein, for example, an ELISA, and then isolated by standard cloning techniques. The stability of the lymphoblastoid cell line producing an anti-mesothelin antibody may be improved by fusing the transformed cell line with a murine

myeloma to produce a mouse-human hybrid cell line according to methods known in the art (see, e.g., Glasky et al., *Hybridoma* 8:377-89 (1989)). Still another method to generate human monoclonal antibodies is in vitro immunization, which includes priming human splenic B-cells with human mesothelin, followed by fusion of primed B-cells with a heterohybrid fusion partner. See, e.g., Boerner et al., 1991 *J. Immunol.* 147:86-95.

[0102] In certain embodiments, a B-cell that is producing an anti-human mesothelin antibody is selected and the light chain and heavy chain variable regions are cloned from the B-cell according to molecular biology techniques known in the art (WO 92/02551; U.S. Pat. No. 5,627,052; Babcook et al., *Proc. Natl. Acad. Sci. USA* 93:7843-48 (1996)) and described herein. B-cells from an immunized animal may be isolated from the spleen, lymph node, or peripheral blood sample by selecting a cell that is producing an antibody that specifically binds to mesothelin. B-cells may also be isolated from humans, for example, from a peripheral blood sample. Methods for detecting single B-cells that are producing an antibody with the desired specificity are well known in the art, for example, by plaque formation, fluorescence-activated cell sorting, in vitro stimulation followed by detection of specific antibody, and the like. Methods for selection of specific antibody-producing B-cells include, for example, preparing a single cell suspension of B-cells in soft agar that contains human mesothelin. Binding of the specific antibody produced by the B-cell to the antigen results in the formation of a complex, which may be visible as an immunoprecipitate. After the B-cells producing the desired antibody are selected, the specific antibody genes may be cloned by isolating and amplifying DNA or mRNA according to methods known in the art and described herein.

[0103] An additional method for obtaining antibodies of the invention is by phage display. See, e.g., Winter et al., 1994 *Annu. Rev. Immunol.* 12:433-55; Burton et al., 1994 *Adv. Immunol.* 57:191-280. Human or murine immunoglobulin variable region gene combinatorial libraries may be created in phage vectors that can be screened to select Ig fragments (Fab, Fv, sFv, or multimers thereof) that bind specifically to TGF-beta binding protein or variant or fragment thereof. See, e.g., U.S. Pat. No. 5,223,409; Huse et al., 1989 *Science* 246: 1275-81; Sastry et al., *Proc. Natl. Acad. Sci. USA* 86:5728-32 (1989); Altling-Mees et al., *Strategies in Molecular Biology* 3:1-9 (1990); Kang et al., 1991 *Proc. Natl. Acad. Sci. USA* 88:4363-66; Hoogenboom et al., 1992 *J. Molec. Biol.* 227: 381-388; Schlebusch et al., 1997 *Hybridoma* 16:47-52 and references cited therein. For example, a library containing a plurality of polynucleotide sequences encoding Ig variable region fragments may be inserted into the genome of a filamentous bacteriophage, such as M13 or a variant thereof, in frame with the sequence encoding a phage coat protein. A fusion protein may be a fusion of the coat protein with the light chain variable region domain and/or with the heavy chain variable region domain. According to certain embodiments, immunoglobulin Fab fragments may also be displayed on a phage particle (see, e.g., U.S. Pat. No. 5,698,426).

[0104] Heavy and light chain immunoglobulin cDNA expression libraries may also be prepared in lambda phage, for example, using λ ImmunoZapTM (H) and λ ImmunoZapTM (L) vectors (Stratagene, La Jolla, Calif.). Briefly, mRNA is isolated from a B-cell population, and used to create heavy and light chain immunoglobulin cDNA expression libraries in the λ ImmunoZap(H) and λ ImmunoZap(L) vectors. These

vectors may be screened individually or co-expressed to form Fab fragments or antibodies (see Huse et al., *supra*; see also Sastry et al., *supra*). Positive plaques may subsequently be converted to a non-lytic plasmid that allows high level expression of monoclonal antibody fragments from *E. coli*.

[0105] In one embodiment, in a hybridoma the variable regions of a gene expressing a monoclonal antibody of interest are amplified using nucleotide primers. These primers may be synthesized by one of ordinary skill in the art, or may be purchased from commercially available sources. (See, e.g., Stratagene (La Jolla, Calif.), which sells primers for mouse and human variable regions including, among others, primers for V_{Ha} , V_{Hb} , V_{Hc} , V_{Hd} , C_{H1} , V_L and C_L regions.) These primers may be used to amplify heavy or light chain variable regions, which may then be inserted into vectors such as ImmunoZAPTM H or ImmunoZAPTM L (Stratagene), respectively. These vectors may then be introduced into *E. coli*, yeast, or mammalian-based systems for expression. Large amounts of a single-chain protein containing a fusion of the V_H and V_L domains may be produced using these methods (see Bird et al., *Science* 242:423-426, 1988).

[0106] Once cells producing antibodies according to the invention have been obtained using any of the above-described immunization and other techniques, the specific antibody genes may be cloned by isolating and amplifying DNA or mRNA therefrom according to standard procedures as described herein. The antibodies produced therefrom may be sequenced and the CDRs identified and the DNA coding for the CDRs may be manipulated as described previously to generate other antibodies according to the invention.

[0107] In certain embodiments, antibodies are generated by first identifying antibodies that bind to cells expressing mesothelin and/or compete for binding with the antibodies described in this application.

[0108] It will be understood by one skilled in the art that some proteins, such as antibodies, may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the protein as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperazine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, R.J. *Journal of Chromatography* 705: 129-134, 1995).

[0109] An alternative method for production of a murine monoclonal antibody is to inject the hybridoma cells into the peritoneal cavity of a syngeneic mouse, for example, a mouse that has been treated (e.g., pristane-primed) to promote formation of ascites fluid containing the monoclonal antibody. Monoclonal antibodies can be isolated and purified by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography (see, for example, Coligan at pages 2.7.1-2.7.12 and pages 2.9.1-2.9.3; Baines et al., "Purification of Immunoglobulin G (IgG)," in *Methods in Molecular Biology*, Vol. 10, pages 79-104 (The Humana Press, Inc. 1992)). Monoclonal antibodies may be purified by affinity chromatography using an appropriate ligand selected based on particular properties of the antibody (e.g., heavy or light chain isotype, binding specificity, etc.). Examples of a suitable ligand, immobilized on a solid support, include Protein A, Protein G, an anticon-

stant region (light chain or heavy chain) antibody, an idiotype antibody, and a TGF-beta binding protein, or fragment or variant thereof.

[0110] Molecular evolution of the complementarity determining regions (CDRs) in the center of the antibody binding site also has been used to isolate antibodies with increased affinity, for example, antibodies having increased affinity for c-erbB-2, as described by Schier et al., 1996, J. Mol. Biol. 263:551. Accordingly, such techniques are useful in preparing antibodies to mesothelin.

[0111] Antigen binding proteins directed against mesothelin can be used, for example, in assays to detect the presence of mesothelin, either in vitro or in vivo.

[0112] Although human, partially human, or humanized antibodies will be suitable for many applications, particularly those involving administration of the antibody to a human subject, other types of antigen binding proteins will be suitable for certain applications. The non-human antibodies of the invention can be, for example, derived from any antibody-producing animal, such as mouse, rat, rabbit, goat, donkey, or non-human primate (for example, monkey such as cynomolgus or rhesus monkey) or ape (e.g., chimpanzee)). Non-human antibodies of the invention can be used, for example, in in vitro and cell-culture based applications, or any other application where an immune response to the antibody of the invention does not occur, is insignificant, can be prevented, is not a concern, or is desired. In one embodiment, a non-human antibody of the invention is administered to a non-human subject. In another embodiment, the non-human antibody does not elicit an immune response in the non-human subject. In another embodiment, the non-human antibody is from the same species as the non-human subject, e.g., a mouse antibody of the invention is administered to a mouse. An antibody from a particular species can be made by, for example, immunizing an animal of that species with the desired immunogen or using an artificial system for generating antibodies of that species (e.g., a bacterial or phage display-based system for generating antibodies of a particular species), or by converting an antibody from one species into an antibody from another species by replacing, e.g., the constant region of the antibody with a constant region from the other species, or by replacing one or more amino acid residues of the antibody so that it more closely resembles the sequence of an antibody from the other species. In one embodiment, the antibody is a chimeric antibody comprising amino acid sequences derived from antibodies from two or more different species.

[0113] Antibodies also may be prepared by any of a number of conventional techniques. For example, they may be purified from cells that naturally express them (e.g., an antibody can be purified from a hybridoma that produces it), or produced in recombinant expression systems, using any technique known in the art. See, for example, *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Kennet et al. (eds.), Plenum Press, New York (1980); and *Antibodies: A Laboratory Manual*, Harlow and Land (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1988). This is discussed in the nucleic acid section below.

[0114] Where it is desired to improve the affinity of antibodies according to the invention containing one or more of the above-mentioned CDRs can be obtained by a number of affinity maturation protocols including maintaining the CDRs (Yang et al., J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks et al., Bio/Technology, 10, 779-783, 1992),

use of mutation strains of *E. coli*. (Low et al., J. Mol. Biol., 250, 350-368, 1996), DNA shuffling (Patten et al., Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson et al., J. Mol. Biol., 256, 7-88, 1996) and additional PCR techniques (Cramer, et al., Nature, 391, 288-291, 1998). All of these methods of affinity maturation are discussed by Vaughan et al. (Nature Biotechnology, 16, 535-539, 1998).

Antibody Fragments

[0115] In another aspect, the present invention provides fragments of an anti-mesothelin antibody of the invention. Such fragments can consist entirely of antibody-derived sequences or can comprise additional sequences. Examples of antigen-binding fragments include Fab, F(ab')₂, single chain antibodies, diabodies, triabodies, tetrabodies, and domain antibodies. Other examples are provided in Lunde et al., 2002, Biochem. Soc. Trans. 30:500-06.

[0116] Single chain antibodies may be formed by linking heavy and light chain variable domain (Fv region) fragments via an amino acid bridge (short peptide linker), resulting in a single polypeptide chain. Such single-chain Fvs (scFvs) have been prepared by fusing DNA encoding a peptide linker between DNAs encoding the two variable domain polypeptides (V_L and V_H). The resulting polypeptides can fold back on themselves to form antigen-binding monomers, or they can form multimers (e.g., dimers, trimers, or tetramers), depending on the length of a flexible linker between the two variable domains (Kortt et al., 1997, Prot. Eng. 10:423; Kortt et al., 2001, Biomol. Eng. 18:95-108). By combining different V_L and V_H-comprising polypeptides, one can form multimeric scFvs that bind to different epitopes (Kriangkum et al., 2001, Biomol. Eng. 18:31-40). Techniques developed for the production of single chain antibodies include those described in U.S. Pat. No. 4,946,778; Bird, 1988, Science 242:423; Huston et al., 1988, Proc. Natl. Acad. Sci. USA 85:5879; Ward et al., 1989, Nature 334:544, de Graaf et al., 2002, Methods Mol. Biol. 178:379-87. Single chain antibodies derived from antibodies provided herein include, but are not limited to, scFvs comprising the variable domain combinations L1H1, L2H2, L3H3, L4H4, L5H5, L6H6, L7H7, L8H8, L9H9, and L10H10 are encompassed by the present invention.

[0117] Antigen binding fragments derived from an antibody can also be obtained, for example, by proteolytic hydrolysis of the antibody, for example, pepsin or papain digestion of whole antibodies according to conventional methods. By way of example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment termed F(ab')₂. This fragment can be further cleaved using a thiol reducing agent to produce 3.5S Fab' monovalent fragments. Optionally, the cleavage reaction can be performed using a blocking group for the sulfhydryl groups that result from cleavage of disulfide linkages. As an alternative, an enzymatic cleavage using papain produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Pat. No. 4,331,647, Nisonoff et al., Arch. Biochem. Biophys. 89:230, 1960; Porter, Biochem. J. 73:119, 1959; Edelman et al., in *Methods in Enzymology* 1:422 (Academic Press 1967); and by Andrews, S. M. and Titus, J. A. in *Current Protocols in Immunology* (Coligan J. E., et al., eds.), John Wiley & Sons, New York (2003), pages 2.8.1-2.8.10 and 2.10A.1-2.10A.5. Other methods for cleaving antibodies, such as separating heavy chains to form monovalent light-heavy chain frag-

ments (Fd), further cleaving of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

[0118] Another form of an antibody fragment is a peptide comprising one or more complementarity determining regions (CDRs) of an antibody. CDRs can be obtained by constructing polynucleotides that encode the CDR of interest. Such polynucleotides are prepared, for example, by using the polymerase chain reaction to synthesize the variable region using mRNA of antibody-producing cells as a template (see, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology* 2:106, 1991; Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies: Production, Engineering and Clinical Application*, Ritter et al. (eds.), page 166 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al. (eds.), page 137 (Wiley-Liss, Inc. 1995)). The antibody fragment further may comprise at least one variable region domain of an antibody described herein. Thus, for example, the V region domain may be monomeric and be a V_H or V_L domain, which is capable of independently binding mesothelin with an affinity at least equal to 10^{-7} M or less as described below.

[0119] The variable region domain may be any naturally occurring variable domain or an engineered version thereof. By engineered version is meant a variable region domain that has been created using recombinant DNA engineering techniques. Such engineered versions include those created, for example, from a specific antibody variable region by insertions, deletions, or changes in or to the amino acid sequences of the specific antibody. Particular examples include engineered variable region domains containing at least one CDR and optionally one or more framework amino acids from a first antibody and the remainder of the variable region domain from a second antibody.

[0120] The variable region domain may be covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof. Thus, for example, a V_H domain that is present in the variable region domain may be linked to an immunoglobulin CH1 domain, or a fragment thereof. Similarly a V_L domain may be linked to a C_K domain or a fragment thereof. In this way, for example, the antibody may be a Fab fragment wherein the antigen binding domain contains associated V_H and V_L domains covalently linked at their C-termini to a CH1 and C_K domain, respectively. The CH1 domain may be extended with further amino acids, for example to provide a hinge region or a portion of a hinge region domain as found in a Fab' fragment, or to provide further domains, such as antibody CH2 and CH3 domains.

Bispecific Single Chain Antibodies (e.g., Bispecific T-Cell Engagers or BiTEs)

[0121] In one embodiment, the invention provides bispecific single chain antibodies, such as, but not limited to, bispecific T-cell engaging molecules (BiTEs). In certain embodiments, the contemplated bispecific single chain antibodies utilize at least two Fv regions to direct binding to target molecules of choice. It is contemplated that two different Fv regions are used, although it is further contemplated that a single Fv region can be used at least twice in a single bispecific single chain antibody. It is contemplated that at least two different target molecules are targeted by the bispecific single

chain antibodies of the invention, although it is further contemplated that the same target molecule can be targeted by the at least two Fv regions of the bispecific single chain antibodies.

[0122] As is well known, Fv, the minimum antibody fragment which contains a complete antigen recognition and binding site, consists of a dimer of one heavy and one light chain variable domain (V_H and V_L) in non-covalent association. In this configuration corresponding to the one found in native antibodies, the three CDRs of each variable domain interact to define an antigen binding site on the surface of the V_H - V_L dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. Frameworks (FRs) flanking the CDRs have a tertiary structure which is essentially conserved in native immunoglobulins of species as diverse as human and mouse. These FRs serve to hold the CDRs in their appropriate orientation. The constant domains are not required for binding function, but may aid in stabilizing V_H - V_L interaction.

[0123] As used herein, CD3 epsilon denotes a molecule expressed as part of the T cell receptor and has the meaning as typically ascribed to it in the prior art. In human, it encompasses in individual or independently combined form all known CD3 subunits, for example CD3 epsilon, CD3 delta, CD3 gamma, CD3 zeta, CD3 alpha and CD3 beta. The non-chimpanzee primate CD3 antigens as referred to herein are, for example, *Macaca fascicularis* CD3 and *Macaca mulatta* CD3. In *Macaca fascicularis*, it encompasses CD3 epsilon FN-18 negative and CD3 epsilon FN-18 positive, CD3 gamma and CD3 delta. In *Macaca mulatta*, it encompasses CD3 epsilon, CD3 gamma and CD3 delta. Preferably, said CD3 as used herein is CD3 epsilon. Additional examples of non-chimpanzee primate CD3 molecules are contemplated, for example, cynomolgus CD3.

[0124] The human CD3 epsilon is indicated in GenBank Accession No. NM-000733. The human CD3 gamma is indicated in GenBank Accession NO. NM-000073. The human CD3 delta is indicated in GenBank Accession No. NM-000732.

[0125] It is also envisaged in the context of the present invention that the bispecific antibody constructs provided in the pharmaceutical composition of the invention are further modified. In particular, it is envisaged that the bispecific single chain antibody construct in the format $V_H(\text{MSLN})$ - $V_L(\text{MSLN})$ - $V_H(\text{CD3})$ - $V_L(\text{CD3})$, $V_H(\text{CD3})$ - $V_L(\text{CD3})$ - $V_H(\text{MSLN})$ - $V_L(\text{MSLN})$ or $V_H(\text{CD3})$ - $V_L(\text{CD3})$ - $V_L(\text{MSLN})$ - $V_H(\text{MSLN})$ as defined herein are deimmunized. In certain embodiments, at least the CD3-binding portion is deimmunized. Deimmunization entails carrying out substitutions of amino acids within potential T cell epitopes.

[0126] In certain embodiments, the bispecific single chain antibodies comprise at least one CDR-3 of a V_H -region of an antibody directed against human CD3, at least one CDR-3 of a V_L -region of an antibody directed against human CD3, at least one CDR-3 of a V_H -region of an antibody directed against human MSLN and at least one CDR-3 of a V_L -region of an antibody directed against human MSLN. In further embodiments, the bispecific single chain antibodies comprise V_H and V_L regions which comprise not only CDR-3 but also CDR1 and/or CDR2 regions. In particular, CDR-regions (e.g., CDRs 1-3 of the V_H and V_L) may be employed to generate further bispecific single chain constructs. In further embodiments, the bispecific single chain antibodies are derived from the parental antibodies as disclosed herein and

share, as disclosed above, at least the CDR-3 domain of the VH-region and the CDR-3 domain of the VL-region with said parental antibodies, and in certain embodiments share CDRs 1-3 of the VH and VL regions of said parental antibodies. It is also envisaged that the bispecific single chain antibodies further comprise modified CDR regions. It is, e.g., envisaged that in particular CDR2 and/or CDR1 regions (or frameworks or linkers between CDRs) are deimmunized. For further disclosure relating to bispecific single chain antibodies, see, for example, U.S. Pat. Nos. 6,723,538; 7,112,324; 7,227,002; 7,235,641; 7,323,440; 7,332,168; 7,635,472; 7,820,166; 7,919,089; 8,017,748; 8,076,459; 8,101,722; 8,236,308; and 8,247,194. See also, for example, U.S. Patent Publication Nos. 20090241202, 20090291072, 20100150918 (WO 2008/119567), 20110262439, 20110293619, 20120034228, and 20120244162.

[0127] In one embodiment, the VH and VL regions of said CD3 specific domain are derived from a CD3 specific antibody selected from the group consisting of X35-3, VIT3, BMA030 (BW264/56), CLB-T3/3, CRIS7, YTH12.5, F111-409, CLB-T3.4.2, WT31, WT32, SPv-T3b, 11D8, XIII-141, XIII-46, XIII-87, 12F6, T3/RW2-8C8, T3/RW2-4B6, OKT3D, M-T301, SMC2 and F101.01. These CD3-specific antibodies are well known in the art and described in Tunnacliffe (1989), *Int. Immunol.* 1, 546-550. In another embodiment, said VH and VL regions of said CD3 specific domain are derived from OKT3 (as described above). In a further embodiment, said VH and VL regions are or are derived from an antibody/antibody derivative specifically directed against CD3 described by Traunecker (1991), *EMBO J.* 10, 3655-3659. In a further embodiment, said VH and VL regions are or are derived from an antibody/antibody derivative specifically directed against CD3 described in U.S. Patent Publication No. 20100150918 (WO 2008/119567). In a specific embodiment, said VH and VL regions are or are derived from an antibody/antibody I2C as described in U.S. Patent Publication No. 20100150918 (WO 2008/119567).

[0128] In accordance with this invention, said VH and VL regions are derived from antibodies/antibody derivatives and the like which are capable of specifically recognizing human CD3 epsilon in the context of other TCR subunits, e.g. in mouse T cells transgenic for human CD3 epsilon. These transgenic mouse cells express human CD3 epsilon in a native or near native conformation. Accordingly, the VH and VL regions derived from a CD3-epsilon-specific antibody are envisioned as further embodiments in accordance with this invention and said (parental) antibodies should be capable of specifically binding epitopes reflecting the native or near native structure or a conformational epitope of human CD3 presented in context of the TCR complex. Such antibodies have been classified by Tunnacliffe (1989) as "group II" antibodies.

[0129] Further classifications in Tunnacliffe (1989) comprise the definition of "group I" and "group III" antibodies directed against CD3. "Group I" antibodies, like UCHT1, recognize CD3 epsilon both expressed as recombinant protein as well as part of the TCR on the cell surface. Therefore, "group I" antibodies are highly specific for CD3 epsilon. In contrast, the herein preferred "group II" antibodies recognize CD3 epsilon only in the native TCR complex in association with other TCR subunits. Without being bound by theory, it is speculated in context of this invention that in "group II" antibodies, the TCR context is required for recognition of CD3 epsilon. CD3 gamma and/or delta, being associated with

epsilon, are also involved in binding of "group II" antibodies. All three subunits express immuno-tyrosine activation motifs (ITAMs) which can be tyrosine phosphorylated by protein tyrosine kinases. For this reason "group II" antibodies induce T cell signaling via CD3 epsilon, gamma and delta, leading to a stronger signal compared to "group I" antibodies selectively inducing T cell signaling via CD3 epsilon. Yet, since for therapeutic applications induction of a strong T cell signaling is desired, the VH (CD3)/VL (CD3)-regions (or parts thereof) to be employed in the bispecific single chain constructs comprised in the inventive pharmaceutical composition, are derived from antibodies directed against human CD3 and classified as "group II" by Tunnacliffe (1989).

Derivatives and Variants of Antigen Binding Proteins

[0130] The nucleotide sequences of the antibodies of the present invention, encoding the corresponding amino acid sequences of the antibodies of the present invention, can be altered, for example, by random mutagenesis or by site-directed mutagenesis (e.g., oligonucleotide-directed site-specific mutagenesis) to create an altered polynucleotide comprising one or more particular nucleotide substitutions, deletions, or insertions as compared to the non-mutated polynucleotide. Examples of techniques for making such alterations are described in Walder et al., 1986, *Gene* 42:133; Bauer et al. 1985, *Gene* 37:73; Craik, *BioTechniques*, January 1985, 12-19; Smith et al., 1981, *Genetic Engineering: Principles and Methods*, Plenum Press; and U.S. Pat. Nos. 4,518,584 and 4,737,462. These and other methods can be used to make, for example, derivatives of anti-mesothelin antibodies that have a desired property, for example, increased affinity, avidity, or specificity for mesothelin increased activity or stability in vivo or in vitro, or reduced in vivo side-effects as compared to the underivatized antibody.

[0131] Other derivatives of anti-mesothelin antibodies within the scope of this invention include covalent or aggregative conjugates of anti-mesothelin antibodies, or fragments thereof, with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an anti-mesothelin antibody polypeptide. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor leader, or a peptide such as an epitope tag. Antigen binding protein-containing fusion proteins can comprise peptides added to facilitate purification or identification of antigen binding protein (e.g., poly-His). An antigen binding protein also can be linked to the FLAG peptide as described in Hopp et al., *Bio/Technology* 6:1204, 1988, and U.S. Pat. No. 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, Mo.).

In another embodiment, oligomers that contain one or more antigen binding proteins may be employed as mesothelin antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more antigen binding protein are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc.

[0132] One embodiment is directed to oligomers comprising multiple antigen binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to the antigen binding proteins. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of antigen binding proteins attached thereto, as described in more detail below.

[0133] In particular embodiments, the oligomers comprise from two to four antigen binding proteins. The antigen binding proteins of the oligomer may be in any form, such as any of the forms described above, e.g., variants or fragments. Preferably, the oligomers comprise antigen binding proteins that have mesothelin binding activity.

[0134] In one embodiment, an oligomer is prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, PNAS USA 88:10535; Byrn et al., 1990, Nature 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in Current Protocols in Immunology, Suppl. 4, pages 10.19.1-10.19.11. One embodiment of the present invention is directed to a dimer comprising two fusion proteins created by fusing a mesothelin binding fragment of an anti-mesothelin antibody to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer.

[0135] The term "Fc polypeptide" as used herein includes native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom) offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns.

[0136] One suitable Fc polypeptide, described in PCT application WO 93/10151 (hereby incorporated by reference), is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035 and in Baum et al., 1994, EMBO J. 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors. In other embodiments, the variable portion of the heavy and/or light chains of an anti-mesothelin antibody may be substituted for the variable portion of an antibody heavy and/or light chain.

[0137] Alternatively, the oligomer is a fusion protein comprising multiple antigen binding proteins, with or without peptide linkers (spacer peptides). Among the suitable peptide linkers are those described in U.S. Pat. Nos. 4,751,180 and 4,935,233.

[0138] Another method for preparing oligomeric antigen binding proteins involves use of a leucine zipper. Leucine zipper domains are peptides that promote oligomerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., 1988, Science 240:1759), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in PCT application WO 94/10308, and the leucine zipper derived from lung surfactant protein D (SPD) described in Hoppe et al., 1994, FEBS Letters 344:191, hereby incorporated by reference. The use of a modified leucine zipper that allows for stable trimerization of a heterologous protein fused thereto is described in Fanslow et al., 1994, Semin. Immunol. 6:267-78. In one approach, recombinant fusion proteins comprising an anti-mesothelin antibody fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric anti-mesothelin antibody fragments or derivatives that form are recovered from the culture supernatant.

[0139] In another embodiment, the antibody derivatives can comprise at least one of the CDRs disclosed herein. For example, one or more CDR may be incorporated into known antibody framework regions (IgG1, IgG2, etc.), or conjugated to a suitable vehicle to enhance the half-life thereof. Suitable vehicles include, but are not limited to Fc, albumin, transferrin, and the like. These and other suitable vehicles are known in the art. Such conjugated CDR peptides may be in monomeric, dimeric, tetrameric, or other form. In one embodiment, one or more water-soluble polymer is bonded at one or more specific position, for example at the amino terminus, of a binding agent. In an example, an antibody derivative comprises one or more water soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. See, e.g., U.S. Pat. Nos. 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192 and 4,179,337. In certain embodiments, a derivative comprises one or more of monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of such polymers. In certain embodiments, one or more water-soluble polymer is randomly attached to one or more side chains. In certain embodiments, PEG can act to improve the therapeutic capacity for a binding agent, such as an antibody. Certain such methods are discussed, for example, in U.S. Pat. No. 6,133,426, which is hereby incorporated by reference for any purpose.

[0140] It will be appreciated that an antigen binding protein or antibody of the present invention may have at least one amino acid substitution, providing that the antigen binding protein or antibody retains binding specificity. Therefore, modifications to the antigen binding protein or antibody structures are encompassed within the scope of the invention. These may include amino acid substitutions, which may be conservative or non-conservative, that do not destroy the mesothelin binding capability of an antigen binding protein or antibody. Conservative amino acid substitutions may encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthe-

sis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties. A conservative amino acid substitution may also involve a substitution of a native amino acid residue with a normative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Non-conservative substitutions may involve the exchange of a member of one class of amino acids or amino acid mimetics for a member from another class with different physical properties (e.g. size, polarity, hydrophobicity, charge). For example, such substituted residues may be introduced into regions of the human antibody that are homologous with non-human antibodies, or into the non-homologous regions of the molecule.

[0141] In certain embodiments, an amino acid substitution is made to improve protein expression, or to improve upon protein stability. For example, but not limited to, in one embodiment, the glutamine (Gln, Q) at the amino terminus of a variable heavy and/or a variable light chain of a binding protein is substituted with glutamic acid (Glu, E).

[0142] Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art. Such variants could be used to gather information about suitable variants. For example, 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.

[0143] A skilled artisan will be able to determine suitable variants of the 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 or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure. Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[0144] 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. A number of scientific publications have

been devoted to the prediction of secondary structure. See Moult 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 (Brenner et al., *Curr. Op. Struct. Biol.*, 7(3):369-376 (1997)) 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.

[0145] Additional methods of predicting secondary structure include "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, variants of antibodies include glycosylation variants wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In certain embodiments, variants comprise a greater or a lesser number of N-linked glycosylation sites than the native protein. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is 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. Additional antibody variants include cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants may be useful when antibodies must be refolded into a biologically active conformation such as after the isolation of insoluble inclusion bodies. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

[0146] 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 antibodies to mesothelin, or to increase or decrease the affinity of the antibodies to mesothelin described herein.

[0147] According to certain embodiments, preferred 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 physiochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid sub-

stitutions (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 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), which are each incorporated herein by reference.

[0148] In certain embodiments, antibodies of the invention may be chemically bonded with polymers, lipids, or other moieties.

[0149] The antigen binding proteins may comprise at least one of the CDRs described herein incorporated into a biocompatible framework structure. In one example, the biocompatible framework structure comprises a polypeptide or portion thereof that is sufficient to form a conformationally stable structural support, or framework, or scaffold, which is able to display one or more sequences of amino acids that bind to an antigen (e.g., CDRs, a variable region, etc.) in a localized surface region. Such structures can be a naturally occurring polypeptide or polypeptide "fold" (a structural motif), or can have one or more modifications, such as additions, deletions or substitutions of amino acids, relative to a naturally occurring polypeptide or fold. These scaffolds can be derived from a polypeptide of any species (or of more than one species), such as a human, other mammal, other vertebrate, invertebrate, plant, bacteria or virus.

[0150] Typically the biocompatible framework structures are based on protein scaffolds or skeletons other than immunoglobulin domains. For example, those based on fibronectin, ankyrin, lipocalin, neocarzinostatin, cytochrome b, CP1 zinc finger, PST1, coiled coil, LACI-D1, Z domain and tendamistat domains may be used (See e.g., Nygren and Uhlen, 1997, *Current Opinion in Structural Biology*, 7, 463-469).

[0151] Additionally, one skilled in the art will recognize that suitable binding agents include portions of these antibodies, such as one or more of heavy chain CDR1, CDR2, CDR3, light chain CDR1, CDR2 and CDR3 as specifically disclosed herein. At least one of the regions of heavy chain CDR1, CDR2, CDR3, CDR1, CDR2 and CDR3 may have at least one amino acid substitution, provided that the antibody or antigen binding protein retains the binding specificity of the non-substituted CDR. The non-CDR portion of the antibody or antigen binding protein may be a non-protein molecule. The non-CDR portion of the antibody or antigen binding protein may be composed of amino acids, wherein the antibody or antigen binding protein is a recombinant binding protein or a synthetic peptide.

Nucleic Acids

[0152] In one aspect, the present invention provides isolated nucleic acid molecules that encode the antigen binding proteins of the present invention. In addition, provided are vectors comprising the nucleic acids, cell comprising the nucleic acids, and methods of making the antigen binding

proteins of the invention. The nucleic acids comprise, for example, polynucleotides that encode all or part of an antigen binding protein, for example, one or both chains of an antibody of the invention, or a fragment, derivative, mutein, or variant thereof, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. The nucleic acids can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

[0153] Nucleic acids encoding antibody polypeptides (e.g., heavy or light chain, variable domain only, or full length) may be isolated from B-cells of mice that have been immunized with mesothelin antigen. The nucleic acid may be isolated by conventional procedures such as polymerase chain reaction (PCR).

[0154] Nucleic acid sequences encoding the variable regions of the heavy and light chain variable regions are shown above. The skilled artisan will appreciate that, due to the degeneracy of the genetic code, each of the polypeptide sequences disclosed herein is encoded by a large number of other nucleic acid sequences. The present invention provides each degenerate nucleotide sequence encoding each antigen binding protein of the invention.

[0155] The invention further provides nucleic acids that hybridize to other nucleic acids (e.g., nucleic acids comprising a nucleotide sequence of any of A1-A14) under particular hybridization conditions. Methods for hybridizing nucleic acids are well-known in the art. See, e.g., *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. As defined herein, for example, a moderately stringent hybridization condition uses a prewashing solution containing 5× sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6×SSC, and a hybridization temperature of 55° C. (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C.), and washing conditions of 60° C., in 0.5×SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6×SSC at 45° C., followed by one or more washes in 0.1×SSC, 0.2% SDS at 68° C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are set forth by, for example, Sambrook, Fritsch, and Maniatis (1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., chapters 9 and 11; and *Current Protocols in Molecular Biology*, 1995, Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4), and can be readily determined by those having ordinary skill in the art based on, for example, the length

and/or base composition of the DNA. Changes can be introduced by mutation into a nucleic acid, thereby leading to changes in the amino acid sequence of a polypeptide (e.g., an antigen binding protein) that it encodes. Mutations can be introduced using any technique known in the art. In one embodiment, one or more particular amino acid residues are changed using, for example, a site-directed mutagenesis protocol. In another embodiment, one or more randomly selected residues is changed using, for example, a random mutagenesis protocol. However it is made, a mutant polypeptide can be expressed and screened for a desired property.

[0156] Mutations can be introduced into a nucleic acid without significantly altering the biological activity of a polypeptide that it encodes. For example, one can make nucleotide substitutions leading to amino acid substitutions at non-essential amino acid residues. In one embodiment, a nucleotide sequence provided herein for of the antibodies of the present invention, or a desired fragment, variant, or derivative thereof, is mutated such that it encodes an amino acid sequence comprising one or more deletions or substitutions of amino acid residues that are shown herein for the light chains of the antibodies of the present invention or the heavy chains of the antibodies of the present invention to be residues where two or more sequences differ. In another embodiment, the mutagenesis inserts an amino acid adjacent to one or more amino acid residues shown herein for the light chains of the antibodies of the present invention or the heavy chains of the antibodies of the present invention to be residues where two or more sequences differ. Alternatively, one or more mutations can be introduced into a nucleic acid that selectively change the biological activity. (e.g., binding to mesothelin) of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity. Examples of quantitative changes include increasing, reducing or eliminating the activity. Examples of qualitative changes include changing the antigen specificity of an antigen binding protein.

[0157] In another aspect, the present invention provides nucleic acid molecules that are suitable for use as primers or hybridization probes for the detection of nucleic acid sequences of the invention. A nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence encoding a full-length polypeptide of the invention, for example, a fragment that can be used as a probe or primer or a fragment encoding an active portion (e.g., a mesothelin binding portion) of a polypeptide of the invention.

[0158] Probes based on the sequence of a nucleic acid of the invention can be used to detect the nucleic acid or similar nucleic acids, for example, transcripts encoding a polypeptide of the invention. The probe can comprise a label group, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used to identify a cell that expresses the polypeptide.

[0159] In another aspect, the present invention provides vectors comprising a nucleic acid encoding a polypeptide of the invention or a portion thereof. Examples of vectors include, but are not limited to, plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors.

[0160] The recombinant expression vectors of the invention can comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. The recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be

used for expression, which is operably linked to the nucleic acid sequence to be expressed. Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cells (e.g., SV40 early gene enhancer, Rous sarcoma virus promoter and cytomegalovirus promoter), those that direct expression of the nucleotide sequence only in certain host cells (e.g., tissue-specific regulatory sequences, see Voss et al., 1986, Trends Biochem. Sci. 11:287, Maniatis et al., 1987, Science 236:1237, incorporated by reference herein in their entireties), and those that direct inducible expression of a nucleotide sequence in response to particular treatment or condition (e.g., the metallothionin promoter in mammalian cells and the tet-responsive and/or streptomycin responsive promoter in both prokaryotic and eukaryotic systems (see id.)). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

[0161] In another aspect, the present invention provides host cells into which a recombinant expression vector of the invention has been introduced. A host cell can be any prokaryotic cell or eukaryotic cell. Prokaryotic host cells include gram negative or gram positive organisms, for example *E. coli* or *bacilli*. Higher eukaryotic cells include insect cells, yeast cells, and established cell lines of mammalian origin. Examples of suitable mammalian host cell lines include Chinese hamster ovary (CHO) cells or their derivatives such as Veggie CHO and related cell lines which grow in serum-free media (see Rasmussen et al., 1998, Cytotechnology 28:31) or CHO strain DXB-11, which is deficient in DHFR (see Urlaub et al., 1980, Proc. Natl. Acad. Sci. USA 77:4216-20). Additional CHO cell lines include CHO-K1 (ATCC#CCL-61), EM9 (ATCC# CRL-1861), and UV20 (ATCC# CRL-1862). Additional host cells include the COS-7 line of monkey kidney cells (ATCC CRL 1651) (see Gluzman et al., 1981, Cell 23:175), L cells, C127 cells, 3T3 cells (ATCC CCL 163), AM-1/D cells (described in U.S. Pat. No. 6,210,924), HeLa cells, BHK (ATCC CRL 10) cell lines, the CV1/EBNA cell line derived from the African green monkey kidney cell line CV1 (ATCC CCL 70) (see McMahan et al., 1991, EMBO J. 10:2821), human embryonic kidney cells such as 293, 293 EBNA or MSR 293, human epidermal A431 cells, human Colo205 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HL-60, U937, HaK or Jurkat cells. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (Cloning Vectors: A Laboratory Manual, Elsevier, New York, 1985).

[0162] Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Additional selectable markers include those which confer resistance to drugs, such as G418, hygromycin and

methotrexate. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die), among other methods.

[0163] The transformed cells can be cultured under conditions that promote expression of the polypeptide, and the polypeptide recovered by conventional protein purification procedures. Polypeptides contemplated for use herein include substantially homogeneous recombinant mammalian anti-mesothelin antibody or antigen binding polypeptides substantially free of contaminating endogenous materials.

[0164] Cells containing the nucleic acid encoding the antigen binding proteins of the present invention also include hybridomas. The production and culturing of hybridomas are discussed in the antibody section above.

Antigen Binding Protein and Antibody Production

[0165] The antigen binding proteins and antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0166] Recombinant expression of an antigen binding protein or antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antigen binding protein or antibody or a fragment of the antibody or antigen binding protein. Once a polynucleotide encoding an antibody or antigen binding protein has been obtained, the vector for the production of the antibody or antigen binding protein may be produced by recombinant DNA technology. An expression vector is constructed containing antibody or antigen binding protein coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

[0167] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody or antigen binding protein of the invention. In one aspect of the invention, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0168] A variety of host-expression vector systems may be utilized to express the antibody or antigen binding protein of the invention as described above. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody or antigen binding protein of the invention *in situ*. Bacterial cells such as *E. coli*, and eukaryotic cells are commonly used for the expression of a recombinant antibody or antigen binding protein, especially for the expression of whole recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[0169] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modi-

fies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include, but are not limited to, CHO, COS, 293, 3T3, or myeloma cells.

[0170] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody or antigen binding protein may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody or antigen binding protein. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody or antigen binding protein.

[0171] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., *Cell* 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, *Proc. Natl. Acad. Sci. USA* 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., *Cell* 22:817 (1980)) genes can be employed in tk, hgp^rt or ap^rt-cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., *Proc. Natl. Acad. Sci. USA* 77:357 (1980); O'Hare et al., *Proc. Natl. Acad. Sci. USA* 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, *Proc. Natl. Acad. Sci. USA* 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 (Wu and Wu, *Biotherapy* 3:87-95 (1991)); and hyg^r, which confers resistance to hygromycin (Santerre et al., *Gene* 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds.), *Current Protocols in Human Genetics*, John Wiley & Sons, NY (1994); Colberre-Garapin et al., *J. Mol. Biol.* 150:1 (1981), which are incorporated by reference herein in their entireties.

[0172] The expression levels of an antibody or antigen binding protein can be increased by vector amplification (for a review, see Bebbington and Hentschel, "The use of vectors

based on gene amplification for the expression of cloned genes in mammalian cells" (DNA Cloning, Vol. 3. Academic Press, New York, 1987)). When a marker in the vector system expressing antibody or antigen binding protein is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody or antigen binding protein will also increase (Crouse et al., *Mol. Cell. Biol.* 3:257 (1983)).

[0173] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, *Nature* 322:52 (1986); Kohler, *Proc. Natl. Acad. Sci. USA* 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0174] Once an antibody or antigen binding protein of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and size-exclusion chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0175] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide. Fused or conjugated antibodies of the present invention may be used for ease in purification. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., *Immunol. Lett.* 39:91-99 (1994); U.S. Pat. No. 5,474,981; Gillies et al., *Proc. Natl. Acad. Sci.* 89:1428-1432 (1992); Fell et al., *J. Immunol.* 146:2446-2452 (1991).

[0176] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

Binding to Mesothelin

[0177] In one embodiment, the present invention provides antigen binding proteins that compete for binding with a reference antibody or antigen binding protein, wherein the

reference antibody or antigen binding protein comprises a combination of light chain and heavy chain variable domain sequences selected from the sequences provided herein. In another embodiment, the present invention provides human antibodies or antigen binding proteins that cross-compete for binding with a reference antibody, wherein the reference antibody is Ab237, Ab1.1.2, Ab1.33.1, Ab1.68.1, Ab1.78.1, Ab1.119.1, or Ab2.69.2. The ability to cross-compete with an antibody can be determined using any suitable assay, with nonlimiting examples further described below.

Epitope

[0178] As described herein, an epitope is the portion of a molecule that is bound by an antigen binding protein (e.g., an antibody). An epitope can comprise non-contiguous portions of the molecule (e.g., in a polypeptide, amino acid residues that are not contiguous in the polypeptide's primary sequence but that, in the context of the polypeptide's tertiary and quaternary structure, are near enough to each other to be bound by an antibody or antigen binding protein). Further, an epitope can comprise or consist of simply a linear, contiguous polypeptide sequence. In determining binding of an antigen binding protein to a target molecule, one skilled in the art can, for example, determine if the antigen binding protein competes for the same epitope as compared to another antigen binding protein or, e.g., the known ligand or receptor of the target molecule.

[0179] The term "compete" or "cross-compete" when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins or neutralizing antigen binding proteins or non-neutralizing antigen binding proteins) that compete for the same epitope means competition between antigen binding proteins as determined by an assay in which the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) being tested prevents or inhibits (e.g., reduces) specific binding of a reference antigen binding protein (e.g., a ligand, or a reference antibody) to a common antigen (e.g., PCSK9 or a fragment thereof).

[0180] Numerous competition assays are well known in the art, with nonlimiting examples being competition ELISA, use of the BiaCore® platform, the Kinexa® platform, or the like. Further examples include: solid phase direct or indirect radioimmunoassay (MA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahl et al., 1983, *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., 1986, *J. Immunol.* 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and Lane, 1988, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, e.g., Morel et al., 1988, *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, et al., 1990, *Virology* 176:546-552); and direct labeled RIA (Moldenhauer et al., 1990, *Scand. J. Immunol.* 32:77-82). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test antigen binding protein and a labeled reference antigen binding protein. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference

antigen binding proteins and antigen binding proteins binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein for steric hindrance to occur. Usually, when a competing antigen binding protein is present in excess, it will inhibit (e.g., reduce) specific binding of a reference antigen binding protein to a target antigen by at least 40-45%, 45-50%, 50-55%, 55-60%, 60-65%, 65-70%, 70-75% or 75% or more. In some embodiments, binding is inhibited by at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. In some embodiments, binding is inhibited by at least 80-85%, 85-90%, 90-95%, 95-97%, or 97% or more.

[0181] Accordingly, the invention provides anti-human mesothelin antibodies that compete for binding with the antibodies of the invention. In one embodiment, the invention provides for antibodies that compete for binding with Ab237. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.1.2. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.33.1. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.33.1y. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.68.1. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.78.1. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.119.1. In one embodiment, the invention provides for antibodies that compete for binding with Ab2.69.2. In one embodiment, the invention provides for antibodies that compete for binding with Ab2.69.2cv. In one embodiment, the invention provides for antibodies that compete for binding with Ab2.69.2s. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.58. In one embodiment, the invention provides for antibodies that compete for binding with Ab1.51.

Activity of Antigen Binding Proteins

[0182] In certain embodiments, the present invention provides antigen binding proteins, in particular human, humanized, or chimeric antibodies, that specifically bind to human mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to cynomolgous mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to murine mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to rat mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to human, cynomolgous, murine and rat mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to human, cynomolgous and murine mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to human and cynomolgous mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to human and murine mesothelin. In another embodiment, the present invention provides antigen binding proteins that specifically bind to human and rat mesothelin. Such antibodies include antagonizing or neutralizing antibodies.

[0183] In certain embodiments, the antigen binding proteins of the invention, such as the human antibodies of the present invention have an IC50 value of 90 nM or less, in another embodiment, an IC50 value of 80 nM or less, in

another embodiment, 70 nM or less, in another embodiment, 60 nM or less, in another embodiment, 50 nM or less, in another embodiment, 40 nM or less, in another embodiment, 30 nM or less, in another embodiment 25 nM or less.

[0184] In certain embodiments, the antigen binding proteins of the invention do not internalize into the cell that expresses MSLN upon binding to MSLN. This is an advantageous and unexpected property, as in certain embodiments it is desirable to keep the antigen binding protein exposed at the cell surface. For example, for effector cell mediated killing of the cell expressing MSLN (e.g., ADCC), it is desirable to maintain the antigen binding protein at the cell surface so that effector cells can bind to, e.g., the Fc region of an antigen binding protein. In another nonlimiting example such as a bispecific single chain antibody that binds to MSLN and CD3, it is desirable to maintain this antibody at the cell surface so that the CD3 expressing effector cells can efficiently be brought into proximity of the MSLN expressing target cell. Determining whether an antigen binding protein of the invention internalizes or not can be readily determined using assays well known in the art.

[0185] In certain embodiments, the antigen binding proteins of the invention do not inhibit or interfere with the MSLN/CA125 interaction. Although the significance of the MSLN and CA125 interaction has not been fully elucidated, as described herein, it is known that this interaction plays a role in cell adhesion and may also play a role in tumor metastasis. Analysis of the MSLN/CA125 interaction can be readily determined using assays well known in the art. Non-limiting examples include using competition assays described herein. In some embodiments the antigen binding proteins of the invention inhibit or interfere with the MSLN/CA125 interaction by less than about 1%, 2%, 3%, 4%, 5%, 10%, 15%, or 20%. In some embodiments, the antigen binding proteins of the invention inhibit or interfere with the MSLN/CA125 interaction by less than about 0.1% to about 1%, less than about 1% to about 5%, less than about 1% to about 10%, less than about 1% to about 15% or less than about 1% to about 20%.

[0186] In certain embodiments, the antibody or antigen binding proteins of the invention specifically bind to MSLN have a dissociation constant or K_d (k_{off}/k_{on}) of less than 10^{-2} M, less than 5×10^{-2} M, less than 10^{-3} M, less than 5×10^{-3} M, less than 10^{-4} M, less than 5×10^{-4} M, less than 10^{-5} M, less than 5×10^{-5} M, less than 10^{-6} M, less than 5×10^{-6} M, less than 10^{-7} M, less than 5×10^{-7} M, less than 10^{-8} M, less than 5×10^{-8} M, less than 10^{-9} M, less than 5×10^{-9} M, less than 10^{-10} M, less than 5×10^{-10} M, less than 10^{-11} M, less than 5×10^{-11} M, less than 10^{-12} M, less than 5×10^{-12} M, less than 10^{-13} M, less than 5×10^{-13} M, less than 10^{-14} M, less than 5×10^{-14} M, less than 10^{-15} M, or less than 5×10^{-15} M. In a further embodiment, an ADC that specifically binds to least on Eph receptor has a dissociation constant or $K_{sub.d}$ ($k_{sub.off}/k_{sub.on}$) of less than about 10^{-2} M, less than about 5×10^{-2} M, less than about 10^{-3} M, less than about 5×10^{-3} M, less than about 10^{-4} M, less than about 5×10^{-4} M, less than about 10^{-5} M, less than about 5×10^{-5} M, less than about 10^{-6} M, less than about 5×10^{-6} M, less than about 10^{-7} M, less than about 5×10^{-7} M, less than about 10^{-8} M, less than about 5×10^{-8} M, less than about 10^{-9} M, less than about 5×10^{-9} M, less than about 10^{-10} M, less than about 5×10^{-10} M, less than about 10^{-11} M, less than about 5×10^{-11} M, less than about 10^{-12} M, less than about 5×10^{-12} M, less than about 10^{-13} M, less than about

5×10^{-13} M, less than about 10^{-14} M, less than about 5×10^{-14} M, less than about 10^{-15} M, or less than about 5×10^{-15} M.

[0187] In another embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of greater than 10^{-9} M, greater than 5×10^{-9} M, greater than 10^{-10} M, greater than 5×10^{-10} M, greater than 10^{-11} M, greater than 5×10^{-11} M, greater than 10^{-12} M, greater than 5×10^{-12} M, greater than 10^{-13} M, greater than 5×10^{-13} M, greater than 10^{-14} M, greater than 5×10^{-14} M or greater than 10^{-14} M. In another embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of greater than about 10^{-9} M, greater than about 5×10^{-9} M, greater than about 10^{-10} M, greater than about 5×10^{-10} M, greater than about 10^{-11} M, greater than about 5×10^{-11} M, greater than about 10^{-12} M, greater than about 5×10^{-12} M, greater than about 10^{-13} M, greater than about 5×10^{-13} M, greater than about 10^{-14} M, greater than about 5×10^{-14} M or greater than about 10^{-14} M.

[0188] In a further embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of between about 10^{-9} M and about 10^{-14} M, between about 10^{-9} M and about 10^{-13} M, between about 10^{-9} M and about 10^{-12} M, between about 10^{-9} M and about 10^{-11} M, or between about 10^{-9} M and about 10^{-10} M. In a further embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of between about 10^{-9} M and about 10^{-14} M, between about 10^{-10} M and about 10^{-14} M, between about 10^{-11} M and about 10^{-14} M, between about 10^{-12} M and about 10^{-14} M, or between about 10^{-13} M and about 10^{-14} M. In a further embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of between 10^{-9} M and 10^{-14} M, between 10^{-9} M and 10^{-13} M, between 10^{-9} M and 10^{-12} M, between 10^{-9} M and 10^{-11} M, or between 10^{-9} M and 10^{-10} M. In a further embodiment, an antibody or antigen binding protein that specifically binds to MSLN has a K_d of between 10^{-9} M and 10^{-14} M, between 10^{-10} M and 10^{-14} M, between 10^{-11} M and 10^{-14} M, between 10^{-12} M and 10^{-14} M, or between 10^{-13} M and 10^{-14} M.

[0189] K_d for the antigen binding proteins of the invention can be readily determined by assays well known in the art. Nonlimiting examples include the BiAcCore® platform or the Kinexa® platform as described herein.

[0190] In certain embodiments, the antigen binding proteins of the invention preferentially bind membrane bound MSLN over soluble MSLN. Membrane bound MSLN refers to the presence of MSLN in or on the cell membrane surface of a cell that expresses MSLN. Soluble MSLN refers to MSLN that is no longer on in or on the cell membrane surface of a cell that expresses or expressed MSLN. In certain instances, the soluble MSLN is present in the blood and/or lymphatic circulation in a subject. In one embodiment, the antigen binding proteins bind membrane-bound mesothelin at least 5 fold, 10 fold, 15 fold, 20 fold, 25 fold, 30 fold, 40 fold, 50 fold, 100 fold, 500 fold, or 1000 fold greater than soluble mesothelin. In one embodiment, the antigen binding proteins of the present invention preferentially bind membrane-bound mesothelin 30 fold greater than soluble mesothelin. Determining the preferential binding of an antigen binding protein to membrane bound MSLN over soluble MSLN can be readily determined using assays well known in the art. Nonlimiting examples are competition assays as described herein.

[0191] In certain embodiments, the antigen binding molecules of the invention reduces the growth of tumor cells in

vivo when administered to a subject who has tumor cells that express MSLN. Measurement of the reduction of the growth of tumor cells can be determined by multiple different methodologies well known in the art. Nonlimiting examples include direct measurement of tumor dimension, measurement of excised tumor mass and comparison to control subjects, measurement via imaging techniques (e.g. CT or MRI) that may or may not use isotopes or luminescent molecules (e.g. luciferase) for enhanced analysis, and the like. In specific embodiments, administration of the antigen binding agents of the invention results in a reduction of in vivo growth of tumor cells as compared to a control antigen binding agent by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 100%, with an about 100% reduction in tumor growth indicating a complete response and disappearance of the tumor. In further embodiments, administration of the antigen binding agents of the invention results in a reduction of in vivo growth of tumor cells as compared to a control antigen binding agent by about 50-100%, about 75-100% or about 90-100%. In further embodiments, administration of the antigen binding agents of the invention results in a reduction of in vivo growth of tumor cells as compared to a control antigen binding agent by about 50-60%, about 60-70%, about 70-80%, about 80-90%, or about 90-100%. Dosing can readily be determined by one skilled in the art and is discussed further herein.

Antibody or Antigen Binding Protein Effector Function

[0192] The present invention provides anti-mesothelin binding molecules with increased effector function. Nonlimiting examples of methods for increasing effector function can be found in U.S. Pat. Nos. 5,624,821, 6,602,684, 7,029,872, U.S. Patent Application Publication Nos. 2006/0067930A1, 2005/0272128A1, 2005/0079605A1, 2005/0123546A1, 2004/0072290A1, 2006/0257399A1, 2004/0261148A1, 2007/0092521, 2006/0040325A1, and 2006/0039904A1, and International Patent Application Publication Nos. WO 04/029207, WO03011878, WO05044859, WO 06071856, and WO 06071280.

[0193] Methods of engineering Fc regions of antibodies so as to alter effector functions are known in the art (e.g., U.S. Patent Publication No. 20040185045 and PCT Publication No. WO 2004/016750, both to Koenig et al., which describe altering the Fc region to enhance the binding affinity for Fc gamma RIIB as compared with the binding affinity for Fc gamma RITA; see, also, PCT Publication Nos. WO 99/58572 to Armour et al., WO 99/51642 to Idusogie et al., and U.S. Pat. No. 6,395,272 to Deo et al.). Methods of modifying the Fc region to decrease binding affinity to Fc gamma RIIB are also known in the art (e.g., U.S. Patent Publication No. 20010036459 and PCT Publication No. WO 01/79299, both to Ravetch et al.). Modified antibodies having variant Fc regions with enhanced binding affinity for Fc gamma RIIIA and/or Fc gamma RITA as compared with a wildtype Fc region have also been described (e.g., PCT Publication Nos. WO 2004/063351, to Stavenhagen et al., the disclosure of which is incorporated herein in its entirety). Throughout the specification, and in particular the examples, the terms "2x" and "3x" in reference to the anti-MSLN antibodies are used. These terms refer to substitutions in the Fc region that result in enhanced ADCC through increased binding affinity to the Fc receptor as described above. In one embodiment, the "2x"

molecule has the following substitutions: S239D/1332E and the “3×” molecule has the following mutations: S239D/1332E/A330L.

[0194] Antibody or antigen binding protein effector function may also be modified through the generation of antibodies with altered glycosylation patterns. In the present invention, such antibodies may be referred to as “low fucose” antibodies. For example, an antibody or antigen binding protein can be made that has an altered type of glycosylation, such as an afucosylated/hypofucosylated antibody or antigen binding protein having reduced amounts of fucosyl residues or an antibody or antigen binding protein having increased bisecting GlcNAc structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody or antigen binding protein in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody or antigen binding protein with altered glycosylation. For example, EP 1,176,195 by Hanai et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lec13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R. L. et al. (2002) *J. Biol. Chem.* 277: 26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNAc structures which results in increased ADCC activity of the antibodies (see also Umana et al. (1999) *Nat. Biotech.* 17:176-180). PCT Publication WO 2009009086 by Collingwood et al. describes the use of zinc finger constructs to inactivate the FUT8 gene in cells.

[0195] Methods for generating antibodies with altered glycoforms are known in the art, and include but are not limited to those described in Umana et al. 1999, *Nat. Biotechnol* 17:176-180; Davies et al., 20017 *Biotechnol Bioeng* 74:288-294; Shields et al. 2002, *J Biol Chem* 277:26733-26740; Shinkawa et al., 2003; *J Biol Chem* 278:3466-3473) U.S. Pat. No. 6,602,684; U.S. Ser. No. 10/277,370; U.S. Ser. No. 10/113,929; PCT WO 00/61739A1; PCT WO 01/292246A1; PCT WO 02/311140A1; PCT WO 02/30954A1; Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb™ glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland). See, e.g., WO 00061739; EA01229125; US 20030115614; Okazaki et al., 2004, *JMB*, 336: 1239-49. It is contemplated that antibodies with altered fucosylation pattern may also be prepared by post-translational removal of fucose (e.g. with a fucosidase enzyme).

Half-Life

[0196] The present invention provides for antibodies or antigen binding protein or fragments thereof that specifically bind to mesothelin which have an extended half-life in vivo. In particular, the present invention provides antibodies or antigen binding protein or fragments thereof which have a

half-life in a mammal (for example, but not limited to, a human), of greater than 3 days, greater than 7 days, greater than 10 days, greater than 15 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months.

[0197] To prolong the serum circulation of antibodies (for example, but not limited to, monoclonal antibodies and single chain antibodies) or antigen binding protein or fragments thereof (for example, but not limited to, Fab fragments) in vivo, for example, inert polymer molecules such as high molecular weight polyethyleneglycol (PEG) can be attached to the antibodies or antigen binding proteins (including fragments thereof) with or without a multifunctional linker either through site-specific conjugation of the PEG to the N- or C-terminus of the antibodies or via epsilon-amino groups present on lysine residues. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody—or antigen binding proteins—PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies or antigen binding proteins (including fragments thereof) can be tested for binding activity as well as for in vivo efficacy using methods known to those of skill in the art, for example, by immunoassays described herein.

[0198] Antibodies having an increased half-life in vivo can also be generated by introducing one or more amino acid modifications (i.e., substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (e.g., Fc or hinge Fc domain fragment). See, e.g., International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Pat. No. 6,277,375, each of which is incorporated herein by reference in its entirety.

Conjugates

[0199] According to certain aspects of the invention, therapeutic agents or toxins can be conjugated to chimerized, human, or humanized anti-mesothelin antibodies for use in the compositions and methods of the invention. In certain embodiments, these conjugates can be generated as fusion proteins. Examples of therapeutic agents and toxins include, but are not limited to, members of the enediyne family of molecules, such as calicheamicin and esperamicin. Chemical toxins can also be taken from the group consisting of duocarmycin (see, e.g., U.S. Pat. No. 5,703,080 and U.S. Pat. No. 4,923,990), methotrexate, doxorubicin, melphalan, chlorambucil, ARA-C, vindesine, mitomycin C, cis-platinum, etoposide, bleomycin and 5-fluorouracil. Examples of chemotherapeutic agents also include Adriamycin, Doxorubicin, 5-Fluorouracil, Cytosine arabinoside (Ara-C), Cyclophosphamide, Thiotepa, Taxotere (docetaxel), Busulfan, Cytosin, Taxol, Methotrexate, Cisplatin, Melphalan, Vinblastine, Bleomycin, Etoposide, Ifosfamide, Mitomycin C, Mitoxantrone, Vincristine, Vinorelbine, Carboplatin, Teniposide, Daunomycin, Caminomycin, Aminopterin, Dactinomycin, Mitomycins, Esperamicins (see, U.S. Pat. No. 4,675,187), Melphalan, and other related nitrogen mustards.

[0200] Other toxins that can be used in the immunoconjugates of the invention include poisonous lectins, plant toxins such as ricin, abrin, modeccin, botulina, and diphtheria toxins. Combinations of the various toxins could also be coupled

to one antibody or antigen binding protein thereby accommodating variable cytotoxicity. Nonlimiting examples of toxins which are suitably employed in the combination therapies of the invention are ricin, abrin, ribonuclease, DNase I, Staphylococcal enterotoxin-A, pokeweed anti-viral protein, gelonin, diphtherin toxin, *Pseudomonas* exotoxin, and *Pseudomonas* endotoxin. See, for example, Pastan et al., Cell, 47:641 (1986), and Goldenberg et al., Cancer Journal for Clinicians, 44:43 (1994). Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, non-binding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolacca americana* proteins (PAPI, PAPII, and PAP-S), *Momordica charantia* inhibitor, curcumin, croton, *Sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the tricothecenes. See, for example, WO 93/21232 published Oct. 28, 1993. Suitable toxins and chemotherapeutic agents are described in Remington's Pharmaceutical Sciences, 19th Ed. (Mack Publishing Co. 1995), and in Goodman And Gilman's The Pharmacological Basis of Therapeutics, 7th Ed. (MacMillan Publishing Co. 1985). Other suitable toxins and/or chemotherapeutic agents are known to those of skill in the art.

[0201] Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as *serratia* protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as beta-galactosidase and neuraminidase useful for converting glycosylated prodrugs into free drugs; beta-lactamase useful for converting drugs derivatized with alpha-lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes," can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, Nature 328:457-458 (1987)). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme as desired to portions of a human affected by a B cell malignancy.

[0202] The enzymes can be covalently bound to the antibodies of the present invention by techniques well-known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen-binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well-known in the art (see, e.g., Neuberger et al., Nature, 312:604-608 (1984)).

[0203] Covalent modifications of the anti-mesothelin antibody or antigen binding proteins of the invention are included within the scope of this invention. They may be made by chemical synthesis or by enzymatic or chemical cleavage of the antibody or antigen binding proteins, if applicable. Other

types of covalent modifications of the anti-mesothelin antibody or antigen binding proteins are introduced into the molecule by reacting targeted amino acid residues of the antibody or antigen binding proteins with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues.

[0204] Cysteiny residues most commonly are reacted with alpha-haloacetates (and corresponding amines), such as chloroacetic acid or chloroacetamide, to give carboxymethyl or carboxyamidomethyl derivatives. Similarly, iodo-reagents may also be used. Cysteiny residues also are derivatized by reaction with bromotrifluoroacetone, alpha-bromo-beta-(5-imidazolyl)propionic acid, chloroacetyl phosphate, N-alkyl-maleimides, 3-nitro-2-pyridyl disulfide, methyl 2-pyridyl disulfide, p-chloromercuribenzoate, 2-chloromercuri-4-nitrophenol, or chloro-7-nitrobenzo-2-oxa-1,3-diazole.

[0205] Histidyl residues are derivatized by reaction with diethylpyrocarbonate at pH 5.5-7.0 because this agent is relatively specific for the histidyl side chain. Para-bromophenacyl bromide also is useful; the reaction is preferably performed in 0.1 M sodium cacodylate at pH 6.0.

[0206] Lysyl and amino-terminal residues are reacted with succinic or other carboxylic acid anhydrides. Derivatization with these agents has the effect of reversing the charge of the lysiny residues. Other suitable reagents for derivatizing .alpha.-amino-containing residues and/or e-amino-containing residues include imidoesters such as methyl picolinimide, pyridoxal phosphate, pyridoxal, chloroborohydride, trinitrobenzenesulfonic acid, O-methylisourea, 2,4-pentanedione, and transaminase-catalyzed reaction with glyoxylate.

[0207] Arginy residues are modified by reaction with one or several conventional reagents, among them phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginy residues generally requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents may react with the epsilon-amino groups of lysine as well as the arginine epsilon-amino group.

[0208] The specific modification of tyrosyl residues may be made, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Tyrosyl residues are iodinated using I¹²⁵ or I¹³¹ to prepare labeled proteins for use in radioimmunoassay.

[0209] Carboxyl side groups (aspartyl or glutamyl) are selectively modified by reaction with carbodiimides (R—N=C=N—R'), where R and R' are different alkyl groups, such as 1-cyclohexyl-3-(2-morpholinyl-4-ethyl)carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl)carbodiimide. Furthermore, aspartyl and glutamyl residues are converted to asparaginy and glutaminy residues by reaction with ammonium ions.

[0210] Glutaminy and asparaginy residues are frequently deamidated to the corresponding glutamyl and aspartyl residues, respectively. These residues are deamidated under neutral or basic conditions. The deamidated form of these residues falls within the scope of this invention.

[0211] Other modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threony residues, methylation of the .alpha.-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman

& Co., San Francisco, pp. 79-86 (1983)), acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

[0212] Another type of covalent modification involves chemically or enzymatically coupling glycosides to the antibody or antigen binding proteins. These procedures are advantageous in that they do not require production of the antibody or antigen binding proteins in a host cell that has glycosylation capabilities for N- or O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in WO 87/05330 published 11 Sep. 1987, and in Aplin and Wriston, *CRC Crit. Rev. Biochem.*, pp. 259-306 (1981).

Methods of Treatment

[0213] In another aspect, a method of treating a subject, comprising administering a therapeutic dosage of the antigen binding proteins of the present invention is provided. In one embodiment, the antigen binding proteins are human antibodies. As used herein the term "subject" refers to a mammal, including humans, and is used interchangeably with the term "patient". The human antibodies, can be used to treat, control or prevent a disorder or condition characterized by cells expressing or overexpressing mesothelin in a subject. These disorders include cancer and other hyperproliferative disorders characterized by expression or overexpression of mesothelin.

[0214] Cancers and related disorders that can be treated, prevented, or managed by methods and compositions of the present invention include but are not limited to cancers of an epithelial cell origin. Examples of such cancers include the following: leukemias, such as but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemias, such as, myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia leukemias and myelodysplastic syndrome; chronic leukemias, such as but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, hairy cell leukemia; polycythemia vera; lymphomas such as but not limited to Hodgkin's disease, non-Hodgkin's disease; multiple myelomas such as but not limited to smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma and extramedullary plasmacytoma; Waldenstrom's macroglobulinemia; monoclonal gammopathy of undetermined significance; benign monoclonal gammopathy; heavy chain disease; bone and connective tissue sarcomas such as but not limited to bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, neurilemmoma, rhabdomyosarcoma, synovial sarcoma; brain tumors such as but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, primary brain lymphoma; breast cancer including but not limited to ductal carcinoma, adenocarcinoma, lobular (small

cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, Paget's disease, and inflammatory breast cancer; adrenal cancer such as but not limited to pheochromocytoma and adrenocortical carcinoma; thyroid cancer such as but not limited to papillary or follicular thyroid cancer, medullary thyroid cancer and anaplastic thyroid cancer; pancreatic cancer such as but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; pituitary cancers such as but limited to Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipidus; eye cancers such as but not limited to ocular melanoma such as iris melanoma, choroidal melanoma, and ciliary body melanoma, and retinoblastoma; vaginal cancers such as squamous cell carcinoma, adenocarcinoma, and melanoma; vulvar cancer such as squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; cervical cancers such as but not limited to, squamous cell carcinoma, and adenocarcinoma; uterine cancers such as but not limited to endometrial carcinoma and uterine sarcoma; ovarian cancers such as but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; esophageal cancers such as but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; stomach cancers such as but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; colon cancers; rectal cancers; liver cancers such as but not limited to hepatocellular carcinoma and hepatoblastoma; gallbladder cancers such as adenocarcinoma; cholangiocarcinomas such as but not limited to papillary, nodular, and diffuse; lung cancers such as non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma and small-cell lung cancer; testicular cancers such as but not limited to germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, choriocarcinoma (yolk-sac tumor), prostate cancers such as but not limited to, prostatic intraepithelial neoplasia, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; penile cancers; oral cancers such as but not limited to squamous cell carcinoma; basal cancers; salivary gland cancers such as but not limited to adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; pharynx cancers such as but not limited to squamous cell cancer, and verrucous; skin cancers such as but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acral lentiginous melanoma; kidney cancers such as but not limited to renal cell carcinoma, adenocarcinoma, hypernephroma, fibrosarcoma, transitional cell cancer (renal pelvis and/or uter); Wilms' tumor; bladder cancers such as but not limited to transitional cell carcinoma, squamous cell cancer, adenocarcinoma, carcinosarcoma. In addition, cancers include myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma and papillary adenocarcinomas (for a review of such disorders, see Fishman et al.,

1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[0215] Accordingly, the methods and compositions of the invention are also useful in the treatment or prevention of a variety of cancers or other abnormal proliferative diseases, including (but not limited to) the following: carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Burkitt's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; other tumors, including melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma; tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas; tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and other tumors, including melanoma, xeroderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma. It is also contemplated that cancers caused by aberrations in apoptosis would also be treated by the methods and compositions of the invention. Such cancers may include but not be limited to follicular lymphomas, carcinomas with p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis, and myelodysplastic syndromes. In specific embodiments, malignancy or dysproliferative changes (such as metaplasias and dysplasias), or hyperproliferative disorders, are treated or prevented in the skin, lung, colon, breast, prostate, bladder, kidney, pancreas, ovary, or uterus. In other specific embodiments, sarcoma, melanoma, or leukemia is treated or prevented.

[0216] In some embodiments, the cancer is malignant and overexpresses mesothelin. In other embodiments, the disorder to be treated is a pre-cancerous condition associated with cells that overexpress mesothelin.

[0217] The term "treatment" encompasses alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. An antigen binding protein, in particular a human antibody according to the present invention, need not effect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. One embodiment of the invention is directed to a method comprising administering to a patient an antigen binding protein such as a human antibody in an

amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

[0218] As is understood in the pertinent field, pharmaceutical compositions comprising the antigen binding proteins of the invention are administered to a subject in a manner appropriate to the indication and the composition. In one embodiment, pharmaceutical compositions comprise the human antibodies of the present invention. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intra-articular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antigen binding protein in aerosol form, and the like. Other alternatives include oral preparations including pills, syrups, or lozenges.

[0219] Advantageously, the antigen binding proteins of the invention, are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents, for example, as described below. In various particular embodiments, the composition comprises one, two, three, four, five, or six physiologically active agents in addition to one or more antigen binding proteins (e.g. human antibodies) of the present invention.

[0220] In one embodiment, the pharmaceutical composition comprises a human antibody or antigen binding protein of the invention together with one or more substances selected from the group consisting of a buffer suitable for antibodies at a suitable pH, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as dextrin, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. In accordance with appropriate industry standards, preservatives may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in Remington's Pharmaceutical Sciences, 16th Ed. (1980) and 20th Ed. (2000), Mack Publishing Company, Easton, Pa.

[0221] Kits for use by medical practitioners are provided including one or more antigen binding proteins of the invention and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more human antibodies, which may be in the form of a composition as disclosed above, and may be in one or more vials.

[0222] Dosages and the frequency of administration may vary according to such factors as the route of administration, the particular antibodies employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the subject. Appropriate dosages can be determined by procedures known in the pertinent art, e.g. in clinical trials that may involve dose escalation studies.

[0223] An antigen binding protein, in particular, the human antibodies, of the invention may be administered, for

example, once or more than once, e.g., at regular intervals over a period of time. In particular embodiments, a human antibody or antigen binding protein is administered over a period of at least once a month or more, e.g., for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, e.g. from one to six weeks, may be sufficient. In general, the human antibody or antigen binding protein is administered until the patient manifests a medically relevant degree of improvement over baseline for the chosen indicator or indicators.

[0224] One example of therapeutic regimens provided herein comprise subcutaneous injection of an antigen binding protein such as a human antibody or antigen binding protein once a week, or once every two weeks, at an appropriate dosage, to treat a condition in which it is desired to target cells expressing mesothelin. Weekly or monthly administration of antigen binding protein would be continued until a desired result is achieved, e.g., the subject's symptoms subside. Treatment may resume as needed, or, alternatively, maintenance doses may be administered. Alternatively, various other routes of administration, such as intravenous, intraperitoneal, or intramuscular injection can be employed.

[0225] For the treatment of the disease, the appropriate dosage of the agent of the present invention depends on the type of disease to be treated, the severity and course of the disease, the responsiveness of the disease, whether the agent is administered for therapeutic or preventative purposes, previous therapy, patient's clinical history, and so on all at the discretion of the treating physician. The agent can be administered one time or over a series of treatments lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved (e.g. reduction in tumor size). Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient and will vary depending on the relative potency of an individual antibody or antigen binding protein or agent. The administering physician can readily determine optimum dosages, dosing methodologies and repetition rates. In certain embodiments, dosage is from 0.01 µg to 100 mg per kg of body weight, and can be given once or more daily, weekly, monthly or yearly. In certain embodiments, the agent is given once every two weeks or once every three weeks. In certain embodiments, the dosage of the agent is from about 0.1 mg to about 20 mg per kg of body weight. The treating physician can estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues.

Combination Therapies

[0226] Particular embodiments of methods and compositions of the invention involve the use of an antigen binding protein such as an anti-mesothelin antibody or antigen binding proteins of the present invention and one or more cancer therapeutics, for example. In one embodiment, antigen binding proteins of the present invention are administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both proteinaceous and non-proteinaceous drugs. When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art. "Co-administration" and combination therapy are not limited to simultaneous administration, but also

include treatment regimens in which an antigen binding protein is administered at least once during a course of treatment that involves administering at least one other therapeutic agent to the patient.

[0227] In another aspect, the present invention provides a method of treating a subject with cancer or a hyperproliferative disorder associated with the expression or overexpression of mesothelin with a therapeutic antigen binding protein of the present invention, such as the fully human therapeutic antibodies described herein, together with one or more other treatments. In one embodiment, such a combination therapy achieves a synergistic effect. The antigen binding proteins may be in combination with one or more of the following treatments currently available. Nonlimiting examples of anticancer agents that can be used in the various embodiments of the invention, including pharmaceutical compositions and dosage forms and kits of the invention, include: acivicin; aclarubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropiramine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cisplatin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; dactinomycin; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziquone; docetaxel; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitrucin; enloplatin; enpromate; epipropidine; epirubicin hydrochloride; erbulozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; floxuridine; fludarabine phosphate; fluorouracil; fluorocitabine; fosquidone; fostriecin sodium; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; ilmofofosine; interleukin II (including recombinant interleukin II, or rIL2), interferon alpha-2a; interferon alpha-2b; interferon alpha-n1 interferon alpha-n3; interferon beta-I a; interferon gamma-I b; ioprolatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedopa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitotane; mitoxantrone hydrochloride; mycophenolic acid; nocodazole; nogalamycin; ormaplatin; oxisuran; paclitaxel; pegaspargase; peliomycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; pipsulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfuroxymycin; prednimustine; procabazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogletimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloxantrone hydrochloride; temoporfin;

teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; tretolone acetate; triceribine phosphate; trimetrexate; trimetrexate glucuronate; triptorelin; tubulazole hydrochloride; uracil mustard; uredepa; vapreotide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinylicinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinzolidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; zorubicin hydrochloride. Other examples of anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstauroporine; beta lactam derivatives; beta-alethine; betaclamyacin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflata; bropiramine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-aminotriazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentan-thraquinones; cycloplatin; cypemycin; cytarabine ocfosfate; cytolytic factor; cytotaxin; dacliximab; decitabine; dehydrodidemin B; desloreline; dexamethasone; dexifosfamide; dextrazoxane; dexverapamil; diaziqune; didemin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docetaxel; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemes-tane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorubicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-I receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting

factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; HMG-CoA reductase inhibitor (such as but not limited to, Lovastatin, Pravastatin, Fluvastatin, Statin, Simvastatin, and Atorvastatin); loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullin; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhodium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B 1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargamostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thali-

blastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; tricyribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; typhostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; Vitaxin®; vorozole; zanoterone; zeniplatin; zilascorb; and zinostatin stimalamer. Additional anti-cancer drugs are 5-fluorouracil and leucovorin. These two agents are particularly useful when used in methods employing thalidomide and a topoisomerase inhibitor. In a specific embodiment, the anti-mesothelin antibodies of the present invention are used in combination with gemcitabine.

Diagnostic Uses

[0228] In one aspect, anti-mesothelin antibodies of the invention are useful for detecting the presence of mesothelin in a biological sample. The term “detecting” as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue. In certain embodiments, such tissues include normal and/or cancerous tissues that express mesothelin at higher levels relative to other tissues.

[0229] In one aspect, the invention provides a method of detecting the presence of mesothelin in a biological sample. In certain embodiments, the method comprises contacting the biological sample with an anti-mesothelin antibody or antigen binding proteins under conditions permissive for binding of the anti-mesothelin antibody or antigen binding protein to mesothelin, and detecting whether a complex is formed between the anti-mesothelin antibody or antigen binding protein and mesothelin.

[0230] In one aspect, the invention provides a method of diagnosing a disorder associated with increased expression of mesothelin. In certain embodiments, the method comprises contacting a test cell with an anti-mesothelin antibody; determining the level of expression (either quantitatively or qualitatively) of mesothelin by the test cell by detecting binding of the anti-mesothelin antibody to mesothelin; and comparing the level of expression of mesothelin by the test cell with the level of expression of mesothelin by a control cell (e.g., a normal cell of the same tissue origin as the test cell or a cell that expresses mesothelin at levels comparable to such a normal cell), wherein a higher level of expression of mesothelin by the test cell as compared to the control cell indicates the presence of a disorder associated with increased expression of mesothelin. In certain embodiments, the test cell is obtained from an individual suspected of having a disorder associated with increased expression of mesothelin. In certain embodiments, the disorder is a cell proliferative disorder, such as a cancer or a tumor.

[0231] In certain embodiments, a method of diagnosis or detection, such as those described above, comprises detecting binding of an anti-mesothelin antibody to mesothelin expressed on the surface of a cell or in a membrane preparation obtained from a cell expressing mesothelin on its surface. In certain embodiments, the method comprises contacting a cell with an anti-mesothelin antibody under conditions permissive for binding of the anti-mesothelin antibody to

mesothelin, and detecting whether a complex is formed between the anti-mesothelin antibody and mesothelin on the cell surface. An exemplary assay for detecting binding of an anti-mesothelin antibody to mesothelin expressed mesothelin on the surface of a cell is a “FACS” assay.

[0232] Certain other methods can be used to detect binding of anti-mesothelin antibodies to mesothelin. Such methods include, but are not limited to, antigen-binding assays that are well known in the art, such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), “sandwich” immunoassays, immunoprecipitation assays, fluorescent immunoassays, protein A immunoassays, and immunohistochemistry (IHC).

[0233] In certain embodiments, anti-mesothelin antibodies are labeled. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, e.g., through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P , ^{14}C , ^{125}I , ^3H , and ^{131}I , fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luciferases, e.g., firefly luciferase and bacterial luciferase (U.S. Pat. No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, beta-galactosidase, glucoamylase, lysozyme, saccharide oxidases, e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

[0234] In certain embodiments, anti-mesothelin antibodies are immobilized on an insoluble matrix. Immobilization entails separating the anti-mesothelin antibody or antigen binding protein from any mesothelin that remains free in solution. This conventionally is accomplished by either insolubilizing the anti-mesothelin antibody or antigen binding protein before the assay procedure, as by adsorption to a water-insoluble matrix or surface (Bennich et al., U.S. Pat. No. 3,720,760), or by covalent coupling (for example, using glutaraldehyde cross-linking), or by insolubilizing the anti-mesothelin antibody or antigen binding protein after formation of a complex between the anti-mesothelin antibody or antigen binding protein and mesothelin, e.g., by immunoprecipitation.

[0235] The invention having been described, the following examples are offered by way of illustration, and not limitation.

EXAMPLES

Example 1

Generation of Anti-Mesothelin Antibodies

Immunization

[0236] Fully human antibodies to human MSLN were generated by immunizing XenoMouse™ transgenic mice (Mendez et al., 1997; Kellerman and Green, 2002). Mice were immunized using routine methods. The full length mesothelin cDNA was cloned into an expression vector in frame with His

and V5 antigen tags. The entire protein was expressed, but the cells subsequently cleaved the 30 kDa MPF fragment. The protein sequence comprising a.a. 1-293 of mesothelin, representing the membrane attached 40 kDa fragment, was injected into the mice.

[0237] The initial immunization was with 10 μ g antigen admixed 1:1 v/v with TiterMax Gold. Subsequent boosts were made with 5 or 10 μ g antigen admixed 1:1 v/v with 100 μ g alum gel in pyrogen-free D-PBS and sometimes with 50% TiterMax Gold, followed by three injections with 10 μ g antigen admixed 1:1 v/v with 10 μ g mesothelin antigen in alum gel, and then a final boost of 10 μ g antigen in PBS. In particular, each mouse was immunized in the footpad by subcutaneous injection. The animals were immunized on days 0, 4, 7, 10, 14, 17, 21, 32, and 45. The animals were bled on days 13 and 20 to obtain sera for harvest selection.

[0238] Anti-mesothelin antibody titers were determined by indirect ELISA. The titer value is the reciprocal of the greatest dilution of sera with an OD reading two-fold that of background. Briefly, mesothelin (84mer; 1 μ g/mL) was coated onto Costar Labcoat Universal Binding Polystyrene 96 well plates overnight at four degrees. The solution containing unbound mesothelin was removed and the plates were treated with UV light (365 nm) for 4 minutes (4000 microjoules). The plates were washed five times with dH₂O. Xenomouse™ mice sera from the mesothelin immunized animals, or naïve Xenomouse™ animals, were titrated in 2% milk/PBS at 1:2 dilutions in duplicate from a 1:100 initial dilution. The last well was left blank. 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 μ g/mL for 1 hour at room temperature. The plates were washed five times with dH₂O. The plates were developed with the addition of TMB for 30 minutes and the ELISA was stopped by the addition of 1 M phosphoric acid. The specific titer of individual Xenomouse™ animals was determined from the optical density at 450 nm. Lymph nodes from all immunized Xenomouse™ animals were harvested for fusion.

[0239] Immunized mice were sacrificed by carbon dioxide asphyxiation, and the lymph nodes harvested and pooled from each cohort. The lymphoid cells were dissociated by grinding in DMEM to release the cells from the tissues and the cells were suspended in DMEM. The cells were counted, and 0.9 ml DMEM per 100 million lymphocytes added to the cell pellet to resuspend the cells gently but completely. Using 100 μ l of CD90+ magnetic beads per 100 million cells, the cells were labeled by incubating the cells with the magnetic beads at 40° C. for 15 minutes. The magnetically labeled cell suspension containing up to 108 positive cells (or up to 2×10^9 total cells) was loaded onto a LS+ column and the column washed with DMEM. The total effluent was collected as the CD90-negative fraction (most of these cells are B cells).

[0240] P3 myeloma cells and B cell-enriched lymph node cells were combined in a ratio of 1:1 (myeloma:lymph nodes) into a 50 ml conical tube in DMEM. The combined cells were centrifuged at 800 $\times$ g (2000 rpm) for 5-7 min. and the supernatant immediately removed from the resulting pellet. Two to four ml of Pronase solution (CalBiochem, Cat. #53702; 0.5 mg/ml in PBS) was added to the cells to resuspend the cell pellet gently. The enzyme treatment was allowed to proceed for no more than two minutes and the reaction stopped by the addition of 3-5 ml of FBS. Enough ECF solution was added to bring the total volume to 40 ml and the mixture was centrifuged at 800 $\times$ g (2000 rpm) for 5-7 min. The supernatant was

removed and the cell pellet gently resuspended with a small volume of ECF solution, followed by enough ECF solution to make a total volume of 40 ml. The cells were mixed well and counted, then centrifuged at 800 $\times$ g (2000 rpm) for 5-7 min. The supernatant was removed and the cells resuspended in a small volume of ECF solution. Enough additional ECF solution was added to adjust the concentration to 2×10^6 cells/ml.

[0241] The cells were then placed in an Electro-Cell-Fusion (ECF) generator (Model ECM2001, Genetronic, Inc., San Diego, Calif.) and fused according to the manufacturer's instructions. After ECF, 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 Medium in DMEM. The cells were incubated for 15-30 minutes at 37° C., then centrifuged at 400 $\times$ g (1000 rpm) for five minutes. The cells were gently resuspended in a small volume of 1/2 HA medium (1 bottle of 50 $\times$ HA from Sigma, Cat. #A9666 and 1 liter of Hybridoma Medium) and the volume adjusted appropriately with more 1/2 HA medium (based on 5×10^6 B cells per 96-well plate and 200 μ l per well). The cells were mixed well and pipetted into 96-well plates and allowed to grow. On day 7 or 10, one-half the medium was removed, and the cells re-fed with 1/2 HA medium.

Screening Antibodies

[0242] 1. Selection of Candidate Antibodies for ELISA.

[0243] After 14 days of culture, hybridoma supernatants were screened for mesothelin-specific monoclonal antibodies. The ELISA plates (Fisher, Cat. No. 12 565 136) were coated with 50 of mesothelin (2 μ g/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) 3 times. 200 μ l/well Blocking Buffer (0.5% BSA, 0.1% Tween 20, 0.01% Thimerosal in 1 $\times$ PBS) were added and the plates incubated at room temperature for 1 hour. After incubation, the plates were washed with Washing Buffer three times. Fifty (50) of hybridoma supernatants, and positive and negative controls were added and the plates incubated at room temperature for 2 hours. The positive control used throughout was XMG2 mesothelin Group 1, fp N160-7 and the negative control was XMG2 KLH Group 1, fp L627-6. After incubation, the plates were washed three times with Washing Buffer. One hundred (100) of detection antibody goat anti-huIgGfc-HRP (Caltag, Cat. #H10507), [and goat anti-hlgk-HRP (Southern Biotechnology, Cat. #2060-05) and goat anti-hlg λ (Southern Biotechnology, Cat. #2070-05) in secondary screening] were added and the plates incubated at room temperature for 1 hour. In the secondary screen, three sets of samples (positives in first screening) were screened, one set for hlgG detection, one set for hKappa detection and one set for hLambda detection. After incubation, the plates were washed three times with Washing Buffer. One hundred (100) μ l/well of TMB (BioFX Lab. Cat. #TMSK-0100-01) were added and the plates allowed to develop for about 10 minutes (until negative control wells barely started to show color), then 50 μ l/well stop solution (TMB Stop Solution (BioFX Lab. Cat. #STPR-0100-01) were added and the plates read on an ELISA plate reader at wavelength 450 nm.

[0244] 2. FACS Analysis

[0245] To ascertain that the antibodies recognizing soluble mesothelin protein also recognized the antigen when bound

to the cell surface, FACS analysis was performed on cells that express mesothelin, OvCar 8, and cells that do not express the antigen, 786-0.

Example 2

Binding Affinity of Anti-Mesothelin Antibodies

[0246] Binding affinity of the anti-MSLN antibodies of the invention was tested using assays well known in the art (Biacore® and Kinexa®) using general procedures outlined by the manufacturers. The data is summarized in FIG. 4.

[0247] The following describes binding activity as assessed by surface plasmon resonance using a BIAcore® biosensor device. Briefly, anti-human Fc (or anti-murine Fc) is covalently coupled to biosensor chips (i.e., a CM5 chip) using a standard amine coupling procedure and reagents according to the manufacturer's instructions. Test antibody or a control antibody is injected over the immobilized anti-Fc, and varying amounts of MSLN (e.g., human, murine, rat, or cyno) are independently passed over an irrelevant antibody-coupled chip (negative control) as well as an anti-MSLN-coated chip using running buffer (e.g. 0.005% P20 surfactant). Regeneration of the chip may be accomplished with one 10-microliter pulse of 100 mM phosphoric acid at 10 microliters/minute. All binding is performed in HBS (10 mM HEPES, 0.15 M NaCl, 3.4 mM EDTA, 0.02% NaN₃, 0.005% surfactant P20, pH 7.4) or equivalent. Binding curves were compared qualitatively for binding signal intensity, as well as for dissociation rates. Antibody binding kinetic parameters (dissociation rate constant "kd") were determined, e.g., by using software provided by the manufacturer (e.g., BIA evaluation 3.0) that allows for global fitting calculations. The lower the dissociation equilibrium constants (expressed in pM), the greater the affinity of the antibody for MSLN.

Example 3

Mesothelin Species Cross-Reactivity of Anti-Mesothelin Antibodies

[0248] Reactivity of the antibodies of the invention against several species of mesothelin (cyno, rat, mouse) was tested using assays well known in the art. The data is summarized in FIG. 4.

[0249] FACS binding assays were performed to evaluate the binding of the anti-Mesothelin antibodies to murine, rat and cynomolgous monkey mesothelin orthologues, using recombinant forms of the various receptors transiently expressed on 293T cells. FACS assays were performed by incubating hybridoma supernatants with 10,000 to 25,000 cells in PBS/2% Fetal bovine serum/2 mM Calcium Chloride at 4° C. for one hour followed by two washes with PBS/2% Fetal bovine serum/2 mM Calcium Chloride. Cells were then treated with fluorochrome-labeled secondary antibodies at 4° C. followed by one wash. The cells were resuspended in 50 µl of PBS/2% FBS and antibody binding was analyzed using a FACSCalibur™ instrument.

Example 4

ELISA Cross-Competition and Binning of Anti-Mesothelin Antibodies

[0250] Cross-competition ELISA assays were performed to evaluate different "bins" of antibodies. The assays utilized

techniques well known in the art. The data is summarized in FIGS. 5 and 6 and indicate that several antibodies bind to a MSLN epitope distinct from MORAb-009; and that Ab237 does not interfere with CA-125 binding while MORAb-009 does.

[0251] Certain antibodies, described herein were binned generally in accordance with the protocol described in U.S. Patent Application Publication No. 20030157730. Mouse anti-hlgG conjugated beads are prepared for coupling to primary antibody. The volume of supernatant needed is calculated using the following formula: $(n+10) \times 50 \text{ uL}$ (where n =total number of samples on plate). Where the concentration is known, 0.5 µg/mL is used. Bead stock is gently vortexed, then diluted in supernatant to a concentration of 2500 of each bead per well or 0.5×10^5 /mL and incubated on a shaker in the dark at RT overnight, or 2 hours if at a known concentration of 0.5 µg/mL. Following aspiration, 50 µL of each bead is added to each well of filter plate, then washed once by adding 100 µL/well wash buffer and aspirating. Antigen and controls are added to filter plate 50 uL/well then covered and allowed to incubate in the dark for 1 hour on shaker. Following a wash step, a secondary unknown antibody is added at 50 µL using the same dilution (or concentration if known) as is used for the primary antibody. The plates are then incubated in the dark for 2 hours at RT on shaker followed by a wash step. Next, 50 µL/well biotinylated mouse anti-hlgG diluted 1:500 is added and allowed to incubate in the dark for one hour on shaker at RT. Following a wash step, 80 µL/well Streptavidin-PE is added at 1:1000 and allowed to incubate in the dark for 15 minutes on shaker at RT. Following a wash step, each well is resuspended in 80 µL blocking buffer and read using Luminex. Results show that the monoclonal antibodies belong to distinct bins. Competitive binding by antibodies from different bins supports antibody specificity for similar or adjacent epitopes. Non competitive binding supports antibody specificity for unique epitopes. Data is summarized in FIG. 5.

Functional Antibody Cross-Competition

[0252] In this antibody binning type set of experiments anti MSLN antibodies were tested for their ability to detect recombinant soluble human MSLN in a solid phase binding assay in which one antibody was used to capture soluble human MSLN in solution and the other antibody was employed to detect bound human MSLN. The ability of the antibodies to detect MSLN in this format indicated that they bound to distinct portions of MSLN (different non-overlapping epitopes) while the inability of a particular antibody pair to detect MSLN showed that they bound so a similar epitope or overlapping epitopes.

[0253] Capture antibodies (or CA125) listed across the top of the table were immobilized on Nalge Nunc Maxisorb 96-well clear Elisa plates in PBS at a concentration of 4 µg/ml overnight at 2-8 C. After washing in PBS-Tween 20 0.05% (PBS-T) 3 times, recombinant soluble MSLN was added in binding medium (PBS, 1% BSA, 10% NGS) to the starting well for titration 100 ng/ml in 100 ul. The soluble MSLN was then tritrated 8-12 well using a two-fold dilution and allowed to incubate with the capture antibody for 1 hour at 25° C. (room temperature). Unbound MSLN was removed by washing wells 3 times employing PBS. The various detection antibodies (listed in the left hand column of the table) were then added to the wells at a concentration of 1 µg/ml and the wells allowed to incubate at room temperature for 1 hour. To

measure binding of bound detection antibodies -mouse anti human MSLN antibodies (MN, MB, OV569, 4H3), the wells were washed 3 times with PBS and then gt anti mouse IgG-HRP (Southern Biotech) was added to the wells for 30 minutes at room temperature. The wells were then washed again 3 times with PBS and the HRP-signal developed by adding 100 u of TMB substrate (K&P). The plate development was stopped by adding 1N sulfuric acid and reading the plate on a dual wave-length optical plate reader (450 nm-572 nm). In the case where the detection antibody was fully human (237, 158, 151) the antibody was added in along with MN or MB and detection of MN or MB was measured.

[0254] The results are summarized in FIG. 6. The results are reported as (+)—detection of soluble MSLN is not altered (≤ 2 fold reduction MSLN binding signal) in presence of competitor or EC50 for binding/detection is ≤ 1 ng/ml with the binding pair being assessed. Results reported as (−) indicates that soluble MSLN is not detected and that significant cross-competition for binding is observed.

Example 5

ADCC Activity of Anti-Mesothelin Antibodies

[0255] Throughout the specification, and in particular the examples, the terms “2x” and “3x” in reference to the anti-MSLN antibodies are used. These terms refer to substitutions in the Fc region that result in enhanced ADCC through increased binding affinity to the Fc receptor. The “2x” molecule has the following substitutions: S239D/I332E and the “3x” molecule has the following mutations: S239D/I332E/A330L.

[0256] 1. Objectives

[0257] Determine the ability of Fc engineered fully human anti-MSLN antibodies to mediate ADCC as compared to the same unmodified, parental fully human anti-MSLN antibody.

[0258] 2. Materials and Methods

[0259] 2.1 Materials

[0260] Effectors: normal in-house donors were leukaphoresed, and NK cells isolated from the leukopack by the Cell Purification Group using the Milteni AutoMacs Pro negative selection system. NK cells were held overnight at 4° C. on a rocker, then washed, counted and resuspended at 4×10^6 cells/mL in complete RPMI for use in the ADCC assay.

[0261] Targets: Tumor cell targets were selected based on MSLN expression. Targets were washed and counted. 6×10^6 targets are resuspended in complete RPMI and labeled in a final concentration of 10 μ M calcein (Sigma #C1359-00UL CALCEIN AM 4MM IN ANHYDROUS DMSO) for 40 minutes at 37 degrees, 5% CO₂. Cells were washed twice in PBS, resuspended in complete RPMI and incubated at 37 degrees, 5% CO₂ for 2 hrs. After labeling, target cells are washed, recounted and resuspended at 0.2×10^6 cells/mL in complete RPMI for use in the ADCC assay

[0262] 2.2 Methods

[0263] Assay was performed in a 96 well round bottom tissue culture plate (Corning 3799). Antibodies were titrated from 20 μ g/mL to 0.0002 μ g/mL by carrying 10 μ L in 100 μ L of complete RPMI containing 10% FCS (a 1:10 dilution). Calcein labeled targets were added, 50 μ L to contain 10,000 cells. Target cells and various concentrations of antibody were incubated for 40 minutes at 4° C., then NK cell effectors added, 50 μ L to contain 100,000 cells (10:1 E:T ratio). Cultures were incubated for 4 hrs at 37° C. then supernatants pulled and assayed for calcein release by measuring fluores-

cence at 485-535 nm on a Wallac Victor II 1420 Multilable HTS counter. 100% lysis values were determined by lysing six wells of labeled targets with Igepal 630 detergent (3 μ L per well) and spontaneous lysis values determined by measuring the fluorescence in supernatants from targets alone.

[0264] 2.3 Statistical Analysis

[0265] Percent (%) specific lysis was defined as (sample fluorescence)–spontaneous lysis fluorescence)/(100% lysis–spontaneous lysis fluorescence). Spontaneous lysis was determined by wells containing only targets and 100% lysis was determined by wells where targets had been lysed with IGEPAL CA 630 detergent. Raw data was entered in an Excel spreadsheet with embedded formulae to calculate % specific lysis and resultant values transferred to graphic program (GraphPad Prism) where the data was transformed in a curve fit graph Subsequent analyses (linear regression calculations) were done in GraphPad to generate EC50 values.

[0266] 3. Results and Discussion

[0267] Effector NK cells in wells incubated with control hlgG1 antibody were unable to mediate killing of the calcein-labeled target cells while effectors in wells with certain fully human anti-MSLN antibodies were, as measured by specific Lytic activity (% specific lysis) able to mediate antibody dependent cellular cytotoxicity.

[0268] 4. Conclusions

[0269] Both ADCC enhanced anti-MSLN and WT anti-MSLN antibodies were able to induce NK mediated killing of target tumor cells expressing MSLN. ADCC enhanced anti-MSLN antibodies mediate a significantly higher level of killing than the parent unmodified anti-MSLN antibodies.

Example 6

CDC Activity of Anti-Mesothelin Antibodies

1. STUDY TITLE: ANTI-MSLN ANTIBODIES MEDIATE COMPLEMENT DEPENDENT CYTOTOXICITY OF MESOTHELIN EXPRESSING TUMOR CELLS

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

[0270] Abbreviation or Term Definition/Explanation

- [0271]** FBS Fetal Bovine Serum
- [0272]** CDC Complement Dependent Cytotoxicity (assay)
- [0273]** CO₂ Carbon Dioxide
- [0274]** mL milliliter
- [0275]** μ L microliter
- [0276]** n number
- [0277]** SEM Standard error of the mean
- [0278]** ° C. Degrees Celsius
- [0279]** PI Propidium Iodide
- [0280]** Ab Antibody
- [0281]** IgG1 immunoglobulin class G1
- [0282]** HuIgG1 Human immunoglobulin class G1
- [0283]** 237 WT Hu-anti-huMesothelin-2.37-IgG1, WT
- [0284]** 237 3x Hu-anti-huMesothelin-237-IgG1, 3x
- [0285]** 237 low fucose Hu-anti-huMesothelin-237-IgG1, clone 6F11
- [0286]** cBU69 WT Chimeric anti-human CD27L IgG1, WT
- [0287]** cBU69 3x Chimeric anti-human CD27L IgG1, 3x

3. OBJECTIVES

[0288] The objective was to determine the ability of Fc-enhanced anti-human mesothelin 237 3x or 237 low fucose to mediate CDC as compared to the wild type anti-Mesothelin antibody 237 WT.

4. MATERIALS AND METHODS

4.1 Materials

4.1.1 Test Materials

[0289]

Antibody Drug Conjugates	Source	Formulation
Human IgG ₁ Kappa from human plasma	Sigma, St. Louis, MO	20 nM tris buffered saline, pH 8.0.
237 WT	Amgen Inc., Seattle, WA	20 nM tris buffered saline, pH 8.0.
237 3x	Amgen Inc., Seattle, WA	
237 low fucose	Amgen Inc., Seattle, WA	
cBU69 WT	Amgen Inc., Seattle, WA	
cBU69 3x	Amgen Inc., Seattle, WA	

4.1.2 Reagents

[0290] Target cells: Ovarc 8, Ovarian Carcinoma cells express Mesothelin (65,000 MSLN/site) and CD27L. Growth medium contained 1 L of DMEM+L-glutamine+10% FBS+10 ml MEM non-essential Amino Acids+10 ml HEPES+1 ml beta-mer captoethanol+5 ml Pen/strep+10 ml sodium pyruvate (=cDMEM)

[0291] Baby rabbit complement (Rt C') (Cederlane, Burlington, Ontario, Canada. Catalog #CL-3441-S. Lot#75540805.)

[0292] Heat inactivated (HI) complement was generated by incubating complement at 56° C. in a water bath for 30 minutes and then returning immediately to 4° C. The heat inactivated complement was used within 1 hr of heat inactivation.

[0293] Assay medium: DMEM (basal medium) with 1% heat inactivated FBS.

[0294] Propidium iodide (PI), (Roche Diagnostics Corporation, Indianapolis, Ind. Catalog #11348639001, lot#93352020).

[0295] Hoechst 33342, (Molecular Probes, Inc. Eugene, Oreg. Catalog#H21492. Lot#24982W).

4.2 Methods

4.2.1 Preparation of Tumor Cells

[0296] Ovarc 8 cells were washed once with assay medium (DMEM plus 1% FBS) and resuspended in assay medium. Cells were seeded in a 96-well tissue culture plate at 100 μ L per well with the cell density at 0.5×10^4 cells per well. Cells were incubated at 37° C., 5% CO₂ overnight.

4.2.2 Treatment of Cells with Complement and Control Antibody

[0297] Two times concentrated complement was prepared in assay medium as outlined in the table below. Medium in cell in 96-well plate was removed with plate washer. Then 2x rabbit complement was added to cells in plates at 50 μ L per well.

Table for preparation of 2x concentrated rabbit complements in assay medium			
2x complements	Complement (ml)	Assay Medium (ml)	Total volume (ml)
20% HI rabbit C' (inactive)	0.5	2	2.5
20% no HI rabbit C' (active)	1.5	6	7.5

[0298] Two times concentrated antibodies were added to cells at 50 μ L per well as shown in the Experimental Design below to get a final concentration at 10 μ g/mL. The total volume in each well at the start of culture was 100 μ L. Cells were continuously incubated at 37° C., 5% CO₂ for five hours.

[0299] Experimental Design: plate map for a 96-well plate. Antibodies were in duplicate wells for each sample with a total volume at 100 μ L/well.

[0300] Note: Data obtained from NB 105783. Rt C' is referred to as baby rabbit complement; Inactive C' is referred to as heat inactivated complement.

4.2.3 Measurement of Cytotoxicity with ArrayScan Plate Reader

[0301] After 5-hour incubation, 150 μ L of warm 2% FBS in PBS were added to each well. The plates were centrifuged at 1000 rpm for 5 min. The medium were discarded with plate washer where its needles were set to a height that allowed 50 μ L of medium left in each well.

[0302] The cocktail of Hoechst 33342 and propidium iodide (PI) which was prepared at 1:1000 dilution in PBS solution containing 2% FBS was added into cells at 100 μ L per well.

[0303] Samples were analyzed on an ArrayScan VTI HCS reader (version 6, Cellomics, Thermo Fisher Scientific, Pittsburgh, Pa.) with BioApplication "Target Activation" employing a 20x objective. The filter setting was indicated in table below. At least 200 cells were counted in each well.

Channel	Target	Label	Fluor	Filter
1	Nucleic acid for all cells	Hoechst 33342	UV/460 nm	DAPI
2	Nucleic acid for dead cells	Propidium iodide	488/>575 nm	TRITC

4.3 Statistical Analysis

[0304] Statistical analysis was performed using Prism 4.01 (GraphPad, San Diego, Calif.). A plot shows % cytotoxicity vs. the log of Ab concentration in μ g/mL. The % cytotoxicity in Y axis is represented with % selected objects from output

feature of ArrayScan reader and expressed as the mean $\pm$ standard error of the mean (SEM) for duplicate measurements (n=2) except control antibodies measured in single wells.

5. SUPPORTING DATA

5.1 Figures

[0305] All WT, 3 $\times$ and Low Fucose of Mesothelin HuG1, Clone 237 did not show any complement-dependent cytotoxicity (CDC) mediated killing with 10% rabbit complement against Ovar 8 after 5 h incubation.

[0306] Ovar8 cells were exposed to doses of anti-Mesothelin WT or Fc-enhanced antibodies or its negative control, huG1 and positive controls cBu69 and cBU69 3 $\times$ starting at 10 μ g/mL (up panel). Then cells were treated with active or inactive (56° C., 30') rabbit complement (Rt C') at final concentration of 10% (up and low panel). After incubation at 37° C., 5% CO₂ for 5 hrs, CDC mediated killing was measured from output feature of ArrayScan reader "% selected objects" to detect % of PI positive vs. Hoechst for % Cytotoxicity. Data are expressed as the mean and standard error of the mean (SEM) for duplicate measurements (n=2) except single wells for controls. The results of this study are summarized in FIGS. 7-9 and indicate that none of the anti-MSLN antibodies demonstrated CDC mediated cell killing.

Example 7

ADCP Activity of Anti-Mesothelin Antibodies

[0307] Anti-MSLN Antibodies Mediate Antibody Dependent Cellular Phagocytosis of Mesothelin Expressing Tumor Cells

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

[0308]

Abbreviation or Term	Definition/Explanation
FBS	Fetal Bovine Serum
RPMI	Roswell Park Memorial Institute
CO ₂	Carbon Dioxide
mL	milliliter
μ L	microliter
n	number
NA	Not applicable
SEM	Standard error of the mean
° C.	Degrees Celsius
ATCC	American Type Culture Collection
RT	Room temperature
Ab	Antibody
IgG1	immunoglobulin class G1
HuIgG1	Human immunoglobulin class G1
ADCP	Antibody Dependent Cellular Phagocytosis (assay)
237 WT	Hu-anti-huMesothelin-237-HuIgG1, WT
237 3x	Hu-anti-huMesothelin-237-HuIgG1, 3x
237 low fucose	Hu-anti-huMesothelin-237-HuIgG1, clone 6F11
EC50	Half maximal effect concentration

2. OBJECTIVES

[0309] Determine the ability of anti-MSLN antibodies to mediate ADCP.

3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Test Materials

Antibody Drug Conjugates

- [0310]** 237 WT
- [0311]** 237 3 $\times$
- [0312]** 237 low fucose
- [0313]** Human IgG1 Kappa from human plasma (Cat. #15154 1 mg; Sigma, St. Louis, Mo.) 20 nM tris buffered saline, pH 8.0

3.1.2 Reagents

- [0314]** Target cells: Ovar 8, Ovarian Carcinoma cells express Mesothelin (65,000 MSLN/site) and CD27L. Growth medium contained 1 L of DMEM+L-glutamine+10% FBS+10 ml MEM non-essential Amino Acids+10 ml HEPES+1 ml beta-mer captoethanol+5 ml Pen/strep+10 ml sodium pyruvate (=cDMEM)
- [0315]** Effectors: normal in-house donor #1193 was monocytes isolated from the human peripheral blood by the Cell Purification Group (Amgen Inc., Seattle, Wash.) using the Milteni AutoMacs Pro negative selection system. Cells were held overnight at 4° C. on a rocker, then washed, counted and resuspended in complete RPMI for use in the ADCP assay.
- [0316]** PKH67 green fluorescent cell linker kit for general cell labeling (Sigma-Aldrich Corporation, St. Louis, Mo. Catalog #PKH67-GL, lot#076K0463).
- [0317]** CD11b-Biotin: mouse anti-human CD11b/Mac-1 monoclonal antibody, clone ICRF44, IgG1, Kappa. (eBioscience, San Diego, Calif. Catalog #13-0118-82, lot# E026682).
- [0318]** Streptavidin, Alexa 568 conjugate (Molecular Probes, Inc. Eugene, Oreg. Catalog #5-11226. Lot#34757A).
- [0319]** Hu M-CSF: recombinant human M-CSF (R&D Systems, Minneapolis, Minn. Catalog #216-MC-025, lot# MVND 16061).

3.2 Methods

- [0320]** Day 0: differentiation of human macrophage cells from purified monocytes
- [0321]** Monocytes were negative selected from human peripheral blood and stored in 4° C. cold room over night with medium RPMI 1640 containing 10% FBS. Then monocytes were seeded to a 48-well tissue culture plate at 200,000 cells per well with 200 μ L of macrophage growth medium (RPMI 1640 containing 10% FBS and 40 ng/ml Hu M-CSF) and incubated at 37° C., 5% CO₂ for 5-7 days to let monocytes differentiate to macrophages.
- [0322]** Day 6: performance of ADCP assay
- [0323]** 1. Labeling target cells with PKH67 green dye at final concentrations of 2×10^{-6} M PKH67 dye
- [0324]** Tumor cells were collected and washed once with PBS by centrifuging the cells (400' g) for 5 minutes.

- [0325] After centrifuging cells, the supernatant was carefully aspirated, but leaving no more than 25 mL of supernatant.
- [0326] Four μL of the PKH67 ethanolic dye solution at stock concentration of 4×10^{-6} M was added to 1 ml of Diluent C from kit in polypropylene tube and mixed well.
- [0327] Cell pellets were re-suspended into 1 mL of Diluent C at a density of 20×10^6 in polypropylene tube.
- [0328] Cells were rapidly transferred to dye work solution with gently pipetting to insure complete dispersion.
- [0329] The mixture was incubated at room temperature for 4 minutes with mixing periodically.
- [0330] Two mL of whole activated FBS was added into cells to stop the staining and incubated at room temp for 1 minute to allow binding of excess dye.
- [0331] Forty mL of RPMI containing 10% FBS was added into cells and washed once by centrifuging the cells (400' g) for 10 minutes.
- [0332] Cell pellets were suspended with 40 mL of medium again and transferred to a new tube.
- [0333] Cells were washed again three times with medium RPMI+10% FBS and $1 \times$ with macrophage growth medium (RPMI 1640 containing 10% FBS and 40 ng/ml Hu M-CSF).
- [0334] Cells were counted and suspended with macrophage growth medium at 1×10^6 cells per mL for T:E at 1:2 ratio.
- [0335] 2. Treatment of tumor cells with antibodies for antibody dependent cellular phagocytosis (ADCP)
- [0336] Antibody dilutions were prepared in macrophage growth medium. These dilutions were concentrated at four times higher than final concentrations.
- [0337] To preincubate PKH67 green labeled target cells with antibodies, 300 μL of $4 \times$ concentrated antibodies was mixed with 300 μL of green labeled tumor cells and incubated at 4°C . for 30 minutes.
- [0338] The mixture of green labeled tumor cells with anti-tumor antibodies was added to macrophage cells in 48-well plate at 200 μL for each well as indicated in the Experiment Design table below. The final volume is 0.4 ml per well. The ratio of target cells to effect cells (macrophages) is 1:2.
- [0339] Cells were incubated at 37°C ., 5% CO_2 for one hour.
- [0340] Experimental design: plate map for 48-well plate. Duplicate for each treatment
- [0341] 3. Counterstaining macrophages with macrophage marker
- [0342] Target cells and macrophages in 48-well plate were detached with Trypsin-Versene mixture.
- [0343] Cells were transferred into a 96-well block with 2.2-ml volume per well and washed once with pre-warmed FACS wash solution by spinning the blocks at 400' g for 5 minutes and then discarding supernatant.
- [0344] Macrophages were stained with their marker, CD11b-Biotin at 1:200 dilution in block solution with 100 μL per well for 10 min on ice.
- [0345] After washing cells once, macrophages were detected with streptavidin Alexa 568 at 1:1000 dilutions for 10 minute on ice.
- [0346] After washing cells $1 \times$ with PBS, cells were fixed with 4% formaldehyde in PBS at room temperature for 20 minutes. Then cells were washed $1 \times$ with dH₂O.

[0347] Cell pellets were resuspended with water at 200 μL per well and transferred to a 96-well plate at 100 μL per well. Plate can be sealed and stored at 4°C . overnight if needed.

[0348] 4. Quantitative measurement of phagocytosis activity on an ArrayScan VTI HCS reader (version 6, Cellomics Inc. Thermo Fisher Scientific, Pittsburgh, Pa.) with Target Activation BioApplication employing a $20 \times$ objective. The filter setting was indicated in table below. At least 200 cells were counted in each well.

Filter setting for ADCP:

Channel	Target	Label	Fluor
1	macrophages	Ms-anti-Hu CD11b Biotin α streptavidin Alexa 568	red
2	Tumor cells	PKH67	green

3.3 Statistical Analysis

[0349] Statistical analysis was performed using Prism 4.01 (GraphPad, San Diego, Calif.). A plot shows % tumor cell phagocytosis vs. the log of antibody concentration in ng/ml. The percentage of tumor cell phagocytosis is represented with percentage of tumor cells that were overlapped with macrophages vs. total macrophages in the selected fields and obtained from output feature of ArrayScan reader “% Object-Counts”. The % values were expressed as the mean $\pm$ standard error of the mean (SEM) for duplicate measurements ($n=2$). The EC50 was determined by using nonlinear regression analysis (Sigmoidal dose response curve fit). Data were normalized to the maximum and minimum signal and fit to a sigmoidal dose-response curve.

4. SUPPORTING DATA

4.1 Anti-MSLN Antibodies Induce Human Macrophages to Phagocytose Ovar 8 Cells

[0350] Anti-MSLN antibodies mediate ADCP activity against Ovar 8 cells. Phagocytosis images were captured using ArrayScan VTI plate reader at $20 \times$ magnification. Green dye labeled tumor cells were exposed to anti-MSLN antibodies (237 Low Fucose MSLN) or its negative control, HuG1. Then cells were mixed with human macrophages at a ratio of 2:1 (effectors:tumor). After incubation at 37°C ., 5% CO_2 for 1 hr, macrophages were detected with the marker CD11b-Biotin plus anti-streptavidin (αSA) Alexa 568 (red). FIG. 10 contains photographic images of these experimental results.

[0351] Fc-Enhanced Anti-Mesothelin HuG1, Clone 237-3 $\times$ and -Low Fucose Enhance Tumor Cell Phagocytosis Compared to 237 WT in Ovar 8 After 1 h Incubation

[0352] Anti-MSLN antibodies mediate ADCP activity by human macrophages. Mesothelin expressing tumor cell line Ovar 8 was exposed to 237 WT, or Fc enhanced Abs, 237 3 $\times$ and 237 low fucose or its negative control, HuG1. Then cells were mixed with human macrophages at a ratio of 2:1 (effectors:tumor). After incubation at 37°C ., 5% CO_2 for 1 hr, macrophages were detected with the marker CD11b. The ADCP activity in Y axis was measured from output feature of ArrayScan VTI reader “% selected objects” to detect % of tumor cells were phagocytized into macrophages. Data are

expressed as the mean and standard error of the mean (SEM) for duplicate measurements (n=2). FIG. 11 summarizes these results.

Example 8

Soluble MSLN vs. Surface MSLN Binding

[0353] Experiments were run to determine binding affinity of the anti-MSLN antibody ab237 against native surface bound MSLN and soluble MSLN. It was determined that ab237 binds native surface bound MSLN with 30-fold higher selectivity as compared to soluble MSLN.

[0354] 237 anti MSLN bind with greater affinity to native human MSLN expressed on the cell surface than recombinant soluble MSLN

		ab237
Binding Affinity	rHuMSLN sol. [#]	97 pM
K _D	Hu MSLN native*	3.5 pM

[0355] Equilibrium binding of 237 antibody was assessed to native human MSLN expressing N87 tumor cells utilizing KinExA technology. The results of binding of 237 to native human MSLN are reported as the equilibrium binding constant or KD in pM. Binding of 237 to recombinant human soluble MSLN (rHuMSLN sol.) was assessed in solution by Biacore analysis. The 237 antibody was captured on the Biacore sensor chip and the solution containing rHuMSLN sol was allowed to flow across the chip until binding equilibrium reached. Both the association and dissociation constants were measured and the results reported as the equilibrium binding constant or KD in pM. The results showed that the 237 mAb bound 30-fold better to native MSLN expressed on the cell surface than it did to soluble MSLN in solution.

Example 9

In Vivo Efficacy of Anti-Mesothelin Antibodies

[0356] In vivo experiments were performed to evaluate the efficacy of the anti-MSLN antibodies of the invention. The data from these experiments is summarized in FIGS. 15-17.

[0357] The ability of Fc-enhanced 237 anti MSLN to mediate anti tumor activity in vivo was assessed in the N87 gastric cancer xenograft model. Prior to implantation mice barcode chips were implanted into CB-17/SCID mice that would receive tumor implants. N87 gastric cancer cells (2×10⁶) in 100 µl were implanted subcutaneously in an equal volume of growth-factor reduced Matrigel (BD). Following implantation, the animals were either immediately treated with 237 mAb or with control mAb as indicated in FIG. 16 (left panel) or starting on the fourth day post tumor implantation FIG. 16 (right panel), FIG. 17 and FIG. 18. When initiation of treatment was delayed to day 4 post tumor implantation, the tumors were measured and the mice randomized into treatment groups of 10 so that the average tumor volume across the groups was similar prior to the start of treatment.

[0358] The control IgG1 antibody, 237 or MorAb-009 (FIG. 17) were administered twice per week i.p. for three weeks at the doses indicated in each figure. Where indicated, Gemcitabine was administered i.p. at the doses indicated on the FIG. 16 (left panel). 17 and 18 on day 4, 7 and 11 post

tumor implant. Tumor volume was assessed twice weekly by taking perpendicular measurements, electronic using calipers and recoding the measure associated with the bar code read in an xls spreadsheet. Control treated N87 tumors typically reached >1000 mm³ by day 28-30 so that is when the studies were designed to end for results presented in FIGS. 16 and 17. In the combination xenograft study (FIG. 18) where 237 was combined with gemcitabine the study was carried out to almost 55 days because the anti tumor effect was more pronounced and one of the outcomes of the experiment was to assess treatment durability. The results are reported as the average tumor volume +/-standard error of the mean over time. Statistical differences between groups was assessed using repeated measures ANOVA followed by post hoc analysis using Dunnett's for multiple comparisons (Graph Pad Prism, 5.0). When comparing the anti-tumor effect of one treatment group to another, a p-value of <0.05 was considered to be indicative a statistical difference between treatment groups.

Example 10

MSLN BiTE Binding

[0359] Binding of MSLN-BiTE to membrane-bound target expressed in cells was determined with an on-cell affinity assay. 3×10⁴ cells per well of a microtiter plate were incubated with MSLN-BiTE protein in a dose response for 16-22 h at 4° C. Cells were washed twice with flow buffer (PBS that contained 2% fetal calf serum and 0.01% sodium azide), and then resuspended in flow buffer and incubated with an anti-His Fab labeled with Alexa Fluor-647 for 50 minutes at 4° C. Cells were fixed after incubation to optimize detection of the fluorescent signal. Cells were then washed twice and resuspended in flow buffer that contained propidium iodide at 1 µg/ml. Cells were analyzed by flow cytometry for live cells that were positive for Alexa Fluor-647. EC₅₀ values were determined from the dose response curve of Alexa Fluor-647 positive cells.

[0360] FIG. 20 shows the results of binding of representative MSLN-BiTE proteins to human MSLN in NCI-N87 gastric cancer cells and to human CD3 in HPB-ALL cells. Solid lines in the graphs below indicate VH-VL orientation and dotted lines indicate the VL-VH orientation. FIG. 22 shows the results of binding of representative MSLN-BiTE proteins to human MSLN in OVCAR-8 ovarian cancer cells and to human or cyno MSLN in 293T cells that are transiently transfected with human MSLN or cyno MSLN.

Example 11

MSLN BiTE T-Cell Activation

[0361] OVCAR-8 cells were incubated at 40,000 cells per well with unstimulated pan-T cells (ALL CELLS) at a 10:1 effector to target cells ratio and BiTE proteins. The T cells are pre-labeled with 5 µM CFSE dye. MEC14-BiTE is directed against murine anti-Mecopropand is a negative control for the assay (Osada et al., Br. J. Cancer 2010). Cetuximab-BiTE is a BiTE generated from the Cetuximab anti-EGFR antibody (Lutterbues et al., PNAS 2010) that serves as a positive control for this assay due to expression of EGFR in OVCAR-8 cells. Both cytokine production and T cell activation were determined from this assay.

[0362] At 24 h, aliquots of supernatants were removed and assayed for the production of cytokines by multiplex ELISA

assays (Meso Scale Discovery). Briefly, spots within wells of a microtiter dish are precoated with an antibody against the target cytokine of interest. Supernatants from the incubation of BiTE, tumor cells and T cells are added to the wells of the cytokine assay plate, and then binding of cytokines to the bound antibody is detected by a chemiluminescent detection reagent. The chemiluminescent signal is quantitated with a plate reader and the EC₅₀ values are calculated from the dose response curves. Cytokines produced by the reaction of BiTE with target-expressing tumor cells and T cells included: IL-6 (shown in FIGS. 23 and 25), TNF- α , IFN- γ , MCP-1, IL-1B, IL-2, IL-4, IL-10, IL-12 and IL-13. Results from the other cytokine assays are summarized in FIG. 23.

[0363] At 48 h, the remaining supernatants were assayed for T cell activation, by increase in CD25⁺ or CD69⁺ T cells. T cells were washed in flow buffer and then incubated with monoclonal antibodies to CD25, CD69 or an isotype control antibody for 30 minutes at room temperature. Cells were then washed twice with flow buffer and analyzed by flow cytometry for gain of CD25-positive or CD69-positive T cells. Dose response curves were obtained by graphing the number of CD25⁺ or CD69⁺ cells at each dose. The increase in CD25⁺ cells is shown in FIGS. 22 and 24. T cell proliferation was also assessed in the flow cytometry experiments by measuring the loss of CFSE signal, a marker for mitotic index (data not shown).

Example 12

MSLN-BiTE Cytotoxicity

[0364] Cytotoxicity assays for the MSLN-BiTE molecules were performed generally as described above in Example 5, except that pan-T cells were used as effector cells. BiTE proteins were incubated with MSLN-expressing tumor cells OVCAR-8 at 2500 cells per well of a microtiter plate, and unstimulated pan-T cells (source: ALL CELLS) in a 10:1 effector to target cells ratio, for 48 h at 37° C., 5% CO₂. Cells were then stained with 10 μ M Hoechst 33342 to visualize the cell nuclei, and 2 μ M propidium iodide to specifically label the nuclei of dead cells. After incubation with the DNA stains for 90 min at 37° C., 5% CO₂, the microplate wells were scanned by high content imaging (ArrayScan) to capture images of the cells. Percent specific cytotoxicity was calculated using the formula: [1 - live target cell count (+BiTE)/live target cell count (-BiTE)] $\times$ 100. Results are summarized in FIGS. 25 and 26.

Example 13

In Vivo Efficacy of MSLN-BiTEs

Admixture Model:

[0365] Athymic nude female mice (Harlan) are implanted subcutaneously in the flank with a mixture of 5 $\times$ 10⁶ NCI-N87

gastric cancer cells and 2.5 $\times$ 10⁶ human PBMCs (1:2 effector: target cell ratio). Mice are dosed with an intraperitoneal (ip) injection of MSLN-BiTE that contains the 2.37 scFv and the 8H9CD3 (P73362) or vehicle control once a day for 10 days. Each dosing group contains 10 mice. Caliper measurement of tumor size is determined every 3-4 days until day 28 when the study is terminated. Body weights are maintained throughout the study. Results are summarized in FIG. 27.

BiTE Screen Model:

[0366] Athymic nude female mice (Harlan) are implanted subcutaneously with four xenograft model cell lines at different sites on the flank (see diagram in FIGS. 29 and 30). Each cancer cell line is labeled with luciferase and mixed 1:1 (5 $\times$ 10⁵ cells each) with human pan-T cells isolated from PBMCs. The BiTE screen model used here tests NCI-N87 cells (53,000 MSLN sites/cell), OVCAR-8 cells (65,000 MSLN sites/cell), SK-OV-3 cells (15,000 MSLN sites/cell) and A2780 cells (MSLN-negative). Baseline cell luciferase signal is measured by Xenogen imaging on Day 1. Mice are dosed intraperitoneally once a day for 11 days with MSLN-BiTE or vehicle, with 5 mice per dosing group. Cell luciferase signal is measured every 3 days (Day 1, 4, 7 and 11) to monitor tumor growth. Tumor growth inhibition is determined by fold change in the luciferase signal.

[0367] In one study, the effect of the MSLN-BiTE that contains the 2.37 scFv and the 8H9CD3 (P73362) was tested. This study showed that the MSLN-BiTE is active in the BiTE screen model. Growth of cancer cell lines that express MSLN is inhibited, and growth of the MSLN-negative cell line A2780 was not affected. Results are summarized in FIG. 28.

[0368] In another study, in vivo activity of the MSLN-BiTE proteins 2.37HL-BiTE and 1.33HL-BiTE, which use the I2C CD3, were tested. Both MSLN-BiTE proteins were active in the BiTE screen, and inhibited tumor growth of the MSLN-expressing cell lines. Results are summarized in FIG. 29.

[0369] Blood plasma pharmacokinetics of the MSLN-BiTE showed increased levels of the BiTE present with higher dose, consistent with the dose-dependent effect on tumor growth (FIG. 30).

[0370] Each reference cited herein is hereby incorporated by reference in its entirety for all that it teaches and for all purposes.

[0371] The present invention is not to be limited in scope by the specific embodiments described herein, which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

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<211> LENGTH: 2135

<212> TYPE: DNA

<213> ORGANISM: Mus musculus

<400> SEQUENCE: 3

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<212> TYPE: PRT

<213> ORGANISM: Mus musculus

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<211> LENGTH: 2099

<212> TYPE: DNA

<213> ORGANISM: Rattus norvegicus

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gtgtttgcat ggattccagc tctgctctca gctttaagac tgagctgaga ccaccactcc 1980
taaggtcctt ggtcccagct ctattgtcga gcccactctt gaccaggagg ggataccagg 2040
ggtcattgcc aaagtttgag gattcttgaa cccaataaac agtggcatgt gccccttg 2099

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<210> SEQ ID NO 6

<211> LENGTH: 625

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 6

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

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210				215				220							
Val 225	Arg	Glu	Val	Leu	Arg 230	Ser	Gly	Arg	Ala	Pro 235	Tyr	Gly	Pro	Pro	Ser 240
Thr	Trp	Ser	Val	Ser 245	Thr	Leu	Asp	Ala	Leu 250	Gln	Gly	Leu	Leu	Val 255	Val
Leu	Asp	Glu	Ser 260	Ile	Val	His	Ser	Ile 265	Pro	Lys	Asp	Val	Ile 270	Thr	Glu
Trp	Leu	Gln	Gly 275	Ile	Ser	Arg	Glu 280	Pro	Ser	Arg	Leu	Gly 285	Ser	Lys	Trp
Thr	Val 290	Thr	His	Pro	Arg	Phe 295	Arg	Arg	Asp	Thr	Glu 300	Gln	Lys	Ala	Cys
Pro 305	Pro	Gly	Lys	Glu	Pro 310	Asn	Val	Val	Asp	Glu 315	Asn	Leu	Ile	Phe	Tyr 320
Gln	Asn	Trp	Glu 325	Leu	Glu	Ala	Cys	Val	Asp 330	Gly	Thr	Leu	Leu	Ala 335	Gly
Gln	Met	Asp	Leu 340	Val	Asn	Glu	Ile	Pro 345	Phe	Thr	Tyr	Glu 350	Gln	Leu	Ser
Ile	Phe 355	Lys	His	Lys	Leu	Asp	Lys 360	Thr	Tyr	Pro	Gln	Gly 365	Tyr	Pro	Glu
Ser	Leu 370	Ile	Lys	Gln	Leu	Gly 375	His	Phe	Phe	Arg	Tyr 380	Val	Ser	Pro	Glu
Asp 385	Ile	Arg	Gln	Trp	Asn 390	Val	Thr	Ser	Pro	Asp 395	Thr	Val	Asn	Thr	Leu 400
Leu	Lys	Val	Ser 405	Lys	Gly	Gln	Lys	Met	Asp 410	Ala	Gln	Val	Ile	Ala 415	Leu
Val	Ala	Cys	Tyr 420	Leu	Arg	Gly	Gly	Gly 425	Lys	Leu	Asp	Glu	Asp 430	Ile	Val
Lys	Ala	Leu 435	Asp	Asn	Ile	Pro	Leu 440	Ser	Tyr	Leu	Cys	Asp 445	Phe	Ser	Pro
Gln	Asp 450	Leu	His	Ala	Ile	Pro 455	Ser	Ser	Val	Met	Trp 460	Leu	Val	Gly	Leu
His 465	Asp	Leu	Asp	Lys	Cys 470	Ser	Gln	Arg	His	Leu 475	Gly	Ile	Leu	Tyr	Gln 480
Lys	Ala	Cys	Ser 485	Ala	Phe	Gln	Asn	Val	Ser	Gly 490	Leu	Glu	Tyr	Phe 495	Glu
Lys	Ile	Arg	Thr 500	Phe	Leu	Gly	Gly	Ala 505	Ser	Arg	Glu	Asp 510	Leu	Arg	Ala
Leu	Ser	Gln 515	His	Asn	Val	Ser	Met 520	Asp	Ile	Ala	Thr	Phe 525	Lys	Lys	Leu
Gln 530	Val	Asp	Ala	Leu	Val	Gly 535	Leu	Ser	Val	Ala	Glu 540	Val	Gln	Lys	Leu
Leu 545	Gly	Pro	His	Ile 550	Gly	Asp	Leu	Lys	Thr	Glu 555	Glu	Asp	Lys	Ser	Pro 560
Val	Arg	Asp	Trp 565	Leu	Phe	Arg	Gln	Gln	Gln 570	Lys	Asp	Leu	Asp	Ser	Leu
Gly	Leu	Gly 580	Leu	Gln	Gly	Gly	Ile 585	Pro	Asn	Gly	Tyr	Leu 590	Ile	Leu	Asp
Phe	Asn 595	Val	Arg	Glu	Ala	Phe	Ser 600	Ser	Gly	Ala	Pro 605	Leu	Leu	Gly	Pro
Gly 610	Phe	Val	Phe	Ala	Trp 615	Ile	Pro	Ala	Leu	Leu 620	Ser	Ala	Leu	Arg	Leu

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Ser
625

<210> SEQ ID NO 7
<211> LENGTH: 1988
<212> TYPE: DNA
<213> ORGANISM: Macaca mulatta

<400> SEQUENCE: 7

atggccttgc caatggctcg acccctgtcg gggctcctgtg ggacccccgc cctcggcagc	60
ctcctgttcc tgctcttcag cctcggatgg gtgcagccct cgagggtcct ggctggagag	120
acaaggcagg ccgcgccccct ggatggaatc ctgaccaatg cacctgacat tgccagcctc	180
tccccacgcc aactccttgg cttcacgtgt gtggaggtgt ccggcctgag cacagagctc	240
gtccaggagc tggctgtggc cttgggacag aagaatgtca agctctccgc agagcagctg	300
cgctgtctgg ctcaccagct ctctgagccc ccgaggacc tggacgcctc cccgctggac	360
ctgctgctct tcctcaaccc agacgcgttc tcggggcccc aggcctgcac ccacttcttc	420
tcccgctcgc cgaagcccaa cgtggacctg ctcccgcggg gggctcctga gagacagagg	480
ctgctgcccc gggctctgac ctgctggggg gtgcgggggt ctctgctgag cgaggctgat	540
gtacgggctc tgggaggcct ggcttgccac ctgcctgggc gctttgtggc cgagtcggca	600
gaagtgggtc taccctggct ggtccgctgc ttgggacccc tggaccagga ccagcaggaa	660
gcagccaggg cggctctgca gagaggagga cccccctacg gccccccgtc aacgtggtct	720
atctccaccc tggacgatct gcagagcctg ttgcctgtgc tgggccagcc cgtcatctct	780
gctcgtctcc agggcatcct ggccgcatgg cggcaacgct cctctcggga cccatcctgg	840
cagcagccgg aacagaccgt cctccggctg aggttccggc gggacgtgga gaggacaacc	900
tgtcccccag agaaaagagg ccacgagata gacgagagcc tcactcttcta caagaagcgg	960
gagctggaag cctgctgga cccagccctg ctggccgccc agatggaccg tgtggacgcc	1020
atccccctta cctacgagca gctggacgtc ctaaagcata aactggatga gctctacca	1080
caaggctacc ccgagctctg gatccggcac ctggggccacc tcttcctcaa gatgagccct	1140
gaggacattc gcaaatggaa cgtgacgtcc ctggagaccc tgaaggctct gctcaaagtc	1200
agcaaggggc atgaaatgag tgctcaggtg gccaccctga ttgaccgctg tgtggtggga	1260
aggggccagc tagacaaaga caccgtagac acgctgactg ccttctgccc cgggtgcctg	1320
tgctccctca gccccgagag gctgagctcc gtgccccca gcgtcatcgg ggcggtcagg	1380
ccccaggacc tggacacgtg tggcccagg cagctggacg tcctctatcc caaggcccg	1440
cttgctttcc agaacatgag cgggtccgaa tacttcgtga agatccggcc cttcctgggt	1500
ggggccccc cggaggatgt gaaggtctc agtcagcaga atgtgagcat ggaactggcc	1560
acgtttcatg agctgcggag ggaagcgtg ctgccgttga ctgtggctga agtgacagaaa	1620
cttctgggac cccacgtgga gggcctgaag gtggaggagc agcacagccc cgtgcgggac	1680
tgatcctaa agcagcggca ggacgacctg gacacactgg ggctggggct acagggcggc	1740
atccccaaag gctacctgat cctagacctc agtgtgcgag aggccctctc ggggacgccc	1800
tgctcctag gacctggacc tgtactcacc gtcttggtt tgctcctggc ctccacctg	1860
gcctgaggac cctactccct tgctggcccc agccctgctg gggatccccg cctggccagg	1920
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tgccccct

1988

<210> SEQ ID NO 8

<211> LENGTH: 514

<212> TYPE: PRT

<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 8

Met Ala Leu Pro Met Ala Arg Pro Leu Ser Gly Ser Cys Gly Thr Pro
1 5 10 15
Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
20 25 30
Pro Ser Arg Val Leu Ala Gly Glu Thr Arg Gln Glu Ala Ala Pro Leu
35 40 45
Asp Gly Ile Leu Thr Asn Ala Pro Asp Ile Ala Ser Leu Ser Pro Arg
50 55 60
Gln Leu Leu Gly Phe Thr Cys Val Glu Val Ser Gly Leu Ser Thr Glu
65 70 75 80
Leu Val Gln Glu Leu Ala Val Ala Leu Gly Gln Lys Asn Val Lys Leu
85 90 95
Ser Ala Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100 105 110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Lys Gln
115 120 125
Ala Ser Val Gln Gly Val Arg Gly Ser Leu Leu Ser Glu Ala Asp Val
130 135 140
Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu Pro Gly Arg Phe Val Ala
145 150 155 160
Glu Ser Ala Glu Val Val Leu Pro Arg Leu Val Arg Cys Leu Gly Pro
165 170 175
Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg Ala Ala Leu Gln Arg Gly
180 185 190
Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp Ser Ile Ser Thr Leu Asp
195 200 205
Asp Leu Gln Ser Leu Leu Pro Val Leu Gly Gln Pro Val Ile His Ser
210 215 220
Ile Pro Gln Gly Ile Leu Ala Ala Trp Arg Gln Arg Ser Ser Arg Asp
225 230 235 240
Pro Ser Trp Gln Gln Pro Glu Gln Thr Val Leu Arg Pro Arg Phe Arg
245 250 255
Arg Asp Val Glu Arg Thr Thr Cys Pro Pro Glu Lys Glu Val His Glu
260 265 270
Ile Asp Glu Asn Leu Ile Phe Tyr Lys Lys Arg Glu Leu Glu Ala Cys
275 280 285
Val Asp Ala Ala Leu Leu Ala Ala Gln Met Asp Arg Val Asp Ala Ile
290 295 300
Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu
305 310 315 320
Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Arg His Leu Gly His
325 330 335
Leu Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr
340 345 350
Ser Leu Glu Thr Leu Lys Ala Leu Leu Lys Val Ser Lys Gly His Glu

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355	360	365
Met Ser Ala Gln Val Ala Thr Leu Ile Asp Arg Val Val Val Gly Arg		
370	375	380
Gly Gln Leu Asp Lys Asp Thr Ala Asp Thr Leu Thr Ala Phe Cys Pro		
385	390	395
Gly Cys Leu Cys Ser Leu Ser Pro Glu Arg Leu Arg Ser Val Pro Pro		
405	410	415
Ser Val Ile Gly Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Gly Pro		
420	425	430
Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn		
435	440	445
Met Ser Gly Ser Glu Tyr Phe Val Lys Ile Arg Pro Phe Leu Gly Gly		
450	455	460
Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met		
465	470	475
Asp Leu Ala Thr Phe Met Lys Leu Arg Arg Glu Ala Val Leu Val Gly		
485	490	495
Arg Ala Gly Gly Gly Ala Ser Gly Gly Gly Asp Asn Arg Gly Arg Glu		
500	505	510

Gly Val

<210> SEQ ID NO 9
 <211> LENGTH: 11
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 9

Arg Ala Ser Gln Ser Ile Asn Asn Tyr Leu Asn
1 5 10

<210> SEQ ID NO 10
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 10

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 11
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 11

Gln Gln Thr Tyr Ser Asn Pro Thr
1 5

<210> SEQ ID NO 12
 <211> LENGTH: 11
 <212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 12

Arg Ala Ser Gln Tyr Ile Gly Ser Asn Leu His
1 5 10

<210> SEQ ID NO 13
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 13

Tyr Ala Ser Gln Ser Phe Ser
1 5

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

<400> SEQUENCE: 14

His Gln Ser Ser Ser Leu Pro Trp Thr
1 5

<210> SEQ ID NO 15
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 15

Gln Ser Ser Leu Ser Leu Gln His Ser Asn Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> SEQ ID NO 16
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 16

Glu Val Ser Asn Arg Phe Ser
1 5

<210> SEQ ID NO 17
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 17

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Met Gln Ser Lys Gln Leu Pro Cys Ser
1 5

<210> SEQ ID NO 18
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 18

Gln Ser Ser Leu Ser Leu Gln His Ser Asn Gly Lys Thr Tyr Leu Tyr
1 5 10 15

<210> SEQ ID NO 19
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 19

Glu Val Ser Asn Arg Phe Ser
1 5

<210> SEQ ID NO 20
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 20

Met Gln Ser Lys Gln Leu Pro Tyr Ser
1 5

<210> SEQ ID NO 21
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 21

Arg Ala Ser Gln Thr Val Ser Ser Ser Tyr Leu Ala
1 5 10

<210> SEQ ID NO 22
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 22

Gly Ala Ser Ile Arg Ala Thr
1 5

<210> SEQ ID NO 23
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 23

Gln Gln Tyr Gly Ser Ser Leu Thr
1 5

<210> SEQ ID NO 24
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 24

Arg Ala Ser Gln Ser Ile Gly Ser Ser Leu His
1 5 10

<210> SEQ ID NO 25
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 25

Tyr Ala Ser Gln Ser Phe Ser
1 5

<210> SEQ ID NO 26
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 26

His Gln Ser Ser Ser Leu Pro Trp Thr
1 5

<210> SEQ ID NO 27
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 27

Arg Ser Ser Gln Ser Leu Val His Ser Asp Arg Asn Thr Tyr Leu Ser
1 5 10 15

<210> SEQ ID NO 28
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 28

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Lys Ile Ser Asn Arg Phe Ser
1 5

<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 29

Met Gln Ala Thr Gln Phe Pro Leu Thr
1 5

<210> SEQ ID NO 30
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 30

Arg Ser Ser Leu Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp
1 5 10 15

<210> SEQ ID NO 31
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 31

Leu Gly Ser Asn Arg Ala Ser
1 5

<210> SEQ ID NO 32
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 32

Met Gln Gly Leu His Thr Pro Pro Ser
1 5

<210> SEQ ID NO 33
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 33

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> SEQ ID NO 34
<211> LENGTH: 7
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 34

Ala Ala Ser Ser Leu Glu Thr
1 5

<210> SEQ ID NO 35
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 35

Gln Gln Tyr Asp Asn Leu Pro
1 5

<210> SEQ ID NO 36
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 36

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> SEQ ID NO 37
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 37

Ala Ala Ser Ser Leu Glu Thr
1 5

<210> SEQ ID NO 38
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 38

Gln Gln Tyr Asp Asn Leu Pro
1 5

<210> SEQ ID NO 39
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 39

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Arg Ala Ser Gln Gly Ile Arg Asn Ala Leu Gly
1 5 10

<210> SEQ ID NO 40
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 40

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 41
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 41

Leu Gln His Asn Ser Tyr Pro Arg Thr
1 5

<210> SEQ ID NO 42
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 42

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu His
1 5 10

<210> SEQ ID NO 43
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 43

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 44
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
peptide

<400> SEQUENCE: 44

Leu Gln His Tyr Ser Tyr Pro Trp Thr
1 5

<210> SEQ ID NO 45
<211> LENGTH: 7
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 45

Asn Asn Asn Tyr Tyr Trp Thr
1 5

<210> SEQ ID NO 46
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 46

Tyr Ile Tyr Tyr Ser Gly Ser Thr Phe Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 47
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 47

Glu Asp Thr Met Thr Gly Leu Asp Val
1 5

<210> SEQ ID NO 48
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 48

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 49
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 49

Ala Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 50
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 50

Asp Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr
1 5 10

<210> SEQ ID NO 51

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 51

Gly Asp Gly His Phe Trp Ser
1 5

<210> SEQ ID NO 52

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 52

Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 53

<211> LENGTH: 9

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 53

Leu Arg Gly Gly Tyr Lys Phe Asp Tyr
1 5

<210> SEQ ID NO 54

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 54

Asn Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 55

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 55

Arg Ile Phe Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 56

-continued

<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 56

Glu Gly Gly His Tyr Gly Ser Ser Gly Tyr Leu Tyr Tyr Tyr Tyr Phe
1 5 10 15

Gly Met Asp Val
20

<210> SEQ ID NO 57
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 57

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 58
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 58

Ala Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 59
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 59

Asp Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr
1 5 10

<210> SEQ ID NO 60
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 60

Ser Gly Gly Tyr Tyr Trp Asn
1 5

<210> SEQ ID NO 61
<211> LENGTH: 16
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 61

Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Arg Gly
1 5 10 15

<210> SEQ ID NO 62
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 62

Asp Gly Gly Asp Ser Tyr Gly Arg Met Asp Val
1 5 10

<210> SEQ ID NO 63
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 63

Ser Asn Ser Val Ala Trp Asn
1 5

<210> SEQ ID NO 64
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 64

Arg Thr Tyr Tyr Arg Ser Lys Trp Tyr Asn Asp Tyr Ala Val Ser Val
1 5 10 15

Lys Ser

<210> SEQ ID NO 65
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 65

Gly Ile Phe Val Val Pro Ala Val Pro Arg Phe Asp Tyr
1 5 10

<210> SEQ ID NO 66
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

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<400> SEQUENCE: 66

Ser His Tyr Trp Ser
1 5

<210> SEQ ID NO 67

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 67

Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 68

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 68

Asp Gly Trp Ser Ala Phe Asp Tyr
1 5

<210> SEQ ID NO 69

<211> LENGTH: 5

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 69

Ser Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 70

<211> LENGTH: 16

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 70

Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 71

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 71

Val Asp Tyr Lys Ala Phe Asp Ile
1 5

<210> SEQ ID NO 72

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<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 72

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

<210> SEQ ID NO 73
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 73

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

<210> SEQ ID NO 74
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 74

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

-continued

Asn	Gly	Lys	Thr	Tyr	Leu	Tyr	Trp	Tyr	Leu	Gln	Lys	Pro	Gly	Gln	Pro
	35						40					45			
Pro	Gln	Leu	Leu	Ile	Tyr	Glu	Val	Ser	Asn	Arg	Phe	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	Ile	Tyr	Tyr	Cys	Met	Gln	Ser
			85					90						95	
Lys	Gln	Leu	Pro	Cys	Ser	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
	100						105						110		

<210> SEQ ID NO 75
 <211> LENGTH: 112
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 75

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

<210> SEQ ID NO 76
 <211> LENGTH: 107
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 76

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	Thr	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	Ile	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	Leu
			85					90						95	

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

<210> SEQ ID NO 77
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 77

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

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

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

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

Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80

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

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

<210> SEQ ID NO 78
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 78

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

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

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

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

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

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

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

<210> SEQ ID NO 79
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

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<400> SEQUENCE: 79

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Leu Ser Leu Leu His Ser
20 25 30
Asn Gly Tyr Asn Tyr Leu Asp Trp Phe 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 Asp 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 Gly
85 90 95
Leu His Thr Pro Pro Ser Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 80

<211> LENGTH: 105

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 80

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

<210> SEQ ID NO 81

<211> LENGTH: 105

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 81

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn 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 Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

-continued

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 Asp Asn Leu Pro Phe
85 90 95
Gly Gln Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 82
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 82

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 Ala
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 Tyr Pro Arg
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Arg Arg
100 105

<210> SEQ ID NO 83
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 83

Asp Ile Gln 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 His 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 Tyr Ser Tyr Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 84
<211> LENGTH: 107

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

<400> SEQUENCE: 84

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

<210> SEQ ID NO 85
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 85

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Trp
1 5 10 15
Leu Arg Gly Ala Arg Cys
20

<210> SEQ ID NO 86
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 86

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 Asn Asn Asn
20 25 30
Asn Tyr Tyr Trp Thr 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 Phe Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Thr 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 Glu Asp Thr Met Thr Gly Leu Asp Val Trp Gly Gln Gly
100 105 110

-continued

Thr Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 87
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 87

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 Ala 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 Met 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 Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 88
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 88

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 Gly Asp
20 25 30
Gly His Phe 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 Leu Arg Gly Gly Tyr Lys Phe Asp Tyr Trp Gly Gln Gly
100 105 110
Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 89
<211> LENGTH: 128

-continued

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

<400> SEQUENCE: 89

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 Asp Ser Ile Asn Asn Tyr
20 25 30
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
35 40 45
Gly Arg Ile Phe Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60
Ser Arg Val Thr Met Ser Ile 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 Glu Gly Gly His Tyr Gly Ser Ser Gly Tyr Leu Tyr Tyr Tyr Tyr
100 105 110
Phe Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 90
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 90

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 Ala 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 Met 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 Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 91
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 91

-continued

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 Asn 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 Arg Gly Arg Leu Ile Ile Ser Val Asp Thr Ser Lys Asn 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 Gly Gly Asp Ser Tyr Gly Arg Met Asp Val Trp Gly
 100 105 110
 Gln Gly Thr Thr Val Thr Val Ser Ala
 115 120

<210> SEQ ID NO 92
 <211> LENGTH: 125
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 92

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

<210> SEQ ID NO 93
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 93

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 Ile Ser His
 20 25 30

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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 Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
 85 90 95
 Arg Asp Gly Trp Ser Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110
 Thr Val Ser Ser
 115

<210> SEQ ID NO 94
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 94

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 Val Asp Tyr Lys Ala Phe Asp Ile Trp Gly Gln Gly Thr Met Val
 100 105 110
 Thr Val Ser Ser
 115

<210> SEQ ID NO 95
 <211> LENGTH: 19
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 peptide

<400> SEQUENCE: 95

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
 1 5 10 15
 Val Leu Ser

<210> SEQ ID NO 96
 <211> LENGTH: 330
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

-continued

<400> SEQUENCE: 96

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1 5 10 15
 Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
 20 25 30
 Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45
 Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
 50 55 60
 Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65 70 75 80
 Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95
 Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100 105 110
 Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115 120 125
 Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130 135 140
 Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145 150 155 160
 Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165 170 175
 Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180 185 190
 His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195 200 205
 Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu
 225 230 235 240
 Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

<210> SEQ ID NO 97

<211> LENGTH: 468

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 97

-continued

Met	Lys	His	Leu	Trp	Phe	Phe	Leu	Leu	Leu	Val	Ala	Ala	Pro	Arg	Trp
1				5					10					15	
Val	Leu	Ser	Gln	Val	Gln	Leu	Gln	Glu	Ser	Gly	Pro	Gly	Leu	Val	Lys
			20					25					30		
Pro	Ser	Gln	Thr	Leu	Ser	Leu	Thr	Cys	Thr	Val	Ser	Gly	Gly	Ser	Ile
		35					40					45			
Asn	Asn	Asn	Asn	Tyr	Tyr	Trp	Thr	Trp	Ile	Arg	Gln	His	Pro	Gly	Lys
	50					55					60				
Gly	Leu	Glu	Trp	Ile	Gly	Tyr	Ile	Tyr	Tyr	Ser	Gly	Ser	Thr	Phe	Tyr
65					70					75					80
Asn	Pro	Ser	Leu	Lys	Ser	Arg	Val	Thr	Ile	Ser	Val	Asp	Thr	Ser	Lys
				85					90					95	
Thr	Gln	Phe	Ser	Leu	Lys	Leu	Ser	Ser	Val	Thr	Ala	Ala	Asp	Thr	Ala
			100					105					110		
Val	Tyr	Tyr	Cys	Ala	Arg	Glu	Asp	Thr	Met	Thr	Gly	Leu	Asp	Val	Trp
		115					120					125			
Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro
	130					135					140				
Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr
145					150					155					160
Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr
				165					170					175	
Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro
			180					185					190		
Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr
		195					200						205		
Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn
	210					215					220				
His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser
225					230					235					240
Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu
				245					250					255	
Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu
			260				265						270		
Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser
		275					280					285			
His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu
	290					295					300				
Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr
305					310					315					320
Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn
				325					330					335	
Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro
			340					345					350		
Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln
		355					360					365			
Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val
		370				375					380				
Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val
385					390					395					400
Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro
				405					410					415	

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

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
435 440 445

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
450 455 460

Ser Pro Gly Lys
465

<210> SEQ ID NO 98

<211> LENGTH: 235

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 98

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Arg Gly Ala Arg Cys Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

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

Ala Pro Thr Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Ala Tyr Phe Cys Gln Gln
100 105 110

Thr Tyr Ser Asn Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

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

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

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

<210> SEQ ID NO 99

<211> LENGTH: 452

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

<400> SEQUENCE: 99

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 Ala 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 Met 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 Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
 115 120 125
 Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
 130 135 140
 Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
 145 150 155 160
 Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
 165 170 175
 Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
 180 185 190
 Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
 195 200 205
 His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
 210 215 220
 Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
 225 230 235 240
 Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
 245 250 255
 Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
 260 265 270
 His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
 275 280 285
 Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
 290 295 300
 Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
 305 310 315 320
 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
 325 330 335
 Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
 340 345 350
 Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
 355 360 365
 Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
 370 375 380
 Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
 385 390 395 400

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Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
405 410 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
420 425 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
435 440 445

Ser Pro Gly Lys
450

<210> SEQ ID NO 100

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 100

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1 5 10 15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Tyr Ile Gly Ser Asn
20 25 30

Leu His Trp Tyr Gln Gln Thr Pro Asp Gln Ser Pro Lys Leu Leu Ile
35 40 45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65 70 75 80

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

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

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

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

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

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

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

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

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 101

<211> LENGTH: 449

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 101

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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	Gly	Asp
			20					25					30		
Gly	His	Phe	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	Leu	Arg	Gly	Gly	Tyr	Lys	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
			100					105					110		
Thr	Leu	Val	Thr	Val	Ser	Ser	Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe
		115					120					125			
Pro	Leu	Ala	Pro	Ser	Ser	Lys	Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu
	130					135					140				
Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp
145					150					155					160
Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu
				165					170					175	
Gln	Ser	Ser	Gly	Leu	Tyr	Ser	Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser
			180					185					190		
Ser	Ser	Leu	Gly	Thr	Gln	Thr	Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro
		195					200					205			
Ser	Asn	Thr	Lys	Val	Asp	Lys	Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys
	210					215					220				
Thr	His	Thr	Cys	Pro	Pro	Cys	Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro
225					230					235					240
Ser	Val	Phe	Leu	Phe	Pro	Pro	Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser
				245					250					255	
Arg	Thr	Pro	Glu	Val	Thr	Cys	Val	Val	Val	Asp	Val	Ser	His	Glu	Asp
			260					265					270		
Pro	Glu	Val	Lys	Phe	Asn	Trp	Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn
	275						280					285			
Ala	Lys	Thr	Lys	Pro	Arg	Glu	Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val
	290					295					300				
Val	Ser	Val	Leu	Thr	Val	Leu	His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu
305					310					315					320
Tyr	Lys	Cys	Lys	Val	Ser	Asn	Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys
			325						330					335	
Thr	Ile	Ser	Lys	Ala	Lys	Gly	Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr
		340						345					350		
Leu	Pro	Pro	Ser	Arg	Glu	Glu	Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr
		355					360					365			
Cys	Leu	Val	Lys	Gly	Phe	Tyr	Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu
	370					375					380				
Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu
385					390					395					400
Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys
				405					410					415	

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Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
435 440 445

Lys

<210> SEQ ID NO 102

<211> LENGTH: 219

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 102

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

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

Asn Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn Arg Phe 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 Ile Tyr Tyr Cys Met Gln Ser
85 90 95

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

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

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

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

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

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

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

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

<210> SEQ ID NO 103

<211> LENGTH: 458

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 103

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 Asp Ser Ile Asn Asn Tyr

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20						25						30					
Tyr	Trp	Ser	Trp	Ile	Arg	Gln	Pro	Ala	Gly	Lys	Gly	Leu	Glu	Trp	Ile		
		35					40					45					
Gly	Arg	Ile	Phe	Thr	Ser	Gly	Ser	Thr	Asn	Tyr	Asn	Pro	Ser	Leu	Lys		
	50					55					60						
Ser	Arg	Val	Thr	Met	Ser	Ile	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	Glu	Gly	Gly	His	Tyr	Gly	Ser	Ser	Gly	Tyr	Leu	Tyr	Tyr	Tyr	Tyr		
			100					105					110				
Phe	Gly	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val	Ser	Ser		
		115					120					125					
Ala	Ser	Thr	Lys	Gly	Pro	Ser	Val	Phe	Pro	Leu	Ala	Pro	Ser	Ser	Lys		
		130				135					140						
Ser	Thr	Ser	Gly	Gly	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr		
145					150					155					160		
Phe	Pro	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser		
				165					170					175			
Gly	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser		
			180					185					190				
Leu	Ser	Ser	Val	Val	Thr	Val	Pro	Ser	Ser	Ser	Leu	Gly	Thr	Gln	Thr		
			195				200					205					
Tyr	Ile	Cys	Asn	Val	Asn	His	Lys	Pro	Ser	Asn	Thr	Lys	Val	Asp	Lys		
	210					215					220						
Lys	Val	Glu	Pro	Lys	Ser	Cys	Asp	Lys	Thr	His	Thr	Cys	Pro	Pro	Cys		
225					230					235					240		
Pro	Ala	Pro	Glu	Leu	Leu	Gly	Gly	Pro	Ser	Val	Phe	Leu	Phe	Pro	Pro		
				245					250					255			
Lys	Pro	Lys	Asp	Thr	Leu	Met	Ile	Ser	Arg	Thr	Pro	Glu	Val	Thr	Cys		
			260					265					270				
Val	Val	Val	Asp	Val	Ser	His	Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn	Trp		
		275					280					285					
Tyr	Val	Asp	Gly	Val	Glu	Val	His	Asn	Ala	Lys	Thr	Lys	Pro	Arg	Glu		
	290					295						300					
Glu	Gln	Tyr	Asn	Ser	Thr	Tyr	Arg	Val	Val	Ser	Val	Leu	Thr	Val	Leu		
305					310					315					320		
His	Gln	Asp	Trp	Leu	Asn	Gly	Lys	Glu	Tyr	Lys	Cys	Lys	Val	Ser	Asn		
			325						330					335			
Lys	Ala	Leu	Pro	Ala	Pro	Ile	Glu	Lys	Thr	Ile	Ser	Lys	Ala	Lys	Gly		
		340						345					350				
Gln	Pro	Arg	Glu	Pro	Gln	Val	Tyr	Thr	Leu	Pro	Pro	Ser	Arg	Glu	Glu		
		355					360					365					
Met	Thr	Lys	Asn	Gln	Val	Ser	Leu	Thr	Cys	Leu	Val	Lys	Gly	Phe	Tyr		
	370					375					380						
Pro	Ser	Asp	Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn		
385					390					395					400		
Asn	Tyr	Lys	Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe		
			405						410					415			
Leu	Tyr	Ser	Lys	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Gln	Gly	Asn		
			420					425					430				

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Val	Phe	Ser	Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr
			435					440					445		

Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys
	450						455		

<210> SEQ ID NO 104

<211> LENGTH: 214

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 104

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	Thr	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	Ile	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	Leu
				85					90					95	

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

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

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

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

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

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

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

Phe	Asn	Arg	Gly	Glu	Cys
	210				

<210> SEQ ID NO 105

<211> LENGTH: 452

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 105

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
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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

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Ser Pro Gly Lys
450

<210> SEQ ID NO 106
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 106

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

<210> SEQ ID NO 107
<211> LENGTH: 451
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 107

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 Asn 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 65	Arg	Gly	Arg	Leu 70	Ile	Ile	Ser	Val	Asp	Thr 75	Ser	Lys	Asn	Gln	Phe 80
Ser	Leu	Arg	Leu 85	Ser	Ser	Val	Thr	Ala	Ala 90	Asp	Thr	Ala	Val	Tyr 95	Tyr
Cys	Ala	Arg	Asp 100	Gly	Gly	Asp	Ser	Tyr 105	Gly	Arg	Met	Asp	Val	Trp	Gly 110
Gln	Gly	Thr 115	Thr	Val	Thr	Val	Ser 120	Ala	Ala	Ser	Thr	Lys 125	Gly	Pro	Ser
Val 130	Phe	Pro	Leu	Ala	Pro	Ser 135	Ser	Lys	Ser	Thr	Ser 140	Gly	Gly	Thr	Ala
Ala 145	Leu	Gly	Cys	Leu	Val 150	Lys	Asp	Tyr	Phe	Pro 155	Glu	Pro	Val	Thr	Val 160
Ser	Trp	Asn	Ser	Gly 165	Ala	Leu	Thr	Ser	Gly 170	Val	His	Thr	Phe	Pro 175	Ala
Val	Leu	Gln	Ser 180	Ser	Gly	Leu	Tyr	Ser 185	Leu	Ser	Ser	Val	Val	Thr	Val 190
Pro	Ser	Ser 195	Ser	Leu	Gly	Thr	Gln 200	Thr	Tyr	Ile	Cys	Asn 205	Val	Asn	His
Lys	Pro	Ser 210	Asn	Thr	Lys 215	Val	Asp	Lys	Lys	Val	Glu 220	Pro	Lys	Ser	Cys
Asp 225	Lys	Thr	His	Thr	Cys 230	Pro	Pro	Cys	Pro	Ala 235	Pro	Glu	Leu	Leu	Gly 240
Gly	Pro	Ser	Val	Phe 245	Leu	Phe	Pro	Pro	Lys 250	Pro	Lys	Asp	Thr	Leu	Met 255
Ile	Ser	Arg	Thr 260	Pro	Glu	Val	Thr	Cys 265	Val	Val	Val	Asp	Val	Ser	His 270
Glu	Asp	Pro	Glu	Val	Lys	Phe	Asn 280	Trp	Tyr	Val	Asp	Gly 285	Val	Glu	Val
His	Asn	Ala	Lys	Thr	Lys	Pro 295	Arg	Glu	Glu	Gln	Tyr 300	Asn	Ser	Thr	Tyr
Arg 305	Val	Val	Ser	Val	Leu 310	Thr	Val	Leu	His	Gln 315	Asp	Trp	Leu	Asn	Gly 320
Lys	Glu	Tyr	Lys 325	Cys	Lys	Val	Ser	Asn	Lys 330	Ala	Leu	Pro	Ala	Pro 335	Ile
Glu	Lys	Thr	Ile 340	Ser	Lys	Ala	Lys	Gly 345	Gln	Pro	Arg	Glu	Pro 350	Gln	Val
Tyr	Thr	Leu 355	Pro	Pro	Ser	Arg	Glu 360	Glu	Met	Thr	Lys	Asn 365	Gln	Val	Ser
Leu	Thr 370	Cys	Leu	Val	Lys 375	Gly	Phe	Tyr	Pro	Ser	Asp 380	Ile	Ala	Val	Glu
Trp 385	Glu	Ser	Asn	Gly 390	Gln	Pro	Glu	Asn	Asn 395	Tyr	Lys	Thr	Thr	Pro	Pro 400
Val	Leu	Asp	Ser 405	Asp	Gly	Ser	Phe	Phe	Leu 410	Tyr	Ser	Lys	Leu	Thr	Val 415
Asp	Lys	Ser	Arg 420	Trp	Gln	Gln	Gly	Asn 425	Val	Phe	Ser	Cys	Ser 430	Val	Met
His	Glu 435	Ala	Leu	His	Asn	His	Tyr 440	Thr	Gln	Lys	Ser	Leu	Ser 445	Leu	Ser
Pro	Gly 450	Lys													

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<210> SEQ ID NO 108
<211> LENGTH: 219
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 108

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

<210> SEQ ID NO 109
<211> LENGTH: 455
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 109

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

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65	70	75	80
Gln Phe Ser Leu Gln Leu Asn Ser Val Thr Pro Glu Asp Thr Ala Val	85	90	95
Tyr Tyr Cys Ala Arg Gly Ile Phe Val Val Pro Ala Val Pro Arg Phe	100	105	110
Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr	115	120	125
Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser	130	135	140
Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu	145	150	155
Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His	165	170	175
Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser	180	185	190
Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys	195	200	205
Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu	210	215	220
Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro	225	230	235
Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys	245	250	255
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val	260	265	270
Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp	275	280	285
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr	290	295	300
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp	305	310	315
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu	325	330	335
Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg	340	345	350
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys	355	360	365
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp	370	375	380
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys	385	390	395
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser	405	410	415
Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser	420	425	430
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser	435	440	445
Leu Ser Leu Ser Pro Gly Lys	450	455	

<210> SEQ ID NO 110

<211> LENGTH: 219

-continued

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

<400> SEQUENCE: 110

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

<210> SEQ ID NO 111
<211> LENGTH: 212
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 111

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 Gln Ala Ser Gln Asp Ile Ser Asn 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 Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Phe

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

<210> SEQ ID NO 112
 <211> LENGTH: 14
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 112

Gly	Ser	Ser	Thr	Gly	Ala	Val	Thr	Ser	Gly	Asn	Tyr	Pro	Asn
1				5					10				

<210> SEQ ID NO 113
 <211> LENGTH: 7
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 113

Gly	Thr	Lys	Phe	Leu	Ala	Pro
1				5		

<210> SEQ ID NO 114
 <211> LENGTH: 9
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 114

Val	Leu	Trp	Tyr	Ser	Asn	Arg	Trp	Val
1				5				

<210> SEQ ID NO 115
 <211> LENGTH: 5
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

-continued

<400> SEQUENCE: 115

Lys Tyr Ala Met Asn
1 5

<210> SEQ ID NO 116

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 116

Arg Ile Arg Ser Lys Tyr Asn Asn Tyr Ala Thr Tyr Tyr Ala Asp Ser
1 5 10 15

Val Lys Asp

<210> SEQ ID NO 117

<211> LENGTH: 14

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 117

His Gly Asn Phe Gly Asn Ser Tyr Ile Ser Tyr Trp Ala Tyr
1 5 10

<210> SEQ ID NO 118

<211> LENGTH: 125

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 118

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

<210> SEQ ID NO 119

<211> LENGTH: 375

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

polynucleotide

<400> SEQUENCE: 119

gagggtgcagc tggctcgagtc tggaggagga ttggtgcagc ctggaggggc attgaaactc 60

tcatgtgcag cctctggatt caccttcaat aagtagcgcca tgaactgggt ccgccaggct 120

ccaggaaagg gtttggaatg ggttgctcgc ataagaagta aatataataa ttatgcaaca 180

tattatgccg attcagtgaag agacagggtc accatctcca gagatgattc aaaaaacact 240

gcctatctac aaatgaacaa ctgaaaact gaggacactg ccgtgtacta ctgtgtgaga 300

catgggaact tcggtaatag ctacatatcc tactgggctt actggggcca agggactctg 360

gtcacctgtct cctca 375

<210> SEQ ID NO 120

<211> LENGTH: 109

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 120

Gln Thr Val Val Thr Gln Glu Pro Ser Leu Thr Val Ser Pro Gly Gly 15

1 5 10

Thr Val Thr Leu Thr Cys Gly Ser Ser Thr Gly Ala Val Thr Ser Gly 30

20 25 30

Asn Tyr Pro Asn Trp Val Gln Gln Lys Pro Gly Gln Ala Pro Arg Gly 45

35 40 45

Leu Ile Gly Gly Thr Lys Phe Leu Ala Pro Gly Thr Pro Ala Arg Phe 60

50 55 60

Ser Gly Ser Leu Leu Gly Gly Lys Ala Ala Leu Thr Leu Ser Gly Val 80

65 70 75 80

Gln Pro Glu Asp Glu Ala Glu Tyr Tyr Cys Val Leu Trp Tyr Ser Asn 95

85 90 95

Arg Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 105

100 105

<210> SEQ ID NO 121

<211> LENGTH: 327

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 121

cagactgttg tgactcagga accttcactc accgtatcac ctggtggaac agtcacactc 60

acttggtggct cctcgactgg ggctgttaca tctggcaact acccaaactg ggtccaacaa 120

aaaccaggtc aggcaccccg tgggtctaata ggtgggacta agttcctcgc ccccggtact 180

cctgccagat tctcaggctc cctgcttgga ggcaaggctg ccctcaccct ctcaggggta 240

cagccagagg atgaggcaga atattactgt gttctatggt acagcaaccg ctgggtgttc 300

ggtggaggaa ccaaactgac tgtccta 327

<210> SEQ ID NO 122

<211> LENGTH: 249

<212> TYPE: PRT

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

<400> SEQUENCE: 122

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

<210> SEQ ID NO 123

<211> LENGTH: 747

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 123

gaggtgcagc tggctcgatc tggaggagga ttggtgcagc ctggaggggc attgaaactc 60
 tcatgtgcag cctctggatt caccttcaat aagtacgccca tgaactgggt ccgccaggct 120
 ccaggaaagg gtttgaatg ggttgctcgc ataagaagta aatataataa ttatgcaaca 180
 tattatgccg attcagtga agacagggtc accatctcca gagatgattc aaaaaacact 240
 gcctatctac aaatgaacaa cttgaaaact gaggacactg ccgtgtacta ctgtgtgaga 300
 catgggaact tcggtaatag ctacatatcc tactgggctt actggggcca agggactctg 360

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gtcaccgtct cctcaggtag tggtagttct ggccggcgcg gtcaggtag tggtagttct 420
cagactgttg tgactcagga acctcactc accgtatcac ctggtggaac agtcacactc 480
acttgtagct cctcagtag ggctgttaca tctggcaact acccaaactg ggtccaacaa 540
aaaccaggtc aggcaccccg tggcttaata ggtgggacta agttcctcgc ccccggtact 600
cctgccagat tctcaggctc cctgcttgga ggcaaggctg ccctcaccct ctcaggggta 660
cagccagagg atgaggcaga atattactgt gttctatggt acagcaaccg ctgggtgttc 720
ggtggaggaa ccaaactgac tgtccta 747

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<210> SEQ ID NO 124

<211> LENGTH: 1578

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 124

```

atgggggtcaa ccgccatcct tggcctctc ctggtgtcc tgcaggagg ggcgcgccag 60
gtgcagctgc aggagtcggg cccaggactg gtgaagcctt cacagacct gtcctcacc 120
tgcactgtct ctggtggctc catcaacaat aataattact actggacctg gatccgccag 180
caccagggga agggcctgga gtggattggg tacatctatt acagtgggag cacctctac 240
aaccgtccc tcaagagtcg agttaccata tcagtcgaca cgtctaagac ccagttctcc 300
ctgaagttga gctctgtgac tgccgcggac acggccgtgt attactgtgc gagagaggat 360
acgatgacgg gcctggagct ctgggggcaa gggaccacgg tcaccgtctc ctcaggaggc 420
ggcggttcag gcggaggtag ctctggcggt ggcggaagtg acatccagat gaccagctc 480
ccatcctccc tgtctgcato tgtaggagac agagtcacca tcacttgccg ggctagtcag 540
agcattaaca actatttaaa ttggtatcag cagaaaccag ggaaagcccc tacgtcctg 600
atctatgctg catccagttt gcaaagtggt gtcccatcaa ggttcagtgg cagtagatct 660
gggacagatt tcaactctac catcagcagt ctgcaacctg aagattttgc agcttacttc 720
tgtcaacaga cttacagtaa cccgacgttc ggccaaggga ccaagggtga agtcaaaggg 780
ggtggaggct cagaggtgca gctggtggag tctgggggag gcctgggtcaa gcctgggggtg 840
tccctgagac tctctgtgac agcctctgga ttcacctca gtagatatgg catgaactgg 900
gtccgccagg ctccagggaa ggggctggag tgggtctcat ccattagtag tagtggtact 960
tacataaagt acgcagactc agtgaagggc cgattacca tctccagaga caacgccaag 1020
aactcactga atctgcaaat gaacagcctg agagccgagg acacggctgt gtattattgt 1080
gcgagagatc gggaccggta tccccctgac tactggggcc agggaaacct ggtcaccgtc 1140
tcctcaggag gcggcggttc aggcggaggt ggctctggcg gtggcggaag ttcctatgag 1200
ctgacacagc caccctcggt gtcagtgtcc ccaggacaaa cgccaggat cacctgctct 1260
ggagatgcat tgccaaaaaa atatgcttat tggtagcagc agaagtcagg ccaggcccct 1320
gtgctggtca tctatgaggc caccaaacga cctccggga ttcctgagag attctctggc 1380
tccagctcag ggacaatggc caccttgact ctgagtgagg ccagggtgga ggatgaagct 1440
gactactact gttactcaac agacagcact aattatcatt ggggtgtcgg cggagggacc 1500
aagctgaccg tcctagcggc cgcagactac aaagacgatg acgacaaggg cagttctcac 1560

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catcaccatc accactaa

1578

<210> SEQ ID NO 125

<211> LENGTH: 525

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 125

```

Met Gly Ser Thr Ala Ile Leu Gly Leu Leu Ala Val Leu Gln Gly
1           5           10           15
Gly Arg Ala Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20           25           30
Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile
35           40           45
Asn Asn Asn Asn Tyr Tyr Trp Thr Trp Ile Arg Gln His Pro Gly Lys
50           55           60
Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Phe Tyr
65           70           75           80
Asn Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys
85           90           95
Thr Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala
100          105          110
Val Tyr Tyr Cys Ala Arg Glu Asp Thr Met Thr Gly Leu Asp Val Trp
115          120          125
Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly
130          135          140
Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser
145          150          155          160
Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
165          170          175
Arg Ala Ser Gln Ser Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys
180          185          190
Pro Gly Lys Ala Pro Thr Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
195          200          205
Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe
210          215          220
Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Ala Tyr Phe
225          230          235          240
Cys Gln Gln Thr Tyr Ser Asn Pro Thr Phe Gly Gln Gly Thr Lys Val
245          250          255
Glu Val Lys Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
260          265          270
Gly Gly Leu Val Lys Pro Gly Val Ser Leu Arg Leu Ser Cys Ala Ala
275          280          285
Ser Gly Phe Thr Phe Ser Arg Tyr Gly Met Asn Trp Val Arg Gln Ala
290          295          300
Pro Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Ser Ser Gly Thr
305          310          315          320
Tyr Ile Lys Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
325          330          335

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Asp	Asn	Ala	Lys	Asn	Ser	Leu	Asn	Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala
			340					345					350		
Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Arg	Asp	Arg	Tyr	Pro
		355					360					365			
Leu	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser	Gly	Gly
		370				375					380				
Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Ser	Tyr	Glu
385					390					395					400
Leu	Thr	Gln	Pro	Pro	Ser	Val	Ser	Val	Ser	Pro	Gly	Gln	Thr	Ala	Arg
				405					410					415	
Ile	Thr	Cys	Ser	Gly	Asp	Ala	Leu	Pro	Lys	Lys	Tyr	Ala	Tyr	Trp	Tyr
			420					425					430		
Gln	Gln	Lys	Ser	Gly	Gln	Ala	Pro	Val	Leu	Val	Ile	Tyr	Glu	Ala	Thr
		435					440					445			
Lys	Arg	Pro	Ser	Gly	Ile	Pro	Glu	Arg	Phe	Ser	Gly	Ser	Ser	Ser	Gly
		450				455					460				
Thr	Met	Ala	Thr	Leu	Thr	Leu	Ser	Gly	Ala	Gln	Val	Glu	Asp	Glu	Ala
465					470				475						480
Asp	Tyr	Tyr	Cys	Tyr	Ser	Thr	Asp	Ser	Thr	Asn	Tyr	His	Trp	Val	Phe
				485					490					495	
Gly	Gly	Gly	Thr	Lys	Leu	Thr	Val	Leu	Ala	Ala	Ala	Asp	Tyr	Lys	Asp
			500					505					510		
Asp	Asp	Asp	Lys	Gly	Ser	Ser	His	His	His	His	His	His			
		515					520					525			

<210> SEQ ID NO 126

<211> LENGTH: 1509

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 126

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcaac aataataatt actactggac ctggatccgc	120
cagcacccag ggaagggcct ggagtggatt ggggtacatct attacagtgg gagcaccttc	180
tacaaccctg ccctcaagag tcgagttacc atatcagtcg acacgtctaa gaccagttc	240
tccttgaagt tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagag	300
gatacagatga cgggccttga cgtctggggc caagggacca cggtcaccgt ctccctcagga	360
ggcgccggtt caggcggagg tggctctggc ggtggcggaa gtgacatcca gatgacccag	420
tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggctagt	480
cagagcatta acaactattt aaattggtat cagcagaaac cagggaaagc ccctacgctc	540
ctgatctatg ctgcatccag tttgcaaagt ggggtcccat caagggtcag tggcagtaga	600
tctgggacag atttcactct caccatcagc agtctgcaac ctgaagattt tgcagettac	660
ttctgtcaac agacttacag taaccgcagc ttcggccaag ggaccaaggt ggaagtcaaa	720
aggtccggag gtggtggatc cgaggtgcag ctggtcgagt ctggaggagg attggtgcag	780
cctggagggt cattgaaact ctcattgtga gcctctggat tcaccttcaa taagtacgcc	840
atgaactggg tccgccaggc tccaggaaag ggtttggaat gggttgcctc cataagaagt	900

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aaatataata attatgcaac atattatgcc gattcagtgga aagacagggt caccatctcc 960
agagatgatt caaaaaaacac tgcctatcta caaatgaaca acttgaagac tgaggacact 1020
gccgtgtact actgtgtgag acatgggaac ttcggtaata gctacatata ctactgggct 1080
tactggggcc aagggactct ggtcaccgtc tctcagggtg gtggtgggtc tggcggcggc 1140
ggctccgggt gtggtgggtc tcagactggt gtgactcagg aaccttcact caccgtatca 1200
cctggtggaa cagtcacact cacttgtggc tctcagactg gggctgttac atctggcaac 1260
taccctaaact gggccaaca aaaaccagggt caggcaccct gtggtctaata aggtgggact 1320
aagttcctcg cccccgttac tctgcccaga ttctcagggt cctgtcttgg aggcaaggct 1380
gccctcaccct tctcaggggt acagccagag gatgaggcag aatattactg tgttctatgg 1440
tacagcaacc gctgggtggt cggtggagga accaaactga ctgtcctaca ccaccatcac 1500
caccactaa 1509

```

<210> SEQ ID NO 127

<211> LENGTH: 502

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 127

```

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 Asn Asn Asn
20          25          30

Asn Tyr Tyr Trp Thr 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 Phe Tyr Asn Pro Ser
50          55          60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Thr 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 Glu Asp Thr Met Thr Gly Leu Asp Val Trp Gly Gln Gly
100         105         110

Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115         120         125

Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser
130         135         140

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
145         150         155         160

Gln Ser Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys
165         170         175

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

Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr
195         200         205

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Ala Tyr Phe Cys Gln Gln
210         215         220

Thr Tyr Ser Asn Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys
225         230         235         240

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<210> SEQ ID NO 128
<211> LENGTH: 1509
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

gacatccaga	tgaccagtc	tccatctctc	ctgtctgcat	ctgtaggaga	cagagtcacc	60
atcaacttgc	gggctagtc	gagcattaac	aactatttaa	attggtatca	gcagaaacca	120
gggaaagccc	ctacgctcct	gatctatgct	gcatccagtt	tgcaaagtgg	ggccccatca	180
aggttcagtg	gcagtagatc	tgggacagat	ttcactctca	ccatcagcag	tctgcaacct	240
gaagattttg	cagcttactt	ctgtcaacag	acttacagta	acccgacgtt	cggccaaggg	300
accaaggttg	aagtcaaaag	gggaggcggc	ggttcaggcg	gaggtggctc	tggcggtggc	360
ggaagtcagg	tcagctgca	ggagtcgggc	ccaggactgg	tgaagccttc	acagaccctg	420

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tcctcacct gcactgtctc tgggtgctcc atcaacaata ataattacta ctggacctgg	480
atccgccagc acccaggga gggcctggag tggattgggt acatctatta cagtgggagc	540
accttctaca acccgtccct caagagtcga gttaccatat cagtcgacac gtctaagacc	600
cagttctccc tgaagtgtag ctctgtgact gccgcggaca cggccgtgta ttactgtgcg	660
agagaggata cgatgacggg cctggacgtc tggggccaag ggaccacggg caccgtctcc	720
tcattccggag gtggtggatc cgaggtgcag ctggtcgagt ctggaggagg attggtgcag	780
cctggagggt cattgaaact ctcattgtga gcctctggat tcacctcaa taagtacgcc	840
atgaactggg tccgccaggc tccaggaaag gggttggaat gggttgctcg cataagaagt	900
aaatataata attatgcaac atattatgcc gattcagtga aagacagggt caccatctcc	960
agagatgatt caaaaaacac tgcctatcta caaatgaaca acttgaagac tgaggacact	1020
gccgtgtact actgtgtgag acatgggaac ttcggtaata gctacatata ctactgggct	1080
tactggggcc aagggaactc ggtcacgtc tctcagggtg gtggtggttc tggcggcggc	1140
ggctccgggt gtggtggttc tcagactgtt gtgactcagg aaccttact caccgtatca	1200
cctggtggaa cagtcacact cacttgtggc tctcagactg gggtgttac atctggcaac	1260
tacccaaact gggccaaca aaaaccagg caggcaccgc gtggtctaata aggtgggact	1320
aagttctctg ccccggtac tctgccaga ttctcaggct ccctgcttg aggcaaggct	1380
gccctcacc tctcagggt acagccagag gatgaggcag aatattactg tgttctatgg	1440
tacagcaacc gctgggtgtt cgggtggagga accaaactga ctgtcctaca ccaccatcac	1500
caccactaa	1509

<210> SEQ ID NO 129

<211> LENGTH: 502

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 129

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	Asn	Asn	Tyr
			20					25						30	
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Thr	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	Arg	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75				80	
Glu	Asp	Phe	Ala	Ala	Tyr	Phe	Cys	Gln	Gln	Thr	Tyr	Ser	Asn	Pro	Thr
			85							90				95	
Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Val	Lys	Arg	Gly	Gly	Gly	Gly	Ser
			100						105					110	
Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Gln	Glu
			115						120					125	
Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln	Thr	Leu	Ser	Leu	Thr	Cys
			130						135					140	
Thr	Val	Ser	Gly	Gly	Ser	Ile	Asn	Asn	Asn	Asn	Tyr	Tyr	Trp	Thr	Trp

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

<210> SEQ ID NO 130

<211> LENGTH: 717

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

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<400> SEQUENCE: 130

```

cagggtgcagc tgcaggagtc ggggccagga ctggtgaagc ctteggagac cctgtccctc   60
acctgcactg tctctggtgg ctccatcata agtcactact ggagctggat ccggcagccc   120
ccaggaaggg gactggagtg gattggatat atctattaca gtgggagcac caactacaac   180
ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg   240
aagctgacct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agacggctgg   300
agcgcccttg actactgggg ccaggaacc ctggtcacg tctcctcagg aggcggcggt   360
tcaggcggag gtggctctgg cgggtggcga agtgacatcc agatgacca gtctccatcc   420
tccctgtctg catctgtagg agacagagtc accatcactt gccgggcaag tcagggcatt   480
agaaatgctt taggctggta tcagcagaaa ccaggaaggg cccctaagcg cctgatctat   540
gtgcatcca gtttgcaaag tggggtecca tcaaggttca gcggcagtgg atctgggaca   600
gaattcactc tcacaatcag cagcctgcag cctgaagatt ttgcaactta ttactgtcta   660
cagcataata gttaccctcg gacgttcggc caagggacca aggtggaaat cagaagg   717

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<210> SEQ ID NO 131

<211> LENGTH: 717

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 131

```

gacatccaga tgaccagtc tccatccctc ctgtctgcat ctgtaggaga cagagtcacc   60
atcacttgcc gggcaagtca gggcattaga aatgctttag gctggatca gcagaaacca   120
gggaaagccc ctaagcgct gatctatgct gcacccagtt tgcaaagtgg ggtcccatca   180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct   240
gaagattttg caactatta ctgtctacag cataatagtt accctcggac gttcggccaa   300
gggaccaagg tggaaatcag aaggggaggg ggcgggttcag gcggaggtgg ctctggcggt   360
ggcggaaagtc aggtgcagct gcaggagtcg gggccaggac tggtagagcc ttcggagacc   420
ctgtccctca cctgcactgt ctctggtggc tccatcataa gtcactactg gagctggatc   480
cggcagcccc caggaagggg actggagtggt attggatata tctattacag tgggagcacc   540
aactacaacc cctccctcaa gactcgagtc accatcagc tagacacgtc caagaaccag   600
ttctccctga agctgacctc tgtgaccgct gcggacacgg ccgtgtatta ctgtgcgaga   660
gacggctgga gcgcctttga ctactggggc caggaacccc tggtcaccgt ctctca   717

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<210> SEQ ID NO 132

<211> LENGTH: 723

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 132

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cagggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc   60
acctgcactg tctctggtgg ctccatcaac aataataatt actactggac ctggatccgc   120
cagcaccag ggaagggcct ggagtggatt gggatcatct attacagtgg gagcaccttc   180

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tacaacccgt cccccaagag tcgagttacc atatcagtcg acacgtctaa gacccagttc	240
tccctgaagt tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagag	300
gatacgatga cgggcctgga cgtctggggc caagggacca cggtcaccgt ctctcagga	360
ggcggcggtt caggcggagg tggctctggc ggtggcggaa gtgacatcca gatgaccag	420
tctccatcct ccctgtctgc atctgtagga gacagagtca ccatcacttg ccgggctagt	480
cagagcatta acaactatct aaattggtat cagcagaaac cagggaagc cctacgctc	540
ctgatctatg ctgcaccag tttgcaaagt ggggtcccat caagggtcag tggcagtaga	600
tctgggacag atttcactct caccatcagc agtctgcaac ctgaagattt tgcagcttac	660
ttctgtcaac agacttacag taaccgcagc ttcggccaag ggaccaaggt ggaagtcaaa	720
agg	723

<210> SEQ ID NO 133
 <211> LENGTH: 723
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 133

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggctagtca gagcattaac aactatttaa attggtatca gcagaaacca	120
gggaaagccc ctacgctcct gatctatgct gcaccagtt tgcaaagtgg ggtcccatca	180
aggttcagtg gcagtagatc tgggacagat ttcactctca ccacagcag tctgcaacct	240
gaagattttg cagcttactt ctgtcaacag acttacagta acccgacgtt cggccaagg	300
accaagggtg aagtcaaaag gggaggcggc ggttcaggcg gaggtggctc tggcgggtggc	360
ggaagtcagg tgcagctgca ggagtcgggc ccaggactgg tgaagccttc acagaccctg	420
tccctcacct gcactgtctc tgggtggctc atcaacaata ataattacta ctggacctgg	480
atccgcagc acccagggaa gggcctggag tggattgggt acatctatta cagtgggagc	540
acctctaca acccgctcct caagagtcga gttaccatat cagtcgacac gtctaagacc	600
cagttctccc tgaagttgag ctctgtgact gcccgggaca cggccgtgta ttactgtgcg	660
agagaggata cgatgacggg cctggacgtc tggggccaag ggaccacggt caccgtctcc	720
tca	723

<210> SEQ ID NO 134
 <211> LENGTH: 741
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 134

cagggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc	60
acctgcactg tctctggcgg ctccatcagc ggtgatggtc acttctggag ctggatccgc	120
cagcaccag ggaagggcct ggagtggatt gggatcatct attacagtgg gagcacctac	180
tacaacccgt cccccaagag tcgagttacc atatcagttg acacgtctaa gaaccagttc	240

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tcctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagatta	300
agagggtggt acaaatttga ctactggggc cagggaaacc tggtcaccgt ctctcagga	360
ggcggcggtt caggcggagg tggctctggc ggtggcgga gtgatattgt gatgaccag	420
actccactct ctctgtccgt cgcctctgga cagccggcct ccatctcttg ccagtctagt	480
ctgagcctcc agcatagtaa tggaaagacc tatttgattt ggtacctgca gaagccaggc	540
cagctccac aactcctgat ctatgaagtt tccaaccggt tctctggagt gccagatagg	600
ttcagtggca gcgggtcagg gacagatttc acgctgaaaa tcagccgggt ggaggctgag	660
gatgttggga ttattactg catgcaaagt aaacagcttc cgtacagttt tggccagggg	720
accaagctgg agatcaaacg a	741

<210> SEQ ID NO 135

<211> LENGTH: 741

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 135

gatattgtga tgaccagac tccactctct ctgtccgtcg cccctggaca gccggcctcc	60
atctcctgcc agtctagtct gaggctccag catagtaatg gaaagaccta ttgtatttg	120
tacctgcaga agccaggcca gcctccacaa ctctgatct atgaagtttc caaccggttc	180
tctggagtgc cagatagggt cagtggcagc gggtcaggga cagatttcac gctgaaaatc	240
agccgggtgg aggtgagga tgttgggatt tattactgca tgcaaagtaa acagcttcctg	300
tacagttttg gccaggggac caagctggag atcaaacgag gagcgggcgg ttcaggcgga	360
ggtggctctg gcggtggcgg aagtcagggt cagctgcagg agtcggggccc aggactggtg	420
aagccttcac agaccctgtc cctcacctgc actgtctctg gcggctccat cagcggtgat	480
ggtcacttct ggagctggat ccgccagcac ccagggaagg gcctggagtg gattgggtac	540
atctattaca gtgggagcac ctactacaac ccgtccctca agagtgcagt taccatatca	600
gttgacacgt ctaagaacca gttctccctg aagctgagct ctgtgactgc cgcggacacg	660
gccgtgtatt actgtgcgag attaagaggt ggctacaaat ttgactactg gggccaggga	720
accctgggtca ccgtctcttc a	741

<210> SEQ ID NO 136

<211> LENGTH: 717

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 136

cagggtcagc tgcaggatc gggcccagga ctggtgaagc cttcgagac cctgtccctc	60
acctgcactg tctctggtgg ctccatcagt agttactact ggagctggat ccggcagccc	120
ccagggaagg gactggagtg gattgggtat atctattaca gtgggagcac caactacaac	180
ccctccctca agagtgcagt caccatatca gtagacacgt ccaagaacca gttctccctg	240
aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtgcgag agttgactac	300
aaggcttttg atatctgggg ccaagggaca atggtcaccg tctcttcagg aggcggcggt	360

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tcaggcggag gtggctctgg cgggtggcga agtgacatcc agatgaccca gtctccatcc	420
tccctgtctg catctgtagg agacagagtc accatcactt gccgggcaag tcagggcatt	480
agaaatgatt tacactggta tcagcagaaa ccagggaag ccctaagcg cctgatctat	540
gtgcatcca gtttgcaag tggggtccca tcaaggttca gcggcagtgg atctgggaca	600
gaattcactc tcacaatcag cagcctgcag cctgaagatt ttgcaactta ttactgtcta	660
cagcattata gttaccctg gacgttcggc caagggacca aggtggaaat caaacga	717

<210> SEQ ID NO 137
 <211> LENGTH: 717
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 137

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc	60
atcacttgcc gggcaagtca gggcattaga aatgatttac actggtatca gcagaaacca	120
gggaaagccc ctaagcgcct gatctatgct gcattccagtt tgcaaagtgg ggtcccatca	180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct	240
gaagattttg caacttatta ctgtctacag cattatagtt acccgtggac gttcggccaa	300
gggaccaagg tggaaatcaa acgaggaggc ggcgggttcag gcggaggtgg ctctggcggg	360
ggcggaagtc aggtgcagct gcaggagtcg ggcccaggac tggtgaaagc ttcggagacc	420
ctgtccctca cctgcactgt ctctggtggc tccatcagta gttactactg gagctggatc	480
cggcagcccc cagggaaggg actggagtgg attgggtata tctattacag tgggagcacc	540
aactacaacc cctccctcaa gagtcgagtc accatatcag tagacacgtc caagaaccag	600
ttctccctga agctgagctc tgtgaccgct gcggacacgg ccgtgtatta ctgtgcgaga	660
gttgactaca aggcctttga tatctggggc caagggacaa tggtcaccgt ctcttca	717

<210> SEQ ID NO 138
 <211> LENGTH: 735
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 138

cagggtgcagc tgggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc	60
tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct	120
ccaggcaagg ggctggagtg ggtggcagct atatggtagt atggaagtaa taaatactat	180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa tatgttgtat	240
ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatctt	300
tcgatttttg gagtggttat tctttctgac tactggggcc aggaaccct ggtcaccgtc	360
tcctcaggag gcggcgggtc aggcggagggt ggctctggcg gtggcggaaag tgaattgtg	420
ctgactcagt ctccagactt tcagtctgtg actccaaagg agaaagtcac catcacctgc	480
cgggccagtc agagcattgg tagtagctta cactgggtacc ggcagaaacc agatcagtct	540

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ccaaagctcc tcatcaagta tgcttccag tcttctcag gggtocttc gaggttcagt    600
ggcgggtggt ctgggacaga ttaccacctc accatcaata gcctggaagc tgaagatgct    660
gcaacgtatt actgtcatca gagtagtagt ttaccgtgga cggtcggcca agggaccaag    720
gtggaaatca aacga                                                    735

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<210> SEQ ID NO 139
<211> LENGTH: 735
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        polynucleotide

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<400> SEQUENCE: 139
gaaattgtgc tgactcagtc tccagacttt cagtctgtga ctccaaagga gaaagtcacc    60
atcacctgcc gggccagtca gagcattggt agtagcttac actggtaccg gcagaaacca    120
gatcagtcct caaagctcct catcaagtat gcttcccagt ccttctcagg ggtcccctcg    180
aggttcagtg gcggtggttc tgggacagat ttcacctca ccatcaatag cctggaagct    240
gaagatgctg caacgtatta ctgtcatcag agtagtagtt tacctgggac gttcggccaa    300
gggaccaagg tggaaatcaa acgaggaggc ggcggttcag gcgaggtgg ctctggcggt    360
ggcggaaagtc aggtgcagct ggtggagtct gggggaggcg tggtcagcc tgggaggtcc    420
ctgagactct cctgtgcagc gtctggattc accttcagta gctatggcat gcaactgggtc    480
cgccaggctc caggcaaggg gctggagtgg gtggcagcta tatggtatga tggaaagtaat    540
aaatactatg cagactccgt gaagggccga ttcaccatct ccagagacaa ttccaagaat    600
atgttgtatc tgcaaatgaa cagcctgaga gccgaggaca cggctgtgta ttactgtgcg    660
agagatcttt cgatttttgg agtggttatt cttctgact actggggcca gggaaacctg    720
gtcacctgct cctca                                                    735

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<210> SEQ ID NO 140
<211> LENGTH: 747
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        polynucleotide

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<400> SEQUENCE: 140
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc    60
acctgcactg tctctggtgg ctccatcagc agtgggtggt actactggaa ctggatccgc    120
cagcacccag ggaagggcct ggagtggatt ggggtacatct attacagtgg gagcacctac    180
tacaacccgt ccctcagggg tcgacttata atatcagtcg acacgtctaa gaaccagttc    240
tccctgaggc tgagctctgt gactgccgcg gacacggcgc tgtattactg tgcgagagat    300
ggtggagaca gctatgggag tatggacgtc tggggccaag ggaccacggt caccgtctcc    360
tcaggaggcg gcggttcagg cggaggtggc tctggcggtg gcggaagtga tattgtcatg    420
accagactc cactctcctc acctgtcacc cttggacagc cggcctccat ctctgcagg    480
tctagtcaaa gcctctgaca cagtgataga aacacctact tgagttggct tcagcagagg    540
ccaggccagc ctccaagact cctaatttat aagatttcta accggttctc tggggtccca    600
gacagattca gtggcagtgg ggcagggaca gatttcacac tgaaaatcag cagggtggaa    660

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gctgaggatg tcgggggttta ttactgcatg caagctacac aatttcctct cactttcggc 720
 ggagggacca aggtggagat caagcga 747

<210> SEQ ID NO 141
 <211> LENGTH: 747
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide

<400> SEQUENCE: 141
 gatattgtca tgaccagac tccactctcc tcacctgtca cccttgaca gccggcctcc 60
 atctcctgca ggtctagtca aagcctcgta cacagtata gaaacaccta cttgagttgg 120
 cttcagcaga ggccaggcca gcctccaaga ctctaatat ataagatttc taaccgggttc 180
 tctgggggtcc cagacagatt cagtggcagt ggggcaggga cagatttcac actgaaaatc 240
 agcagggtgg aagctgagga tgcgggggtt tattactgca tgcaagctac acaatttcct 300
 ctcaatttcg gcggaggggac caagtgagg atcaagcgag gagcgggcgg ttcaggcggga 360
 ggtggctctg gcggtggcgg aagtcagggtg cagctgcagg agtcggggccc aggactgggtg 420
 aagccttcac agacctgtc cctcacctgc actgtctctg gtggctccat cagcagtggt 480
 ggttactact ggaactggat ccgccagcac ccagggaagg gcctggagtg gattgggtac 540
 atctattaca gtgggagcac ctactacaac ccgtccctca ggggtcgact tataatatca 600
 gtcgacacgt ctaagaacca gttctccctg aggctgagct ctgtgactgc cgcggacacg 660
 gccgtgtatt actgtgcgag agatgggtgga gacagctatg gccgtatgga cgtctggggc 720
 caagggacca cggtcaccgt ctccctca 747

<210> SEQ ID NO 142
 <211> LENGTH: 753
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polynucleotide

<400> SEQUENCE: 142
 cagggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcgagac cctgtccctc 60
 acctgcactg tctctggtga ctccatcaat aattactact ggagctggat ccggcagccc 120
 gccgggaagg gactggagtg gattgggctg atctttacca gtgggagcac caactacaac 180
 ccctccctca agagtcgagt caccatgtca atagacacgt ccaagaacca gttctccctg 240
 aagctgagct ctgtgaccgc cgcggacacg gccgtgtatt actgtgcgag agagggggga 300
 cactatggta gtagtgggta tctatactat tactatttcg gtatggacgt ctggggccaa 360
 gggaccacgg tcaccgtctc ctcaggagggc ggcggttcag gcggaggtgg ctctggcggc 420
 ggcggaagtg aaattgtgtt gacgcagtct ccaggcacc tgtctttgtc tccaggggaa 480
 agagccaccc tctctgcgag ggccagtcag actgttagca gcagctactt agcctggtag 540
 cagcagaaac ctggccaggc tcccaggctc ctcactctat gtgcattcat caggggccact 600
 ggcatccag acaggttcag tggcagtggt tctgggacag acttcactct caccatcagc 660
 agactggagc ctgaagattt tgcagtgtat tactgtcagc agtatggtag ctcactcact 720

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ttcggcggag ggaccaaggt ggagatcaaa cga 753

<210> SEQ ID NO 143
 <211> LENGTH: 753
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 143
 gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagagccacc 60
 ctctcctgca gggccagtca gactgttagc agcagctact tagcctggta ccagcagaaa 120
 cctggccagg ctcccaggct cctcatctat ggtgcatcca tcagggccac tggcatccca 180
 gacaggttca gtggcagtggt gtctgggaca gacttcactc tcaccatcag cagactggag 240
 cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gctcactcac ttctggcgga 300
 gggaccaagg tggagatcaa acgaggaggc ggcggttcag gcggaggtgg ctctggcggt 360
 ggcggaagtc aggtgcagct gcaggagtcg ggcccaggac tggagaagcc ttcggagacc 420
 ctgtccctca cctgcactgt ctctggtgac tccatcaata attactactg gagctggatc 480
 cggcagcccg ccgggaaggg actggagtggt attgggcgta tctttaccag tgggagcacc 540
 aactacaacc cctccctcaa gagtgcagtc accatgtcaa tagacacgtc caagaaccag 600
 ttctccctga agctgagctc tgtgaccgac gcggacacgg ccgtgtatta ctgtgcgaga 660
 gagggggggac actatggtag tagtggttat ctatactatt actatttcgg tatggacgtc 720
 tggggccaag ggaccacggt caccgtctcc tca 753

<210> SEQ ID NO 144
 <211> LENGTH: 759
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 144
 caggtagcgc tgcagcagtc aggtccagga ctggtgaagc cctgcagac cctctcactc 60
 acctgtgcca tctccgggga cagtgtctct agcaacagtg ttgcttggaa ctggatcagg 120
 cagtcccat cgagaggcct tgagtggctg ggaaggacat actacaggtc caagtgggtat 180
 aatgattatg cagtatctgt gaaaagtcga ataaccatca acccagacac atccaagaac 240
 cagttctccc tgcagctgaa ctctgtgact cccgaggaca cggctgtgta ttactgtgca 300
 agaggtatct tcgtagtgc agctgttctt aggtttgact actggggcca ggaaccctg 360
 gtcaccgtct cctcaggagg cggcggttca ggccgaggtg gctctggcgg tggcggaagt 420
 gatattgtga tgactcagtc tccactctct ctgtccgta cccctggaga gccggcctcc 480
 atctcctgca ggtctagtct gagcctcctg catagtaatg gatacaacta tttggattgg 540
 ttctctcaga agccagggca gtctccacag ctctgatct atttgggttc taatcggggc 600
 tccgggggtcc ctgacagggt cagtggcagt gggtcagaca cagattttac gctgaaaatc 660
 agcagagtggt aggtcagga tgttgggtt tattactgca tgcaaggtct acatactcct 720
 cctagttttg gccaggggac caagctggag atcaaacga 759

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<210> SEQ ID NO 145
<211> LENGTH: 759
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 145

gatattgtga tgactcagtc tccactctct ctgtccgta cccctggaga gccggcctcc	60
atctcctgca ggtctagtct gagcctctcg catagtaatg gatacaacta ttggattgg	120
ttcctgcaga agccagggca gtctccacag ctctgatct atttgggttc taatcgggcc	180
tccgggggtcc ctgacagggt cagtggcagt gggtcagaca cagattttac gctgaaaatc	240
agcagagtgg aggctgagga tgttgggggt tattactgca tgcaaggctc acatactcct	300
cctagttttg gccaggggac caagctggag atcaaacgag gagcgggcgg ttcaggcggga	360
ggtggctctg gcggtggcgg aagtcaggta cagctgcagc agtcaggctc aggactggtg	420
aagccctcgc agaccctctc actcacctgt gccatctccg gggacagtgt ctctagcaac	480
agtgttgctt ggaactggat caggcagctc ccacgagag gccttgagtg gctgggaagg	540
acatactaca ggtccaagtg gtataatgat tatgcagtat ctgtgaaaag tcgaataacc	600
atcaaccag acacatccaa gaaccagttc tccctgcagc tgaactctgt gactcccgag	660
gacacggctg tgtattactg tgcaagaggt attttcgtag tgccagctgt tctaggttt	720
gactactggg gccagggaac cctggtcacc gtctctca	759

<210> SEQ ID NO 146
<211> LENGTH: 726
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 146

caagtgcagc ttgtggaaa gggaggcggg gtctgtgcaac ccggacgctc actgcgcctg	60
agctgtgccg cctctgggtt cacctctctc taccacgggc tgcatgggt gagacaagca	120
cccggaaaag gcctggaatg ggtcgccgtg atctgggtatg acgtaataa caagaattac	180
gctgatagcg tgaagggtcg gtttactatc tcacgcgaca attccaagaa caccctgttt	240
ctccaaatga actctctgag ggccgaggac accgccgtgt actactgcgc tcggaaggga	300
tctggcaaa gatgcatgga tgtgtgggga caggggacca cgtgactgt cagctctggt	360
ggaggagggt ccgggggagg tgggagcggc ggagggggaa gcgaaattgt cctgactcaa	420
tcacctggca ccctgagcct ttcaccagga gagagggcaa ccctcagctg tcggggttca	480
cagagcgtgt ccttcagcta tctggcttgg tatcagcaaa agcctggaca ggccccaga	540
cttctcatct acggagcctc ttcacgggcc accggcatcc ctgaccgctt ctctggtagc	600
gggtcaggaa ccgacttcac cctcaccatt tcacgccttg agccagagga cttgcagctc	660
tactattgcc agcattacga tgggtctatt acttttgac cggggactaa ggtggacatt	720
gaaaga	726

<210> SEQ ID NO 147
<211> LENGTH: 726
<212> TYPE: DNA

-continued

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 147

```
gaaattgtcc tgactcaatc acctggcacc ctgagccttt caccaggaga gagggcaacc      60
ctcagctgtc gggcttcaca gagcgtgtcc ttcagctatc tggcttggtg tcagcaaaag     120
cctggacagg cccccagact tctcatctac ggagcctett cacgggccac cggcatccct     180
gaccgcttct ctggtagcgg gtcaggaacc gacttcaccc tcaccatttc acgccttgag     240
ccagaggact tcgcagtcta ctattgccag cattacgatg ggtctattac ttttgaccg      300
gggactaagg tggacattga aagaggtgga ggagggtccg ggggaggtgg gagcgcgga      360
gggggaagcc aagtgcagct tgtggaagc ggaggcgagg tcgtgcaacc cggacgctca     420
ctgcgcctga gctgtgccgc ctctgggttc accttctcct accacgggct gcattgggtg     480
agacaagcac ccgaaaaagg cctggaatgg gtcgccgtga tctggtatga cggtaataac     540
aagaattacg ctgatagcgt gaagggtcgg ttactatct caccgcacaa ttccaagaac     600
acctgtttc tccaaatgaa ctctctgagg gccgaggaca ccgccgtgta ctactgcgct     660
cggaagggat ctggcaaaag atgcatggat gtgtggggac aggggaccac cgtgactgtc     720
agctca                                           726
```

<210> SEQ ID NO 148

<211> LENGTH: 726

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 148

```
caagtccagc tcgaacaatc agggggagggt gtggtccaac ccggcagatc actgaggctc      60
tcatgtgctg catcagggtt taccttctca tcttatggta tgcattgggt cagacaggct     120
ccagggaagg ggcttgatgt ggtggccgtg atttggtagc acggaacaa taaggactac     180
cgggacagcg tgactggtcg gttcaccatc tcacgggata acagcaagaa taccctctac     240
cttcaaatgt catcacttcg cgctgaagat accgccgtgt attactgcgc caggaaggga     300
tctggtaaa gttgcatgga cgtgtggggg cggggaacta ccgtgaccgt gtcactcggg     360
ggaggcggct ccgggggtgg aggaagcggc ggaggagggt ccgagattgt cctcaccag      420
tctcccgaa ctctttccct gagccctggt gacagagcaa ccctgtcatg ccgcgttct      480
cagtccgtgt cttttagctt tctggcctgg tatcagcaga cccagggca ggcacccgc      540
cttctgatct acggagccta ctctagggt accggcattc ccgacagggt ctctggtagc     600
ggcagcggca ccgacttcgc cctcactatt tcacgccttg agccggaaga tttcgcagtg     660
tactactgcc agcattatgg aacctctatc accttcggtc ctggcactaa ggtggacctt     720
aaaagg                                           726
```

<210> SEQ ID NO 149

<211> LENGTH: 726

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

polynucleotide

<400> SEQUENCE: 149

gagattgtcc tcacccagtc tcccggaaact ctttccctga gccctggtga cagagcaacc	60
ctgtcatgcc gcgcttctca gtccgtgtct tttagcttcc tggcctggta tcagcagacc	120
ccagggcagg cacccegcct tctgatctac ggagcctact ctagggtac cggcattccc	180
gacaggttct ctggtagcgg cagcggcacc gacttcgccc tcaactattc acgccttgag	240
ccggaagatt tcgcagtgtg ctactgccag cattatggaa cctctatcac cttcggtcct	300
ggcactaagg tggaccttaa aaggggtgga ggcggctccg ggggtggagg aagcggcgga	360
ggaggggtccc aagtccagct cgaacaatca gggggagggg tggccaacc cggcagatca	420
ctgaggctct catgtgctgc atcaggggtt accttctcat cttatggtat gcattgggtc	480
agacaggctc caggggaagg gcttgagtgg gtggccgtga tttggtacga cggaaacaat	540
aaggactacc gggacagcgt gactggctcg ttcaccatct cacgggataa cagcaagaat	600
acctctacc ttcaaatgct atcacttcgc gctgaagata ccgccgtgta ttactgcgcc	660
aggaagggat ctggtaaagg ttgcatggac gtgtggggtc ggggaactac cgtgaccgtg	720
tcattct	726

<210> SEQ ID NO 150
<211> LENGTH: 726
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 150

caagtgaac tcgtcgagtc aggagggggg gtggtccagc ctggacgctc actcagactt	60
tcattgcgctg catctggggt cactttttcc agctacggga tgcattgggt gcggcaggct	120
ccgggaaaag gtctggaatg ggtgactgtg atttggtagc acgggaataa caaagactat	180
gccgattccg tgaagggaag attcaccatt agcagggaact cctcaaagaa caccctttat	240
ctccaaatga atagccttcg cgctgaggac accgccgtct actattgtgc caggaagggg	300
tcaggaaagg ggtgcatgga tgtgtgggga caggggacta ccgtcactgt ctcatcaggc	360
ggaggcggat ctggcgggtg agggctctgt gggggaggct cagaaatcgt gctgaccag	420
agcccaggca ccctcagcct gtcacccgga gagcgggcca ccctgtcatg tcgggccagc	480
cagtcagtct cttactcttt cctcgcttgg tatcagcaga agcctggtca agcccctgc	540
ctcctgatct acgccgcctc atcacgggct actggtatcc cagatcggtt ttctggtagc	600
ggcagcggaa ccgacttcac cctgaccatt tcccgcctgg aaccgagga ctttgtgtg	660
tactactgcc aacattacgg atcttctatc accttcggtc cgggcaccaa ggtggacatt	720
aagagg	726

<210> SEQ ID NO 151
<211> LENGTH: 726
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 151

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gaaatcgtgc tgaccagag cccaggcacc ctgagcctgt caccgagaga gcgggccacc    60
ctgtcatgtc gggccagcca gtcagtctct tactctttcc tcgcttggtg tcagcagaag    120
cctggtaag cccctgcct cctgatctac gccgectcat cacgggctac tggatccca    180
gatcggtttt ctggtagcgg cagcggaacc gacttcaccc tgaccatttc ccgectggaa    240
cccaggact ttgctgtgta ctactgcaa cattacggat cttctatcac ctteggtccg    300
ggaccaagg tggacattaa gagggcgga ggcgatctg gcggtggagg gtctggtggg    360
ggaggctcac aagtgaact cgtcgagtc ggaggggtg tggccagcc tggacgctca    420
ctcagacttt catgcgctgc atctgggttc actttttcca gctacgggat gcattgggtg    480
cggcaggctc cgggaaaagg tctggaatgg gtgactgtga tttggtacga cgggaataac    540
aaagactatg ccgattccgt gaagggaaga ttcaccatta gcagggactc ctcaaagaac    600
acctttatc tccaaatgaa tagccttcgc gctgaggaca ccgccgtcta ctattgtgcc    660
aggaaggggt caggaaagg gtgcatggat gtgtggggac aggggactac cgtcactgtc    720
tcatct                                           726

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<210> SEQ ID NO 152
<211> LENGTH: 738
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

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<400> SEQUENCE: 152

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```

gaagtccagc ttgaacagag cgggtggagg ctctgcaac caggtgggag ccttcgctg    60
agctgcgccg catcagggtt caccttctca tcatacgata tgcattgggt ccgccaggcc    120
accgggaagg gcctggaatg ggtgagcgtg attggcaccg ctggcgacac ttattacccc    180
gactccgtga agggacgctt taccatttca agggagaacg ccaaaaactc tctttacctc    240
caaatgaact cccttcgggc tggggatact gccgtctatt actgcgtccg gggaggtgga    300
tggaattatg gatactacta ttacggaatg gacgtgtggg gacagtggac caccgtgact    360
gtgtcaagcg gaggaggggg ttcaggcggt gggggcagcg ggggagcg atcagacatc    420
caaatgacct agagcccctc atcactgtca gcctctgtgg gagacagagt gactatcact    480
tgtcgggcct cagagtcaat caggcgctat ctgaattggt atcaagaaaa gccaggaaaa    540
gctcctaagc tgctgatcta cgcagcttcc agcagccaaa gcggggtgcc atcacggttc    600
tctggtagcg gatctggaac tgacttcacc ctgaccatct ctagcctcca gccggaggat    660
ttcgccactt actactgcca gcagtcctac attaataccg ccaccttgg acagggaacc    720
aaggtcgaga ttaagaga                                           738

```

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<210> SEQ ID NO 153
<211> LENGTH: 738
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

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<400> SEQUENCE: 153

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gacatccaaa tgaccagag cccctcatca ctgtcagcct ctgtgggaga cagagtgact    60

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-continued

atcacttgtc gggcctcaga gtoaacacagg cgtatctga attggtatca agaaaagcca	120
ggaaaagctc ctaagctgct gatctacgca gcttccagca gccaaagcgg ggtgccatca	180
cggttctctg gtagcggatc tggaactgac ttcaccctga ccatctctag cctccagccg	240
gaggatttcg ccacttacta ctgccagcag tctacatta atccgcccac ctttgacag	300
ggaaccaagg tgcagattaa gagaggagga ggggggttcag gcggtggggg cagcggggga	360
ggcggatcag aagtcacgtc tgaacagagc ggtggagggc tctgcaacc aggtgggagc	420
cttcgcctga gctgcgccgc atcagggttc accttctcat catacgatat gcattgggtc	480
cgccaggcca ccgggaaggg cctggaatgg gtgagcgtga ttggcacgcg tggcgacact	540
tattaccccg actccgtgaa gggacgcttt accatttcaa gggagaacgc caaaaactct	600
ctttacctcc aaatgaacte ccttcgggct ggggatactg ccgtctatta ctgcgtccg	660
ggaggtggat ggaattatgg atactactat tacggaatgg acgtgtgggg acagtggacc	720
accgtgactg tgtcaagc	738

<210> SEQ ID NO 154

<211> LENGTH: 735

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 154

caagtccagc tgaacagtc tggcccaggg cttgtgaagc cctcccagac cctcagcctg	60
acttgcactg tgcaggagg ttccattagc tccggcggat attactggtc atggatcagg	120
cagcatcccg gaaagggcct ggaatggatt ggatacatct acttcagcgg gaacactaat	180
tacaatccct ctctgaaatc tgggtcact atcagcgtgg ataccagcaa gaaccagttc	240
tccctgaagc tcagctcagt gaccgtgct gacaccgcg tctactactg tgctagagaa	300
tactgcgacg atgactgcta tggcttcgac tactggggtc agggaaccct tgtgaccgtc	360
agctctggag gaggggggtc tggcgggtga ggctcagggg gagcggatc agacattcaa	420
gtgactcaat ctctagctc tctgtcagcc tcagtggcg accgcgtcac catcacctgt	480
cgggcatccc agggaatccg caatgacctc ggggtgtatc aacagaaacc aggaaaggcc	540
ccgaagagac ttatctacgc agcctcctct ctccaaagcg gtgtgccatc tcgcttttct	600
ggctctggca gcggaaccga gttcaccctg actatttcat ctctgcagcc ggaggacttc	660
gcaacctatt actgctgca atattcaatc tacccacgca cctttgggca ggggaccaag	720
gtcgagatta agcgg	735

<210> SEQ ID NO 155

<211> LENGTH: 734

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 155

gacattcaag tgactcaatc tctagctct ctgtcagcct cagtgggcca ccgcgtcacc	60
atcacctgtc gggcatccca gggaatccgc aatgacctcg ggtggtatca acagaaacca	120
ggaaaggccc cgaagagact tatctacgca gctcctctc tccaaagcgg tgtgccatct	180

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```

cgcttttctg gctctggcag cggaaccgag ttcaccctga ctatttcac tctgcagccg 240
gaggacttcg caacctatta ctgctgcaa tattcaatct acccacgcac ctttgggcag 300
gggaccaag gtcagattaa ggggggagga ggggttctg gcggtggagg ctcaggggga 360
ggcggatcac aagtcacgt cgaacagtct ggcccagggc ttgtgaagcc ctcccagacc 420
ctcagcctga cttgcactgt gtcaggaggt tccattagct ccggcggata ttactggcca 480
tggatcaggc agcatcccg aaagggcctg gaatggattg gatacatcta cttcagcggg 540
aacactaatt acaatccctc tctgaaatct cgggtcacta tcagcgtgga taccagcaag 600
aaccagttct ccctgaagct cagctcagtg accgctgctg acaccgccgt ctactactgt 660
gctagagaat actgcgacga tgactgctat ggcttcgact actggggtca gggaaacctt 720
gtgaccgtca gctc 734

```

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<210> SEQ ID NO 156
<211> LENGTH: 735
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        polynucleotide

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<400> SEQUENCE: 156

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```

caagtccagc ttgtcgagag cgggtggggc gtggtccagc ccggacgctc acttaggctg 60
tcatgcgccg caagcggttt caccttttca tcatacgga tgcactgggt ccggcaggcc 120
ccaggaag gctggaatg ggtggccgtg atctggtacg atgggtcaaa taagtactat 180
gcagattcag tgaagggtcg gtttaccatc tctagggaca atagcaaaaa caccctctac 240
ctccaaatga acagcctcag agccgaggac accgccgtgt attactgtgc ccgcgacctg 300
tcaattttcg gggctgtggt gctgtctgac tactggggtc aaggtactct cgtgaccgtg 360
tctagcgggg gaggaggaag cggagggggg gggtcaggcg gaggcgggtc tgaattgtg 420
ctgactcaat caccgcactt ccaatccgtc acccctaagg agaaagtac tattacctgt 480
cgggcctccc agtacatcgg gtctaattct cattgggtac agcagacccc cgaccagtca 540
cctaagctcc tgattaagta cgctctcag tcttttagcg gagtcccatc tcgcttctct 600
ggatcaggat ctggaactga ttctactctg accatcaact cacttgaagc tgaggacgct 660
gctacctact actgccatca atcatcatca cttccgtgga ccttcggaca gggcaccaag 720
gtggaaatca agaga 735

```

```

<210> SEQ ID NO 157
<211> LENGTH: 735
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
        polynucleotide

```

```

<400> SEQUENCE: 157

```

```

gaaattgtgc tgactcaatc acccgacttc caatccgtca cccctaagga gaaagtgact 60
attacctgtc gggcctccca gtacatcggg tctaattctc attggtatca gcagaccccc 120
gaccagtcac ctaagctcct gattaagtac gcctctcagt ctttttagcg agtcccatct 180
cgcttctctg gatcaggatc tggaactgat ttcactctga ccatcaactc acttgaagct 240

```

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```

gaggacgctg ctacctacta ctgccatcaa tcatcatcac ttccgtggac cttcggacag 300
ggcaccaagg tggaaatcaa gagaggggga ggaggaagcg gaggggtgg gtcaggcgga 360
ggcggtcttc aagtccagct tgtcgagagc ggtgggggagc tggtcagcc cggacgctca 420
cttaggctgt catgcgccgc aagcggtttc accttttcat catacggcat gcactgggtc 480
cggcaggccc cagggaaggg cctggaatgg gtggccgtga tctggtacga tgggtcaaat 540
aagtactatg cagattcagt gaagggtcgg tttaccatct ctagggacaa tagcaaaaac 600
acctctacc tccaaatgaa cagcctcaga gccgaggaca ccgccgtgta ttactgtgcc 660
cgcgacctgt caattttcgg ggtcgtggtg ctgtctgact actggggtca aggtactctc 720
gtgaccgtgt cttca 735

```

<210> SEQ ID NO 158

<211> LENGTH: 239

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 158

```

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 Ile Ser His
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 Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85          90          95
Arg Asp Gly Trp Ser Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100         105         110
Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
115         120         125
Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala
130         135         140
Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile
145         150         155         160
Arg Asn Ala Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
165         170         175
Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg
180         185         190
Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser
195         200         205
Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser
210         215         220
Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Arg Arg
225         230         235

```

<210> SEQ ID NO 159

<211> LENGTH: 239

-continued

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

<400> SEQUENCE: 159

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 Ala
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 Tyr Pro Arg
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Arg Arg Gly Gly Gly Gly
100 105 110
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln
115 120 125
Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr
130 135 140
Cys Thr Val Ser Gly Gly Ser Ile Ile Ser His Tyr Trp Ser Trp Ile
145 150 155 160
Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile Tyr Tyr
165 170 175
Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Ile
180 185 190
Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Thr Ser Val
195 200 205
Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asp Gly Trp Ser
210 215 220
Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
225 230 235

<210> SEQ ID NO 160
<211> LENGTH: 241
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 160

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 Asn Asn Asn
20 25 30
Asn Tyr Tyr Trp Thr 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 Phe Tyr Asn Pro Ser
50 55 60
Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Thr Gln Phe

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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 Glu Asp Thr Met Thr Gly Leu Asp Val Trp Gly Gln Gly	100	105	110
Thr Thr Val Thr Val Ser Ser Gly Gly Gly Ser Gly Gly Gly Gly	115	120	125
Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser	130	135	140
Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser	145	150	155
Gln Ser Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys	165	170	175
Ala Pro Thr Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val	180	185	190
Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr	195	200	205
Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Ala Tyr Phe Cys Gln Gln	210	215	220
Thr Tyr Ser Asn Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Val Lys	225	230	235
			240

Arg

<210> SEQ ID NO 161

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 161

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

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Tyr Tyr Ser Gly Ser Thr Phe Tyr Asn Pro Ser Leu Lys Ser Arg Val
180 185 190

Thr Ile Ser Val Asp Thr Ser Lys Thr Gln Phe Ser Leu Lys Leu Ser
195 200 205

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Asp
210 215 220

Thr Met Thr Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
225 230 235 240

Ser Ser

<210> SEQ ID NO 162

<211> LENGTH: 247

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 162

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 Gly Asp
20 25 30

Gly His Phe 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 Leu Arg Gly Gly Tyr Lys Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
115 120 125

Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro Leu Ser
130 135 140

Leu Ser Val Ala Pro Gly Gln Pro Ala Ser Ile Ser Cys Gln Ser Ser
145 150 155 160

Leu Ser Leu Gln His Ser Asn Gly Lys Thr Tyr Leu Tyr Trp Tyr Leu
165 170 175

Gln Lys Pro Gly Gln Pro Pro Gln Leu Leu Ile Tyr Glu Val Ser Asn
180 185 190

Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr
195 200 205

Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Ile
210 215 220

Tyr Tyr Cys Met Gln Ser Lys Gln Leu Pro Tyr Ser Phe Gly Gln Gly
225 230 235 240

Thr Lys Leu Glu Ile Lys Arg
245

<210> SEQ ID NO 163

<211> LENGTH: 247

-continued

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

<400> SEQUENCE: 163

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

<210> SEQ ID NO 164
<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 164

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

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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 Val Asp Tyr Lys	Ala Phe Asp Ile Trp Gly	Gln Gly Thr Met Val
	100	105 110
Thr Val Ser Ser Gly	Gly Gly Ser Gly	Gly Gly Ser Gly Gly
	115	120 125
Gly Gly Ser Asp Ile	Gln Met Thr Gln Ser	Pro Ser Ser Leu Ser Ala
	130	135 140
Ser Val Gly Asp Arg	Val Thr Ile Thr Cys	Arg Ala Ser Gln Gly Ile
	145	150 155 160
Arg Asn Asp Leu His	Trp Tyr Gln Gln Lys	Pro Gly Lys Ala Pro Lys
	165	170 175
Arg Leu Ile Tyr Ala	Ala Ser Ser Leu Gln	Ser Gly Val Pro Ser Arg
	180	185 190
Phe Ser Gly Ser Gly	Ser Gly Thr Glu Phe	Thr Leu Thr Ile Ser Ser
	195	200 205
Leu Gln Pro Glu Asp	Phe Ala Thr Tyr Tyr	Cys Leu Gln His Tyr Ser
	210	215 220
Tyr Pro Trp Thr Phe	Gly Gln Gly Thr Lys	Val Glu Ile Lys Arg
	225	230 235

<210> SEQ ID NO 165

<211> LENGTH: 239

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 165

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 His 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 Tyr Ser Tyr Pro Trp
	85	90 95
Thr Phe Gly Gln Gly	Thr Lys Val Glu Ile	Lys Arg Gly Gly Gly Gly
	100	105 110
Ser Gly Gly Gly Gly	Ser Gly Gly Gly	Ser Gln Val Gln Leu Gln
	115	120 125
Glu Ser Gly Pro Gly	Leu Val Lys Pro	Ser Glu Thr Leu Ser Leu Thr
	130	135 140
Cys Thr Val Ser Gly	Gly Ser Ile Ser Ser	Tyr Tyr Trp Ser Trp Ile
	145	150 155 160
Arg Gln Pro Pro Gly	Lys Gly Leu Glu Trp	Ile Gly Tyr Ile Tyr Tyr

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<210> SEQ ID NO 166
<211> LENGTH: 245
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide
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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 Ala 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 Met 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 Leu Ser Ile Phe Gly Val Val Ile Leu Ser Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
130 135 140

Pro Asp Phe Gln Ser Val Thr Pro Lys Glu Lys Val Thr Ile Thr Cys
145 150 155 160

Arg Ala Ser Gln Ser Ile Gly Ser Ser Leu His Trp Tyr Arg Gln Lys
165 170 175

Pro Asp Gln Ser Pro Lys Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe
180 185 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly Thr Asp Phe
195 200 205

Thr Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr

Cys His Gln Ser Ser Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys
235 236 237 238 239 240 241 242 243 244 245 246 247 248 249

Val Glu Ile Lys Arg
245

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<211> LENGTH: 2
<212> TYPE: PRT
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-continued

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 167

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

<210> SEQ ID NO 168

<211> LENGTH: 249

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 168

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30Gly Tyr Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

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Leu Arg Gly Arg Leu Ile Ile Ser Val Asp Thr Ser Lys Asn 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 Gly Gly Asp Ser Tyr Gly Arg Met Asp Val Trp Gly
            100              105              110

Gln Gly Thr Thr Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly Gly
            115              120              125

Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Val Met Thr Gln Thr Pro
            130              135              140

Leu Ser Ser Pro Val Thr Leu Gly Gln Pro Ala Ser Ile Ser Cys Arg
145              150              155              160

Ser Ser Gln Ser Leu Val His Ser Asp Arg Asn Thr Tyr Leu Ser Trp
            165              170              175

Leu Gln Gln Arg Pro Gly Gln Pro Pro Arg Leu Leu Ile Tyr Lys Ile
            180              185              190

Ser Asn Arg Phe Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ala
            195              200              205

Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val
            210              215              220

Gly Val Tyr Tyr Cys Met Gln Ala Thr Gln Phe Pro Leu Thr Phe Gly
225              230              235              240

Gly Gly Thr Lys Val Glu Ile Lys Arg
            245

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<210> SEQ ID NO 169
<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
                        polypeptide

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<400> SEQUENCE: 169

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

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

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

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

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

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

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

Arg Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
            115              120              125

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
            130              135              140

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
145              150              155              160

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Gly Tyr Trp Asn Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
165 170 175
Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
180 185 190
Leu Arg Gly Arg Leu Ile Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
195 200 205
Ser Leu Arg Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
210 215 220
Cys Ala Arg Asp Gly Gly Asp Ser Tyr Gly Arg Met Asp Val Trp Gly
225 230 235 240
Gln Gly Thr Thr Val Thr Val Ser Ser
245

<210> SEQ ID NO 170
<211> LENGTH: 251
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 170

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

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<210> SEQ ID NO 171
<211> LENGTH: 251
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 171

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 Thr 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 Ile 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 Leu
 85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
 100 105 110
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Gln
 115 120 125
Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu Thr Leu Ser Leu Thr
 130 135 140
Cys Thr Val Ser Gly Asp Ser Ile Asn Asn Tyr Tyr Trp Ser Trp Ile
145 150 155 160
Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile Gly Arg Ile Phe Thr
 165 170 175
Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val Thr Met
 180 185 190
Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser Ser Val
 195 200 205
Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Gly Gly His
 210 215 220
Tyr Gly Ser Ser Gly Tyr Leu Tyr Tyr Tyr Tyr Phe Gly Met Asp Val
225 230 235 240
Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 245 250

<210> SEQ ID NO 172
<211> LENGTH: 253
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 172

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

-continued

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

<210> SEQ ID NO 173

<211> LENGTH: 253

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 173

Asp	Ile	Val	Met	Thr	Gln	Ser	Pro	Leu	Ser	Leu	Ser	Val	Thr	Pro	Gly
1				5					10				15		
Glu	Pro	Ala	Ser	Ile	Ser	Cys	Arg	Ser	Ser	Leu	Ser	Leu	Leu	His	Ser
		20					25					30			
Asn	Gly	Tyr	Asn	Tyr	Leu	Asp	Trp	Phe	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	Asp	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	Gly
			85					90						95	
Leu	His	Thr	Pro	Pro	Ser	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys
	100						105					110			
Arg	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser
	115					120					125				

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Gln	Val	Gln	Leu	Gln	Gln	Ser	Gly	Pro	Gly	Leu	Val	Lys	Pro	Ser	Gln
130						135					140				
Thr	Leu	Ser	Leu	Thr	Cys	Ala	Ile	Ser	Gly	Asp	Ser	Val	Ser	Ser	Asn
145					150					155					160
Ser	Val	Ala	Trp	Asn	Trp	Ile	Arg	Gln	Ser	Pro	Ser	Arg	Gly	Leu	Glu
				165					170					175	
Trp	Leu	Gly	Arg	Thr	Tyr	Tyr	Arg	Ser	Lys	Trp	Tyr	Asn	Asp	Tyr	Ala
			180					185					190		
Val	Ser	Val	Lys	Ser	Arg	Ile	Thr	Ile	Asn	Pro	Asp	Thr	Ser	Lys	Asn
		195					200					205			
Gln	Phe	Ser	Leu	Gln	Leu	Asn	Ser	Val	Thr	Pro	Glu	Asp	Thr	Ala	Val
	210					215					220				
Tyr	Tyr	Cys	Ala	Arg	Gly	Ile	Phe	Val	Val	Pro	Ala	Val	Pro	Arg	Phe
225					230					235					240
Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	Ser			
				245					250						

<210> SEQ ID NO 174

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 174

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

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His	Tyr	Asp	Gly	Ser	Ile	Thr	Phe	Gly	Pro	Gly	Thr	Lys	Val	Asp	Ile
225					230					235					240

Glu Arg

<210> SEQ ID NO 175

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 175

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	Phe	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	His	Tyr	Asp	Gly	Ser	Ile
			85						90					95	

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

Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val
	115					120						125			

Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	Ser	Leu	Arg	Leu	Ser
	130					135					140				

Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Tyr	His	Gly	Leu	His	Trp	Val
145					150					155				160	

Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Val	Ile	Trp	Tyr
		165						170						175	

Asp	Gly	Asn	Asn	Lys	Asn	Tyr	Ala	Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr
		180						185					190		

Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Phe	Leu	Gln	Met	Asn	Ser
	195					200						205			

Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Lys	Gly	Ser
	210					215					220				

Gly	Lys	Gly	Cys	Met	Asp	Val	Trp	Gly	Gln	Gly	Thr	Thr	Val	Thr	Val
225					230					235					240

Ser Ser

<210> SEQ ID NO 176

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 176

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

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

<210> SEQ ID NO 177

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 177

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

-continued

115					120					125					
Gln	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	Ser	Leu	Arg	Leu	Ser
130					135					140					
Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly	Met	His	Trp	Val
145					150					155					160
Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Val	Ile	Trp	Tyr
				165					170					175	
Asp	Gly	Asn	Asn	Lys	Asp	Tyr	Arg	Asp	Ser	Val	Thr	Gly	Arg	Phe	Thr
		180						185					190		
Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	Gln	Met	Ser	Ser
	195					200					205				
Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Lys	Gly	Ser
210					215					220					
Gly	Lys	Gly	Cys	Met	Asp	Val	Trp	Gly	Arg	Gly	Thr	Thr	Val	Thr	Val
225					230					235					240
Ser	Ser														

<210> SEQ ID NO 178

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 178

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			
Thr	Val	Ile	Trp	Tyr	Asp	Gly	Asn	Asn	Lys	Asp	Tyr	Ala	Asp	Ser	Val
		50				55					60				
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Ser	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	Lys	Gly	Ser	Gly	Lys	Gly	Cys	Met	Asp	Val	Trp	Gly	Gln	Gly
			100				105						110		
Thr	Thr	Val	Thr	Val	Ser	Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly
		115					120					125			
Ser	Gly	Gly	Gly	Gly	Ser	Glu	Ile	Val	Leu	Thr	Gln	Ser	Pro	Gly	Thr
	130					135					140				
Leu	Ser	Leu	Ser	Pro	Gly	Glu	Arg	Ala	Thr	Leu	Ser	Cys	Arg	Ala	Ser
145					150					155				160	
Gln	Ser	Val	Ser	Tyr	Ser	Phe	Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly
			165						170					175	
Gln	Ala	Pro	Arg	Leu	Leu	Ile	Tyr	Ala	Ala	Ser	Ser	Arg	Ala	Thr	Gly
			180				185						190		
Ile	Pro	Asp	Arg	Phe	Ser	Gly	Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu
	195					200						205			
Thr	Ile	Ser	Arg	Leu	Glu	Pro	Glu	Asp	Phe	Ala	Val	Tyr	Tyr	Cys	Gln
210						215					220				

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His Tyr Gly Ser Ser Ile Thr Phe Gly Pro Gly Thr Lys Val Asp Ile
225 230 235 240

Lys Arg

<210> SEQ ID NO 179

<211> LENGTH: 242

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 179

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 Tyr Ser
20 25 30

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

Ile Tyr Ala 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 His Tyr Gly Ser Ser Ile
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Gly Gly Gly Gly
100 105 110

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gln Val Gln Leu Val
115 120 125

Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser
130 135 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Gly Met His Trp Val
145 150 155 160

Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Thr Val Ile Trp Tyr
165 170 175

Asp Gly Asn Asn Lys Asp Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr
180 185 190

Ile Ser Arg Asp Ser Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser
195 200 205

Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Lys Gly Ser
210 215 220

Gly Lys Gly Cys Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val
225 230 235 240

Ser Ser

<210> SEQ ID NO 180

<211> LENGTH: 246

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 180

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

-continued

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

<210> SEQ ID NO 181

<211> LENGTH: 246

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 181

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 Glu Ser Ile Arg Arg Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Glu Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Ser 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 Ile Asn Pro Pro
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Gly Gly Gly Gly
 100 105 110

-continued

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Glu
 115 120 125

Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser
 130 135 140

Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Asp Met His Trp Val
 145 150 155 160

Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val Ser Val Ile Gly Thr
 165 170 175

Ala Gly Asp Thr Tyr Tyr Pro Asp Ser Val Lys Gly Arg Phe Thr Ile
 180 185 190

Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu
 195 200 205

Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Val Arg Gly Gly Gly Trp
 210 215 220

Asn Tyr Gly Tyr Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Trp Thr
 225 230 235 240

Thr Val Thr Val Ser Ser
 245

<210> SEQ ID NO 182
 <211> LENGTH: 245
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<400> SEQUENCE: 182

Gln Val Gln Leu Glu Gln 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 Phe Ser Gly Asn Thr Asn 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 Glu Tyr Cys Asp Asp Asp Cys Tyr Gly Phe Asp Tyr Trp
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125

Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Val Thr Gln Ser
 130 135 140

Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
 145 150 155 160

Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys
 165 170 175

Pro Gly Lys Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln
 180 185 190

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe
 195 200 205

-continued

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
210 215 220

Cys Leu Gln Tyr Ser Ile Tyr Pro Arg Thr Phe Gly Gln Gly Thr Lys
225 230 235 240

Val Glu Ile Lys Arg
245

<210> SEQ ID NO 183

<211> LENGTH: 245

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 183

Asp Ile Gln Val 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 Tyr Ser Ile Tyr Pro Arg
85 90 95

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

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln Leu Glu
115 120 125

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

Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly Gly Tyr Tyr Trp Ser
145 150 155 160

Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu Trp Ile Gly Tyr Ile
165 170 175

Tyr Phe Ser Gly Asn Thr Asn Tyr Asn Pro Ser Leu Lys Ser Arg Val
180 185 190

Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu Ser
195 200 205

Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu Tyr
210 215 220

Cys Asp Asp Asp Cys Tyr Gly Phe Asp Tyr Trp Gly Gln Gly Thr Leu
225 230 235 240

Val Thr Val Ser Ser
245

<210> SEQ ID NO 184

<211> LENGTH: 245

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

-continued

<400> SEQUENCE: 184

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 Asp Leu Ser Ile Phe Gly Val Val Val Leu Ser Asp Tyr Trp
 100 105 110
 Gly Gln Gly Thr Leu Val Thr Val Ser Ser Gly Gly Gly Gly Ser Gly
 115 120 125
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu Thr Gln Ser
 130 135 140
 Pro Asp Phe Gln Ser Val Thr Pro Lys Glu Lys Val Thr Ile Thr Cys
 145 150 155 160
 Arg Ala Ser Gln Tyr Ile Gly Ser Asn Leu His Trp Tyr Gln Gln Thr
 165 170 175
 Pro Asp Gln Ser Pro Lys Leu Leu Ile Lys Tyr Ala Ser Gln Ser Phe
 180 185 190
 Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
 195 200 205
 Thr Leu Thr Ile Asn Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr
 210 215 220
 Cys His Gln Ser Ser Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys
 225 230 235 240
 Val Glu Ile Lys Arg
 245

<210> SEQ ID NO 185

<211> LENGTH: 245

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 185

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

-continued

Glu	Asp	Ala	Ala	Thr	Tyr	Tyr	Cys	His	Gln	Ser	Ser	Ser	Leu	Pro	Trp
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Gly	Gly	Gly	Gly
			100					105					110		
Ser	Gly	Gly	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Ser	Gln	Val	Gln	Leu	Val
			115				120					125			
Glu	Ser	Gly	Gly	Gly	Val	Val	Gln	Pro	Gly	Arg	Ser	Leu	Arg	Leu	Ser
			130				135					140			
Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	Gly	Met	His	Trp	Val
					150					155					160
Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Val	Ile	Trp	Tyr
				165					170					175	
Asp	Gly	Ser	Asn	Lys	Tyr	Tyr	Ala	Asp	Ser	Val	Lys	Gly	Arg	Phe	Thr
			180					185						190	
Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	Leu	Gln	Met	Asn	Ser
			195				200					205			
Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys	Ala	Arg	Asp	Leu	Ser
			210				215				220				
Ile	Phe	Gly	Val	Val	Val	Leu	Ser	Asp	Tyr	Trp	Gly	Gln	Gly	Thr	Leu
			225			230				235					240
Val	Thr	Val	Ser	Ser											
				245											

<210> SEQ ID NO 186

<211> LENGTH: 981

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 186

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gctagcacca agggcccatc ggtcttcccc ctggcgccct gctccaggag cacctccgag      60
agcacagcgg ccctgggctg cctgggtcaag gactacttcc ccgaaccggg gacgggtgtcg    120
tggaactcag gcgctctgac cagcggcgctg cacaccttcc cagctgtcct acagtccctca    180
ggactctact ccctcagcag cgtggtgacc gtgccctcca gcaacttcgg caccagacc      240
tacacctgca acgtagatca caagcccagc aacaccaagg tggacaagac agttgagcgc      300
aaatgttgtg tcgagtgcgc accgtgcccc gcaccacctg tggcaggacc gtcagtcttc      360
cttttcccc caaaacccaa ggacaccctc atgatctccc ggaccctga ggtcacgtgc      420
gtggtggtgg acgtgagcca cgaagacccc gaggtccagt tcaactggta cgtggacggc      480
gtggagggtg ataatgccaa gacaaagcca cgggaggagc agttcaacag caggttccgt      540
gtggtcagcg tcctcaccgt tgtgcaccag gactggctga acggcaagga gtacaagtgc      600
aaggctctca acaaaggcct ccagccccc atcgagaaaa ccatctccaa aaccaaaggg      660
cagccccgag aaccacaggt gtacaccctg ccccatccc gggaggagat gaccaagaac      720
caggtcagcc tgacctgctt ggtcaaaggc ttctacccca gcgacatcgc cgtggagtgg      780
gagagcaatg ggcagccgga gaacaactac aagaccacac ctcccatgct ggactccgac      840
ggctccttct tcctctacag caagctcacc gtggacaaga gcagggtggc gcagggggaa      900
gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca gaagagcctc      960
tccctgtctc cgggtaaatg a

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-continued

<210> SEQ ID NO 187
<211> LENGTH: 326
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 187

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
1 5 10 15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
20 25 30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
35 40 45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
50 55 60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Asn Phe Gly Thr Gln Thr
65 70 75 80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
85 90 95
Thr Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
100 105 110
Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
115 120 125
Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
130 135 140
Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly
145 150 155 160
Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn
165 170 175
Ser Thr Phe Arg Val Val Ser Val Leu Thr Val Val His Gln Asp Trp
180 185 190
Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro
195 200 205
Ala Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu
210 215 220
Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
225 230 235 240
Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
245 250 255
Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
260 265 270
Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
275 280 285
Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
290 295 300
Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
305 310 315 320
Ser Leu Ser Pro Gly Lys
325

<210> SEQ ID NO 188

-continued

<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 188

cgtaagggtgg ctgcaccatc tgtcttcac ttcccggccat ctgatgagca gttgaaatct 60
ggaactgcct ctgttggtg cctgctgaat aacttctatc ccagagaggc caaagtacag 120
tggaagggtgg ataacgccct ccaatcgggt aactcccagg agagtgtcac agagcaggac 180
agcaaggaca gcacctacag cctcagcagc accctgacgc tgagcaaagc agactacgag 240
aaacacaaag tctacgctg cgaagtcacc catcagggcc tgagctcgcc cgtcacaaag 300
agcttcaaca ggggagagtg tttag 324

<210> SEQ ID NO 189
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 189

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

<210> SEQ ID NO 190
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 190

ggccaaccga aagcggcgcc ctcggtcact ctgttcccgc cctcctctga ggagcttcaa 60
gccaacaagg ccactgtgt gtgtctcata agtgacttct acccgggagc cgtgacagtg 120
gcctggaagg cagatagcag ccccgtaag gcgggagtgg agaccaccac accctccaaa 180
caaagcaaca acaagtacgc ggccagcagc tatctgagcc tgacgcctga gcagtggag 240
tcccacagaa gctacagctg ccaggtcacg catgaaggga gcaccgtgga gaagacagtg 300
gccctacag aatgttcata g 321

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<210> SEQ ID NO 191
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 191

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

Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp
 20             25             30

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

Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn
 50             55             60

Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys
 65             70             75             80

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

Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
 100             105

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<210> SEQ ID NO 192
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 192

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1             5             10             15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35             40             45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
 65             70             75             80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85             90             95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
 100            105            110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
 115            120            125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
 130            135            140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
 145            150            155            160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
 165            170            175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
 180            185            190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
 195            200            205

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-continued

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
 210 215 220
 Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
 225 230 235 240
 Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
 245 250 255
 Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
 260 265 270
 Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
 275 280 285
 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
 290 295 300
 Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
 305 310 315 320
 Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
 325 330

<210> SEQ ID NO 193

<211> LENGTH: 326

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 193

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

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<210> SEQ ID NO 194
<211> LENGTH: 377
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 194
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Ala 1	Ser	Thr	Lys	Gly 5	Pro	Ser	Val	Phe	Pro 10	Leu	Ala	Pro	Cys	Ser 15	Arg
Ser	Thr	Ser	Gly 20	Gly	Thr	Ala	Ala	Leu 25	Gly	Cys	Leu	Val	Lys 30	Asp	Tyr
Phe	Pro	Glu 35	Pro	Val	Thr	Val	Ser 40	Trp	Asn	Ser	Gly	Ala 45	Leu	Thr	Ser
Gly	Val 50	His	Thr	Phe	Pro	Ala 55	Val	Leu	Gln	Ser	Ser 60	Gly	Leu	Tyr	Ser
Leu 65	Ser	Ser	Val	Val	Thr 70	Val	Pro	Ser	Ser	Ser 75	Leu	Gly	Thr	Gln	Thr 80
Tyr	Thr	Cys	Asn 85	Val	Asn	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Arg	Val	Glu	Leu 100	Lys	Thr	Pro	Leu	Gly 105	Asp	Thr	Thr	His	Thr 110	Cys	Pro
Arg	Cys	Pro 115	Glu	Pro	Lys	Ser	Cys 120	Asp	Thr	Pro	Pro	Pro 125	Cys	Pro	Arg
Cys	Pro 130	Glu	Pro	Lys	Ser	Cys 135	Asp	Thr	Pro	Pro	Pro 140	Cys	Pro	Arg	Cys
Pro 145	Glu	Pro	Lys	Ser	Cys 150	Asp	Thr	Pro	Pro	Pro 155	Cys	Pro	Arg	Cys	Pro 160
Ala	Pro	Glu	Leu	Leu 165	Gly	Gly	Pro	Ser	Val 170	Phe	Leu	Phe	Pro	Pro 175	Lys
Pro	Lys	Asp	Thr 180	Leu	Met	Ile	Ser	Arg 185	Thr	Pro	Glu	Val	Thr 190	Cys	Val
Val	Val	Asp 195	Val	Ser	His	Glu	Asp 200	Pro	Glu	Val	Gln	Phe 205	Lys	Trp	Tyr
Val 210	Asp	Gly	Val	Glu	Val	His 215	Asn	Ala	Lys	Thr	Lys 220	Pro	Arg	Glu	Glu
Gln 225	Tyr	Asn	Ser	Thr	Phe 230	Arg	Val	Val	Ser	Val 235	Leu	Thr	Val	Leu	His
Gln	Asp	Trp	Leu	Asn 245	Gly	Lys	Glu	Tyr	Lys 250	Cys	Lys	Val	Ser	Asn 255	Lys
Ala	Leu	Pro	Ala 260	Pro	Ile	Glu	Lys	Thr 265	Ile	Ser	Lys	Thr	Lys 270	Gly	Gln

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Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
 275 280 285

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
 290 295 300

Ser Asp Ile Ala Val Glu Trp Glu Ser Ser Gly Gln Pro Glu Asn Asn
 305 310 315 320

Tyr Asn Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe Leu
 325 330 335

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Ile
 340 345 350

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln
 355 360 365

Lys Ser Leu Ser Leu Ser Pro Gly Lys
 370 375

<210> SEQ ID NO 195

<211> LENGTH: 327

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 195

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1 5 10 15

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

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
 35 40 45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
 65 70 75 80

Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
 85 90 95

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
 100 105 110

Glu Phe Glu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
 115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
 130 135 140

Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
 145 150 155 160

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
 165 170 175

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
 180 185 190

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
 195 200 205

Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
 210 215 220

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
 225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
 245 250 255

-continued

Ile	Ala	Val	Glu	Trp	Glu	Ser	Asn	Gly	Gln	Pro	Glu	Asn	Asn	Tyr	Lys
			260					265						270	
Thr	Thr	Pro	Pro	Val	Leu	Asp	Ser	Asp	Gly	Ser	Phe	Phe	Leu	Tyr	Ser
		275					280					285			
Arg	Leu	Thr	Val	Asp	Lys	Ser	Arg	Trp	Gln	Glu	Gly	Asn	Val	Phe	Ser
	290				295						300				
Cys	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His	Tyr	Thr	Gln	Lys	Ser
305					310				315					320	
Leu	Ser	Leu	Ser	Leu	Gly	Lys									
				325											

What is claimed is:

1. An isolated anti-mesothelin human antibody or antigen binding protein or fragment thereof, wherein said antibody has at least one of the following properties:

- binds to a different epitope than the MORAb-009 antibody;
- competes for binding with Ab237;
- specifically binds to human, cyno, rat and murine mesothelin;
- does not internalize upon binding to mesothelin;
- when bound to mesothelin, does not inhibit CA125 interaction with mesothelin;
- has a binding affinity K_D of at least 5.0 pM against human mesothelin;
- has enhanced effector function;
- binds to membrane-bound mesothelin preferentially over soluble mesothelin;
- reduces the growth of mesothelin expressing tumor cells in vivo.

2. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least two of the listed properties.

3. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least three of the listed properties.

4. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least four of the listed properties.

5. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least five of the listed properties.

6. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least six of the listed properties.

7. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least seven of the listed properties.

8. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits at least eight of the listed properties.

9. The antibody or antigen binding protein of claim 1, wherein said antibody or antigen binding protein exhibits nine of the listed properties.

10. An isolated antibody or antigen binding protein or fragment thereof, wherein the antibody or antigen binding protein or fragment thereof specifically binds to mesothelin and comprises 3 heavy chain CDRs and 3 light chain CDRs with sequences selected from the group consisting of:

- SEQ ID NOs: 45, 46, 47 of the heavy chain and SEQ ID NOs: 9, 10, 11 of the light chain;
- SEQ ID NOs: 48, 49, 50 of the heavy chain and SEQ ID NOs: 12, 13, 14 of the light chain;
- SEQ ID NOs: 51, 52, 53 of the heavy chain and SEQ ID NOs: 15, 16, 17 of the light chain;
- SEQ ID NOs: 51, 52, 53 of the heavy chain and SEQ ID NOs: 18, 19, of the light chain;
- SEQ ID NOs: 54, 55, 56 of the heavy chain and SEQ ID NOs: 21, 22, 23 of the light chain;
- SEQ ID NOs: 57, 58, 59 of the heavy chain and SEQ ID NOs: 24, 25, 26 of the light chain;
- SEQ ID NOs: 60, 61, 62 of the heavy chain and SEQ ID NOs: 27, 28, 29 of the light chain;
- SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 30, 31, 32 of the light chain;
- SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 33, 34, of the light chain; and
- SEQ ID NOs: 63, 64, 65 of the heavy chain and SEQ ID NOs: 36, 37, 38 of the light chain

wherein each of said CDRs are identical to or comprise 1, 2, or 3 amino acid residue substitutions relative to their specified sequence.

11. An isolated antibody or antigen binding protein or fragment thereof, wherein the antibody or antigen binding protein or fragment thereof specifically binds mesothelin and comprises a heavy chain variable domain and a light chain variable domain selected from the group consisting of:

- a heavy chain variable domain comprising SEQ ID NO: 86 and a light chain variable domain comprising SEQ ID NO: 72;
- a heavy chain variable domain comprising SEQ ID NO: 87 and a light chain variable domain comprising SEQ ID NO: 73;
- a heavy chain variable domain comprising SEQ ID NO: 88 and a light chain variable domain comprising SEQ ID NO: 74;
- a heavy chain variable domain comprising SEQ ID NO: 88 and a light chain variable domain comprising SEQ ID NO: 75;
- a heavy chain variable domain comprising SEQ ID NO: 89 and a light chain variable domain comprising SEQ ID NO: 76;
- a heavy chain variable domain comprising SEQ ID NO: 90 and a light chain variable domain comprising SEQ ID NO: 77;

- g. a heavy chain variable domain comprising SEQ ID NO: 91 and a light chain variable domain comprising SEQ ID NO: 78;
- h. a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 79;
- i. a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 80;
- j. a heavy chain variable domain comprising SEQ ID NO: 92 and a light chain variable domain comprising SEQ ID NO: 81;
- k. a heavy chain variable domain comprising SEQ ID NO: 93 and a light chain variable domain comprising SEQ ID NO: 82;
- l. a heavy chain variable domain comprising SEQ ID NO: 94 and a light chain variable domain comprising SEQ ID NO: 83;

wherein each of said heavy chain variable domain and light chain variable domain have at least 90% identity relative to their specified sequence.

12. The isolated antibody or antigen binding protein or fragment thereof of claim **11**, wherein said heavy chain variable domain and light chain variable domain have at least 95% identity relative to their specified sequence.

13. The isolated antibody or antigen binding protein or fragment thereof of claim **11**, wherein said heavy chain variable domain and light chain variable domain are 100% identical to their specified sequence.

14. The antibody of claim **1**, wherein said antibody or antigen binding protein or fragment thereof is a bispecific antibody and binds an additional target other than MSLN.

15. The antibody or antigen binding protein or fragment thereof of claim **14**, wherein said additional target is CD3.

16. The antibody or antigen binding protein or fragment thereof of claim **15**, wherein said CD3 is human and/or cynomolgus CD3.

17. The antibody or antigen binding protein or fragment thereof of claim **15**, wherein said CD3 is human and/or mouse and/or rat and/or cynomolgus CD3.

18. The antibody or antigen binding protein or fragment thereof of claim **15**, wherein said antibody further comprises a variable heavy chain region (VH) as set forth in SEQ ID NO: 118 and a variable light chain region (VL) as set forth in SEQ ID NO: 120.

19. The antibody or antigen binding protein or fragment thereof of claim **15**, wherein said antibody further comprises

- a. a VH CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 115;
- b. a VH CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 116;
- c. a VH CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 117;
- d. a VL CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 112;
- e. a VL CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 113; and

- f. a VL CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 114.

20. The antibody or antigen binding protein or fragment thereof of claim **15**, wherein said antibody further comprises a VH and VL set forth in SEQ ID NO: 122.

21. A bispecific single chain antibody, said bispecific single chain antibody comprising binding domains specific for CD3 and MSLN, wherein the corresponding variable heavy chain regions (V_H) and the corresponding variable light chain regions (V_L) regions are arranged, from N-terminus to C-terminus, in the order, $V_H(\text{MSLN})-V_L(\text{MSLN})-V_H(\text{CD3})-V_L(\text{CD3})$, or $V_H(\text{CD3})-V_L(\text{CD3})-V_H(\text{MSLN})-V_L(\text{MSLN})$, or $V_L(\text{MSLN})-V_H(\text{MSLN})-V_H(\text{CD3})-V_L(\text{CD3})$, or $V_H(\text{CD3})-V_L(\text{CD3})-V_L(\text{MSLN})-V_H(\text{MSLN})$, or $VL(\text{MSLN})-V_H(\text{MSLN})-V_L(\text{CD3})-V_H(\text{CD3})$, or $V_L(\text{CD3})-V_H(\text{CD3})-V_L(\text{MSLN})-V_H(\text{MSLN})$, or $V_H(\text{MSLN})-V_L(\text{MSLN})-V_L(\text{CD3})-V_H(\text{CD3})$, or $V_L(\text{CD3})-V_H(\text{CD3})-V_H(\text{MSLN})-V_L(\text{MSLN})$.

22. The bispecific single chain antibody of claim **21**, wherein said CD3 is human and/or cynomolgus and/or mouse and/or rat CD3 and said MSLN is human and/or cynomolgus and/or mouse and/or rat MSLN.

23. The bispecific single chain antibody of claim **21**, wherein said $V_H(\text{MSLN})$ are set forth in SEQ ID NOs: 86-94, said $V_L(\text{MSLN})$ are set forth in SEQ ID NOs: 72-83, said VH (CD3) are set forth in SEQ ID NO: 118, and said VL (CD3) are set forth in SEQ ID NO: 120.

24. The bispecific single chain antibody of claim **21**, wherein said VH (MSLN) comprises CDRs 1-3 having the sequences set forth in SEQ ID NOs: 45, 46, and 47, respectively, said VL (MSLN) comprises CDRs 1-3 having the sequences set forth in SEQ ID NOs: 9, 10, and 11, respectively, said VH (CD3) comprises CDRs 1-3 having the sequences set forth in SEQ ID NOs: 115, 116, and 117, respectively, and said VL(CD3) comprises CDRs 1-3 having the sequences set forth in SEQ ID NOs: 112, 113, and 114, respectively.

25. A bispecific single chain antibody that comprises a first VH as set forth in SEQ ID NO: 86, a first VL as set forth in SEQ ID NO: 72, a second VH as set forth in SEQ ID NO: 118, and a second VL as set forth in SEQ ID NO: 120.

26. A bispecific single chain antibody that comprises:

- a. a first VH CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 45;
- b. a first VH CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 46;
- c. a first VH CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 47;
- d. a first VL CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 9;
- e. a first VL CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 10;
- f. a first VL CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 11;
- g. a second VH CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 115;

- h. a second VH CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 116;
 - i. a second VH CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 117;
 - j. a second VL CDR1 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 112;
 - k. a second VL CDR2 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 113; and
 - l. a second VL CDR3 having an amino acid sequence identical to or comprising 1, 2, or 3 amino acid residue substitutions relative to SEQ ID NO: 114.
- 27.** A bispecific single chain antibody having the sequence is set forth in SEQ ID NO: 127 or SEQ ID NO: 129.
- 28.** A bispecific single chain antibody comprising any of SEQ ID NOs: 158-185 and further comprising SEQ ID NO: 122.
- 29.** An isolated antibody or antigen binding protein or fragment thereof which competes for binding with the antibody of claim 1.
- 30.** The antibody or antigen binding protein or fragment thereof of claim 1, wherein the antibody further comprises and IgG heavy chain constant domain and an IgG light chain constant domain.
- 31.** The antibody or antigen binding protein or fragment thereof of claim 1, wherein the antibody is a monoclonal antibody.
- 32.** The antibody or antigen binding protein or fragment thereof of claim 1, wherein the antibody is a chimeric antibody, a humanized antibody, or a fully human antibody.
- 33.** A sterile composition comprising the isolated antibody or or antigen binding protein or fragment thereof of any one of claim 1.
- 34.** The composition of claim 33 further comprising a pharmaceutically acceptable carrier.
- 35.** An isolated nucleic acid encoding the antibody or antigen binding protein or fragment thereof of claims 1.
- 36.** A vector comprising the nucleic acid of claim 35.
- 37.** A host cell comprising the nucleic acid of claim 35.
- 38.** A host cell comprising the vector of claim 36.
- 39.** A method for producing an antibody or antigen binding protein or fragment thereof comprising culturing the host cell of claim 37 under suitable conditions and recovering said antibody.
- 40.** A method for producing an antibody or antigen binding protein or fragment thereof comprising culturing the host cell of claim 38 under suitable conditions and recovering said antibody.
- 41.** A method of inhibiting or reducing the growth of mesothelin expressing tumor cells in an animal, comprising administering to said animal a therapeutically effective dose of the antibody or antigen binding protein or fragment thereof of claim 1.
- 42.** A method of treating cancer in a subject in need thereof, comprising administering to said subject a therapeutically effective dose of the antibody or antigen binding protein or fragment thereof of claim 1.
- 43.** The method of claim 41, wherein said animal is human.
- 44.** A method of determining if a subject has mesothelin expressing tumor cells, comprising:
- a. contacting a tumor sample from the subject with the antibody or antigen binding protein or fragment thereof of claim 1; and
 - b. detecting binding of the antibody or antigen binding protein or fragment thereof to the sample, wherein an increase in binding of the antibody or antigen binding protein or fragment thereof to the sample as compared to binding of the antibody or antigen binding protein or fragment thereof to a control sample identifies the subject as having mesothelin expressing tumor cells.
- 45.** The method of claim 44, wherein the isolated human monoclonal antibody or antigen binding protein or fragment thereof is directly labeled.

* * * * *