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(54) **PLECTIN-1 BINDING ANTIBODIES AND USES THEREOF**

(71) Applicant: **ITI HEALTH, INC.**, Crozet, VA (US)

(72) Inventors: **Kimberly A. Kelly**, Goochland, VA (US); **Julien Dimastromatteo**, Charlottesville, VA (US)

(73) Assignee: **iTi Health, Inc. d/b/a ZielBio**, Charlottesville, VA (US)

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

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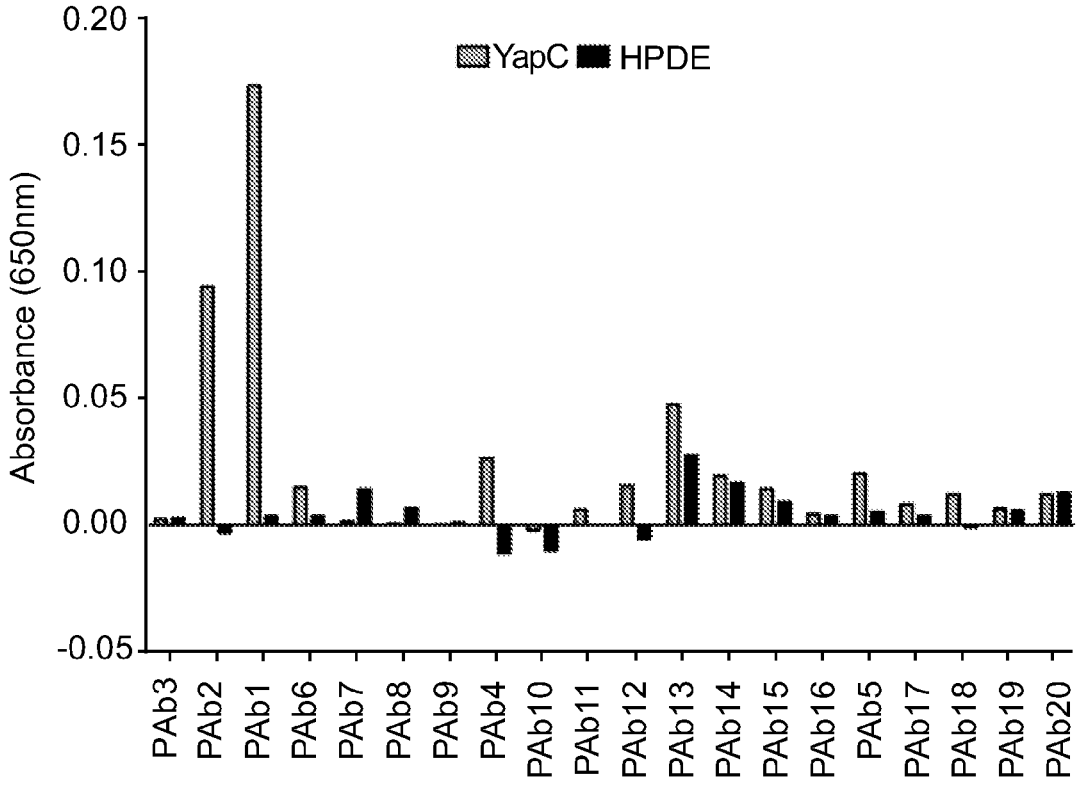
(57) **ABSTRACT**

Aspects of the disclosure provide compositions and methods for treating cancer characterized by surface expression of plectin-1. In some embodiments, the disclosure provides anti-plectin-1 antibodies. In some embodiments, the anti-plectin-1 antibodies are conjugated to a targeted moiety (e.g., a therapeutic moiety or a detectable label).

Specification includes a Sequence Listing.



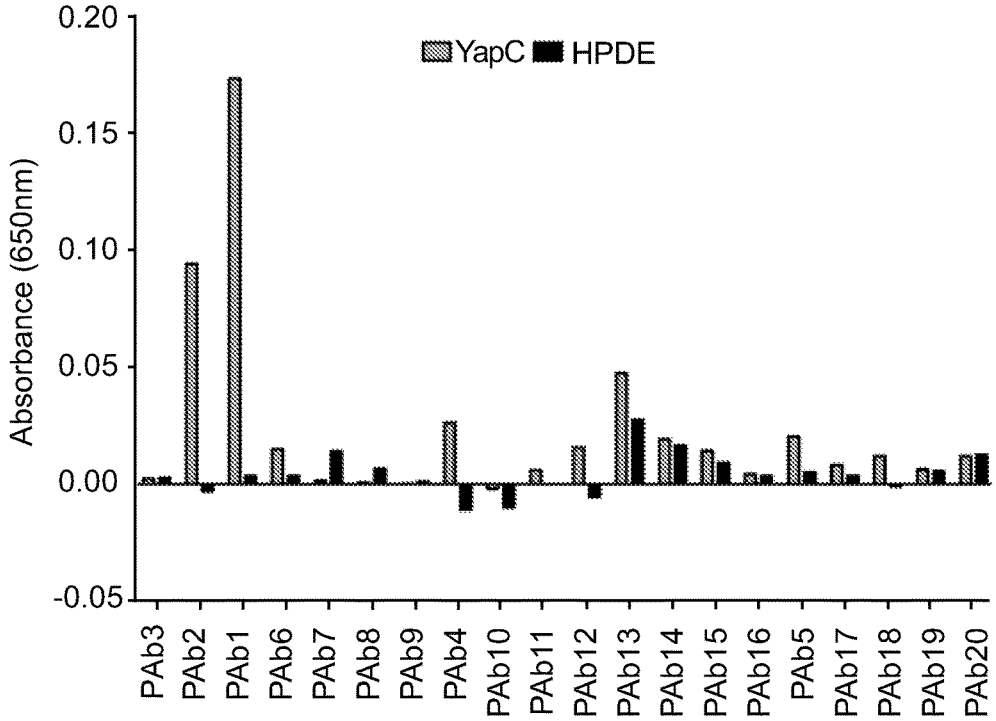

YapC
HPDE
Absorbance (650nm)
0.20
0.15
0.10
0.05
0.00
-0.05
PAb3
PAb2
PAb1
PAb6
PAb7
PAb8
PAb9
PAb4
PAb10
PAb11
PAb12
PAb13
PAb14
PAb15
PAb16
PAb5
PAb17
PAb18
PAb19
PAb20

FIG. 1

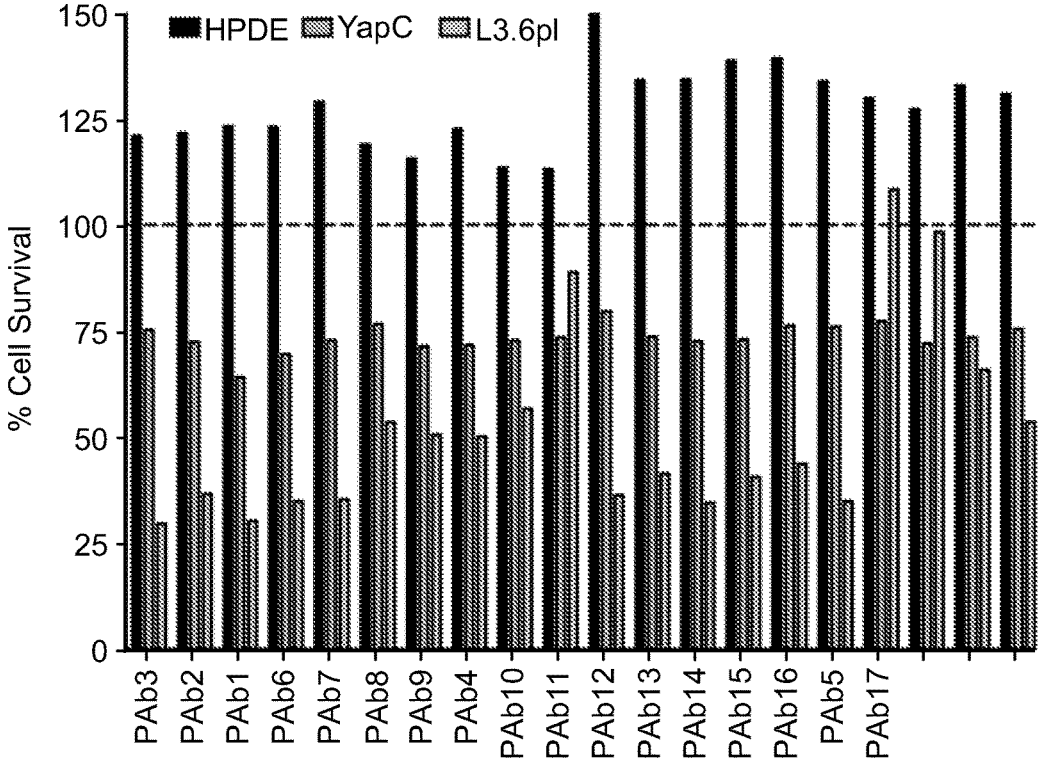

HPDE
YapC
L3.6pl
% Cell Survival
150
125
100
75
50
25
0
PAb3
PAb2
PAb1
PAb6
PAb7
PAb8
PAb9
PAb4
PAb10
PAb11
PAb12
PAb13
PAb14
PAb15
PAb16
PAb5
PAb17

FIG. 2

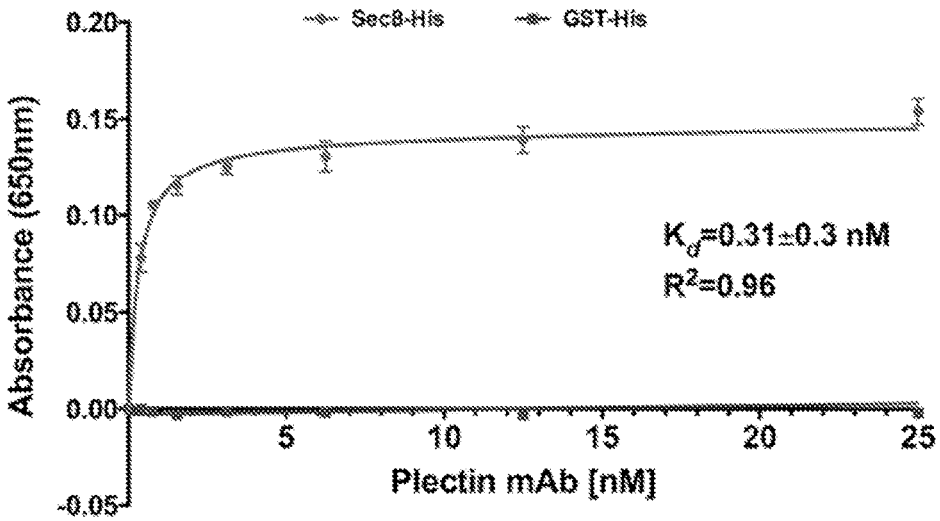

Sec8-His
GST-His
0.20
0.15
0.10
0.05
0.00
-0.05
Absorbance (650nm)
K_d=0.31±0.3 nM
R^2=0.96
5
10
15
20
25
Plectin mAb [nM]

FIG. 3A

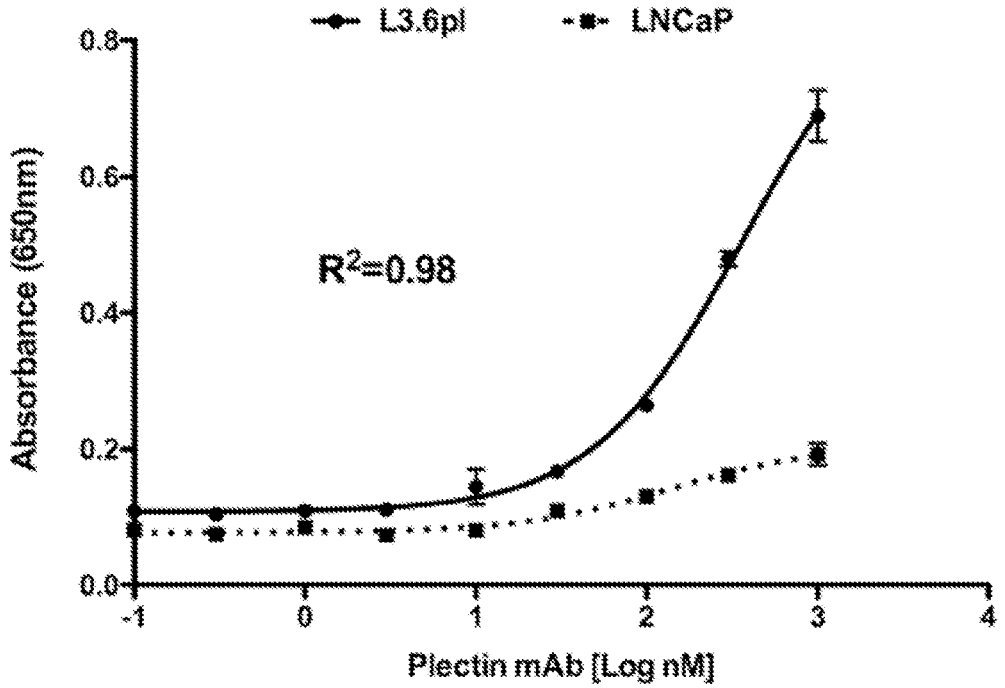

L3.6pl
LNCaP
0.8
0.6
0.4
0.2
0.0
Absorbance (650nm)
R^2=0.98
-1
0
1
2
3
4
Plectin mAb [Log nM]

FIG. 3B

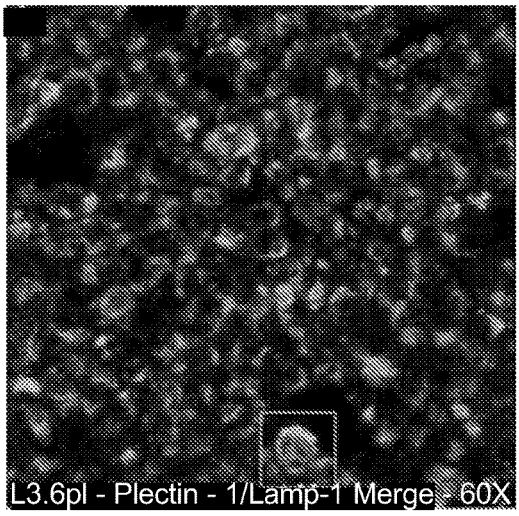


FIG. 4A

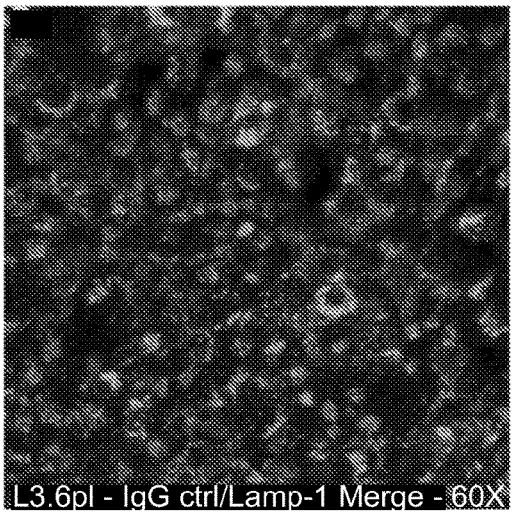


FIG. 4B

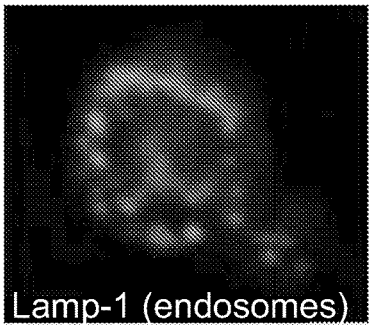


FIG. 4C

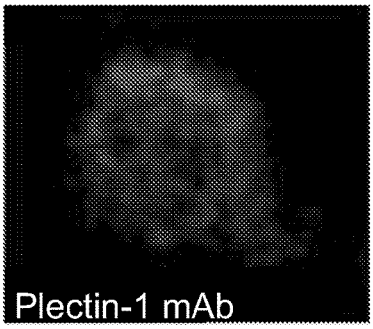


FIG. 4D

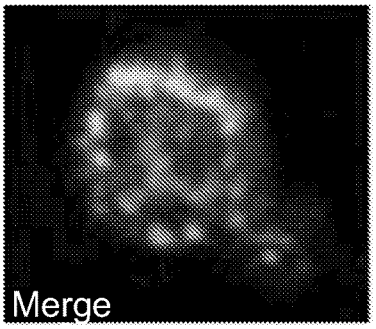


FIG. 4E

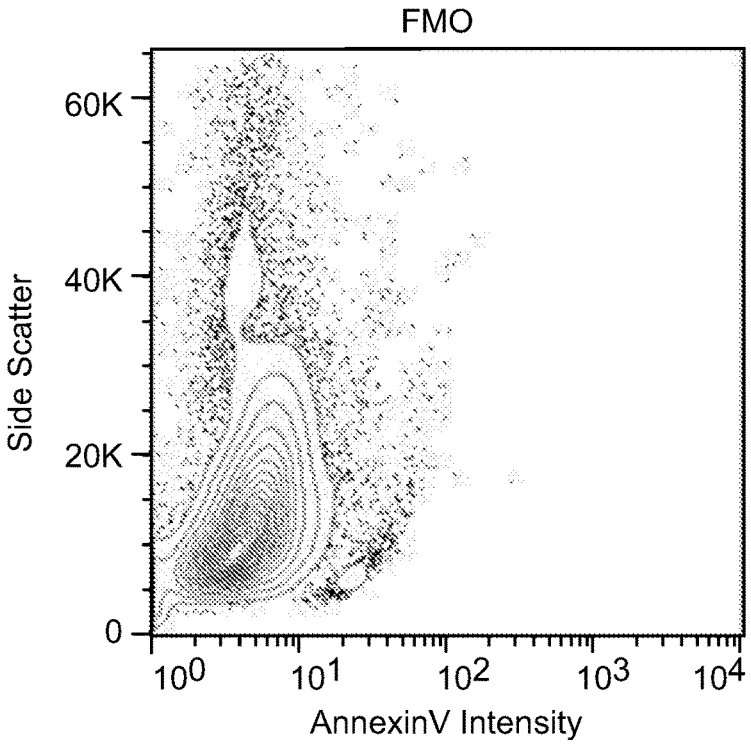

FMO
60K
40K
20K
0
Side Scatter
10^0
10^1
10^2
10^3
10^4
AnnexinV Intensity

FIG. 5A

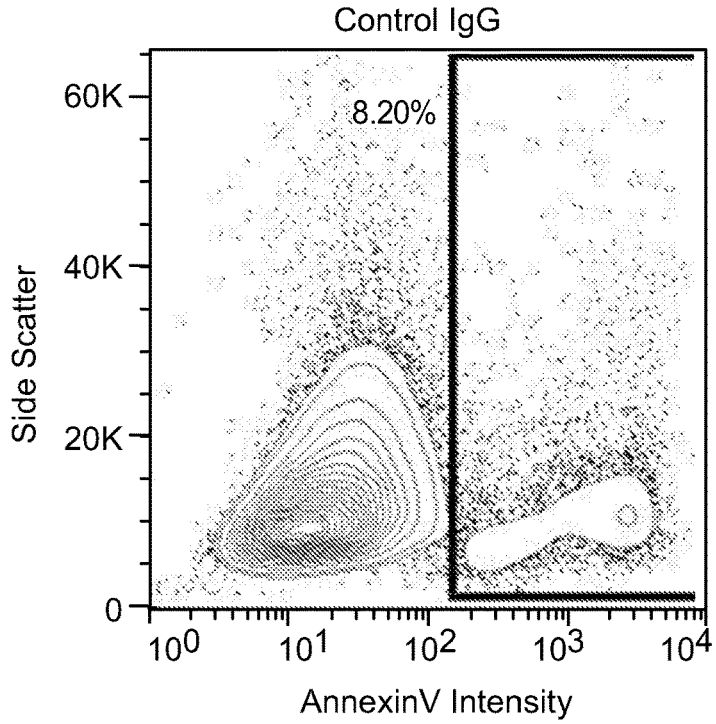

Control IgG
8.20%
60K
40K
20K
0
Side Scatter
10^0
10^1
10^2
10^3
10^4
AnnexinV Intensity

FIG. 5B

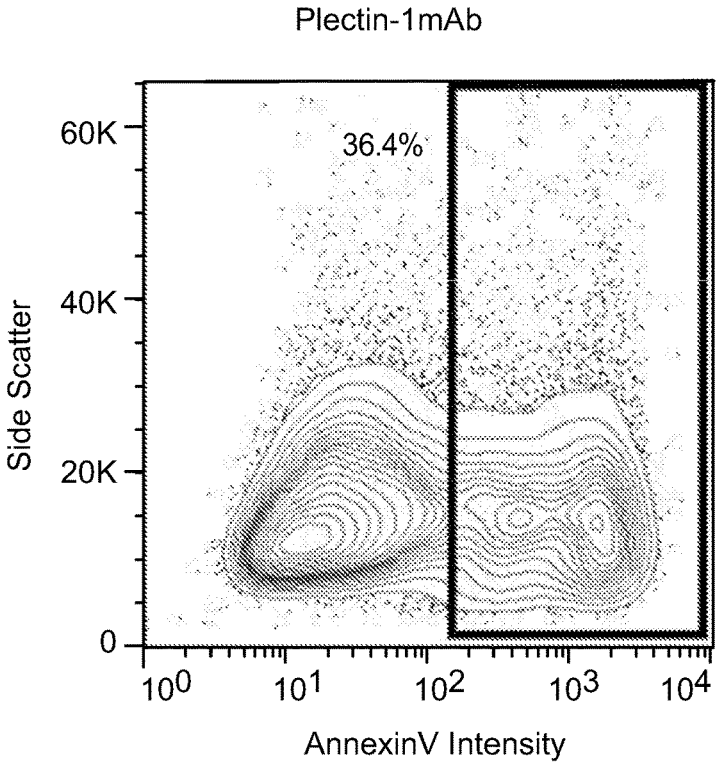

Plectin-1mAb
36.4%
60K
40K
20K
0
Side Scatter
10^0
10^1
10^2
10^3
10^4
AnnexinV Intensity

FIG. 5C

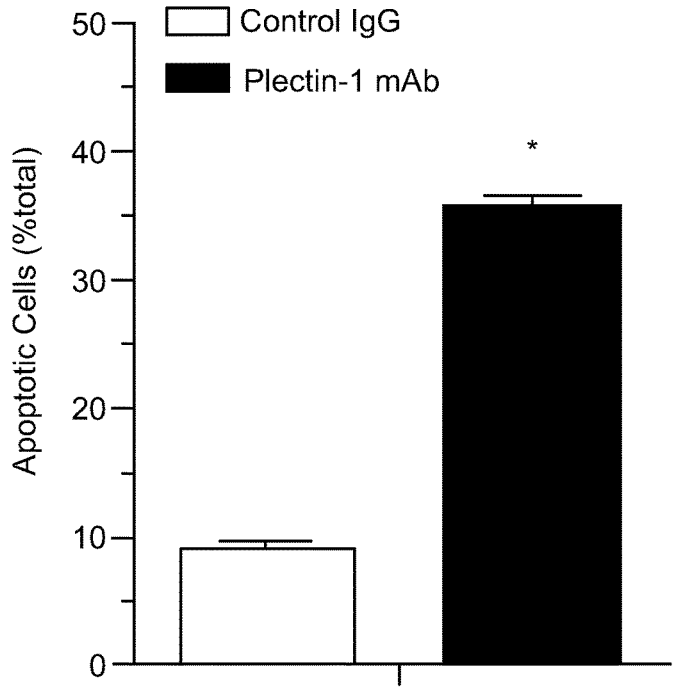

Control IgG
Plectin-1 mAb
*
50
40
30
20
10
0
Apoptotic Cells (%total)

FIG. 5D

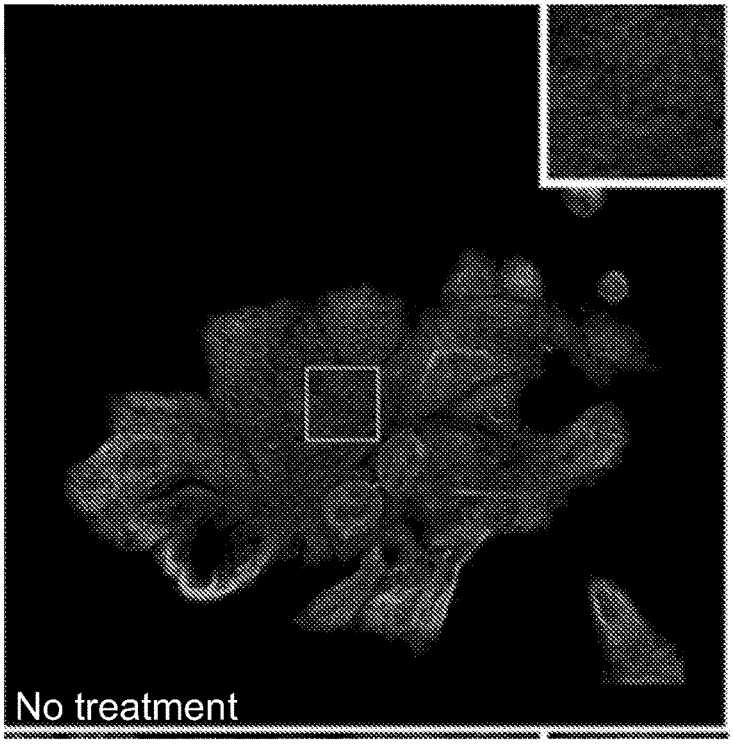


FIG. 6A

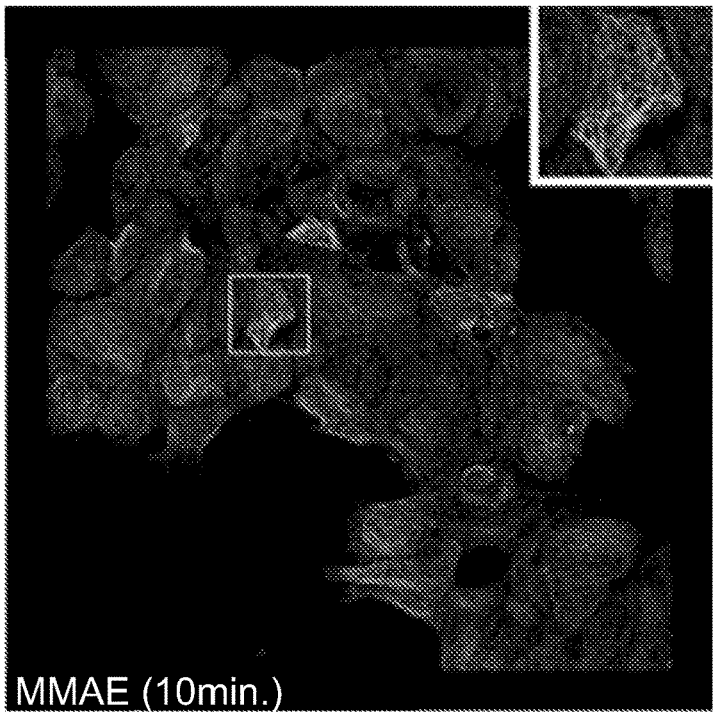


FIG. 6B

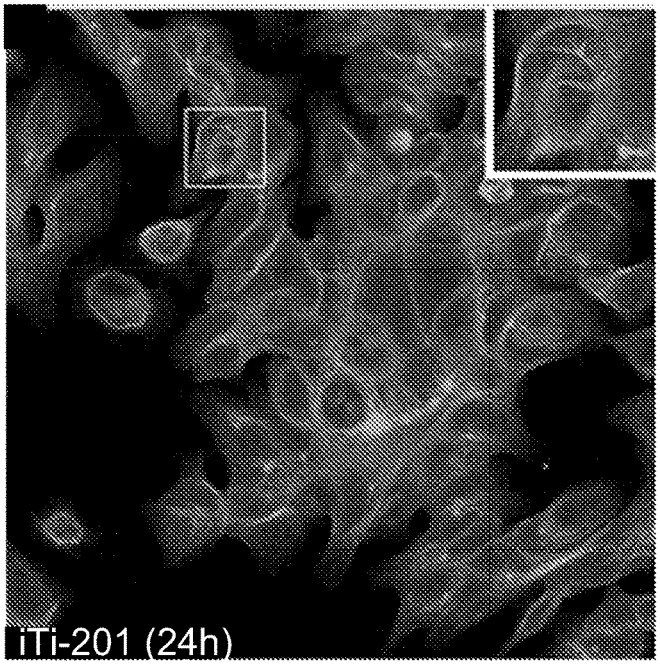

iTi-201 (24h)

FIG. 6C

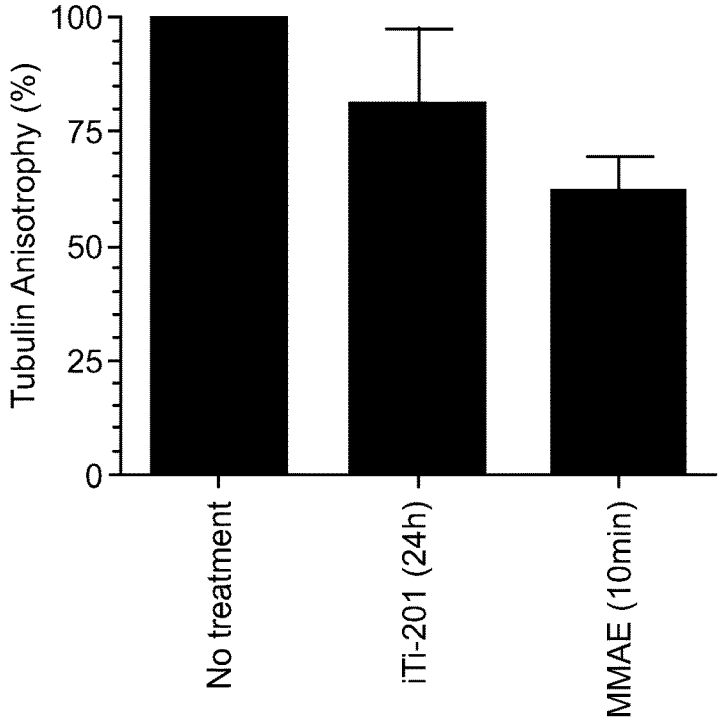

Tubulin Anisotrophy (%)
100
75
50
25
0
No treatment
iTi-201 (24h)
MMAE (10min)

FIG. 6D

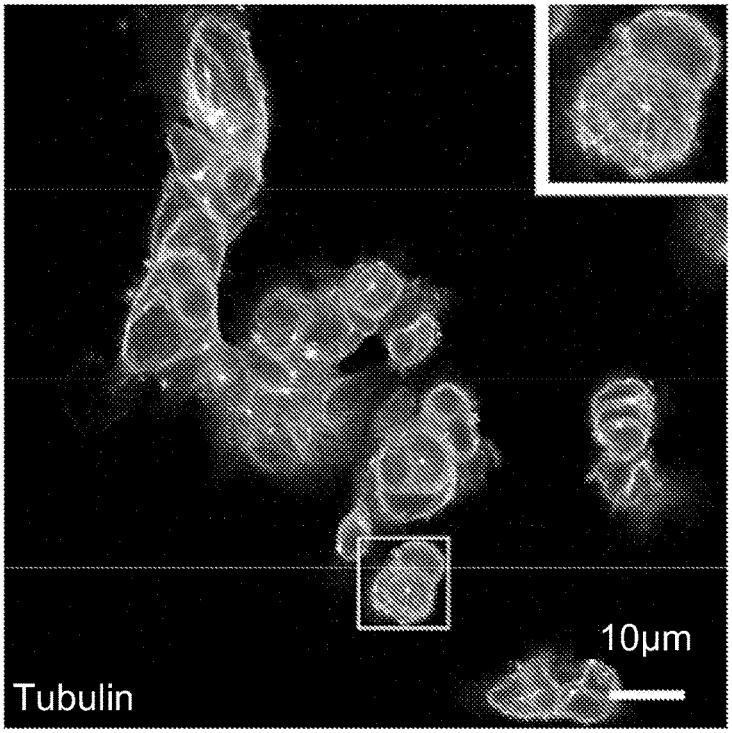


FIG. 7A

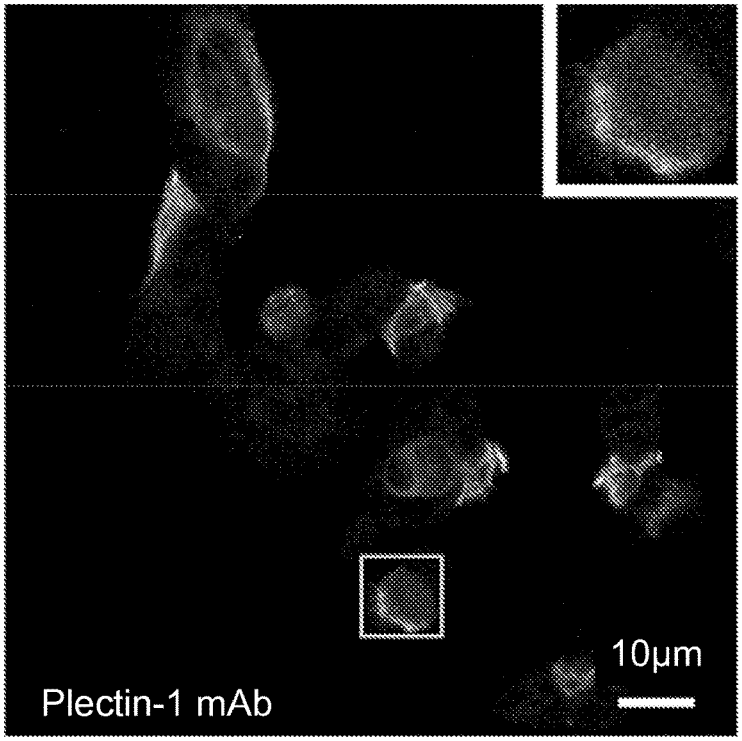


FIG. 7B

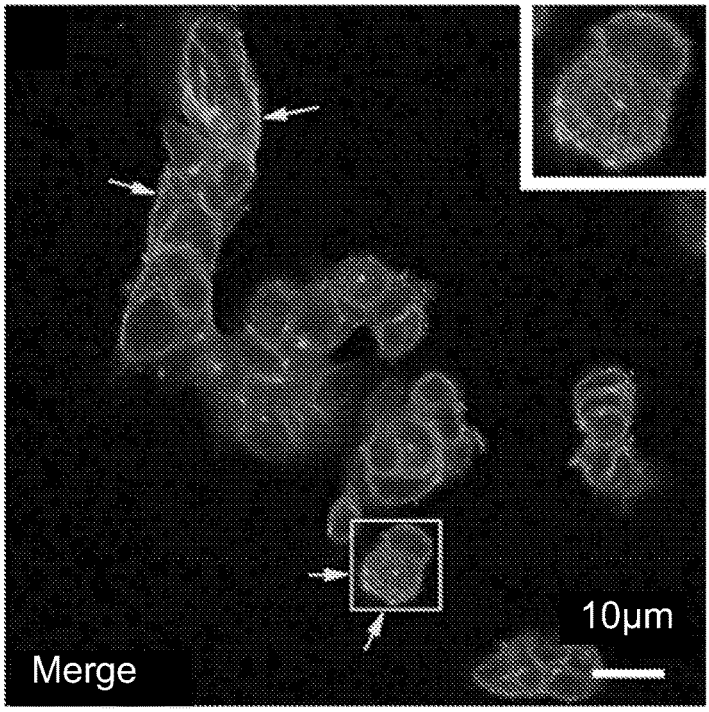

10μm
Merge

FIG. 7C

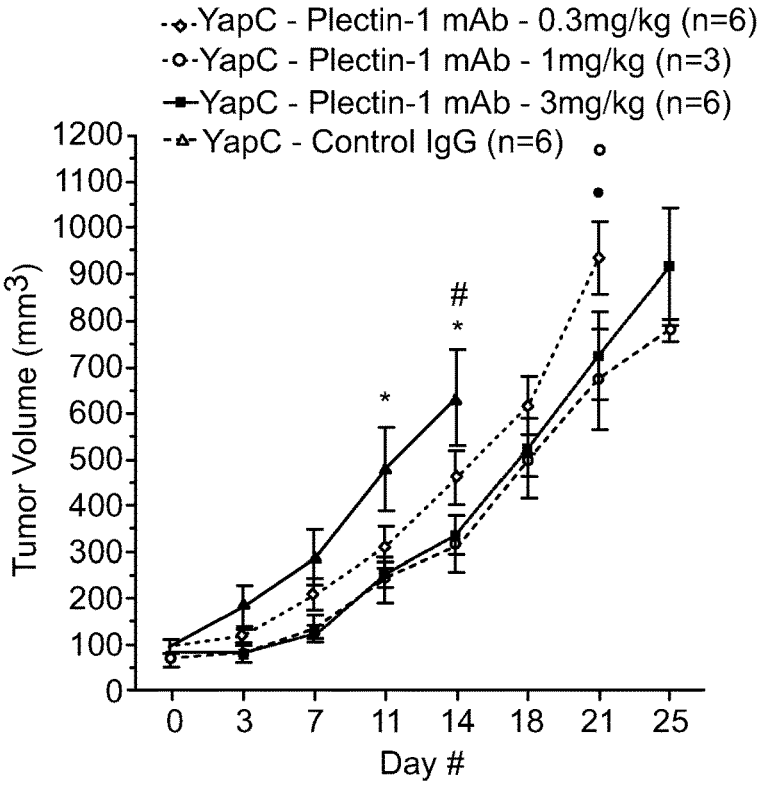

YapC - Plectin-1 mAb - 0.3mg/kg (n=6)
YapC - Plectin-1 mAb - 1mg/kg (n=3)
YapC - Plectin-1 mAb - 3mg/kg (n=6)
YapC - Control IgG (n=6)
Tumor Volume (mm3)
Day #
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
0
3
7
11
14
18
21
25
*
*
#

FIG. 8A

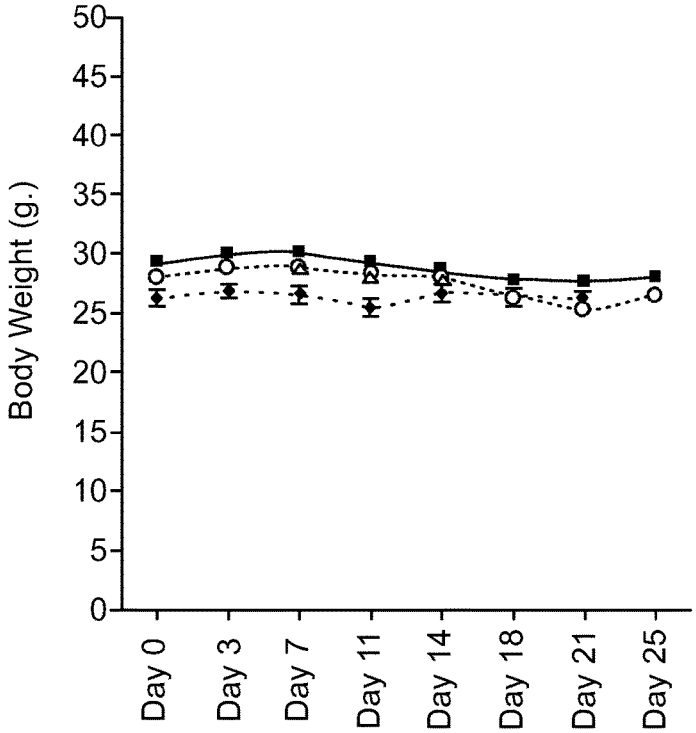


FIG. 8B

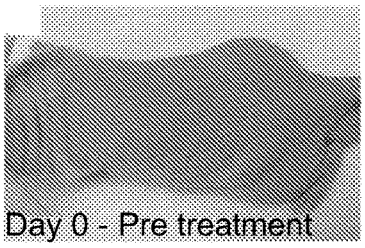


FIG. 8C

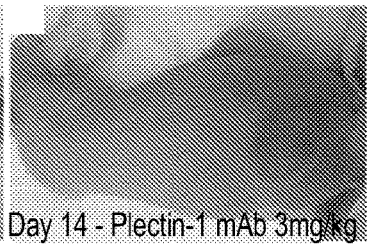


FIG. 8D

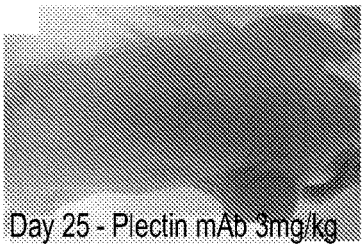


FIG. 8E

PLECTIN-1 BINDING ANTIBODIES AND USES THEREOF

RELATED APPLICATIONS

[0001] This Application claims the benefit of the filing date under 35 U.S.C. § 119(e) of U.S. provisional Application Ser. No. 62/320,117, filed Apr. 8, 2016, entitled "PLECTIN-1 BINDING ANTIBODIES AND USES THEREOF", the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] Pancreatic ductal adenocarcinoma (PDAC) is the 4th leading cause of cancer death in the United States showing a rapid clinical course leading to death. Once diagnosed, PDAC has a median survival of 6 months and a 5-year survival rate of only 3 percent (Li et al., Lancet 363:1049-1057 (2004)).

[0003] As chemotherapy and radiotherapy have only modest benefits, and surgery is only possible in 20% of patients, early detection that allows surgical resection offers the best hope for longer survival (Yeo et al., Ann Surg 222:580-588 (1995); discussion 588-592). Indeed, the detection of PDAC or high-grade precursors in high-risk patient groups (e.g., hereditary cancer syndromes, chronic pancreatitis, and new-onset diabetes) represents a critical unmet need in the cancer diagnostic portfolio (Brentnall et al., Ann. Intern. Med. 131:247-255 (1999); Canto et al., Clin. Gastroenterol. Hepatol. 2:606-621 (2004)).

[0004] Serum CA-19-9 is the clinically used biomarker; however, it lacks the sensitivity needed to detect early-stage PDAC (Goggins, J. Clin. Oncol. 23:4524-4531 (2005)). In addition, cross-sectional abdominal imaging has proven to be unreliable to detect early-stage PDAC in high-risk patients (Pelaez-Luna et al., Am J Gastroenterol 102:2157-2163 (2007)).

[0005] Thus a high priority in this field of medicine is the identification of biomarkers for the development of binding ligands as diagnostics, such as imaging probes for detecting pre-neoplastic/early invasive lesions and for use in treatments.

SUMMARY

[0006] Aspects of the present disclosure relate to a recognition that successful development of clinically useful antibody-based agents, such as antibody drug conjugates (ADCs), is influenced by the specificity and selectivity of the agent for its target. Plectin-1 is a useful biomarker for a variety of cancers, including ovarian, esophageal, and head and neck squamous cells carcinomas, as well as pancreatic ductal adenocarcinoma. In contrast with antibody targets, such as CD30, which is targeted by Brentuximab vedotin, and Her2, which is targeted by Ado-trastuzumab Emtansine, plectin-1 is a particularly useful target because it is present on the cell surface exclusively in certain cancer cells (e.g., pancreatic ductal adenocarcinoma cells, ovarian cancer cells, etc.), thus giving exquisite specificity and selectivity. Accordingly, in some embodiments, the disclosure relates to antibodies and antigen binding fragments that bind specifically to plectin-1 on the surface of cancer cells, and methods of use thereof. In some embodiments, binding of an anti-plectin-1 antibody as described by the disclosure to a plectin-1 expressing cell induces death (e.g., triggers apoptosis) of the cell.

[0007] In some aspects, the disclosure provides an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 92. In some aspects, the disclosure provides an antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 90%, at least 95%, at least 96%, at least 97% at least 98% or at least 99% identity to SEQ ID NO: 92. In some embodiments, the antibody specifically binds an amino acid sequence set forth as: SEQ ID NO: 92.

[0008] In some aspects, the disclosure provides an antibody, or antigen binding fragment, that specifically binds to cell-surface exposed plectin-1 antigen and that comprises six complementarity determining regions (CDRs): CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 18, CDRH2 comprises a sequence as set forth in SEQ ID NO: 20, CDRH3 comprises a sequence as set forth in SEQ ID NO: 22, CDRL1 comprises a sequence as set forth in SEQ ID NO: 40, CDRL2 comprises a sequence as set forth in SEQ ID NO: 42, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 44; or wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 62, CDRH2 comprises a sequence as set forth in SEQ ID NO: 64, CDRH3 comprises a sequence as set forth in SEQ ID NO: 66, CDRL1 comprises a sequence as set forth in SEQ ID NO: 84, CDRL2 comprises a sequence as set forth in SEQ ID NO: 86, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 88.

[0009] In some embodiments, CDRH1 comprises a sequence as set forth in SEQ ID NO: 18, CDRH2 comprises a sequence as set forth in SEQ ID NO: 20, CDRH3 comprises a sequence as set forth in SEQ ID NO: 22, CDRL1 comprises a sequence as set forth in SEQ ID NO: 40, CDRL2 comprises a sequence as set forth in SEQ ID NO: 42, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 44.

[0010] In some aspects, the disclosure provides an antibody or antigen binding fragment that specifically binds to cell-surface exposed plectin-1, wherein the antibody or antigen binding fragment comprises variable heavy chain region comprising a complementarity determining region 3 (CDRH3) having a sequence set forth as: SEQ ID NO: 22 or SEQ ID NO: 66. In some embodiments, the antibody further comprises a light chain variable region comprising a complementarity determining region 3 (CDRL3) having a sequence set forth as: SEQ ID NO: 44 or SEQ ID NO: 88.

[0011] In some embodiments, the antibody, or antigen binding fragment comprises the heavy chain variable domain sequence of SEQ ID NO: 24. In some embodiments, the antibody, or antigen binding fragment comprises the light chain variable domain sequence of SEQ ID NO: 46. In some embodiments, the antibody, or antigen binding fragment comprises the heavy chain variable domain sequence of SEQ ID NO: 24 and the light chain variable domain sequence of SEQ ID NO: 46.

[0012] In some embodiments, the antibody, or antigen binding fragment CDRH1 comprises a sequence as set forth in SEQ ID NO: 62, CDRH2 comprises a sequence as set forth in SEQ ID NO: 64, CDRH3 comprises a sequence as set forth in SEQ ID NO: 66, CDRL1 comprises a sequence

as set forth in SEQ ID NO: 84, CDRL2 comprises a sequence as set forth in SEQ ID NO: 86, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 88.

[0013] In some embodiments, the antibody, or antigen binding fragment comprises the heavy chain variable domain sequence of SEQ ID NO: 68. In some embodiments, the antibody, or antigen binding fragment comprises the light chain variable domain sequence of SEQ ID NO: 90. In some embodiments, the antibody, or antigen binding fragment comprises the heavy chain variable domain sequence of SEQ ID NO: 68 and the light chain variable domain sequence of SEQ ID NO: 90.

[0014] In some aspects, the disclosure provides an antibody or antigen binding fragment that specifically binds to a cell-surface exposed plectin-1, wherein the antibody or antigen binding fragment comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 24 or SEQ ID NO: 68. In some embodiments, the antibody or antigen binding fragment further comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 46 or SEQ ID NO: 90.

[0015] In some embodiments, the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 24 and a light chain variable region having a sequence set forth as: SEQ ID NO: 46.

[0016] In some embodiments, the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 68 and a light chain variable region having a sequence set forth as: SEQ ID NO: 90.

[0017] In some aspects, the disclosure provides an antibody that comprises a heavy chain variable region having a sequence set that shares at least 85% identity with SEQ ID NO: 15 and a light chain variable region that shares at least 85% identity with SEQ ID NO: 37. In some aspects, the disclosure provides an antibody that comprises a heavy chain variable region having a sequence set that shares at least 90% (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identity with SEQ ID NO: 15 and a light chain variable region that shares at least 90% (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identity with SEQ ID NO: 37.

[0018] In some aspects, the disclosure provides an antibody that comprises a heavy chain variable region having a sequence set that shares at least 85% identity with SEQ ID NO: 59 and a light chain variable region that shares at least 85% identity with SEQ ID NO: 81. In some aspects, the disclosure provides an antibody that comprises a heavy chain variable region having a sequence set that shares at least 90% (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identity with SEQ ID NO: 59 and a light chain variable region that shares at least 90% (e.g., at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) identity with SEQ ID NO: 81.

[0019] In some embodiments, an antibody, or antigen binding fragment described by the disclosure comprises a heavy chain constant domain having a sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 59.

[0020] In some embodiments, an antibody, or antigen binding fragment as described by the disclosure comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains.

[0021] In some embodiments, an antibody, or antigen binding fragment described by the disclosure is a monoclonal antibody, a humanized antibody, a diabody, a chimeric antibody, a Fab fragment, a F(ab')2 fragment, an affibody, or an Fv fragment.

[0022] In some embodiments, the disclosure relates to antibody-drug conjugates targeted against plectin-1. In some embodiments, an antibody described by the disclosure (e.g., an anti-plectin-1 antibody) is coupled to a targeted agent. In some embodiments, the targeted agent is a detectable moiety. In some embodiments, the detectable moiety is selected from the group consisting of a radioactive isotope, a magnetic compound, an x-ray absorber, a chemical compound, a biological tag, and a fluorescent molecule.

[0023] In some embodiments, the targeted agent is a therapeutic agent. In some embodiments, the therapeutic agent is a cytotoxic moiety or an immunomodulatory moiety.

[0024] In some embodiments, the antibody is coupled to the targeted agent via a linker. In some embodiments, the linker is a flexible amino acid sequence. In some embodiments, the linker is a photolinker.

[0025] In some embodiments, the targeted agent comprises a physiologically inert nanoparticle. In some embodiments, the nanoparticle is magnetic, fluorescent, or radioactive. In some embodiments, the targeted agent comprises a fluorochrome.

[0026] In some aspects, the disclosure provides an antibody, or antigen binding fragment, that competes or cross-competes for binding to an amino acid sequence set forth as: SEQ ID NO: 92 with an antibody, or antigen binding fragment as described by the disclosure (e.g., an anti-plectin-1 antibody). In some embodiments, the antibody or antigen binding fragment competes or cross-competes with an equilibrium dissociation constant, Kd, of less than 10^{-6} M between the antibody or antigen binding fragment, and its antigen.

[0027] In some aspects, the disclosure provides a composition comprising an antibody as described by the disclosure (e.g., an anti-plectin-1 antibody), optionally further comprising a pharmaceutically acceptable excipient.

[0028] In some aspects, the disclosure provides an isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRH1, CDRH2, and CDRH3, wherein CDRH3 comprises a sequence as set forth in SEQ ID NO: 22. In some embodiments, CDRH1 comprises a sequence as set forth in SEQ ID NO: 18. In some embodiments, CDRH2 comprises a sequence as set forth in SEQ ID NO: 20.

[0029] In some aspects, the disclosure provides an isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRL1, CDRL2, and CDRL3, wherein CDRL3 comprises a sequence as set forth in SEQ ID NO: 44. In some embodiments, CDRL1 comprises a sequence as set forth in SEQ ID NO: 40. In some embodiments, CDRL2 comprises a sequence as set forth in SEQ ID NO: 42.

[0030] In some aspects, the disclosure provides an isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRH1, CDRH2, and CDRH3, wherein CDRH3 comprises a sequence as set forth in SEQ ID NO: 66. In some embodiments, CDRH1 comprises a sequence as set forth in SEQ ID NO: 62. In some embodiments, CDRH2 comprises a sequence as set forth in SEQ ID NO: 64.

[0031] In some aspects, the disclosure provides an isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRL1, CDRL2, and CDRL3, wherein CDRL3 comprises a sequence as set forth in SEQ ID NO: 88. In some embodiments, CDRL1 comprises a sequence as set forth in SEQ ID NO: 84. In some embodiments, CDRL2 comprises a sequence as set forth in SEQ ID NO: 86.

[0032] In some aspects, the disclosure provides an isolated nucleic acid comprising a sequence as set forth in a sequence selected from the group consisting of SEQ ID NO: 15, 24, 37, 46, 59, 68, 81, or 90.

[0033] In some aspects, the disclosure provides an isolated cell (e.g., a host cell) comprising a nucleic acid as described by the disclosure. In some embodiments, the isolated cell is a bacterial cell, a yeast cell, a mammalian cell, or an insect cell. In some embodiments, the cell is a hybridoma cell.

[0034] In some aspects, the disclosure provides a method for targeting an agent to a cancer cell in a subject, the method comprising administering to the subject an antibody or composition as described by the disclosure (e.g., an anti-plectin-1 antibody or a composition comprising an anti-plectin-1 antibody), coupled to a targeted agent, wherein the antibody binds to plectin-1 on the surface of the cancer cell in the subject.

[0035] In some aspects, the disclosure provides a method for treating cancer, the method comprising administering to a subject having cancer an effective amount an antibody or composition as described by the disclosure (e.g., an anti-plectin-1 antibody or a composition comprising an anti-plectin-1 antibody).

[0036] In some aspects, the disclosure provides a method for detecting a cancer cell, the method comprising administering to a subject having cancer an effective amount of the method comprising administering to the subject an antibody or composition as described by the disclosure (e.g., an anti-plectin-1 antibody or a composition comprising an anti-plectin-1 antibody).

[0037] In some embodiments of methods described by the disclosure, the antibody or composition is administered at a dose in a range of 1 ng/kg and 100 mg/kg.

[0038] In some embodiments of methods described by the disclosure, the cancer cell is an ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell. In some embodiments, the cancer cell is a pancreatic ductal adenocarcinoma cell. In some embodiments of methods described by the disclosure, the subject is a mammal, optionally a human.

BRIEF DESCRIPTION OF DRAWINGS

[0039] FIG. **1** shows the in vitro validation of different clones on YapC- or HPDE-coated plates.

[0040] FIG. **2** shows further in vitro validation of the cell lines using a cell killing assay.

[0041] FIGS. **3**A-**3**B show PAb1 binding specificity on recombinant human C-terminal portion of Plectin-1 protein (FIG. **3**A, Sec8-His) and plectin-1-positive L3.6pl cancer cells (FIG. **3**B).

[0042] FIGS. **4**A-**4**G show internalization of PAb1 in L3.6pl plectin-1-positive cancer cells. FIGS. **4**A-**4**B show representative confocal images of L3.6pl after staining of PAb1 (FIG. **4**A) and IgG ctrl (FIG. **4**B) merged with endosomal marker Lamp-1. Staining of Lamp-1 (FIG. **4**C), PAb1 (FIG. **4**D) and co-localization of LAMP-1 and PAb1 (FIG. **4**E) are shown. FIG. **4**F shows data indicating that a significant portion of PAb1 merged with Lamp-1 whereas IgG control did not. FIG. **4**G shows quantification of internalized ^{125}I-PAb1 radioactivity after incubation at 37° C., 4° C. or in combination with excess of cold PAb1 in L3.6pl plectin-1-positive cells and LNCap plectin-1-negative cells; Comp. refers to competition assay.

[0043] FIGS. **5**A-**5**D show induction of cancer cell death by apoptosis after treatment with PAb1. FIG. **5**A shows fluorescent minus one (FMO) flow cytometry data of L3.6pl cells. FIG. **5**B shows L3.6pl AnnexinV positive cells after 72 h control IgG treatment. FIG. **5**C shows L3.6pl AnnexinV positive cells after 72 h PAb1 treatment. FIG. **5**D shows L3.6pl cancer cells experienced significantly more apoptosis after PAb1 treatment compared to control IgG (D).*, $p<0.05$.

[0044] FIGS. **6**A-**6**D show effects of PAb1 treatment on tubulin anisotropy of YapC cancer cells. FIG. **6**A shows confocal microscopy images of YapC after tubulin staining without treatment. FIG. **6**B shows confocal microscopy images of YapC after tubulin staining 10 min. post monomethyl auristatin E (MMAE) treatment. FIG. **6**C shows confocal microscopy images of YapC after tubulin staining 24 h post PAb1 treatment. FIG. **6**D shows a decrease of anisotropy in cells treated with PAb1 compared to non-treated controls.

[0045] FIGS. **7**A-**7**C show co-localization of PAb1 with tubulin in YapC cancer cells. FIG. **7**A shows confocal microscopy images of YapC cells after tubulin staining. FIG. **7**B shows confocal microscopy images of YapC cells after PAb1 staining. FIG. **7**C shows co-localization (arrows) of tubulin staining and PAb1 staining.

[0046] FIGS. **8**A-**8**E show in vivo PAb1 dose-escalating treatment of immunocompromised mice bearing a subcutaneous YapC tumor. FIG. **8**A shows that after 11 days of treatment, tumor volume is significantly lower in mice administered 3 mg/kg PAb1 than control IgG mice. 1 mg/kg PAb1 treatment group elicited a significant reduction of tumor volume at day 14. The two higher doses of PAb1 showed a significantly lower tumor volume compared to 0.3 mg/kg group. *, $p<0.05$, IgG vs 3 mg/kg PAb1; #, $p<0.05$, IgG vs 1 mg/kg PAb1; °, $p<0.05$, 0.3 vs 3 mg/kg PAb1; •, $p<0.05$, 0.3 vs 1 mg/kg PAb1. FIG. **8**B shows the average body weight of the animal of each group. Note that the animal did not lose weight during the entire duration of the treatment.

DETAILED DESCRIPTION

[0047] Antibodies that Bind Plectin-1

[0048] The present disclosure provides antibodies and antigen binding fragments that bind to plectin-1 on the surface of cancer cells. The monoclonal antibodies of the disclosure may be murine, humanized or chimeric or in other forms. A detailed description of the antibodies of the disclosure as well as methods for the production and identification of the antibodies of the disclosure is provided herein.

[0049] Plectin-1 is a high molecular weight protein (500 kDa) that links intermediate filaments to microtubules and microfilaments, in addition to anchoring the cytoskeleton the plasma and nuclear membranes (reviewed in Sonnenberg, et al., Exp Cell Res 313:2189-2203 (2007)).

[0050] Generally, plectin-1 levels are low in normal pancreatic ductal cells but its expression is upregulated in cells having certain cancers (e.g., precursor pancreatic intraepithelial neoplasis (PanINs), pancreatic ductal adenocarci-

noma cells (PDACs), ovarian cancer cells, etc.). Plectin-1 exhibits distinct cytoplasm and nuclear localization in normal fibroblasts, whereas an aberrant expression on the cell membrane is observed in cells having certain cancers (e.g., PDACs). Altered subcellular localization of plectin-1 has also been observed in an autoimmune condition, paraneoplastic pemphigus, and in the associated lymphoproliferative neoplasm, Castleman's disease (Aho et al., J Invest Dermatol 113:422-423 (1999)). Plectin-1 also has important roles in signal transduction. Thus, plectin-1 in cells having certain cancers (e.g., precursor pancreatic intraepithelial neoplasis (PanINs), pancreatic ductal adenocarcinoma cells (PDACs), ovarian cancer cells, etc.) may have an impact on signaling pathways that regulate cell migration, polarity and energy metabolism related to carcinogenesis. Accordingly, in some embodiments, the disclosure provides antibodies and antigen binding fragments that bind to plectin-1 on the surface of cancer cells.

[0051] In some embodiments, antibodies, also known as immunoglobulins, are tetrameric glycosylated proteins composed of two light (L) chains of approximately 25 kDa each and two heavy (H) chains of approximately 50 kDa each. Two types of light chain, termed lambda and kappa, may be found in antibodies. Depending on the amino acid sequence of the constant domain of heavy chains, immunoglobulins can be assigned to five major classes: A, D, E, G, and M, and several of these may be further divided into subclasses (isotypes), e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. Each light chain typically includes an N-terminal variable (V) domain (V_L) and a constant (C) domain (C_L). Each heavy chain typically includes an N-terminal V domain (V_H), three or four C domains (C_H1-3), and a hinge region. The C_H domain most proximal to V_H is designated as C_H1. The V_H and V_L domains consist of four regions of relatively conserved sequences called framework regions (FR1, FR2, FR3, and FR4), which form a scaffold for three regions of hypervariable sequences (complementarity determining regions, CDRs). The CDRs contain most of the residues responsible for specific interactions of the antibody with the antigen. CDRs are referred to as CDR1, CDR2, and CDR3. Accordingly, CDR constituents on the heavy chain are referred to as CDRH1, CDRH2, and CDRH3, while CDR constituents on the light chain are referred to as CDRL1, CDRL2, and CDRL3. The CDRs typically refer to the Kabat CDRs, as described in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services (1991), eds. Kabat et al. Another standard for characterizing the antigen binding site is to refer to the hypervariable loops as described by Chothia. See, e.g., Chothia, D. et al. (1992) J. Mol. Biol. 227:799-817; and Tomlinson et al. (1995) EMBO J. 14:4628-4638. Still another standard is the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, generally, e.g., Protein Sequence and Structure Analysis of Antibody Variable Domains. In: Antibody Engineering Lab Manual (Ed.: Duebel, S, and Kontermann, R., Springer-Verlag, Heidelberg). Embodiments described with respect to Kabat CDRs can alternatively be implemented using similar described relationships with respect to Chothia hypervariable loops or to the AbM-defined loops, or combinations of any of these methods.

[0052] In some embodiments, anti-plectin-1 antibodies of the present disclosure and the nucleic acid molecules of the present disclosure that encode the antibodies include the CDR amino acid and nucleic acid sequences shown in Table 1 below.

TABLE 1

	Antibody					
	CDRH1	CDRH2	CDRH3	CDRL1	CDRL2	CDRL3
Pab2						
Amino acid:	(SEQ ID NO: 18)	(SEQ ID NO: 20)	(SEQ ID NO: 22)	(SEQ ID NO: 40)	(SEQ ID NO: 42)	(SEQ ID NO: 44)
Nuc. Acid:	(SEQ ID NO: 7)	(SEQ ID NO: 9)	(SEQ ID NO: 11)	(SEQ ID NO: 29)	(SEQ ID NO: 31)	(SEQ ID NO: 33)
Pab1						
Amino acid:	(SEQ ID NO: 62)	(SEQ ID NO: 64)	(SEQ ID NO: 66)	(SEQ ID NO: 84)	(SEQ ID NO: 86)	(SEQ ID NO: 88)
Nuc. Acid:	(SEQ ID NO: 51)	(SEQ ID NO: 53)	(SEQ ID NO: 55)	(SEQ ID NO: 73)	(SEQ ID NO: 75)	(SEQ ID NO: 77)

[0053] In some embodiments, anti-plectin-1 binding agents (e.g., anti-plectin-1 antibodies) of the disclosure include any antibody or antigen binding fragment that includes a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3, or combinations thereof, as provided for any one of the antibodies shown in Table 1. In some embodiments, anti-plectin-1 binding agents include the CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3 of any one of the antibodies shown in Table 1. The disclosure also includes any nucleic acid sequence that encodes a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3 as provided for any one of the antibodies shown in Table 1. Antibody heavy and light chain CDR3 domains may play a particularly important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, the anti-plectin-1 antibodies of the disclosure, or the nucleic acid molecules thereof, may include at least the heavy and/or light chain CDR3s of antibodies as shown in Table 1 or as set forth by SEQ ID NOs: 15, 22, 24, 37, 44, 46, 59, 66, 68, 81, 88 or 90.

[0054] The complete amino acid and nucleic acid sequences for the heavy chain variable region and light chain variable region of the antibodies listed in Table 2.

TABLE 2

Antibody	Heavy Chain Variable Region	Light Chain Variable Region
PAb2		
Amino acid:	SEQ ID NO: 24	SEQ ID NO: 46
Nuc. Acid:	SEQ ID NO: 13	SEQ ID NO: 35

TABLE 2-continued

Antibody	Heavy Chain Variable Region	Light Chain Variable Region
PAb1		
Amino acid:	SEQ ID NO: 68	SEQ ID NO: 90
Nuc. Acid:	SEQ ID NO: 57	SEQ ID NO: 79

[0055] In some embodiments, anti-plectin antibodies of the disclosure include any antibody that includes a heavy chain variable domain or a light chain variable domain or both as shown in Table 1, or as described in the sequence listing of this disclosure (e.g., SEQ ID NOs: 15, 24, 37, 46, 59, 68, 81, or 90). The disclosure also includes any nucleic acid molecule encoding an antibody that includes a heavy chain variable domain or a light chain variable domain nucleic acid sequence, or both, as shown in Table 1 or as described in the sequence listing of this disclosure (e.g., SEQ ID NOs: 4, 13, 26, 35, 48, 57, 70, or 79).

[0056] Anti-plectin-1 antibodies of this disclosure may optionally comprise antibody constant regions or parts thereof. For example, a V_L domain may be attached at its C-terminal end to a light chain constant domain like Cκ or Cλ. Similarly, a V_H domain or portion thereof may be attached to all or part of a heavy chain like IgA, IgD, IgE, IgG, and IgM, and any isotype subclass. Antibodies may include suitable constant regions (see, for example, Kabat et al., Sequences of Proteins of Immunological Interest, No. 91-3242, National Institutes of Health Publications, Bethesda, Md. (1991)). Therefore, antibodies within the scope of this may disclosure include V_H and V_L domains, or an antigen binding portion thereof, combined with constant regions known in the art. In some embodiments, anti-plectin-1 antibodies of the disclosure comprise a heavy chain constant region comprising a sequence represented by SEQ ID NOs: 4, 14, 26, 36, 48, 58, 70, or 80.

[0057] In certain embodiments, the V_H and/or V_L domains may be reverted to germline sequence, e.g., the FR of these domains are mutated using conventional molecular biology techniques to match those produced by the germline cells. In other embodiments, the FR sequences remain diverged from the consensus germline sequences.

[0058] In some embodiments, anti-plectin-1 antibodies or antigen binding fragments may or may not include the framework region of the antibodies, for example as set forth in SEQ ID NOs: 6, 8, 10, 12, 17, 19, 21, 23, 28, 30, 32, 34, 39, 41, 43, 45, 50, 52, 54, 56, 61, 63, 65, 67, 72, 74, 76, 78, 83, or 85. In some embodiments, anti-plectin-1 antibodies are murine antibodies. In some embodiments, anti-plectin-1 antibodies are chimeric or humanized antibodies.

[0059] It should be appreciated that, in some embodiments, the disclosure contemplates variants (e.g., homologs) of amino acid and nucleic acid sequences for the heavy chain variable region and light chain variable region of the antibodies. "Homology" refers to the percent identity between two polynucleotides or two polypeptide moieties. The term "substantial homology", when referring to a nucleic acid, or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in about 90 to 100% of the aligned sequences. For example, in some embodiments, nucleic acid sequences sharing substantial homology are at least 90%, at least 91%, at least 92% at least 93%, at least 94%, at least 95%, at least 96% at least 97%, at least 98% at least 99% sequence identity. When referring to a polypeptide, or fragment thereof, the term "substantial homology" indicates that, when optimally aligned with appropriate gaps, insertions or deletions with another polypeptide, there is nucleotide sequence identity in about 90 to 100% of the aligned sequences. The term "highly conserved" means at least 80% identity, preferably at least 90% identity, and more preferably, over 97% identity. For example, in some embodiments, highly conserved proteins share at least 85%, at least 90%, at least 91%, at least 92% at least 93%, at least 94%, at least 95%, at least 96% at least 97%, at least 98% at least 99% identity. In some cases, highly conserved may refer to 100% identity. Identity is readily determined by one of skill in the art by, for example, the use of algorithms and computer programs known by those of skill in the art.

[0060] In some embodiments, an anti-plectin-1 antibodies of the disclosure can bind to plectin-1 with high affinity, e.g., with a Kd less than 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M or lower. For example, anti-plectin-1 antibodies or antigen binding fragments thereof can bind to plectin-1 with an affinity between 5 pM and 500 nM, e.g., between 50 pM and 100 nM, e.g., between 500 pM and 50 nM. The disclosure also includes antibodies or antigen binding fragments that compete with any of the antibodies described herein for binding to plectin-1 and that have an affinity of 50 nM or lower (e.g., 20 nM or lower, 10 nM or lower, 500 pM or lower, 50 pM or lower, or 5 pM or lower). The affinity and binding kinetics of the anti-plectin-1antibody can be tested using any method known in the art including but not limited to biosensor technology (e.g., OCTET or BIACORE).

[0061] As used herein, the term "antibody" generally refers to an immunoglobulin. All derivatives thereof which maintain or possess specific binding ability are also provided herein. An antibody preparation may be monoclonal or polyclonal.

[0062] As used herein, the term "antibody fragment" or "antigen binding fragment" refers to any derivative of an antibody which is less than full-length. Generally, an antigen binding fragment retains at least a significant portion of the full-length antibody's specific binding ability. Examples of antigen binding fragments include, but are not limited to, Fab, Fab', F(ab')2, scFv, Fv, dsFv diabody, affibodies, and Fd fragments. Antigen binding fragments may be produced by any appropriate means. For instance, an antigen binding fragment may be enzymatically or chemically produced by fragmentation of an intact antibody or it may be recombinantly produced from a gene encoding the partial antibody sequence. Alternatively, an antigen binding fragment may be wholly or partially synthetically produced. An antigen binding fragment may optionally be a single chain antibody fragment. Alternatively, a fragment may comprise multiple chains which are linked together, for instance, by disulfide linkages. An antigen binding fragment may also optionally be a multimolecular complex. A functional antigen binding fragment will typically comprise at least about 50 amino acids and more typically will comprise at least about 200 amino acids.

[0063] Single-chain Fvs (scFvs) are recombinant antigen binding fragments consisting of only the variable light chain (VL) and variable heavy chain (VH) covalently connected to one another by a polypeptide linker. Either VL or VH may be the NH2-terminal domain. The polypeptide linker may be

of variable length and composition so long as the two variable domains are bridged without serious steric interference. Typically, the linkers are comprised primarily of stretches of glycine and serine residues with some glutamic acid or lysine residues interspersed for solubility.

[0064] Diabodies are dimeric scFvs. The components of diabodies typically have shorter peptide linkers than most scFvs, and they show a preference for associating as dimers.

[0065] A Fv fragment is an antigen binding fragment which consists of one VH and one VL domain held together by noncovalent interactions. The term dsFv is used herein to refer to an Fv with an engineered intermolecular disulfide bond to stabilize the VH-VL pair.

[0066] A F(ab')2 fragment is an antigen binding fragment essentially equivalent to that obtained from immunoglobulins (typically IgG) by digestion with an enzyme pepsin at pH 4.0-4.5. The fragment may be recombinantly produced.

[0067] A Fab fragment is an antigen binding fragment essentially equivalent to that obtained by reduction of the disulfide bridge or bridges joining the two heavy chain pieces in the F(ab')2 fragment. The Fab' fragment may be recombinantly produced.

[0068] A Fab fragment is an antigen binding fragment essentially equivalent to that obtained by digestion of immunoglobulins (typically IgG) with the enzyme papain. The Fab fragment may be recombinantly produced. The heavy chain segment of the Fab fragment is the Fd piece.

[0069] An affibody is a small protein comprising a three-helix bundle that functions as an antigen binding molecule (e.g., an antibody mimetic). Generally, affibodies are approximately 58 amino acids in length and have a molar mass of approximately 6 kDa. Affibody molecules with unique binding properties are acquired by randomization of 13 amino acids located in two alpha-helices involved in the binding activity of the parent protein domain. Specific affibody molecules binding a desired target protein can be isolated from pools (libraries) containing billions of different variants, using methods such as phage display.

[0070] Production of Antibodies that Bind Plectin-1

[0071] Numerous methods may be used for obtaining antibodies, or antigen binding fragments thereof, of the disclosure. For example, antibodies can be produced using recombinant DNA methods. Monoclonal antibodies may also be produced by generation of hybridomas (see e.g., Kohler and Milstein (1975) Nature, 256: 495-499) in accordance with known methods. Hybridomas formed in this manner are then screened using standard methods, such as enzyme-linked immunosorbent assay (ELISA) and surface plasmon resonance (e.g., OCTET or BIACORE) analysis, to identify one or more hybridomas that produce an antibody that specifically binds with a specified antigen. Any form of the specified antigen may be used as the immunogen, e.g., recombinant antigen, naturally occurring forms, any variants or fragments thereof, as well as antigenic peptide thereof (e.g., any of the epitopes described herein as a linear epitope or within a scaffold as a conformational epitope). One exemplary method of making antibodies includes screening protein expression libraries that express antibodies or fragments thereof (e.g., scFv), e.g., phage or ribosome display libraries. Phage display is described, for example, in Ladner et al., U.S. Pat. No. 5,223,409; Smith (1985) Science 228: 1315-1317; Clackson et al. (1991) Nature, 352: 624-628; Marks et al. (1991) J. Mol. Biol., 222: 581-597WO92/18619; WO 91/17271; WO 92/20791; WO 92/15679; WO 93/01288; WO 92/01047; WO 92/09690; and WO 90/02809.

[0072] In addition to the use of display libraries, the specified antigen (e.g., plectin-1) can be used to immunize a non-human animal, e.g., a rodent, e.g., a mouse, hamster, or rat. In one embodiment, the non-human animal is a mouse.

[0073] In another embodiment, a monoclonal antibody is obtained from the non-human animal, and then modified, e.g., made chimeric, using recombinant DNA techniques known in the art. A variety of approaches for making chimeric antibodies have been described. See e.g., Morrison et al., Proc. Natl. Acad. Sci. U.S.A. 81:6851, 1985; Takeda et al., Nature 314:452, 1985, Cabilly et al., U.S. Pat. No. 4,816,567; Boss et al., U.S. Pat. No. 4,816,397; Tanaguchi et al., European Patent Publication EP171496; European Patent Publication 0173494, United Kingdom Patent GB 2177096B.

[0074] Antibodies can also be humanized by methods known in the art. For example, monoclonal antibodies with a desired binding specificity can be commercially humanized (Scotgene, Scotland; and Oxford Molecular, Palo Alto, Calif.). Fully humanized antibodies, such as those expressed in transgenic animals are within the scope of the invention (see, e.g., Green et al. (1994) Nature Genetics 7, 13; and U.S. Pat. Nos. 5,545,806 and 5,569,825).

[0075] For additional antibody production techniques, see Antibodies: A Laboratory Manual, Second Edition. Edited by Edward A. Greenfield, Dana-Farber Cancer Institute, ©2014. The present disclosure is not necessarily limited to any particular source, method of production, or other special characteristics of an antibody.

[0076] Some aspects of the present invention relate to isolated cells (e.g., host cells) transformed with a polynucleotide or vector. Host cells may be a prokaryotic or eukaryotic cell. The polynucleotide or vector which is present in the host cell may either be integrated into the genome of the host cell or it may be maintained extrachromosomally. The host cell can be any prokaryotic or eukaryotic cell, such as a bacterial, insect, fungal, plant, animal or human cell. In some embodiments, fungal cells are, for example, those of the genus *Saccharomyces*, in particular those of the species *S. cerevisiae*. The term "prokaryotic" includes all bacteria which can be transformed or transfected with a DNA or RNA molecules for the expression of an antibody or the corresponding immunoglobulin chains. Prokaryotic hosts may include gram negative as well as gram positive bacteria such as, for example, *E. coli, S. typhimurium, Serratia marcescens* and *Bacillus subtilis*. The term "eukaryotic" includes yeast, higher plants, insects and vertebrate cells, e.g., mammalian cells, such as NSO and CHO cells. Depending upon the host employed in a recombinant production procedure, the antibodies or immunoglobulin chains encoded by the polynucleotide may be glycosylated or may be non-glycosylated. Antibodies or the corresponding immunoglobulin chains may also include an initial methionine amino acid residue.

[0077] In some embodiments, once a vector has been incorporated into an appropriate host, the host may be maintained under conditions suitable for high level expression of the nucleotide sequences, and, as desired, the collection and purification of the immunoglobulin light chains, heavy chains, light/heavy chain dimers or intact antibodies, antigen binding fragments or other immunoglobulin forms

may follow; see, Beychok, Cells of Immunoglobulin Synthesis, Academic Press, N.Y., (1979). Thus, polynucleotides or vectors are introduced into the cells which in turn produce the antibody or antigen binding fragments. Furthermore, transgenic animals, preferably mammals, comprising the aforementioned host cells may be used for the large scale production of the antibody or antibody fragments.

[0078] The transformed host cells can be grown in fermenters and cultured according to techniques known in the art to achieve optimal cell growth. Once expressed, the whole antibodies, their dimers, individual light and heavy chains, other immunoglobulin forms, or antigen binding fragments, can be purified according to standard procedures of the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like; see, Scopes, "Protein Purification", Springer Verlag, N.Y. (1982). The antibody or antigen binding fragments can then be isolated from the growth medium, cellular lysates, or cellular membrane fractions. The isolation and purification of the, e.g., microbially expressed antibodies or antigen binding fragments may be by any conventional means such as, for example, preparative chromatographic separations and immunological separations such as those involving the use of monoclonal or polyclonal antibodies directed, e.g., against the constant region of the antibody.

[0079] Aspects of the disclosure relate to a hybridoma, which provides an indefinitely prolonged source of monoclonal antibodies. As used herein, "hybridoma cell" refers to an immortalized cell derived from the fusion of B lymphoblasts with a myeloma fusion partner. For preparing monoclonal antibody-producing cells (e.g., hybridoma cells), an individual animal whose antibody titer has been confirmed (e.g., a mouse) is selected, and 2 days to 5 days after the final immunization, its spleen or lymph node is harvested and antibody-producing cells contained therein are fused with myeloma cells to prepare the desired monoclonal antibody producer hybridoma. Measurement of the antibody titer in antiserum can be carried out, for example, by reacting the labeled protein, as described hereinafter and antiserum and then measuring the activity of the labeling agent bound to the antibody. The cell fusion can be carried out according to known methods, for example, the method described by Kochler and Milstein (Nature 256:495 (1975)). As a fusion promoter, for example, polyethylene glycol (PEG) or Sendai virus (HVJ), preferably PEG is used.

[0080] Examples of myeloma cells include NS-1, P3U1, SP2/0, AP-1 and the like. The proportion of the number of antibody producer cells (spleen cells) and the number of myeloma cells to be used is preferably about 1:1 to about 20:1. PEG (preferably PEG 1000-PEG 6000) is preferably added in concentration of about 10% to about 80%. Cell fusion can be carried out efficiently by incubating a mixture of both cells at about 20° C. to about 40° C., preferably about 30° C. to about 37° C. for about 1 minute to 10 minutes.

[0081] Various methods may be used for screening for a hybridoma producing the antibody (e.g., against a tumor antigen or autoantibody of the present invention). For example, where a supernatant of the hybridoma is added to a solid phase (e.g., microplate) to which antibody is adsorbed directly or together with a carrier and then an anti-immunoglobulin antibody (if mouse cells are used in cell fusion, anti-mouse immunoglobulin antibody is used) or Protein A labeled with a radioactive substance or an enzyme is added to detect the monoclonal antibody against the protein bound to the solid phase. Alternately, a supernatant of the hybridoma is added to a solid phase to which an anti-immunoglobulin antibody or Protein A is adsorbed and then the protein labeled with a radioactive substance or an enzyme is added to detect the monoclonal antibody against the protein bound to the solid phase.

[0082] Selection of the monoclonal antibody can be carried out according to any known method or its modification. Normally, a medium for animal cells to which HAT (hypoxanthine, aminopterin, thymidine) are added is employed. Any selection and growth medium can be employed as long as the hybridoma can grow. For example, RPMI 1640 medium containing 1% to 20%, preferably 10% to 20% fetal bovine serum, GIT medium containing 1% to 10% fetal bovine serum, a serum free medium for cultivation of a hybridoma (SFM-101, Nissui Seiyaku) and the like can be used. Normally, the cultivation is carried out at 20° C. to 40° C., preferably 37° C. for about 5 days to 3 weeks, preferably 1 week to 2 weeks under about 5% CO_2 gas. The antibody titer of the supernatant of a hybridoma culture can be measured according to the same manner as described above with respect to the antibody titer of the anti-protein in the antiserum.

[0083] As an alternative to obtaining immunoglobulins directly from the culture of hybridomas, immortalized hybridoma cells can be used as a source of rearranged heavy chain and light chain loci for subsequent expression and/or genetic manipulation. Rearranged antibody genes can be reverse transcribed from appropriate mRNAs to produce cDNA. If desired, the heavy chain constant region can be exchanged for that of a different isotype or eliminated altogether. The variable regions can be linked to encode single chain Fv regions. Multiple Fv regions can be linked to confer binding ability to more than one target or chimeric heavy and light chain combinations can be employed. Any appropriate method may be used for cloning of antibody variable regions and generation of recombinant antibodies.

[0084] In some embodiments, an appropriate nucleic acid that encodes variable regions of a heavy and/or light chain is obtained and inserted into an expression vectors which can be transfected into standard recombinant host cells. A variety of such host cells may be used. In some embodiments, mammalian host cells may be advantageous for efficient processing and production. Typical mammalian cell lines useful for this purpose include CHO cells, 293 cells, or NSO cells. The production of the antibody or antigen binding fragment may be undertaken by culturing a modified recombinant host under culture conditions appropriate for the growth of the host cells and the expression of the coding sequences. The antibodies or antigen binding fragments may be recovered by isolating them from the culture. The expression systems may be designed to include signal peptides so that the resulting antibodies are secreted into the medium; however, intracellular production is also possible.

[0085] The disclosure also includes a polynucleotide encoding at least a variable region of an immunoglobulin chain of the antibodies described herein. In some embodiments, the variable region encoded by the polynucleotide comprises at least one complementarity determining region (CDR) of the VH and/or VL of the variable region of the antibody produced by any one of the above described hybridomas.

[0086] Polynucleotides encoding antibody or antigen binding fragments may be, e.g., DNA, cDNA, RNA or

synthetically produced DNA or RNA or a recombinantly produced chimeric nucleic acid molecule comprising any of those polynucleotides either alone or in combination. In some embodiments, a polynucleotide is part of a vector. Such vectors may comprise further genes such as marker genes which allow for the selection of the vector in a suitable host cell and under suitable conditions.

[0087] In some embodiments, a polynucleotide is operatively linked to expression control sequences allowing expression in prokaryotic or eukaryotic cells. Expression of the polynucleotide comprises transcription of the polynucleotide into a translatable mRNA. Regulatory elements ensuring expression in eukaryotic cells, preferably mammalian cells, are well known to those skilled in the art. They may include regulatory sequences that facilitate initiation of transcription and optionally poly-A signals that facilitate termination of transcription and stabilization of the transcript. Additional regulatory elements may include transcriptional as well as translational enhancers, and/or naturally associated or heterologous promoter regions. Possible regulatory elements permitting expression in prokaryotic host cells include, e.g., the PL, Lac, Trp or Tac promoter in *E. coli*, and examples of regulatory elements permitting expression in eukaryotic host cells are the AOX1 or GAL1 promoter in yeast or the CMV-promoter, SV40-promoter, RSV-promoter (Rous sarcoma virus), CMV-enhancer, SV40-enhancer or a globin intron in mammalian and other animal cells.

[0088] Beside elements which are responsible for the initiation of transcription such regulatory elements may also include transcription termination signals, such as the SV40-poly-A site or the tk-poly-A site, downstream of the polynucleotide. Furthermore, depending on the expression system employed, leader sequences capable of directing the polypeptide to a cellular compartment or secreting it into the medium may be added to the coding sequence of the polynucleotide and are well known in the art. The leader sequence(s) is (are) assembled in appropriate phase with translation, initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein, or a portion thereof, into, for example, the extracellular medium. Optionally, a heterologous polynucleotide sequence can be used that encode a fusion protein including a C- or N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product.

[0089] In some embodiments, polynucleotides encoding at least the variable domain of the light and/or heavy chain may encode the variable domains of both immunoglobulin chains or only one. Likewise, a polynucleotides may be under the control of the same promoter or may be separately controlled for expression. Furthermore, some aspects relate to vectors, particularly plasmids, cosmids, viruses and bacteriophages used conventionally in genetic engineering that comprise a polynucleotide encoding a variable domain of an immunoglobulin chain of an antibody or antigen binding fragment; optionally in combination with a polynucleotide that encodes the variable domain of the other immunoglobulin chain of the antibody.

[0090] In some embodiments, expression control sequences are provided as eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells, but control sequences for prokaryotic hosts may also be used. Expression vectors derived from viruses such as retroviruses, vaccinia virus, adeno-associated virus, herpes viruses, or bovine papilloma virus, may be used for delivery of the polynucleotides or vector into targeted cell population (e.g., to engineer a cell to express an antibody or antigen binding fragment). A variety of appropriate methods can be used to construct recombinant viral vectors. In some embodiments, polynucleotides and vectors can be reconstituted into liposomes for delivery to target cells. The vectors containing the polynucleotides (e.g., the heavy and/or light variable domain(s) of the immunoglobulin chains encoding sequences and expression control sequences) can be transferred into the host cell by suitable methods, which vary depending on the type of cellular host.

[0091] Modifications

[0092] Some aspects of the disclosure relate to antibody-drug conjugates targeted against plectin-1. As used herein, "antibody drug conjugate" refers to molecules comprising an antibody, or antigen binding fragment thereof, linked to a targeted molecule (e.g., a biologically active molecule, such as a therapeutic molecule, and/or a detectable label). Accordingly, in some embodiments, antibodies or antigen binding fragments of the disclosure may be modified with a detectable label, including, but not limited to, an enzyme, prosthetic group, fluorescent material, luminescent material, bioluminescent material, radioactive material, positron emitting metal, nonradioactive paramagnetic metal ion, and affinity label for detection and isolation of plectin-1. The detectable substance may be coupled or conjugated either directly to the polypeptides of the disclosure or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. Non-limiting examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, glucose oxidase, or acetylcholinesterase; non-limiting examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; non-limiting examples of suitable fluorescent materials include biotin, umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride, or phycoerythrin; an example of a luminescent material includes luminol; non-limiting examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include a radioactive metal ion, e.g., alpha-emitters or other radioisotopes such as, for example, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115}mIn, ^{113}mIn, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99}mTc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{86}R, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, and tin (^{113}Sn, ^{117}Sn). The detectable substance may be coupled or conjugated either directly to the anti-plectin-1 antibodies of the disclosure or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. Anti-plectin-1 antibodies conjugated to a detectable substance may be used for diagnostic assays as described herein.

[0093] In some embodiments, antibodies or antigen binding fragments of the disclosure may be modified with a therapeutic moiety (e.g., therapeutic agent). As used herein, the term "therapeutic agent" refers to chemicals or drugs or proteins that are able to inhibit cell function, inhibit cell replication or kill mammalian cells, preferably human cells.

Examples of therapeutic agents include but are not limited to cytotoxic moieties, radioisotopes, molecules of plant, fungal, or bacterial origin (e.g., plant-derived toxins (e.g., secondary metabolites), glycosides, antimicrobial compounds (e.g., streptomycin, penicillin, etc.), biological proteins (e.g., protein toxins), particles (e.g., recombinant viral particles, e.g., via a viral coat protein), or mixtures thereof. The therapeutic agent can be an intracellularly active drug or other agent, such as short-range radiation emitters, including, for example, short-range, high-energy alpha-emitters (e.g., ^{131}I).

[0094] In some embodiments, the therapeutic agent is an immunomodulatory moiety (e.g., immunomodulatory agent). As used herein, "immunomodulatory agent" refers to a compound or molecule that increases or decreases the immune response of a subject in response to the agent. For example, an immunomodulatory agent may enhance the immune response of a subject to a tumor, e.g., increase the level of inflammatory cytokines such as interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α). Examples of immunomodulatory agents that increase the immune response of a subject include granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod, cellular membrane fractions from bacteria, certain interleukins and cytokines (e.g., IL-1β, IL-6, and TNF-α), and immune checkpoint inhibitors (e.g., PD-1 inhibitors, PD1-L inhibitors, etc.). In some embodiments, an immunomodulatory agent may decrease the immune response of a subject (e.g., mediate or achieve immunosuppression). Examples of immunosuppressive immunomodulators include but are not limited to immunosuppressive drugs (e.g., glucococorticoids, cytostatics, anti-inflammatory monoclonal antibodies (e.g., anti-IL-2 receptor antibodies), and drugs targeting immunophilins (e.g., ciclosporin, sirolimus, etc.). In some embodiments, the antibody is coupled to the targeted agent via a linker. As used herein, the term "linker" refers to a molecule or sequence, such as an amino acid sequence, that attaches, as in a bridge, one molecule or sequence to another molecule or sequence. "Linked," "conjugated," or "coupled" means attached or bound by covalent bonds, or non-covalent bonds, or other bonds, such as van der Waals forces. Antibodies described by the disclosure can be linked to the targeted agent (e.g., therapeutic moiety or detectable moiety) directly, e.g., as a fusion protein with protein or peptide detectable moieties (with or without an optional linking sequence, e.g., a flexible linker sequence) or via a chemical coupling moiety. A number of such coupling moieties are known in the art, e.g., a peptide linker or a chemical linker, e.g., as described in International Patent Application Publication No. WO 2009/036092. In some embodiments, the linker is a flexible amino acid sequence. Examples of flexible amino acid sequences include glycine and serine rich linkers, which comprise a stretch of two or more glycine residues, (e.g., GGGS; SEQ ID NO: 93). In some embodiments, the linker is a photolinker. Examples of photolinkers include ketyl-reactive benzophenone (BP), anthraquinone (AQ), nitrene-reactive nitrophenyl azide (NPA), and carbene-reactive phenyl-(trifluoromethyl)diazirine (PTD).

[0095] In some embodiments, the targeted agent comprises a physiologically inert nanoparticle. Examples of nanoparticles developed and used for imaging cancer cells, include magnetic nanoparticles and their magnetofluorescent analogues (see, e.g., Weissleder et al., Nat. Biotechnol., 19:316-317 (2001); McCarthy et al., Nanomedicine, 2:153-167 (2007); Hogemann et al., Bioconjug. Chem., 11:941-946 (2000), and Josephson et al., Bioconjug. Chem., 10:186-191 (1999)) which are contemplated for use with isolated peptide ligands and phage displayed peptides. Multimodal nanoparticles are known that incorporate both magnetic and fluorescent molecules within the same molecule and are used for fluorescent microscopy (which detects the fluorescent part of this very small particle) and MRI (which detects its magnetic portion). In some embodiments, the nanoparticle is magnetic, fluorescent, or radioactive. In some embodiments, the targeted agent comprises a fluorochrome.

[0096] Pharmaceutical Compositions

[0097] In some aspects, the disclosure relates to pharmaceutical compositions comprising anti-plectin-1 antibodies. In some embodiments, the composition comprises an anti-plectin-1 antibody and a pharmaceutically acceptable carrier. As used herein the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions. Pharmaceutical compositions can be prepared as described below. The active ingredients may be admixed or compounded with any conventional, pharmaceutically acceptable carrier or excipient. The compositions may be sterile.

[0098] Typically, pharmaceutical compositions are formulated for delivering an effective amount of an agent (e.g., an anti-plectin-1 antibody or antibody drug conjugate comprising an anti-plectin-1 antibody and a targeted agent). In general, an "effective amount" of an active agent refers to an amount sufficient to elicit the desired biological response (e.g., killing of a cancerous cell or suppression of tumor growth). An effective amount of an agent may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the disease being treated (e.g., certain cancers characterized by surface expression of plectin-1), the mode of administration, and the patient.

[0099] A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, 18th Ed. (1990).

[0100] It will be understood by those skilled in the art that any mode of administration, vehicle or carrier conventionally employed and which is inert with respect to the active agent may be utilized for preparing and administering the pharmaceutical compositions of the present disclosure. Illustrative of such methods, vehicles and carriers are those described, for example, in Remington's Pharmaceutical Sciences, 4th ed. (1970), the disclosure of which is incorporated herein by reference. Those skilled in the art, having been exposed to the principles of the disclosure, will experience no difficulty in determining suitable and appropriate vehicles, excipients and carriers or in compounding the

active ingredients therewith to form the pharmaceutical compositions of the disclosure.

[0101] An effective amount, also referred to as a therapeutically effective amount, of a compound (for example, an anti-plectin-1 antibody or antibody drug conjugate comprising an anti-plectin-1 antibody and a targeted agent) is an amount sufficient to ameliorate at least one adverse effect associated with cancer (e.g., tumor growth, metastasis). The therapeutically effective amount to be included in pharmaceutical compositions depends, in each case, upon several factors, e.g., the type, size and condition of the patient to be treated, the intended mode of administration, the capacity of the patient to incorporate the intended dosage form, etc. Generally, an amount of active agent is included in each dosage form to provide from about 0.1 to about 250 mg/kg, and preferably from about 0.1 to about 100 mg/kg. One of ordinary skill in the art would be able to determine empirically an appropriate therapeutically effective amount.

[0102] Combined with the teachings provided herein, by choosing among the various active compounds and weighing factors such as potency, relative bioavailability, patient body weight, severity of adverse side-effects and selected mode of administration, an effective prophylactic or therapeutic treatment regimen can be planned which does not cause substantial toxicity and yet is entirely effective to treat the particular subject. The effective amount for any particular application can vary depending on such factors as the disease or condition being treated, the particular therapeutic agent being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art can empirically determine the effective amount of a particular nucleic acid and/or other therapeutic agent without necessitating undue experimentation.

[0103] In some cases, compounds of the disclosure are prepared in a colloidal dispersion system. Colloidal dispersion systems include lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. In some embodiments, a colloidal system of the disclosure is a liposome. Liposomes are artificial membrane vessels which are useful as a delivery vector in vivo or in vitro. It has been shown that large unilamellar vesicles (LUVs), which range in size from 0.2-4.0 μm can encapsulate large macromolecules.

[0104] Liposomes may be targeted to a particular tissue by coupling the liposome to a specific ligand such as a monoclonal antibody, sugar, glycolipid, or protein. Ligands which may be useful for targeting a liposome to, for example, an smooth muscle cell include, but are not limited to: intact or fragments of molecules which interact with smooth muscle cell specific receptors and molecules, such as antibodies, which interact with the cell surface markers of cancer cells. Such ligands may easily be identified by binding assays well known to those of skill in the art. In still other embodiments, the liposome may be targeted to a tissue by coupling it to an antibody known in the art.

[0105] Compounds described by the disclosure may be administered alone (e.g., in saline or buffer) or using any delivery vehicle known in the art. For instance the following delivery vehicles have been described: cochleates; Emulsomes; ISCOMs; liposomes; live bacterial vectors (e.g., *Salmonella, Escherichia coli, Bacillus* Calmette-Guérin, *Shigella, Lactobacillus*); live viral vectors (e.g., Vaccinia, adenovirus, Herpes simplex); microspheres; nucleic acid vaccines; polymers (e.g., carboxymethylcellulose, chitosan); polymer rings; proteosomes; sodium fluoride; transgenic plants; virosomes; and, virus-like particles.

[0106] The formulations of the disclosure are administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

[0107] The term pharmaceutically-acceptable carrier means one or more compatible solid or liquid filler, diluents or encapsulating substances which are suitable for administration to a human or other vertebrate animal. The term carrier denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions also are capable of being commingled with the compounds of the present disclosure, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

[0108] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0109] In addition to the formulations described herein, the compounds may also be formulated as a depot preparation. Such long-acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0110] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[0111] Suitable liquid or solid pharmaceutical preparation forms are, for example, aqueous or saline solutions for inhalation, microencapsulated, encochleated, coated onto microscopic gold particles, contained in liposomes, nebulized, aerosols, pellets for implantation into the skin, or dried onto a sharp object to be scratched into the skin. The pharmaceutical compositions also include granules, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, flavorings, sweeteners or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer R (1990) Science 249:1527-1533, which is incorporated herein by reference.

[0112] The compounds may be administered per se (neat) or in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may

conveniently be used to prepare pharmaceutically acceptable salts thereof. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

[0113] Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

[0114] The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the compounds into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product. Liquid dose units are vials or ampoules. Solid dose units are tablets, capsules and suppositories.

[0115] Treatment Methods

[0116] Aspects of the disclosure relate to the discovery of antibodies that specifically bind to plectin-1 on the surface of certain cancer cells. In some embodiments, binding of an anti-plectin-1 antibody as described by the disclosure to certain cancer cells induces death (e.g., triggers apoptosis) of the cells. Without wishing to be bound by any particular theory, antibodies described by the disclosure are useful, in some embodiments, for treating cancer characterized by surface expression of plectin-1. As used herein, "treating cancer" refers to decreasing the number of cancer cells in a patient, slowing the growth of cancer cells in a patient, reducing the metastasis of cancer cells in a patient and includes any type of response for either relieving cancer symptoms or increasing the life-span of a patient.

[0117] Examples of cancers characterized by surface expression of plectin-1 include but are not limited to ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell (e.g., pancreatic ductal adenocarcinoma (PDAC)). However, it should be appreciated that other cancers (such as lung cancer, bladder cancer, breast cancer, esophageal cancer, mouth cancer, tongue cancer, gum cancer, skin cancer (e.g., melanoma, basal cell carcinoma, Kaposi's sarcoma, etc.), muscle cancer, heart cancer, liver cancer, bronchial cancer, cartilage cancer, bone cancer, stomach cancer, prostate cancer, testicular cancer, cervical cancer, endometrial cancer, uterine cancer, colon cancer, colorectal, gastric cancer, kidney cancer, bladder cancer, lymphoma cancer, spleen cancer, thymus cancer, thyroid cancer, brain cancer, neuronal cancer, mesothelioma, gall bladder cancer, ocular cancer (e.g., cancer of the cornea, cancer of uvea, cancer of the choroids, cancer of the macula, vitreous humor cancer, etc.), joint cancer (such as synovium cancer), glioblastoma, white blood cell cancer (e.g., lymphoma, leukemia, etc.), hereditary non-polyposis cancer (HNPC), colitis-associated cancer, etc. Cancers are further exemplified by sarcomas (such as osteosarcoma and Kaposi's sarcoma) may be treated using anti-plectin-1 antibodies described by the disclosure.

[0118] In some aspects, the disclosure provides a method for treating cancer, the method comprising administering to a subject having cancer an effective amount an antibody or composition as described by the disclosure (e.g., an anti-plectin-1 antibody or a composition comprising an anti-plectin-1 antibody). In some embodiments, the subject is a mammal. In some embodiments, the subject is a human.

[0119] Generally, antibodies and pharmaceutical compositions of the disclosure preferably contain a pharmaceutically acceptable carrier or excipient suitable for rendering the compound or mixture administrable orally as a tablet, capsule or pill, or parenterally, intravenously, intradermally, intramuscularly or subcutaneously, or transdermally.

[0120] The pharmaceutical compositions containing an anti-plectin-1 antibody and/or other compounds can be administered by any suitable route for administering medications. A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular agent or agents selected, the particular condition being treated, and the dosage required for therapeutic efficacy. The methods of this disclosure, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces therapeutic effect without causing clinically unacceptable adverse effects. Various modes of administration are discussed herein. For use in therapy, an effective amount of the anti-plectin-1 antibody and/or other therapeutic agent can be administered to a subject by any mode that delivers the agent to the desired surface, e.g., mucosal, systemic.

[0121] Administering the pharmaceutical composition of the present disclosure may be accomplished by any means known to the skilled artisan. Routes of administration include but are not limited to oral, parenteral, intravenous, intramuscular, intraperitoneal, intranasal, sublingual, intratracheal, inhalation, subcutaneous, ocular, vaginal, and rectal. Systemic routes include oral and parenteral. Several types of devices are regularly used for administration by inhalation. These types of devices include metered dose inhalers (MDI), breath-actuated MDI, dry powder inhaler (DPI), spacer/holding chambers in combination with MDI, and nebulizers.

[0122] For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject to be treated. Pharmaceutical preparations for oral use can be obtained as solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. Optionally the oral formulations

may also be formulated in saline or buffers for neutralizing internal acid conditions or may be administered without any carriers.

[0123] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Microspheres formulated for oral administration may also be used. Such microspheres have been well defined in the art. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner. For administration by inhalation, the compounds for use according to the present disclosure may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g., gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0124] The compounds, when it is desirable to deliver them systemically, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

[0125] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0126] Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0127] The compounds may also be formulated in rectal or vaginal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0128] Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the compounds, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer base systems such as poly(lactide-glycolide), copolyoxalates, polycaprolactones, polyesteramides, polyorthoesters, polyhydroxybutyric acid, and polyanhydrides. Microcapsules of the foregoing polymers containing drugs are described in, for example, U.S. Pat. No. 5,075,109. Delivery systems also include non-polymer systems that are: lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di-, and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings; compressed tablets using conventional binders and excipients; partially fused implants; and the like. Specific examples include, but are not limited to: (a) erosional systems in which an agent of the disclosure is contained in a form within a matrix such as those described in U.S. Pat. Nos. 4,452,775, 4,675,189, and 5,736,152, and (b) diffusional systems in which an active component permeates at a controlled rate from a polymer such as described in U.S. Pat. Nos. 3,854,480, 5,133,974 and 5,407,686. In addition, pump-based hardware delivery systems can be used, some of which are adapted for implantation.

[0129] The anti-plectin-1 antibodies and compositions described by the disclosure can be administered to a subject (e.g., a subject having cancer) on multiple occasions. In some embodiments, the number of occasions in which an antibody or composition of the disclosure is delivered to a subject is in a range of 2 to 10 times (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 times). In some embodiments, a heterologous nucleic acid is delivered to a subject more than 10 times.

[0130] In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per calendar day (e.g., a 24-hour period). In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per 2, 3, 4, 5, 6, or 7 calendar days. In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per calendar week (e.g., 7 calendar days). In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than bi-weekly (e.g., once in a two calendar week period). In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per calendar month (e.g., once in 30 calendar days). In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per six calendar months. In some embodiments, a dose of an antibody or composition of the disclosure is administered to a subject no more than once per calendar year (e.g., 365 days or 366 days in a leap year).

[0131] Immunoassays

[0132] In some embodiments, the disclosure relates to a method for detecting a plectin-1 on the surface of cells, e.g., cancer cells, in situ or in vitro. In some embodiments, the disclosure relates to a method for detecting plectin-1 on the surface of cells in a sample obtained from a subject. The sample may be obtained from a subject, for example, by extracting a tumor or portion thereof from a subject. In some embodiments, cells may be isolated from the tumor. However, in some embodiments, cells may be examined in the context of an isolated tumor.

[0133] In some embodiments, a method for detecting a plectin-1 in situ involve delivering to a subject a plectin-1 antibody or antigen binding fragment conjugated to a label (e.g., a radioactive label) under conditions in which the antibody or antigen binding fragment is able to form binding complexes with an accessible epitope of plectin-1 on cells, e.g., cancer cells, in the subject; and detecting the label in the subject (e.g., using autoradiography or other nuclear medicines detection techniques, including single photon emission computed tomography (SPECT), positron emission tomography (PET) and scintigraphy).

[0134] In some embodiments, a method for detecting a plectin-1 in a tumor sample obtained from a subject involve (a) contacting the sample with the antibody or antigen binding fragment under conditions suitable for binding of the antibody or antigen binding fragment to the antigen, if the antigen is present in the sample, thereby forming binding complexes; and (b) determining the level of the antibody or antigen binding fragment bound to the antigen (e.g., determining the level of the binding complexes), e.g., at the surface of a cell of the tumor.

[0135] As used herein a binding complex refers to a biomolecular complex of antibody or antigen binding fragments bound to antigen (e.g., plectin-1 protein). Binding complexes may comprise antibodies or antigen binding fragments with a single specificity or two or more antibodies or antigen binding fragments with different specificities. In one embodiment, a binding complex comprises two or more antibodies recognizing different antigenic sites on the same antigen. In some instances, an antibody or antigen binding fragment may be bound to an antigen, having bound to it other biomolecules such as RNA, DNA, polysaccharides or proteins. In one embodiment, a binding complex comprises two or more antibodies recognizing different antigens. In some embodiments, an antibody or antigen binding fragment in a binding complex (e.g., an immobilized antibody or antigen binding fragment bound to antigen), may itself by bound, as an antigen, to an antibody or antigen binding fragment (e.g., a detectably labeled antibody or antigen binding fragment). Thus, binding complexes may, in some instances, comprise multiple antigens and multiple antibodies or antigen binding fragments. Antigens present in binding complexes may or may not be in their native in situ conformation. In some embodiments, a binding complex is formed between an antibody or antigen binding fragment and a purified protein antigen, or isolated proteins comprising antigen, in which the antigen is not in its native in situ conformation. In some embodiments, a binding complex is formed between an antibody or antigen binding fragment and a purified protein antigen, in which the antigen is not in its native in situ conformation and is immobilized on solid support (e.g., a PVDF membrane). In some embodiments, a binding complex is formed with an antibody or antigen binding fragment and, for example, a cell surface protein that is present in situ in a native confirmation (e.g., on the surface of a cell). Antibodies or antigen binding fragments in binding complexes may or may not be detectably labeled. In some embodiments, binding complexes comprise detectably labeled antibodies or antigen binding fragments and non-labeled antibodies or antigen binding fragments. In some embodiments, binding complexes comprise detectably labeled antigen. In some embodiments, antibodies or antigen binding fragments, in binding complexes, are immobilized to one or more solid supports. In some embodiments, antigens, in binding complexes, are immobilized to one or more solid supports. Exemplary solid supports are disclosed herein and will be apparent to one of ordinary skill in the art. The foregoing examples of binding complexes are not intended to be limiting. Other examples of binding complexes will be apparent to one or ordinary skill in the art.

[0136] In any of the detection, diagnosis, and monitoring methods, the antibody, or antigen binding fragments, or antigen may be conjugated to a solid support surface, either directly or indirectly. Methods for conjugation to solid supports are standard and can be accomplished via covalent and non-covalent interactions. Non-limiting examples of conjugation methods include: adsorption, cross-linking, protein A/G-antibody interactions, and streptavidin-biotin interactions. Other methods of conjugation will be readily apparent to one of ordinary skill in the art.

[0137] In some aspects, the foregoing detection, diagnosis, and monitoring methods include comparing the level of the antibody or antigen binding fragment bound to the antigen (e.g., binding complexes) to one or more reference standards. The reference standard may be, for example, the level of a corresponding plectin-1 in a subject that does or does not have preeclampsia. In one embodiment, the reference standard is the level of plectin-1 detected in a sample that does not contain plectin-1 (e.g., a background level). Alternatively, a background level can be determined from a sample that contains a particular plectin-1, by contacting the sample with non-specific antibodies (e.g., antibodies obtained from non-immune serum). Then again, the reference standard may be the level of plectin-1 detected in a sample that does contain plectin-1 (e.g., a positive control). In some cases, the reference standard may be a series of levels associated with varying concentrations of plectin-1 in a sample and useful for quantifying the concentration of plectin-1 in the test sample. The foregoing examples of reference standards are not limiting and other suitable reference standard will be readily apparent to one of ordinary skill in the art.

[0138] Another embodiment relates to a diagnostic composition comprising any one of the above described antibodies, antigen binding fragments, polynucleotides, vectors or cells and optionally suitable means for detection. The antibodies or antigen binding fragments are, for example, suited for use in immunoassays in which they can be utilized in liquid phase or bound to a solid phase carrier. Examples of immunoassays which can utilize the antibody or antigen binding fragments are competitive and non-competitive immunoassays in either a direct or indirect format. Examples of such immunoassays are the Enzyme Linked Immunoassay (ELISA), radioimmunoassay (RIA), the sandwich (immunometric assay), flow cytometry, the western blot assay, immunoprecipitation assays, immunohistochemistry, immuno-microscopy, lateral flow immuno-chromatographic assays, and proteomics arrays. The antigens and antibodies or antigen binding fragments can be bound to many different solid supports (e.g., carriers, membrane, columns, proteomics array, etc.). Examples of solid support materials include glass, polystyrene, polyvinyl chloride, polyvinylidene difluoride, polypropylene, polyethylene, polycarbonate, dextran, nylon, amyloses, natural and modified celluloses, such as nitrocellulose, polyacrylamides, agaroses, and magnetite. The nature of the support can be either fixed or suspended in a solution (e.g., beads).

[0139] By a further embodiment, antibodies and antigen binding fragments provided herein may also be used in a method for evaluating plectin-1 expression in a subject by obtaining a biological sample from the subject which may be a blood sample, any other appropriate body fluid sample (e.g., lymph fluid), or a tissue sample (e.g., pancreatic tissue, ovarian tissue, tissue from the head or neck of a subject, breast tissue, lung tissue, etc.). The procedure may comprise contacting the sample (e.g., pancreatic tissue), or protein sample isolated therefrom, with an antibody, or antigen binding fragment, under conditions enabling the formation of binding complexes between antibody or antigen binding fragment and antigen. The level of such binding complexes may then be determined by methods known in the art.

[0140] In some embodiments, the biological sample is contacted with the antibody or antigen binding fragment under conditions suitable for binding of the antibody or antigen binding fragment to a plectin-1 protein, if the antigen is present in the sample, and formation of binding complexes consisting of antibody, or antigen binding fragment, bound to the antigen. This contacting step is typically performed in a reaction chamber, such as a tube, plate well, membrane bath, cell culture dish, microscope slide, and the like. In some embodiments, the antibody or antigen binding fragment is immobilized on a solid support. In some embodiments, the antigen is immobilized on a solid support. In some embodiments, the solid support is the surface of a the reaction chamber. In some embodiments, the solid support is of a polymeric membrane (e.g., nitrocellulose strip, Polyvinylidene Difluoride (PVDF) membrane, etc.). Other appropriate solid supports may be used.

[0141] In some embodiments, the antibody and antigen binding fragment is immobilized on the solid support prior to contacting with the antigen. In other embodiments, immobilization of the antibody and antigen binding fragment is performed after formation of binding complexes. In still other embodiments, antigen is immobilized on a solid support prior to formation of binding complexes. In some embodiments, a detection reagent is added to the reaction chamber to detect immobilized binding complexes. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the antigen. In some embodiments, the primary antibody or antigen binding fragment is itself detectable labeled, and is thereby the detection reagent.

[0142] In one aspect, detection methods comprise the steps of immobilizing antibodies or antigen binding fragments to a solid support; applying a sample (e.g., a biological sample or isolated protein sample) to the solid support under conditions that permit binding of antigen to the antibodies or antigen binding fragment, if present in the sample; removing the excess sample from the solid support; applying detectably labeled antibodies or antigen binding fragments under conditions that permit binding of the detectably labeled antibodies or antigen binding fragments to the antigen-bound immobilized antibodies or antigen binding fragments; washing the solid support and assaying for the presence of label on the solid support.

[0143] In some embodiments, the antigen is immobilized on the solid support, such as a PVDF membrane, prior to contacting with the antibody and antigen binding fragment in a reaction chamber (e.g., a membrane bath). A detection reagent is added to the reaction chamber to detect immobilized binding complexes. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the antigen. In some embodiments, the detection reagent comprises a detectably labeled secondary antibody directed against the primary antibody or antigen binding fragment. As disclosed herein, the detectable label may be, for example, a radioisotope, a fluorophore, a luminescent molecule, an enzyme, a biotin-moiety, an epitope tag, or a dye molecule. In some embodiments, the primary antibody or antigen binding fragment is itself detectable labeled, and is thereby the detection reagent. Suitable detectable labels are described herein, and will be readily apparent to one of ordinary skill in the art.

[0144] Accordingly, diagnostic kits, suitable for home or clinical use (point of care service), are provided that comprise (a) detectably labeled and/or non-labeled antibodies or antigen binding fragments, as antigen binding reagents (e.g., plectin-1 binding reagents); (b) a detection reagent; and, optionally, (c) complete instructions for using the reagents to detect antigens in a sample. In some embodiments, the diagnostic kit includes the antibody, or antigen binding fragment, and/or plectin-1 immobilized on a solid support. Any of the solid supports described herein are suitable for incorporation in the diagnostic kits. In a preferred embodiment, the solid support is the surface of a reaction chamber of a plate well. Typically, the plate well is in a multi-well plate having a number of wells selected from: 6, 12, 24, 96, 384, and 1536, but it is not so limited. In other embodiments, the diagnostic kits provide a detectably labeled antibody or antigen binding fragment. Diagnostic kits are not limited to these embodiments and other variations in kit composition will be readily apparent to one of ordinary skill in the art.

[0145] The present disclosure is further illustrated by the following Examples, which in no way should be construed as further limiting. The entire contents of all of the references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated by reference.

EXAMPLES

[0146] Expression and Purification of Human Plectin-1 in *E. coli*

[0147] Expression-ready constructs, both His-tagged vectors (15 mg/L, SEQ ID NO: 2) and GST-tagged vectors (30 mg/L, SEQ ID NO: 3), were used to generate monoclonal antibodies. To evaluate expression, the plasmids were transformed in strain B of *E. coli*. The trials were conducted in 4 mL test tubes, and the following variables were examined: temperature, expression time, and concentration of isopropyl β-D-1-thiogalactopyranoside (IPTG).

[0148] Cells were harvested by centrifugation. Cell pellets were lysed by sonication and target protein was obtained with one-step purification using a nickel column. Fractions were pooled and dialyzed against the storage buffer. Different storage buffers were used to determine which yielded the most stable protein with a concentration greater than 0.4 mg/mL. Proteins were analyzed by SDS-PAGE and Western blot using standard protocols to obtain molecular weight and purity measurements. The concentration of the protein was determined with a Bradford protein assay, using bovine serum albumin (BSA) as a standard.

[0149] Monoclonal Development of Anti-human Plectin-1 Protein

[0150] A specific panel of anti-human plectin-1 protein monoclonal antibodies which recognize the target protein (underlined in SEQ ID NO: 1; set forth in SEQ ID NO: 92) was developed.

[0151] First, five BALB/c mice were immunized with GenScript's MonoExpress immunization protocol and observed for two weeks.

[0152] Electrofusion was used to perform two fusions. The average fusion efficiency using this process is around 1 hybridoma/5000 B cells. The anticipated yield of hybridoma clones was 2×10^4, and the fused cells were plated into 96-well plates. An ELISA was performed to screen the

fusion proteins for positive clones. Supernatants from the positive clones were then further screened by ELISA against the target protein. 10*His-tagged protein was used as the counter screen. Selected clones were positive against the target protein and negative against the 10*His-tagged protein. The positive clones were expanded into 24-well plates coated with human recombinant Sec 8 (plectin-1 Section 8) and 2mL of supernatant for each clone was collected before the cells were frozen for storage. Table 3 shows the OD_{450nm} for cell lines grown on plates coated with human recombinant plectin-1 section 8.

TABLE 3

OD450 Results for Experimental Cell Lines

	OD 450		Host
Cell Line	A	B	Strain
PAb3	2.647	0.084	
PAb2	2.428	0.082	
PAb1	2.323	0.117	
PAb6	2.484	0.093	
PAb7	2.400	0.109	
PAb8	2.257	0.085	
PAb9	2.616	0.113	MOUSE
PAb4	2.484	0.118	
PAb10	2.326	0.132	
PAb11	2.418	0.110	
PC (antiserum 1:1k)	2.254	0.215	
PAb12	2.422	0.107	
PAb13	2.223	0.093	
PAb14	2.292	0.084	
PAb15	2.498	0.086	
PAb16	2.223	0.087	
PAb5	2.453	0.097	
PAb17	2.546	0.086	
PAb18	2.589	0.098	
PAb19	2.552	0.081	
PAb20	2.558	0.073	
NC (medium)	0.068	0.073	

[0153] Positive primary clones from the two fusions were sub-cloned by limiting dilution to ensure the sub-clones were derived from a single parental cell. The clones were grown for three generations. The sub-clones were further screened by ELISA. Based on the results of the ELISA, two stable sub-clonal cell lines of each primary clone were cryopreserved.

[0154] Clones PAb1 and PAb2, exhibited the highest specific plectin binding potential (FIG. **1**). Clones PAb3, PAb4, and PAb5 also demonstrated ability to kill cancer cells (FIG. **2**).

[0155] Roller bottles were used to produce the antibodies at a concentration of approximately 15 mg/L. The antibody proteins were further purified using protein A/G affinity column chromatography and dialyzed into PBS buffer for storage. For quality control, the antibodies underwent a purity test by SDS-PAGE, concentration determination by absorption at OD_{280nm}, and antigen reactivity by ELISA.

[0156] Selected antibodies were subjected to standard full length antibody sequencing. The antibodies underwent total RNA extraction, RT-PCR, and 5' RACE and 3' RACE PCR. The target PCR fragments of the variable and constant regions were gel-purified and cloned into sequencing vectors. At least five independent positive clones of each chain were sequenced in order to deduce the consensus sequence.

[0157] Monoclonal Antibody Sequencing of PAb1 and PAb2

[0158] PAb1 and PAb2 were sequenced using the following procedure. Total RNA was isolated from the hybridoma cells recovered by GenScript using TRIzol® reagent (Ambion, Cat. No.: 15596-026) and the procedure from the technical manual of TRIzol® reagent. The total RNA was then analyzed by agarose gel electrophoresis. Isotype-specific anti-sense primers or universal primers were used to reverse transcribe the total RNA into cDNA with the PrimeScript™ 1st Strand cDNA Synthesis Kit using the manufacturer's protocol. The antibody fragments of V_H, V_L, C_H, and C_L were amplified. Amplified antibody fragments were then separately cloned into a standard cloning vector using standard molecular cloning procedures. Colony PCR was performed to identify clones with inserts of correct sizes. More than five single colonies with inserts of correct sizes were sequenced for each antibody fragment.

[0159] Ultimately, five single colonies with correct V_H, V_L, C_H, C_L insert sizes were sent for sequencing. The V_H, V_L, C_H, C_L genes of five different clones were found to be nearly identical. The PAb1 and PAb2 consensus sequences, listed in the Sequences section below, represent the sequences of the PAb1 and PAb2 antibodies.

[0160] In Vitro Assays Using PAb1

[0161] In vitro binding assays were performed. FIG. **3**A shows PAb1 binds specifically to a recombinant human C-terminal portion of plectin-1 protein. Data indicate that PAb1 binds selectively to recombinant human Sec8-His protein with high affinity (e.g., a K_d<1 nM). FIG. **3**B shows PAb1 binding specificity on plectin-1 positive L3.6pl cancer cells; PAb1 did not bind to plectin-1 negative LNCaP cells.

[0162] FIGS. **4**A-**4**G show internalization of PAb1 in L3.6pl plectin-1 positive cancer cells. Representative confocal microscopy images demonstrating staining of L3.6pl cells with PAb1 (FIG. **4**A) or IgG control (FIG. **4**B), merged with endosomal marker LAMP-1, are shown. Co-localization of PAb1 and LAMP-1 was observed (FIGS. **4**C-**4**E). Quantification assays indicated that a significant portion of PAb1 merged with LAMP-1, whereas IgG control did not. Measurement of internalized ^{125}I-PAb1 radioactivity after incubation at 37° C., 4° C., or in combination with cold PAb1 in L3.6pl cells, indicated a decrease in radioactivity in both cell lines at 4° C. vs. 37 4° C., while internalization activity decreased only in the L3.6pl cells during competition with cold PAb1 (Comp.), as shown in FIG. **4**G.

[0163] FIGS. **5**A-**5**D show data relating to induction of cancer cell death by apoptosis after treatment with PAb1. FIG. **5**A shows a fluorescence minus one control experiment of L3.6pl cells by flow cytometry. FIG. **5**B shows L3.6pl Annexin V-positive cells 72 hours after treatment with IgG control. FIG. **5**C shows L3.6pl Annexin V-positive cells 72 hours after treatment with PAb1. Data indicate PAb1-treated L3.6pl cells experienced significantly more apoptosis (as assessed by Annexin V) compared to control IgG-treated cells (FIG. **5**D).

[0164] Survival of cancer cell types and healthy cell types was measured 72 hours after treatment with either PAb1 or IgG control. EC50s were calculated by logistical nonlinear regression and reported as the concentration of mAb (nM) that reduced cell viability by 50%. Data are shown in Table 4 (below).

TABLE 4

Cell name	Origin	Phenotype	Tissue type	Plectin-1mAb EC50 (nM)	Plectin-1 mAb Cell survival min. (%)	IgG EC50 (nM)	IgG Cell survival min. (%)
Keratinocyte	Human	Normal	Skin	500	80	no fit	90
HPDE	Human	Normal	Pancreas	300	80	330	64
RL14	Human	Normal	Heart	4020	55	345	82
HEK293T	Human	Normal	Kidney	324	32	65	95
L3.6pl	Human	Cancer	Pancreas	34	23	5049	9
YapC	Human	Cancer	Pancreas	43	19	225	38
OVCAR8	Human	Cancer	Ovary	63	16	no fit	100
SKOV3	Human	Cancer	Ovary	53	6	no fit	83

[0165] The effect of PAb1 treatment on tubulin anisotropy of YapC cancer cells was examined by confocal microscopy. FIG. **6**A shows tubulin staining in YapC cells that were not treated with PAb1. FIG. **6**B shows tubulin staining 10 minutes post monomethyl auristatin E (MMAE) treatment; MMAE blocks tubulin polymerization. FIG. **6**C shows tubulin staining 24 hours post PAb1 treatment. Data indicate a decrease in anisotropy in cells treated with PAb1 compared to untreated control cells (FIG. **6**D).

[0166] Co-localization of PAb1 with tubulin in YapC cancer cells was also investigated. Representative confocal microscopy images of YapC after tubulin staining (FIG. **7**A) and PAb1 staining (FIG. **7**B) are shown. Data indicate that tubulin and PAb1 co-localize (FIG. **7**C; arrows) on the surface of dying cells. Increased PAb1 staining was also observed on couple cells.

[0167] In Vitro Assays Using PAb1

[0168] Immunocompromised mice bearing a subcutaneous YapC tumor were administered either PAb1 or IgG control. Data indicated that after 11 days, the mice treated with 3 mg/kg PAb1 had a significantly smaller tumor volume than mice treated with the IgG control (FIG. **8**A). Data also indicated that 1 mg/kg PAb1 of mice elicited a significant reduction of tumor volume at day 14. Two higher doses (1 mg/kg and 3 mg/kg) of PAb1 resulted in a significantly lower tumor volume compared to the mice treated with 0.3 mg/kg PAb1 (FIG. **8**A), indicating a dose-dependent effect. Data also indicated that animals treated with PAb1 did not lose weight during the entire duration of treatment (FIG. **8**B). Photos of mice treated with 3 mg/kg PAb1 at Day 0, Day 14 and Day 25 are also shown (FIGS. **8**C-**8**E).

SEQUENCES

[0169]

-Plectin (hemidesmosomal protein 1), *Homo sapiens*;
target protein underlined

>SEQ ID NO: 1

MVAGMLMPRDQLRAIYEVLFREGVMVAKKDRRPRSLHPHVPGVTNLQVMRAMASLRARG

LVRETFAWCHFYWYLTNEGIAHLRQYLHLPPEIVPASLQRVRRPVAMVMPARRTPHVQAVQ

GPLGSPPKRGPLPTEEQRVYRRKELEEVSPETPVVPATTQRTLARPGPEPAPATDERDRVQKK

TFTKWVNKHLIKAQRHISDLYEDLRDGHNLISLLEVLSGDSLPREKGRMRFHKLQNVQIALD

YLRHRQVKLVNIRNDDIADGNPKLTLGLIWTIILHFQISDIQVSGQSEDMTAKEKLLLWSQRM

VEGYQGLRCDNFTSSWRDGRLFNAIIHRHKPLLIDMNKVYRQTNLENLDQAFSVAERDLGVT

RLLDPEDVDVPQPDEKSIITYVSSLYDAMPRVPDVQDGVRANELQLRWQEYRELVLLLLQW

MRHHTAAFEERRFPSSFEEIEILWSQFLKFKEMELPAKEADKNRSKGIYQSLEGAVQAGQLKV

PPGYHPLDVEKEWGKLHVAILEREKQLRSEFERLECLQRIVTKLQMEAGLCEEQLNQADALL

QSDVRLLAAGKVPQRAGEVERDLDKADSMIRLLFNDVQTLKDGRHPQGEQMYRRVYRLHE

RLVAIRTEYNLRLKAGVAAPATQVAQVTLQSVQRRPELEDSTLRYLQDLLAWVEENQHRVD

GAEWGVDLPSVEAQLGSHRGLHQSIEEFRAKIERARSDEGQLSPATRGAYRDCLGRLDLQYA

KLLNSSKARLRSLESLHSFVAAATKELMWLNEKEEEEVGFDWSDRNTNMTAKKESYSALMR

ELELKEKKIKELQNAGDRLLREDHPARPTVESFQAALQTQWSWMLQLCCCIEAHLKENAAY

FQFFSDVREAEGQLQKLQEALRRKYSCDRSATVTRLEDLLQDAQDEKEQLNEYKGHLSGLA

KRAKAVVQLKPRHPAHPMRGRLPLLAVCDYKQVEVTVHKGDECQLVGPAQPSHWKVLSSS

GSEAAVPSVCFLVPPPNQEAQEAVTRLEAQHQALVTLWHQLHVDMKSLLAWQSLRRDVQLI

RSWSLATFRTLKPEEQRQALHSLELHYQAFLRDSQDAGGFGPEDRLMAEREYGSCSHHYQQ

-continued

LLQSLEQGAQEESRCQRCISELKDIRLQLEACETRTVHRLRLPLDKEPARECAQRIAEQQKAQ

AEVEGLGKGVARLSAEAEKVLALPEPSPAAPTLRSELELTLGKLEQVRSLSAIYLEKLKTISLV

IRGTQGAEEVLRAHEEQLKEAQAVPATLPELEATKASLKKLRAQAEAQQPTFDALRDELRGA

QEVGERLQQRHGERDVEVERWRERVAQLLERWQAVLAQTDVRQRELEQLGRQLRYYRESA

DPLGAWLQDARRRQEQIQAMPLADSQAVREQLRQEQALLEEIERHGEKVEECQRFAKQYIN

AIKDYELQLVTYKAQLEPVASPAKKPKVQSGSESVIQEYVDLRTHYSELTTLTSQYIKFISETL

RRMEEEERLAEQQRAEERERLAEVEAALEKQRQLAEAHAQAKAQAEREAKELQQRMQEEV

VRREEAAVDAQQQKRSIQEELQQLRQSSEAEIQAKARQAEAAERSRLRIEEEIRVVRLQLEAT

ERQRGGAEGELQALRARAEEAEAQKRQAQEEAERLRRQVQDESQRKRQAEVELASRVKAE

AEAAREKQRALQALEELRLQAEEAERRLRQAEVERARQVQVALETAQRSAEAELQSKRASF

AEKTAQLERSLQEEHVAVAQLREEAERRAQQQAEAERAREEAERELERWQLKANEALRLRL

QAEEVAQQKSLAQAEAEKQKEEAEREARRRGKAEEQAVRQRELAEQELEKQRQLAEGTAQ

QRLAAEQELIRLRAETEQGEQQRQLLEEELARLQREAAAATQKRQELEAELAKVRAEMEVL

LASKARAEEESRSTSEKSKQRLEAEAGRFRELAEEAARLRALAEEAKRQRQLAEEDAARQRA

EAERVLAEKLAAIGEATRLKTEAEIALKEKEAENERLRRLAEDEAFQRRRLEEQAAQHKADI

EERLAQLRKASDSELERQKGLVEDTLRQRRQVEEEILALKASFEKAAAGKAELELELGRIRSN

AEDTLRSKEQAELEAARQRQLAAEEERRRREAEERVQKSLAAEEEAARQRKAALEEVERLK

AKVEEARRLRERAEQESARQLQLAQEAAQKRLQAEEKAHAFAVQQKEQELQQTLQQEQSV

LDQLRGEAEAARRAAEEAEEARVQAEREAAQSRRQVEEAERLKQSAEEQAQARAQAQAAA

EKLRKEAEQEAARRAQAEQAALRQKQAADAEMEKHKKFAEQTLRQKAQVEQELTTLRLQL

EETDHQKNLLDEELQRLKAEATEAARQRSQVEEELFSVRVQMEELSKLKARIEAENRALILR

DKDNTQRFLQEEAEKMKQVAEEAARLSVAAQEAARLRQLAEEDLAQQRALAEKMLKEKM

QAVQEATRLKAEAELLQQQKELAQEQARRLQEDKEQMAQQLAEETQGFQRTLEAERQRQL

EMSAEAERLKLRVAEMSRAQARAEEDAQRFRKQAEEIGEKLHRTELATQEKVTLVQTLEIQR

QQSDHDAERLREAIAELEREKEKLQQEAKLLQLKSEEMQTVQQEQLLQETQALQQSFLSEKD

SLLQRERFIEQEKAKLEQLFQDEVAKAQQLREEQQRQQQQMEQERQRLVASMEEARRRQHE

AEEGVRRKQEELQQLEQQRRQQEELLAEENQRLREQLQLLEEQHRAALAHSEEVTASQVAA

TKTLPNGRDALDGPAAEAEPEHSFDGLRRKVSAQRLQEAGILSAEELQRLAQGHTTVDELAR

REDVRHYLQGRSSIAGLLLKATNEKLSVYAALQRQLLSPGTALILLEAQAASGFLLDPVRNRR

LTVNEAVKEGVVGPELHHKLLSAERAVTGYKDPYTGQQISLFQAMQKGLIVREHGIRLLEAQ

IATGGVIDPVHSHRVPVDVAYRRGYFDEEMNRVLADPSDDTKGFFDPNTHENLTYLQLLERC

VEDPETGLCLLPLTDKAAKGGELVYTDSEARDVFEKATVSAPFGKFQGKTVTIWEIINSEYFT

AEQRRDLLRQFRTGRITVEKIIKIIITVVEEQEQKGRLCFEGLRSLVPAAELLESRVIDRELYQQ

LQRGERSVRDVAEVDTVRRALRGANVIAGVWLEEAGQKLSIYNALKKDLLPSDMAVALLEA

QAGTGHIIDPATSARLTVDEAVRAGLVGPEFHEKLLSAEKAVTGYRDPYTGQSVSLFQALKK

GLIPREQGLRLLDAQLSTGGIVDPSKSHRVPLDVACARGCLDEETSRALSAPRADAKAYSDPS

TGEPATYGELQQRCRPDQLTGLSLLPLSEKAARARQEELYSELQARETFEKTPVEVPVGGFK

GRTVTVWELISSEYFTAEQRQELLRQFRTGKVTVEKVIKILITIVEEVETLRQERLSFSGLRAPV

PASELLASGVLSRAQFEQLKDGKTTVKDLSELGSVRTLLQGSGCLAGIYLEDTKEKVSIYEAM

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RRGLLRATTAALLLEAQAATGFLVDPVRNQRLYVHEAVKAGVVGPELHEQLLSAEKAVTGY

RDPYSGSTISLFQAMQKGLVLRQHGIRLLEAQIATGGIIDPVHSHRVPVDVAYQRGYFSEEMN

RVLADPSDDTKGFFDPNTHENLTYRQLLERCVEDPETGLRLLPLKGAEKAEVVETTQVYTEE

ETRRAFEETQIDIPGGGSHGGSTMSLWEVMQSDLIPEEQRAQLMADFQAGRVTKERMIIIIIEII

EKTEIIRQQGLASYDYVRRRLTAEDLFEARIISLETYNLLREGTRSLREALEAESAWCYLYGTG

SVAGVYLPGSRQTLSIYQALKKGLLSAEVARLLLEAQAATGFLLDPVKGERLTVDEAVRKGL

VGPELHDRLLSAERAVTGYRDPYTEQTISLFQAMKKELIPTEEALRLLDAQLATGGIVDPRLG

FHLPLEVAYQRGYLNKDTHDQLSEPSEVRSYVDPSTDERLSYTQLLRRCRRDDGTGQLLLPL

SDARKLTFRGLRKQITMEELVRSQVMDEATALQLREGLTSIEEVTKNLQKFLEGTSCIAGVFV

DATKERLSVYQAMKKGIIRPGTAFELLEAQAATGYVIDPIKGLKLTVEEAVRMGIVGPEFKD

KLLSAERAVTGYKDPYSGKLISLFQAMKKGLILKDHGIRLLEAQIATGGIIDPEESHRLPVEVA

YKRGLFDEEMNEILTDPSDDTKGFFDPNTEENLTYLQLMERCITDPQTGLCLLPLKEKKRERK

TSSKSSVRKRRVVIVDPETGKEMSVYEAYRKGLIDHQTYLELSEQECEWEEITISSSDGVVKS

MIIDRRSGRQYDIDDAIAKNLIDRSALDQYRAGTLSITEFADMLSGNAGGFRSRSSSVGSSSSY

PISPAVSRTQLASWSDPTEETGPVAGILDTETLEKVSITEAMHRNLVDNITGQRLLEAQACTG

GIIDPSTGERFPVTDAVNKGLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQALKKGWLY

YEAGQRFLEVQYLTGGLIEPDTPGRVPLDEALQRGTVDARTAQKLRDVGAYSKYLTCPKTK

LKISYKDALDRSMVEEGTGLRLLEAAAQSTKGYYSPYSVSGSGSTAGSRTGSRTGSRAGSRR

GSFDATGSGFSMTFSSSSYSSSGYGRRYASGSSASLGGPESAVA

-pET-10NC-Plec C term: His tag-EK cleavage site-Human plectin 1 (section 8)-stop codon (344 amino acids; MW = 36959.2; predicted pI = 8.80)

>SEQ ID NO: 2

MR*SHHHHHHHHHH*RSGTG**DDDDK**AMADIGSEFELRRQACGFRSRSSSVGSSSSYPIS

PAVSRTQLASWSDPTEETGPVAGILDTETLEKVSITEAMHRNLVDNITGQRLLEAQAC

TGGIIDPSTGERFPVTDAVNKGLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQAL

KKGWLYYEAGQRFLEVQYLTGGLIEPDTPGRVPLDEALQRGTVDARTAQKLRDVG

AYSKYLTCPKTKLKISYKDALDRSMVEEGTGLRLLEAAAQSTKGYYSPYSVSGSGST

AGSRTGSRTGSRAGSRRGSFDATGSGFSMTFSSSSYSSSGYGRRYASGSSSLGGPESA

VA.

-pGEX2t-Section 8: GST tag-Thrombin cleavage site-Human plectin 1 (section 8)-stop codon (540 amino acids; MW = 59809.3; predicted pI = 8.15)

>SEQ ID NO: 3

MSPILGYWKIKGLVQPTRLLLEYLEEKYEEHLYERDEGDKWRNKKFELGLEFPNLPYYIDGDVKLT

QSMAIIRYIADKHNMLGGCPKERAEISMLEGAVLDIRYGVSRIAYSKDFETLKVDFLSKLPEMLKMF

EDRLCHKTYLNGDHVTHPDFMLYDALDVVLYMDPMCLDAFPKLVCFKKRIEAIPQIDKYLKSSKYI

*AWPLQGWQATFGGGDHPPK*SD**LVPRGS**EFELRRQACGFRSRSSSVGSSSSYPISPAVSRTQLA

SWSDPTEETGPVAGILDTETLEKVSITEAMHRNLVDNITGQRLLEAQACTGGIIDPSTGERFPV

TDAVNKGLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQALKKGWLYYEAGQRFLEVQY

LTGGLIEPDTPGRVPLDEALQRGTVDARTAQKLRDVGAYSKYLTCPKTKLKISYKDALDRSM

VEEGTGLRLLEAAAQSTKGYYSPYSVSGSGSTAGSRTGSRTGSRAGSRRGSFDATGSGFSMT

FSSSSYSSSGYGRRYASGSSSLGGPESAVA.

Pab2 Sequences

[0170]

Name	Sequence	SEQ ID NO:
Pab2 Heavy Chain	ATGAACTTCGGGCTCAGCTTGATTTTCCTTGCCCTCATTTTA AAAGGTGTCCAGTGTGAGGTGCAGCTGGTGGAGTCTGGGG GAGACTTGGTGAAGCCTGGAGGGTCCCTGAAACTCTCCTGT GCAGCCTCTGGATTCACTTTCAGTAGGTATGGCATGTCTTG GGTTCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCGCA ACCATTAGTATTGGTGGTACTTACACCTACTATCCAGACAG TATGAAGGGGCGATTCACCATCTCCAGAGACAATGCCAAG AACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGG ACACAGCCATGTATTACTGTGCAAGACGGGGGTATGGTAA CTACTCTTACTATGGTATGGACTACTGGGGTCAAGGAACCT CAGTCACCGTCTCCTCAGCCAAAACGACACCCCCATCTGTC TATCCACTGGCCCCTGGATCTGCTGCCCAAACTAACTCCAT GGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGC CAGTGACAGTGACCTGGAACTCTGGATCCCTGTCCAGCGGT GTGCACACCTTCCCAGCTGTCCTGCAGTCTGACCTCTACAC TCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCA GCGAGACCGTCACCTGCAACGTTGCCCACCCGGCCAGCAG CACCAAGGTGGACAAGAAAATTGTGCCCAGGGATTGTGGT TGTAAGCCTTGCATATGTACAGTCCCAGAAGTATCATCTGT CTTCATCTTCCCCCCAAAGCCCAAGGATGTGCTCACCATTA CTCTGACTCCTAAGGTCACGTGTGTTGTGGTAGACATCAGC AAGGATGATCCCGAGGTCCAGTTCAGCTGGTTTGTAGATGA TGTGGAGGTGCACACAGCTCAGACGCAACCCCGGGAGGAG CAGTTCAACAGCACTTTCCGCTCAGTCAGTGAACTTCCCAT CATGCACCAGGACTGGCTCAATGGCAAGGAGTTCAAATGC AGGGTCAACAGTGCAGCTTTCCCTGCCCCCATCGAGAAAA CCATCTCCAAAACCAAAGGCAGACCGAAGGCTCCACAGGT GTACACCATTCCACCTCCCAAGGAGCAGATGGCCAAGGAT AAAGTCAGTCTGACCTGCATGATAACAGACTTCTTCCCTGA AGACATTACTGTGGAGTGGCAGTGGAATGGGCAGCCAGCG GAGAACTACAAGAACACTCAGCCCATCATGGACACAGATG GCTCTTACTTCGTCTACAGCAAGCTCAATGTGCAGAAGAGC AACTGGGAGGCAGGAAATACTTTCACCTGCTCTGTGTTACA TGAGGGCCTGCACAACCACCATACTGAGAAGAGCCTCTCC CACTCTCCTGGTAAATGA	4
Pab2 Heavy Chain Leader	ATGAACTTCGGGCTCAGCTTGATTTTCCTTGCCCTCATTTTA AAAGGTGTCCAGTGT	5
Pab2 Heavy Chain FR1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGC CTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATTC ACTTTCAGT	6
Pab2 Heavy Chain CDR1	AGGTATGGCATGTCT	7
Pab2 Heavy Chain FR2	TGGGTTCGCCAGACTCCAGACAAGAGGCTGGAGTGGGTCG CA	8
Pab2 Heavy Chain CDR2	ACCATTAGTATTGGTGGTACTTACACCTACTATCCAGACAG TATGAAGGGG	9
Pab2 Heavy Chain FR3	CGATTCACCATCTCCAGAGACAATGCCAAGAACACCCTGT ACCTGCAAATGAGCAGTCTGAAGTCTGAGGACACAGCCAT GTATTACTGTGCAAGA	10
Pab2 Heavy Chain CDR3	CGGGGGTATGGTAACTACTCTTACTATGGTATGGACTAC	11
Pab2 Heavy Chain FR4	TGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA	12

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Name	Sequence	SEQ ID NO:
Pab2 Heavy Chain Variable Region	GAGGTGCAGCTGGTGGAGTCTGGGGGAGACTTGGTGAAGC CTGGAGGGTCCCTGAAACTCTCCTGTGCAGCCTCTGGATTC ACTTTCAGTAGGTATGGCATGTCTTGGGTTCGCCAGACTCC AGACAAGAGGCTGGAGTGGGTCGCAACCATTAGTATTGGT GGTACTTACACCTACTATCCAGACAGTATGAAGGGGCGATT CACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTG CAAATGAGCAGTCTGAAGTCTGAGGACACAGCCATGTATT ACTGTGCAAGACGGGGGTATGGTAACTACTCTTACTATGGT ATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTC A	13
Pab2 Heavy Chain Constant Region	GCCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTGG ATCTGCTGCCCAAACTAACTCCATGGTGACCCTGGGATGCC TGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGTGACCTGG AACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGC TGTCCTGCAGTCTGACCTCTACACTCTGAGCAGCTCAGTGA CTGTCCCCTCCAGCACCTGGCCCAGCGAGACCGTCACCTGC AACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGA AAATTGTGCCCAGGGATTGTGGTTGTAAGCCTTGCATATGT ACAGTCCCAGAAGTATCATCTGTCTTCATCTTCCCCCCAAA GCCCAAGGATGTGCTCACCATTACTCTGACTCCTAAGGTCA CGTGTGTTGTGGTAGACATCAGCAAGGATGATCCCGAGGT CCAGTTCAGCTGGTTTGTAGATGATGTGGAGGTGCACACAG CTCAGACGCAACCCCGGGAGGAGCAGTTCAACAGCACTTT CCGCTCAGTCAGTGAACTTCCCATCATGCACCAGGACTGGC TCAATGGCAAGGAGTTCAAATGCAGGGTCAACAGTGCAGC TTTCCCTGCCCCCATCGAGAAAACCATCTCCAAAACCAAAG GCAGACCGAAGGCTCCACAGGTGTACACCATTCCACCTCCC AAGGAGCAGATGGCCAAGGATAAAGTCAGTCTGACCTGCA TGATAACAGACTTCTTCCCTGAAGACATTACTGTGGAGTGG CAGTGGAATGGGCAGCCAGCGGAGAACTACAAGAACACTC AGCCCATCATGGACACAGATGGCTCTTACTTCGTCTACAGC AAGCTCAATGTGCAGAAGAGCAACTGGGAGGCAGGAAATA CTTTCACCTGCTCTGTGTTACATGAGGGCCTGCACAACCAC CATACTGAGAAGAGCCTCTCCCACTCTCCTGGTAAA	14
Pab2 Heavy Chain	MNFGLSLIFLALILKGVQCEVQLVESGGDLVKPGGSLKLSCAA SGFTFSRYGMSWVRQTPDKRLEWVATISIGGTYTYYPDSMKG RFTISRDNAKNTLYLQMSSLKSEDTAMYYCARRGYGNYSYY GMDYWGQGTSVTVSSAKTTPPSVYPLAPGSAAQTNSMVTLG CLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSD	15
Pab2 Heavy Chain Leader	MNFGLSLIFLALILKGVQC	16
Pab2 Heavy Chain FR1	EVQLVESGGDLVKPGGSLKLSCAASGFTFS	17
Pab2 Heavy Chain CDR1	RYGMS	18
Pab2 Heavy Chain FR2	WVRQTPDKRLEWVA	19
Pab2 Heavy Chain CDR2	TISIGGTYTYYPDSMKG	20
Pab2 Heavy Chain FR3	RFTISRDNAKNTLYLQMSSLKSEDTAMYYCAR	21
Pab2 Heavy Chain CDR3	RGYGNYSYYGMDY	22
Pab2 Heavy Chain FR4	WGQGTSVTVSS	23
Pab2 Heavy Chain Variable Region	EVQLVESGGDLVKPGGSLKLSCAASGFTFSRYGMSWVRQTPD KRLEWVATISIGGTYTYYPDSMKGRFTISRDNAKNTLYLQMS SLKSEDTAMYYCARRGYGNYSYYGMDYWGQGTSVTVSS	24

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Name	Sequence	SEQ ID NO:
Pab2 Heavy Chain Constant Region	AKTTPPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWN SGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVA HPASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTI TLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTQPREEQ FNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKT KGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQ WNGQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTF TCSVLHEGLHNHHTEKSLSHSPGK	25
Pab2 Light Chain	ATGAGGTTCTCTGCTCAGCTTCTGGGGCTGCTTGTGCTCTG GATCCCTGGATCCACTGCAGATATTGTGATGACGCAGGCTG CATTCTCCAATCCAGTCACTCTTGGAACATCAGCTTCCATC TCCTGCAGGTCTAGTAAGAGTCTCCTACATAGTAATGGCAT CACTTATTTGTATTGGTATCTGCAGAAGCCAGGCCAGTCTC CTCAGCTCCTGATTTATCAGATGTCCAACCTTGCCTCAGGA GTCCCAGACAGGTTCAGTAGCAGTGGGTCAGGAACTGATT TCACACTGAGAATCAGCAGAGTGGAGGCTGAGGATGTGGG TGTTTATTACTGTGCTCAAAATCTAGAACTTCCGCTCACGTT CGGTGCTGGGACCAAGCTGGAGCTGAAACGGGCTGATGCT GCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTT AACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACT TCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGG CAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGAT CAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCC TCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTA TACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG TCAAGAGCTTCAACAGGAATGAGTGTTAG	26
Pab2 Light Chain Leader	ATGAGGTTCTCTGCTCAGCTTCTGGGGCTGCTTGTGCTCTG GATCCCTGGATCCACTGCA	27
Pab2 Light Chain FR1	GATATTGTGATGACGCAGGCTGCATTCTCCAATCCAGTCAC TCTTGGAACATCAGCTTCCATCTCCTGC	28
Pab2 Light Chain CDR1	AGGTCTAGTAAGAGTCTCCTACATAGTAATGGCATCACTTA TTTGTAT	29
Pab2 Light Chain FR2	TGGTATCTGCAGAAGCCAGGCCAGTCTCCTCAGCTCCTGAT TTAT	30
Pab2 Light Chain CDR2	CAGATGTCCAACCTTGCCTCA	31
Pab2 Light Chain FR3	GGAGTCCCAGACAGGTTCAGTAGCAGTGGGTCAGGAACTG ATTTCACACTGAGAATCAGCAGAGTGGAGGCTGAGGATGT GGGTGTTTATTACTGT	32
Pab2 Light Chain CDR3	GCTCAAAATCTAGAACTTCCGCTCACG	33
Pab2 Light Chain FR4	TTCGGTGCTGGGACCAAGCTGGAGCTGAAA	34
Pab2 Light Chain Variable Region	GATATTGTGATGACGCAGGCTGCATTCTCCAATCCAGTCAC TCTTGGAACATCAGCTTCCATCTCCTGCAGGTC TAGTAAGAGTCTCCTACATAGTAATGGCATCACTTATTTGT ATTGGTATCTGCAGAAGCCAGGCCAGTCTCCTCAGCTCCTG ATTTATCAGATGTCCAACCTTGCCTCAGGAGTCCCAGACAG GTTCAGTAGCAGTGGGTCAGGAACTGATTTCACACTGAGA ATCAGCAGAGTGGAGGCTGAGGATGTGGGTGTTTATTACT GTGCTCAAAATCTAGAACTTCCGCTCACGTTCGGTGCTGGG ACCAAGCTGGAGCTGAAA	35

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Name	Sequence	SEQ ID NO:
Pab2 Light Chain Constant Region	CTGTGCTCAAAATCTAGAACTTCCGCTCACGTTCGGTGCTG GGACCAAGCTGGAGCTGAAACGGGCTGATGCTGCACCAAC TGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTG GAGGTGCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCC AAAGACATCAATGTCAAGTGGAAGATTGATGGCAGTGAAC GACAAAATGGCGTCCTGAACAGTTGGACTGATCAGGACAG CAAAGACAGCACCTACAGCATGAGCAGCACCCTCACGTTG ACCAAGGACGAGTATGAACGACATAACAGCTATACCTGTG AGGCCACTCACA AGACATCAACTTCACCCATTGTCAAGAGCTTCAACAGGAAT GAGTGT	36
Pab2 Light Chain	MRFSAQLLGLLVLWIPGSTADIVMTQAAFSNPVTLGTSASISC RSSKSLLHSNGITYLYWYLQKPGQSPQLLIYQMSNLASGVPDR FSSSGSGTDFTLRISRVEAEDVGVYYCAQNLELPLTFGAGTKL ELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVK WKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYER HNSYTCEATHKTSTSPIVKSFNRNEC	37
Pab2 Light Chain Leader	MRFSAQLLGLLVLWIPGSTA	38
Pab2 Light Chain FR1	DIVMTQAAFSNPVTLGTSASISC	39
Pab2 Light Chain CDR1	RSSKSLLHSNGITYLY	40
Pab2 Light Chain FR2	WYLQKPGQSPQLLIY	41
Pab2 Light Chain CDR2	QMSNLAS	42
Pab2 Light Chain FR3	GVPDRFSSSGSGTDFTLRISRVEAEDVGVYYC	43
Pab2 Light Chain CDR3	AQNLELPLT	44
Pab2 Light Chain FR4	FGAGTKLELK	45
Pab2 Light Chain Variable Region	DIVMTQAAFSNPVTLGTSASISCRSSKSLLHSNGITYLYWYLQ KPGQSPQLLIYQMSNLASGVPDRFSSSGSGTDFTLRISRVEAED VGVYYCAQNLELPLTFGAGTKLELK	46
Pab2 Light Chain Constant Region	RADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNS YTCEATHKTSTSPIVKSFNRNEC	47

[0171] Pab1 Sequences

Name	Sequence	SEQ ID NO:
Pab1 Heavy Chain	ATGGCTTGGGTGTGGACCTTGCTATTCCTGATGGCAGCTGC CCAAAGTATCCAAGCACAGATCCAGTTGGTGCAGTCTGGA CCTGAGCTGAAGAAGCCTGGAGAGACAGTCAAGATCTCCT GCAAGGCTTCTGGTTATACCTTCACAGACTATTCAATGCAC TGGGTGAAGCAGGCTCCAGGAAAGGGTTTAAAGTGGATGG GCTGGATAAACACTGAGACTGGTGAGCCAACATATGCAGA TGACTTCAAGGGACGGTTTGCCTTCTCTTTGGAAACCTCTG CCAGCACTGCCTATTTGCAGATCAACAACCTCAAAAATGA GGACACGGCTAC ATATTTCTGTGCCCCCGGAGGGTTTGCTTACTGGGGCCAAG GGACTCTGGTCACTGTCTCTGCAGCCAAAACAACACCCCCA	48

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Name	Sequence	SEQ ID NO:
	TCAGTCTATCCACTGGCCCCTGGGTGTGGAGATACAACTGG TTCCTCCGTGACTCTGGGATGCCTGGTCAAGGGCTACTTCC CTGAGTCAGTGACTGTGACTTGGAACTCTGGATCCCTGTCC AGCAGTGTGCACACCTTCCCAGCTCTCCTGCAGTCTGGACT CTACACTATGAGCAGCTCAGTGACTGTCCCCTCCAGCACCT GGCCAAGTCAGACCGTCACCTGCAGCGTTGCTCACCCAGCC AGCAGCACCACGGTGGACAAAAAACTTGAGCCCAGCGGGC CCATTTCAACAATCAACCCCTGTCCTCCATGCAAGGAGTGT CACAAATGCCCAGCTCCTAACCTCGAGGGTGGACCATCCGT CTTCATCTTCCCTCCAAATATCAAGGATGTACTCATGATCT CCCTGACACCCAAGGTCACGTGTGTGGTGGTGGATGTGAG CGAGGATGACCCAGACGTCCAGATCAGCTGGTTTGTGAAC AACGTGGAAGTACACACAGCTCAGACACAAACCCATAGAG AGGATTACAACAGTACTATCCGGGTGGTCAGCACCCTCCCC ATCCAGCACCAGGACTGGATGAGTGGCAAGGAGTTCAAAT GCAAGGTCAACAACAAAGACCTCCCATCACCCATCGAGAG AACCATCTCAAAAATTAAAGGGCTAGTCAGAGCTCCACAA GTATACATCTTGCCGCCACCAGCAGAGCAGTTGTCCAGGA AAGATGTCAGTCTCACTTGCCTGGTCGTGGGCTTCAACCCT GGAGACATCAGTGTGGAGTGGACCAGCAATGGGCATACAG AGGAGAACTACAAGGACACCGCACCAGTCCTGGACTCTGA CGGTTCTTACTTCATATATAGCAAGCTCAATATGAAAACAA GCAAGTGGGAGAAAACAGATTCCTTCTCATG CAACGTGAGACACGAGGGTCTGAAAAATTACTACCTGAAG AAGACCATCTCCCGGTCTCCGGGTAAATGA	
Pab1 Heavy Chain Leader	ATGGCTTGGGTGTGGACCTTGCTATTCCTGATGGCAGCTGC CCAAAGTATCCAAGCA	49
Pab1 Heavy Chain FR1	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAAGAAGC CTGGAGAGACAGTCAAGATCTCCTGCAAGGCTTCTGGTTAT ACCTTCACA	50
Pab1 Heavy Chain CDR1	GACTATTCAATGCAC	51
Pab1 Heavy Chain FR2	TGGGTGAAGCAGGCTCCAGGAAAGGGTTTAAAGTGGATGG GC	52
Pab1 Heavy Chain CDR2	TGGATAAACACTGAGACTGGTGAGCCAACATATGCAGATG ACTTCAAGGGA	53
Pab1 Heavy Chain FR3	CGGTTTGCCTTCTCTTTGGAAACCTCTGCCAGCACTGCCTAT TTGCAGATCAACAACCTCAAAAATGAGGACACGGCTACAT ATTTCTGTGCCCCC	54
Pab1 Heavy Chain CDR3	GGAGGGTTTGCTTAC	55
Pab2 Heavy Chain FR4	TGGGGCCAAGGGACTCTGGTCACTGTCTCTGCA	56
Pab1 Heavy Chain Variable Region	CAGATCCAGTTGGTGCAGTCTGGACCTGAGCTGAAGAAGC CTGGAGAGACAGTCAAGATCTCCTGCAAGGCTTCTGGTTAT ACCTTCACAGACTATTCAATGCACTGGGTGAAGCAGGCTCC AGGAAAGGGTTTAAAGTGGATGGGCTGGATAAACACTGAG ACTGGTGAGCCAACATATGCAGATGACTTCAAGGGACGGT TTGCCTTCTCTTTGGAAACCTCTGCCAGCACTGCCTATTTGC AGATCAACAACCTCAAAAATGAGGACACGGCTACATATTT CTGTGCCCCCGGAGGGTTTGCTTACTGGGGCCAAGGGACTC TGGTCACTGTCTCTGCA	57
Pab1 Heavy Chain Constant Region	GCCAAAACAACACCCCCATCAGTCTATCCACTGGCCCCTGG GTGTGGAGATACAACTGGTTCCTCCGTGACTCTGGGATGCC TGGTCAAGGGCTACTTCCCTGAGTCAGTGACTGTGACTTGG AACTCTGGATCCCTGTCCAGCAGTGTGCACACCTTCCCAGC TCTCCTGCAGTCTGGACTCTACACTATGAGCAGCTCAGTGA CTGTCCCCTCCAGCACCTGGCCAAGTCAGACCGTCACCTGC AGCGTTGCTCACCCAGCCAGCAGCACCACGGTGGACAAAA AACTTGAGCCCAGCGGGCCCATTTCAACAATCAACCCCTGT CCTCCATGCAAGGAGTGTCACAAATGCCCAGCTCCTAACCT CGAGGGTGGACCATCCGTCTTCATCTTCCCTCCAAATATCA	58

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Name	Sequence	SEQ ID NO:
	AGGATGTACTCATGATCTCCCTGACACCCAAGGTCACGTGT GTGGTGGTGGATGTGAGCGAGGATGACCCAGACGTCCAGA TCAGCTGGTTTGTGAACAACGTGGAAGTACACACAGCTCA GACACAAACCCATAGAGAGGATTACAACAGTACTATCCGG GTGGTCAGCACCCTCCCCATCCAGCACCAGGACTGGATGA GTGGCAAGGAGTTCAAATGCAAGGTCAACAACAAAGACCT CCCATCACCCATCGAGAGAACCATCTCAAAAATTAAAGGG CTAGTCAGAGCTCCACAAGTATACATCTTGCCGCCACCAGC AGAGCAGTT GTCCAGGAAAGATGTCAGTCTCACTTGCCTGGTCGTGGGCT TCAACCCTGGAGACATCAGTGTGGAGTGGACCAGCAATGG GCATACAGAGGAGAACTACAAGGACACCGCACCAGTCCTG GACTCTGACGGTTCTTACTTCATATATAGCAAGCTCAATAT GAAAACAAGCAAGTGGGAGAAAACAGATTCCTTCTCATGC AACGTGAGACACGAGGGTCTGAAAAATTACTACCTGAAGA AGACCATCTCCCGGTCTCCGGGTAAA	
Pab1 Heavy Chain	MAWVWTLLFLMAAAQSIQAQIQLVQSGPELKKPGETVKISCK ASGYTFTDYSMHWVKQAPGKGLKWMGWINTETGEPTYADD FKGRFAFSLETSASTAYLQINNLKNEDTATYFCAPGGFAYWG QGTLVTVSAAKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYF PESVTVTWNSGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWP SQTVTCSVAHPASSTTVDKKLEPSGPISTINPCPPCKECHKCPA PNLEGGPSVFIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQI SWFVNNVEVHTAQTQTHREDYNSTIRVVSTLPIQHQDWMSG KEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSR KDVSLTCLVVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDG SYFIYSKLNMKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSP GK	59
Pab1 Heavy Chain Leader	MAWVWTLLFLMAAAQSIQA	60
Pab1 Heavy Chain FR1	QIQLVQSGPELKKPGETVKISCKASGYTFT	61
Pab1 Heavy Chain CDR1	DYSMH	62
Pab1 Heavy Chain FR2	WVKQAPGKGLKWMG	63
Pab1 Heavy Chain CDR2	WINTETGEPTYADDFKG	64
Pab1 Heavy Chain FR3	RFAFSLETSASTAYLQINNLKNEDTATYFCAP	65
PAb1 Heavy Chain CDR3	GGFAY	66
PAb1 Heavy Chain FR4	WGQGTLVTVSA	67
PAb1 Heavy Chain Variable Region	QIQLVQSGPELKKPGETVKISCKASGYTFTDYSMHWVKQAPG KGLKWMGWINTETGEPTYADDFKGRFAFSLETSASTAYLQIN NLKNEDTATYFCAPGGFAYWGQGTLVTVSA	68
PAb1 Heavy Chain Constant Region	AKTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPESVTVTWN SGSLSSSVHTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCSVA HPASSTTVDKKLEPSGPISTINPCPPCKECHKCPAPNLEGGPSV FIFPPNIKDVLMISLTPKVTCVVVDVSEDDPDVQISWFVNNVE VHTAQTQTHREDYNSTIRVVSTLPIQHQDWMSGKEFKCKVN NKDLPSPIERTISKIKGLVRAPQVYILPPPAEQLSRKDVSLTCLV VGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFIYSKLN MKTSKWEKTDSFSCNVRHEGLKNYYLKKTISRSPGK	69
PAb1 Light Chain	ATGAGGTGCCTAGCTGAGTTCCTGGGGCTGCTTGTGCTCTG GATCCCTGGAGCCATTGGGGATATTGTGATGACTCAGGCTG CACCCTCTGTACCTGTCACTCCTGGAGAGTCAGTATCCATC TCCTGCAGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAA CACTTACTTGTATTGGTTCCTGCAGAGGCCAGGCCAGTCTC	70

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Name	Sequence	SEQ ID NO:
	CTCAGCTCCTGATATATCGGATGTCCAACCTTGCCTCAGGA GTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTGCTTT CACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGTGGGT GTTTATTACTGTATGCAACATCTAGAATATCCGCTCACGTT CGGTGCTGGGACCAAGCTGGAGCTGAAACGGGCTGATGCT GCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTT AACATCTGGAGGTGCCTCAGTCGTGTGCTTCTTGAACAACT TCTACCCCAAAGACATCAATGTCAAGTGGAAGATTGATGG CAGTGAACGACAAAATGGCGTCCTGAACAGTTGGACTGAT CAGGACAGCAAAGACAGCACCTACAGCATGAGCAGCACCC TCACGTTGACCAAGGACGAGTATGAACGACATAACAGCTA TACCTGTGAGGCCACTCACAAGACATCAACTTCACCCATTG TCAAGAGCTTCAACAGGAATGAGTGTTAG	
PAb1 Light Chain Leader	ATGAGGTGCCTAGCTGAGTTCCTGGGGCTGCTTGTGCTCTG GATCCCTGGAGCCATTGGG	71
PAb1 Light Chain FR1	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCAC TCCTGGAGAGTCAGTATCCATCTCCTGC	72
PAb1 Light Chain CDR1	AGGTCTAGTAAGAGTCTCCTGCATAGTAATGGCAACACTTA CTTGTAT	73
PAb1 Light Chain FR2	TGGTTCCTGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGAT ATAT	74
PAb1 Light Chain CDR2	CGGATGTCCAACCTTGCCTCA	75
PAb1 Light Chain FR3	GGAGTCCCAGACAGGTTCAGTGGCAGTGGGTCAGGAACTG CTTTCACACTGAGAATCAGTAGAGTGGAGGCTGAGGATGT GGGTGTTTATTACTGT	76
PAb1 Light Chain CDR3	ATGCAACATCTAGAATATCCGCTCACG	77
PAb1 Light Chain FR4	TTCGGTGCTGGGACCAAGCTGGAGCTGAAA	78
PAb1 Light Chain Variable Region	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCAC TCCTGGAGAGTCAGTATCCATCTCCTGCAGGTCTAGTAAGA GTCTCCTGCATAGTAATGGCAACACTTACTTGTATTGGTTC CTGCAGAGGCCAGGCCAGTCTCCTCAGCTCCTGATATATCG GATGTCCAACCTTGCCTCAGGAGTCCCAGACAGGTTCAGTG GCAGTGGGTCAGGAACTGCTTTCACACTGAGAATCAGTAG AGTGGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAAC ATCTAGAATATCCGCTCACGTTCGGTGCTGGGACCAAGCTG GAGCTGAAA	79
PAb1 Light Chain Constant Region	CGGGCTGATGCTGCACCAACTGTATCCATCTTCCCACCATC CAGTGAGCAGTTAACATCTGGAGGTGCCTCAGTCGTGTGCT TCTTGAACAACTTCTACCCCAAAGACATCAATGTCAAGTGG AAGATTGATGGCAGTGAACGACAAAATGGCGTCCTGAACA GTTGGACTGATCAGGACAGCAAAGACAGCACCTACAGCAT GAGCAGCACCCTCACGTTGACCAAGGACGAGTATGAACGA CATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAA CTTCACCCATTGTCAAGAGCTTCAACAGGAATGAGTGT	80
PAb1 Light Chain	MRCLAEFLGLLVLWIPGAIGDIVMTQAAPSVPVTPGESVSISC RSSKSLLHSNGNTYLYWFLQRPGQSPQLLIYRMSNLASGVPD RFSGSGSGTAFTLRISRVEAEDVGVYYCMQHLEYPLTFGAGT KLELKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINV KWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYE RHNSYTCEATHKTSTSPIVKSFNRNEC	81
PAb1 Light Chain Leader	MRCLAEFLGLLVLWIPGAIG	82
PAb1 Light Chain FR1	DIVMTQAAPSVPVTPGESVSISC	83

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Name	Sequence	SEQ ID NO:
PAb1 Light Chain CDR1	RSSKSLLHSNGNTYLY	84
PAb1 Light Chain FR2	WFLQRPGQSPQLLIY	85
PAb1 Light Chain CDR2	RMSNLAS	86
PAb1 Light Chain FR3	GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC	87
PAb1 Light Chain CDR3	MQHLEYPLT	88
PAb1 Light Chain FR4	FGAGTKLELKR	89
PAb1 Light Chain Variable Region	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQ RPGQSPQLLIYRMSNLASGVPDRFSGSGSGTAFTLRISRVEAED VGVYYCMQHLEYPLTFGAGTKLELKR	90
PAb1 Light Chain Constant Region	ADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKID GSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYT CEATHKTSTSPIVKSFNRNEC	91

-Plectin (hemidesmosomal protein 1), *Homo sapiens*; target protein underlined

>SEQ ID NO: 92

SSSDGVVKSMIIDRRSGRQYDIDDAIAKNLIDRSALDQYRAGTLSITEFA

DMLSGNAGGFRSRSSSVGSSSSYPISPAVSRTQLASWSDPTEETGPVAGI

LDTETLEKVSITEAMHRNLVDNITGQRLLEAQACTGGIIDPSTGERFPVT

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DAVNKGLVDKIMVDRINLAQKAFCGFEDPRTKTKMSAAQALKKGWLYYEA

GQRFLEVQYLTGGLIEPDTPGRVPLDEALQRGTVDARTAQKLRDVGAYSK

YLTCPKTKLKISYKDALDRSMVEEGTGLRLLEAAAQSTKGYYSPYSVSGS

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GSSASLGGPESAVA

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 93

<210> SEQ ID NO 1
<211> LENGTH: 4684
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1

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1 5 10 15

Glu Val Leu Phe Arg Glu Gly Val Met Val Ala Lys Lys Asp Arg Arg
20 25 30

Pro Arg Ser Leu His Pro His Val Pro Gly Val Thr Asn Leu Gln Val
35 40 45

Met Arg Ala Met Ala Ser Leu Arg Ala Arg Gly Leu Val Arg Glu Thr
50 55 60

Phe Ala Trp Cys His Phe Tyr Trp Tyr Leu Thr Asn Glu Gly Ile Ala
65 70 75 80

His Leu Arg Gln Tyr Leu His Leu Pro Pro Glu Ile Val Pro Ala Ser
85 90 95

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Leu Gln Arg Val Arg Arg Pro Val Ala Met Val Met Pro Ala Arg Arg
            100                 105                 110

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

Arg Gly Pro Leu Pro Thr Glu Glu Gln Arg Val Tyr Arg Arg Lys Glu
    130                 135                 140

Leu Glu Glu Val Ser Pro Glu Thr Pro Val Val Pro Ala Thr Thr Gln
145                 150                 155                 160

Arg Thr Leu Ala Arg Pro Gly Pro Glu Pro Ala Pro Ala Thr Asp Glu
                165                 170                 175

Arg Asp Arg Val Gln Lys Lys Thr Phe Thr Lys Trp Val Asn Lys His
            180                 185                 190

Leu Ile Lys Ala Gln Arg His Ile Ser Asp Leu Tyr Glu Asp Leu Arg
        195                 200                 205

Asp Gly His Asn Leu Ile Ser Leu Leu Glu Val Leu Ser Gly Asp Ser
    210                 215                 220

Leu Pro Arg Glu Lys Gly Arg Met Arg Phe His Lys Leu Gln Asn Val
225                 230                 235                 240

Gln Ile Ala Leu Asp Tyr Leu Arg His Arg Gln Val Lys Leu Val Asn
                245                 250                 255

Ile Arg Asn Asp Asp Ile Ala Asp Gly Asn Pro Lys Leu Thr Leu Gly
            260                 265                 270

Leu Ile Trp Thr Ile Ile Leu His Phe Gln Ile Ser Asp Ile Gln Val
        275                 280                 285

Ser Gly Gln Ser Glu Asp Met Thr Ala Lys Glu Lys Leu Leu Leu Trp
    290                 295                 300

Ser Gln Arg Met Val Glu Gly Tyr Gln Gly Leu Arg Cys Asp Asn Phe
305                 310                 315                 320

Thr Ser Ser Trp Arg Asp Gly Arg Leu Phe Asn Ala Ile Ile His Arg
                325                 330                 335

His Lys Pro Leu Leu Ile Asp Met Asn Lys Val Tyr Arg Gln Thr Asn
            340                 345                 350

Leu Glu Asn Leu Asp Gln Ala Phe Ser Val Ala Glu Arg Asp Leu Gly
        355                 360                 365

Val Thr Arg Leu Leu Asp Pro Glu Asp Val Asp Val Pro Gln Pro Asp
    370                 375                 380

Glu Lys Ser Ile Ile Thr Tyr Val Ser Ser Leu Tyr Asp Ala Met Pro
385                 390                 395                 400

Arg Val Pro Asp Val Gln Asp Gly Val Arg Ala Asn Glu Leu Gln Leu
                405                 410                 415

Arg Trp Gln Glu Tyr Arg Glu Leu Val Leu Leu Leu Leu Gln Trp Met
            420                 425                 430

Arg His His Thr Ala Ala Phe Glu Glu Arg Arg Phe Pro Ser Ser Phe
        435                 440                 445

Glu Glu Ile Glu Ile Leu Trp Ser Gln Phe Leu Lys Phe Lys Glu Met
    450                 455                 460

Glu Leu Pro Ala Lys Glu Ala Asp Lys Asn Arg Ser Lys Gly Ile Tyr
465                 470                 475                 480

Gln Ser Leu Glu Gly Ala Val Gln Ala Gly Gln Leu Lys Val Pro Pro
                485                 490                 495

Gly Tyr His Pro Leu Asp Val Glu Lys Glu Trp Gly Lys Leu His Val
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            500                 505                 510

Ala Ile Leu Glu Arg Glu Lys Gln Leu Arg Ser Glu Phe Glu Arg Leu
        515                 520                 525

Glu Cys Leu Gln Arg Ile Val Thr Lys Leu Gln Met Glu Ala Gly Leu
    530                 535                 540

Cys Glu Glu Gln Leu Asn Gln Ala Asp Ala Leu Leu Gln Ser Asp Val
545                 550                 555                 560

Arg Leu Leu Ala Ala Gly Lys Val Pro Gln Arg Ala Gly Glu Val Glu
                565                 570                 575

Arg Asp Leu Asp Lys Ala Asp Ser Met Ile Arg Leu Leu Phe Asn Asp
            580                 585                 590

Val Gln Thr Leu Lys Asp Gly Arg His Pro Gln Gly Glu Gln Met Tyr
        595                 600                 605

Arg Arg Val Tyr Arg Leu His Glu Arg Leu Val Ala Ile Arg Thr Glu
    610                 615                 620

Tyr Asn Leu Arg Leu Lys Ala Gly Val Ala Ala Pro Ala Thr Gln Val
625                 630                 635                 640

Ala Gln Val Thr Leu Gln Ser Val Gln Arg Arg Pro Glu Leu Glu Asp
                645                 650                 655

Ser Thr Leu Arg Tyr Leu Gln Asp Leu Leu Ala Trp Val Glu Glu Asn
            660                 665                 670

Gln His Arg Val Asp Gly Ala Glu Trp Gly Val Asp Leu Pro Ser Val
        675                 680                 685

Glu Ala Gln Leu Gly Ser His Arg Gly Leu His Gln Ser Ile Glu Glu
    690                 695                 700

Phe Arg Ala Lys Ile Glu Arg Ala Arg Ser Asp Glu Gly Gln Leu Ser
705                 710                 715                 720

Pro Ala Thr Arg Gly Ala Tyr Arg Asp Cys Leu Gly Arg Leu Asp Leu
                725                 730                 735

Gln Tyr Ala Lys Leu Leu Asn Ser Ser Lys Ala Arg Leu Arg Ser Leu
            740                 745                 750

Glu Ser Leu His Ser Phe Val Ala Ala Ala Thr Lys Glu Leu Met Trp
        755                 760                 765

Leu Asn Glu Lys Glu Glu Glu Glu Val Gly Phe Asp Trp Ser Asp Arg
    770                 775                 780

Asn Thr Asn Met Thr Ala Lys Lys Glu Ser Tyr Ser Ala Leu Met Arg
785                 790                 795                 800

Glu Leu Glu Leu Lys Glu Lys Lys Ile Lys Glu Leu Gln Asn Ala Gly
                805                 810                 815

Asp Arg Leu Leu Arg Glu Asp His Pro Ala Arg Pro Thr Val Glu Ser
            820                 825                 830

Phe Gln Ala Ala Leu Gln Thr Gln Trp Ser Trp Met Leu Gln Leu Cys
        835                 840                 845

Cys Cys Ile Glu Ala His Leu Lys Glu Asn Ala Ala Tyr Phe Gln Phe
    850                 855                 860

Phe Ser Asp Val Arg Glu Ala Glu Gly Gln Leu Gln Lys Leu Gln Glu
865                 870                 875                 880

Ala Leu Arg Arg Lys Tyr Ser Cys Asp Arg Ser Ala Thr Val Thr Arg
                885                 890                 895

Leu Glu Asp Leu Leu Gln Asp Ala Gln Asp Glu Lys Glu Gln Leu Asn
            900                 905                 910
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Glu Tyr Lys Gly His Leu Ser Gly Leu Ala Lys Arg Ala Lys Ala Val
        915                 920                 925

Val Gln Leu Lys Pro Arg His Pro Ala His Pro Met Arg Gly Arg Leu
    930                 935                 940

Pro Leu Leu Ala Val Cys Asp Tyr Lys Gln Val Glu Val Thr Val His
945                 950                 955                 960

Lys Gly Asp Glu Cys Gln Leu Val Gly Pro Ala Gln Pro Ser His Trp
                965                 970                 975

Lys Val Leu Ser Ser Ser Gly Ser Glu Ala Ala Val Pro Ser Val Cys
            980                 985                 990

Phe Leu Val Pro Pro Pro Asn Gln  Glu Ala Gln Glu Ala  Val Thr Arg
        995                 1000                1005

Leu Glu  Ala Gln His Gln Ala  Leu Val Thr Leu Trp  His Gln Leu
    1010                1015                1020

His Val  Asp Met Lys Ser Leu  Leu Ala Trp Gln Ser  Leu Arg Arg
    1025                1030                1035

Asp Val  Gln Leu Ile Arg Ser  Trp Ser Leu Ala Thr  Phe Arg Thr
    1040                1045                1050

Leu Lys  Pro Glu Glu Gln Arg  Gln Ala Leu His Ser  Leu Glu Leu
    1055                1060                1065

His Tyr  Gln Ala Phe Leu Arg  Asp Ser Gln Asp Ala  Gly Gly Phe
    1070                1075                1080

Gly Pro  Glu Asp Arg Leu Met  Ala Glu Arg Glu Tyr  Gly Ser Cys
    1085                1090                1095

Ser His  His Tyr Gln Gln Leu  Leu Gln Ser Leu Glu  Gln Gly Ala
    1100                1105                1110

Gln Glu  Glu Ser Arg Cys Gln  Arg Cys Ile Ser Glu  Leu Lys Asp
    1115                1120                1125

Ile Arg  Leu Gln Leu Glu Ala  Cys Glu Thr Arg Thr  Val His Arg
    1130                1135                1140

Leu Arg  Leu Pro Leu Asp Lys  Glu Pro Ala Arg Glu  Cys Ala Gln
    1145                1150                1155

Arg Ile  Ala Glu Gln Gln Lys  Ala Gln Ala Glu Val  Glu Gly Leu
    1160                1165                1170

Gly Lys  Gly Val Ala Arg Leu  Ser Ala Glu Ala Glu  Lys Val Leu
    1175                1180                1185

Ala Leu  Pro Glu Pro Ser Pro  Ala Ala Pro Thr Leu  Arg Ser Glu
    1190                1195                1200

Leu Glu  Leu Thr Leu Gly Lys  Leu Glu Gln Val Arg  Ser Leu Ser
    1205                1210                1215

Ala Ile  Tyr Leu Glu Lys Leu  Lys Thr Ile Ser Leu  Val Ile Arg
    1220                1225                1230

Gly Thr  Gln Gly Ala Glu Glu  Val Leu Arg Ala His  Glu Glu Gln
    1235                1240                1245

Leu Lys  Glu Ala Gln Ala Val  Pro Ala Thr Leu Pro  Glu Leu Glu
    1250                1255                1260

Ala Thr  Lys Ala Ser Leu Lys  Lys Leu Arg Ala Gln  Ala Glu Ala
    1265                1270                1275

Gln Gln  Pro Thr Phe Asp Ala  Leu Arg Asp Glu Leu  Arg Gly Ala
    1280                1285                1290
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Gln Glu  Val Gly Glu Arg Leu  Gln Gln Arg His Gly  Glu Arg Asp
    1295                 1300                 1305

Val Glu  Val Glu Arg Trp Arg  Glu Arg Val Ala Gln  Leu Leu Glu
    1310                 1315                 1320

Arg Trp  Gln Ala Val Leu Ala  Gln Thr Asp Val Arg  Gln Arg Glu
    1325                 1330                 1335

Leu Glu  Gln Leu Gly Arg Gln  Leu Arg Tyr Tyr Arg  Glu Ser Ala
    1340                 1345                 1350

Asp Pro  Leu Gly Ala Trp Leu  Gln Asp Ala Arg Arg  Arg Gln Glu
    1355                 1360                 1365

Gln Ile  Gln Ala Met Pro Leu  Ala Asp Ser Gln Ala  Val Arg Glu
    1370                 1375                 1380

Gln Leu  Arg Gln Glu Gln Ala  Leu Leu Glu Glu Ile  Glu Arg His
    1385                 1390                 1395

Gly Glu  Lys Val Glu Glu Cys  Gln Arg Phe Ala Lys  Gln Tyr Ile
    1400                 1405                 1410

Asn Ala  Ile Lys Asp Tyr Glu  Leu Gln Leu Val Thr  Tyr Lys Ala
    1415                 1420                 1425

Gln Leu  Glu Pro Val Ala Ser  Pro Ala Lys Lys Pro  Lys Val Gln
    1430                 1435                 1440

Ser Gly  Ser Glu Ser Val Ile  Gln Glu Tyr Val Asp  Leu Arg Thr
    1445                 1450                 1455

His Tyr  Ser Glu Leu Thr Thr  Leu Thr Ser Gln Tyr  Ile Lys Phe
    1460                 1465                 1470

Ile Ser  Glu Thr Leu Arg Arg  Met Glu Glu Glu Glu  Arg Leu Ala
    1475                 1480                 1485

Glu Gln  Gln Arg Ala Glu Glu  Arg Glu Arg Leu Ala  Glu Val Glu
    1490                 1495                 1500

Ala Ala  Leu Glu Lys Gln Arg  Gln Leu Ala Glu Ala  His Ala Gln
    1505                 1510                 1515

Ala Lys  Ala Gln Ala Glu Arg  Glu Ala Lys Glu Leu  Gln Gln Arg
    1520                 1525                 1530

Met Gln  Glu Glu Val Val Arg  Arg Glu Glu Ala Ala  Val Asp Ala
    1535                 1540                 1545

Gln Gln  Gln Lys Arg Ser Ile  Gln Glu Glu Leu Gln  Gln Leu Arg
    1550                 1555                 1560

Gln Ser  Ser Glu Ala Glu Ile  Gln Ala Lys Ala Arg  Gln Ala Glu
    1565                 1570                 1575

Ala Ala  Glu Arg Ser Arg Leu  Arg Ile Glu Glu Glu  Ile Arg Val
    1580                 1585                 1590

Val Arg  Leu Gln Leu Glu Ala  Thr Glu Arg Gln Arg  Gly Gly Ala
    1595                 1600                 1605

Glu Gly  Glu Leu Gln Ala Leu  Arg Ala Arg Ala Glu  Glu Ala Glu
    1610                 1615                 1620

Ala Gln  Lys Arg Gln Ala Gln  Glu Glu Ala Glu Arg  Leu Arg Arg
    1625                 1630                 1635

Gln Val  Gln Asp Glu Ser Gln  Arg Lys Arg Gln Ala  Glu Val Glu
    1640                 1645                 1650

Leu Ala  Ser Arg Val Lys Ala  Glu Ala Glu Ala Ala  Arg Glu Lys
    1655                 1660                 1665

Gln Arg  Ala Leu Gln Ala Leu  Glu Glu Leu Arg Leu  Gln Ala Glu
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    1670                1675                1680

Glu Ala  Glu Arg Arg Leu Arg  Gln Ala Glu Val Glu  Arg Ala Arg
    1685                1690                1695

Gln Val  Gln Val Ala Leu Glu  Thr Ala Gln Arg Ser  Ala Glu Ala
    1700                1705                1710

Glu Leu  Gln Ser Lys Arg Ala  Ser Phe Ala Glu Lys  Thr Ala Gln
    1715                1720                1725

Leu Glu  Arg Ser Leu Gln Glu  Glu His Val Ala Val  Ala Gln Leu
    1730                1735                1740

Arg Glu  Glu Ala Glu Arg Arg  Ala Gln Gln Gln Ala  Glu Ala Glu
    1745                1750                1755

Arg Ala  Arg Glu Glu Ala Glu  Arg Glu Leu Glu Arg  Trp Gln Leu
    1760                1765                1770

Lys Ala  Asn Glu Ala Leu Arg  Leu Arg Leu Gln Ala  Glu Glu Val
    1775                1780                1785

Ala Gln  Gln Lys Ser Leu Ala  Gln Ala Glu Ala Glu  Lys Gln Lys
    1790                1795                1800

Glu Glu  Ala Glu Arg Glu Ala  Arg Arg Arg Gly Lys  Ala Glu Glu
    1805                1810                1815

Gln Ala  Val Arg Gln Arg Glu  Leu Ala Glu Gln Glu  Leu Glu Lys
    1820                1825                1830

Gln Arg  Gln Leu Ala Glu Gly  Thr Ala Gln Gln Arg  Leu Ala Ala
    1835                1840                1845

Glu Gln  Glu Leu Ile Arg Leu  Arg Ala Glu Thr Glu  Gln Gly Glu
    1850                1855                1860

Gln Gln  Arg Gln Leu Leu Glu  Glu Glu Leu Ala Arg  Leu Gln Arg
    1865                1870                1875

Glu Ala  Ala Ala Ala Thr Gln  Lys Arg Gln Glu Leu  Glu Ala Glu
    1880                1885                1890

Leu Ala  Lys Val Arg Ala Glu  Met Glu Val Leu Leu  Ala Ser Lys
    1895                1900                1905

Ala Arg  Ala Glu Glu Glu Ser  Arg Ser Thr Ser Glu  Lys Ser Lys
    1910                1915                1920

Gln Arg  Leu Glu Ala Glu Ala  Gly Arg Phe Arg Glu  Leu Ala Glu
    1925                1930                1935

Glu Ala  Ala Arg Leu Arg Ala  Leu Ala Glu Glu Ala  Lys Arg Gln
    1940                1945                1950

Arg Gln  Leu Ala Glu Glu Asp  Ala Ala Arg Gln Arg  Ala Glu Ala
    1955                1960                1965

Glu Arg  Val Leu Ala Glu Lys  Leu Ala Ala Ile Gly  Glu Ala Thr
    1970                1975                1980

Arg Leu  Lys Thr Glu Ala Glu  Ile Ala Leu Lys Glu  Lys Glu Ala
    1985                1990                1995

Glu Asn  Glu Arg Leu Arg Arg  Leu Ala Glu Asp Glu  Ala Phe Gln
    2000                2005                2010

Arg Arg  Arg Leu Glu Glu Gln  Ala Ala Gln His Lys  Ala Asp Ile
    2015                2020                2025

Glu Glu  Arg Leu Ala Gln Leu  Arg Lys Ala Ser Asp  Ser Glu Leu
    2030                2035                2040

Glu Arg  Gln Lys Gly Leu Val  Glu Asp Thr Leu Arg  Gln Arg Arg
    2045                2050                2055
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Gln Val  Glu Glu Glu Ile Leu  Ala Leu Lys Ala Ser  Phe Glu Lys
    2060                2065                2070

Ala Ala  Ala Gly Lys Ala Glu  Leu Glu Leu Glu Leu  Gly Arg Ile
    2075                2080                2085

Arg Ser  Asn Ala Glu Asp Thr  Leu Arg Ser Lys Glu  Gln Ala Glu
    2090                2095                2100

Leu Glu  Ala Ala Arg Gln Arg  Gln Leu Ala Ala Glu  Glu Glu Arg
    2105                2110                2115

Arg Arg  Arg Glu Ala Glu Glu  Arg Val Gln Lys Ser  Leu Ala Ala
    2120                2125                2130

Glu Glu  Glu Ala Ala Arg Gln  Arg Lys Ala Ala Leu  Glu Glu Val
    2135                2140                2145

Glu Arg  Leu Lys Ala Lys Val  Glu Glu Ala Arg Arg  Leu Arg Glu
    2150                2155                2160

Arg Ala  Glu Gln Glu Ser Ala  Arg Gln Leu Gln Leu  Ala Gln Glu
    2165                2170                2175

Ala Ala  Gln Lys Arg Leu Gln  Ala Glu Glu Lys Ala  His Ala Phe
    2180                2185                2190

Ala Val  Gln Gln Lys Glu Gln  Glu Leu Gln Gln Thr  Leu Gln Gln
    2195                2200                2205

Glu Gln  Ser Val Leu Asp Gln  Leu Arg Gly Glu Ala  Glu Ala Ala
    2210                2215                2220

Arg Arg  Ala Ala Glu Glu Ala  Glu Glu Ala Arg Val  Gln Ala Glu
    2225                2230                2235

Arg Glu  Ala Ala Gln Ser Arg  Arg Gln Val Glu Glu  Ala Glu Arg
    2240                2245                2250

Leu Lys  Gln Ser Ala Glu Glu  Gln Ala Gln Ala Arg  Ala Gln Ala
    2255                2260                2265

Gln Ala  Ala Ala Glu Lys Leu  Arg Lys Glu Ala Glu  Gln Glu Ala
    2270                2275                2280

Ala Arg  Arg Ala Gln Ala Glu  Gln Ala Ala Leu Arg  Gln Lys Gln
    2285                2290                2295

Ala Ala  Asp Ala Glu Met Glu  Lys His Lys Lys Phe  Ala Glu Gln
    2300                2305                2310

Thr Leu  Arg Gln Lys Ala Gln  Val Glu Gln Glu Leu  Thr Thr Leu
    2315                2320                2325

Arg Leu  Gln Leu Glu Glu Thr  Asp His Gln Lys Asn  Leu Leu Asp
    2330                2335                2340

Glu Glu  Leu Gln Arg Leu Lys  Ala Glu Ala Thr Glu  Ala Ala Arg
    2345                2350                2355

Gln Arg  Ser Gln Val Glu Glu  Glu Leu Phe Ser Val  Arg Val Gln
    2360                2365                2370

Met Glu  Glu Leu Ser Lys Leu  Lys Ala Arg Ile Glu  Ala Glu Asn
    2375                2380                2385

Arg Ala  Leu Ile Leu Arg Asp  Lys Asp Asn Thr Gln  Arg Phe Leu
    2390                2395                2400

Gln Glu  Glu Ala Glu Lys Met  Lys Gln Val Ala Glu  Glu Ala Ala
    2405                2410                2415

Arg Leu  Ser Val Ala Ala Gln  Glu Ala Ala Arg Leu  Arg Gln Leu
    2420                2425                2430
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Ala Glu  Glu Asp Leu Ala Gln  Gln Arg Ala Leu Ala  Glu Lys Met
    2435                 2440                 2445

Leu Lys  Glu Lys Met Gln Ala  Val Gln Glu Ala Thr  Arg Leu Lys
    2450                 2455                 2460

Ala Glu  Ala Glu Leu Leu Gln  Gln Gln Lys Glu Leu  Ala Gln Glu
    2465                 2470                 2475

Gln Ala  Arg Arg Leu Gln Glu  Asp Lys Glu Gln Met  Ala Gln Gln
    2480                 2485                 2490

Leu Ala  Glu Glu Thr Gln Gly  Phe Gln Arg Thr Leu  Glu Ala Glu
    2495                 2500                 2505

Arg Gln  Arg Gln Leu Glu Met  Ser Ala Glu Ala Glu  Arg Leu Lys
    2510                 2515                 2520

Leu Arg  Val Ala Glu Met Ser  Arg Ala Gln Ala Arg  Ala Glu Glu
    2525                 2530                 2535

Asp Ala  Gln Arg Phe Arg Lys  Gln Ala Glu Glu Ile  Gly Glu Lys
    2540                 2545                 2550

Leu His  Arg Thr Glu Leu Ala  Thr Gln Glu Lys Val  Thr Leu Val
    2555                 2560                 2565

Gln Thr  Leu Glu Ile Gln Arg  Gln Gln Ser Asp His  Asp Ala Glu
    2570                 2575                 2580

Arg Leu  Arg Glu Ala Ile Ala  Glu Leu Glu Arg Glu  Lys Glu Lys
    2585                 2590                 2595

Leu Gln  Gln Glu Ala Lys Leu  Leu Gln Leu Lys Ser  Glu Glu Met
    2600                 2605                 2610

Gln Thr  Val Gln Gln Glu Gln  Leu Leu Gln Glu Thr  Gln Ala Leu
    2615                 2620                 2625

Gln Gln  Ser Phe Leu Ser Glu  Lys Asp Ser Leu Leu  Gln Arg Glu
    2630                 2635                 2640

Arg Phe  Ile Glu Gln Glu Lys  Ala Lys Leu Glu Gln  Leu Phe Gln
    2645                 2650                 2655

Asp Glu  Val Ala Lys Ala Gln  Gln Leu Arg Glu Glu  Gln Gln Arg
    2660                 2665                 2670

Gln Gln  Gln Gln Met Glu Gln  Glu Arg Gln Arg Leu  Val Ala Ser
    2675                 2680                 2685

Met Glu  Glu Ala Arg Arg Arg  Gln His Glu Ala Glu  Glu Gly Val
    2690                 2695                 2700

Arg Arg  Lys Gln Glu Glu Leu  Gln Gln Leu Glu Gln  Gln Arg Arg
    2705                 2710                 2715

Gln Gln  Glu Glu Leu Leu Ala  Glu Glu Asn Gln Arg  Leu Arg Glu
    2720                 2725                 2730

Gln Leu  Gln Leu Leu Glu Glu  Gln His Arg Ala Ala  Leu Ala His
    2735                 2740                 2745

Ser Glu  Glu Val Thr Ala Ser  Gln Val Ala Ala Thr  Lys Thr Leu
    2750                 2755                 2760

Pro Asn  Gly Arg Asp Ala Leu  Asp Gly Pro Ala Ala  Glu Ala Glu
    2765                 2770                 2775

Pro Glu  His Ser Phe Asp Gly  Leu Arg Arg Lys Val  Ser Ala Gln
    2780                 2785                 2790

Arg Leu  Gln Glu Ala Gly Ile  Leu Ser Ala Glu Glu  Leu Gln Arg
    2795                 2800                 2805

Leu Ala  Gln Gly His Thr Thr  Val Asp Glu Leu Ala  Arg Arg Glu
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    2810                2815                2820

Asp Val  Arg His Tyr Leu Gln  Gly Arg Ser Ser Ile  Ala Gly Leu
    2825                2830                2835

Leu Leu  Lys Ala Thr Asn Glu  Lys Leu Ser Val Tyr  Ala Ala Leu
    2840                2845                2850

Gln Arg  Gln Leu Leu Ser Pro  Gly Thr Ala Leu Ile  Leu Leu Glu
    2855                2860                2865

Ala Gln  Ala Ala Ser Gly Phe  Leu Leu Asp Pro Val  Arg Asn Arg
    2870                2875                2880

Arg Leu  Thr Val Asn Glu Ala  Val Lys Glu Gly Val  Val Gly Pro
    2885                2890                2895

Glu Leu  His His Lys Leu Leu  Ser Ala Glu Arg Ala  Val Thr Gly
    2900                2905                2910

Tyr Lys  Asp Pro Tyr Thr Gly  Gln Gln Ile Ser Leu  Phe Gln Ala
    2915                2920                2925

Met Gln  Lys Gly Leu Ile Val  Arg Glu His Gly Ile  Arg Leu Leu
    2930                2935                2940

Glu Ala  Gln Ile Ala Thr Gly  Gly Val Ile Asp Pro  Val His Ser
    2945                2950                2955

His Arg  Val Pro Val Asp Val  Ala Tyr Arg Arg Gly  Tyr Phe Asp
    2960                2965                2970

Glu Glu  Met Asn Arg Val Leu  Ala Asp Pro Ser Asp  Asp Thr Lys
    2975                2980                2985

Gly Phe  Phe Asp Pro Asn Thr  His Glu Asn Leu Thr  Tyr Leu Gln
    2990                2995                3000

Leu Leu  Glu Arg Cys Val Glu  Asp Pro Glu Thr Gly  Leu Cys Leu
    3005                3010                3015

Leu Pro  Leu Thr Asp Lys Ala  Ala Lys Gly Gly Glu  Leu Val Tyr
    3020                3025                3030

Thr Asp  Ser Glu Ala Arg Asp  Val Phe Glu Lys Ala  Thr Val Ser
    3035                3040                3045

Ala Pro  Phe Gly Lys Phe Gln  Gly Lys Thr Val Thr  Ile Trp Glu
    3050                3055                3060

Ile Ile  Asn Ser Glu Tyr Phe  Thr Ala Glu Gln Arg  Arg Asp Leu
    3065                3070                3075

Leu Arg  Gln Phe Arg Thr Gly  Arg Ile Thr Val Glu  Lys Ile Ile
    3080                3085                3090

Lys Ile  Ile Ile Thr Val Val  Glu Glu Gln Glu Gln  Lys Gly Arg
    3095                3100                3105

Leu Cys  Phe Glu Gly Leu Arg  Ser Leu Val Pro Ala  Ala Glu Leu
    3110                3115                3120

Leu Glu  Ser Arg Val Ile Asp  Arg Glu Leu Tyr Gln  Gln Leu Gln
    3125                3130                3135

Arg Gly  Glu Arg Ser Val Arg  Asp Val Ala Glu Val  Asp Thr Val
    3140                3145                3150

Arg Arg  Ala Leu Arg Gly Ala  Asn Val Ile Ala Gly  Val Trp Leu
    3155                3160                3165

Glu Glu  Ala Gly Gln Lys Leu  Ser Ile Tyr Asn Ala  Leu Lys Lys
    3170                3175                3180

Asp Leu  Leu Pro Ser Asp Met  Ala Val Ala Leu Leu  Glu Ala Gln
    3185                3190                3195
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Ala Gly  Thr Gly His Ile Ile  Asp Pro Ala Thr Ser  Ala Arg Leu
    3200                3205                3210

Thr Val  Asp Glu Ala Val Arg  Ala Gly Leu Val Gly  Pro Glu Phe
    3215                3220                3225

His Glu  Lys Leu Leu Ser Ala  Glu Lys Ala Val Thr  Gly Tyr Arg
    3230                3235                3240

Asp Pro  Tyr Thr Gly Gln Ser  Val Ser Leu Phe Gln  Ala Leu Lys
    3245                3250                3255

Lys Gly  Leu Ile Pro Arg Glu  Gln Gly Leu Arg Leu  Leu Asp Ala
    3260                3265                3270

Gln Leu  Ser Thr Gly Gly Ile  Val Asp Pro Ser Lys  Ser His Arg
    3275                3280                3285

Val Pro  Leu Asp Val Ala Cys  Ala Arg Gly Cys Leu  Asp Glu Glu
    3290                3295                3300

Thr Ser  Arg Ala Leu Ser Ala  Pro Arg Ala Asp Ala  Lys Ala Tyr
    3305                3310                3315

Ser Asp  Pro Ser Thr Gly Glu  Pro Ala Thr Tyr Gly  Glu Leu Gln
    3320                3325                3330

Gln Arg  Cys Arg Pro Asp Gln  Leu Thr Gly Leu Ser  Leu Leu Pro
    3335                3340                3345

Leu Ser  Glu Lys Ala Ala Arg  Ala Arg Gln Glu Glu  Leu Tyr Ser
    3350                3355                3360

Glu Leu  Gln Ala Arg Glu Thr  Phe Glu Lys Thr Pro  Val Glu Val
    3365                3370                3375

Pro Val  Gly Gly Phe Lys Gly  Arg Thr Val Thr Val  Trp Glu Leu
    3380                3385                3390

Ile Ser  Ser Glu Tyr Phe Thr  Ala Glu Gln Arg Gln  Glu Leu Leu
    3395                3400                3405

Arg Gln  Phe Arg Thr Gly Lys  Val Thr Val Glu Lys  Val Ile Lys
    3410                3415                3420

Ile Leu  Ile Thr Ile Val Glu  Glu Val Glu Thr Leu  Arg Gln Glu
    3425                3430                3435

Arg Leu  Ser Phe Ser Gly Leu  Arg Ala Pro Val Pro  Ala Ser Glu
    3440                3445                3450

Leu Leu  Ala Ser Gly Val Leu  Ser Arg Ala Gln Phe  Glu Gln Leu
    3455                3460                3465

Lys Asp  Gly Lys Thr Thr Val  Lys Asp Leu Ser Glu  Leu Gly Ser
    3470                3475                3480

Val Arg  Thr Leu Leu Gln Gly  Ser Gly Cys Leu Ala  Gly Ile Tyr
    3485                3490                3495

Leu Glu  Asp Thr Lys Glu Lys  Val Ser Ile Tyr Glu  Ala Met Arg
    3500                3505                3510

Arg Gly  Leu Leu Arg Ala Thr  Thr Ala Ala Leu Leu  Leu Glu Ala
    3515                3520                3525

Gln Ala  Ala Thr Gly Phe Leu  Val Asp Pro Val Arg  Asn Gln Arg
    3530                3535                3540

Leu Tyr  Val His Glu Ala Val  Lys Ala Gly Val Val  Gly Pro Glu
    3545                3550                3555

Leu His  Glu Gln Leu Leu Ser  Ala Glu Lys Ala Val  Thr Gly Tyr
    3560                3565                3570
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Arg Asp  Pro Tyr Ser Gly Ser  Thr Ile Ser Leu Phe  Gln Ala Met
    3575                 3580                 3585

Gln Lys  Gly Leu Val Leu Arg  Gln His Gly Ile Arg  Leu Leu Glu
    3590                 3595                 3600

Ala Gln  Ile Ala Thr Gly Gly  Ile Ile Asp Pro Val  His Ser His
    3605                 3610                 3615

Arg Val  Pro Val Asp Val Ala  Tyr Gln Arg Gly Tyr  Phe Ser Glu
    3620                 3625                 3630

Glu Met  Asn Arg Val Leu Ala  Asp Pro Ser Asp Asp  Thr Lys Gly
    3635                 3640                 3645

Phe Phe  Asp Pro Asn Thr His  Glu Asn Leu Thr Tyr  Arg Gln Leu
    3650                 3655                 3660

Leu Glu  Arg Cys Val Glu Asp  Pro Glu Thr Gly Leu  Arg Leu Leu
    3665                 3670                 3675

Pro Leu  Lys Gly Ala Glu Lys  Ala Glu Val Val Glu  Thr Thr Gln
    3680                 3685                 3690

Val Tyr  Thr Glu Glu Glu Thr  Arg Arg Ala Phe Glu  Glu Thr Gln
    3695                 3700                 3705

Ile Asp  Ile Pro Gly Gly Gly  Ser His Gly Gly Ser  Thr Met Ser
    3710                 3715                 3720

Leu Trp  Glu Val Met Gln Ser  Asp Leu Ile Pro Glu  Glu Gln Arg
    3725                 3730                 3735

Ala Gln  Leu Met Ala Asp Phe  Gln Ala Gly Arg Val  Thr Lys Glu
    3740                 3745                 3750

Arg Met  Ile Ile Ile Ile Ile  Glu Ile Ile Glu Lys  Thr Glu Ile
    3755                 3760                 3765

Ile Arg  Gln Gln Gly Leu Ala  Ser Tyr Asp Tyr Val  Arg Arg Arg
    3770                 3775                 3780

Leu Thr  Ala Glu Asp Leu Phe  Glu Ala Arg Ile Ile  Ser Leu Glu
    3785                 3790                 3795

Thr Tyr  Asn Leu Leu Arg Glu  Gly Thr Arg Ser Leu  Arg Glu Ala
    3800                 3805                 3810

Leu Glu  Ala Glu Ser Ala Trp  Cys Tyr Leu Tyr Gly  Thr Gly Ser
    3815                 3820                 3825

Val Ala  Gly Val Tyr Leu Pro  Gly Ser Arg Gln Thr  Leu Ser Ile
    3830                 3835                 3840

Tyr Gln  Ala Leu Lys Lys Gly  Leu Leu Ser Ala Glu  Val Ala Arg
    3845                 3850                 3855

Leu Leu  Leu Glu Ala Gln Ala  Ala Thr Gly Phe Leu  Leu Asp Pro
    3860                 3865                 3870

Val Lys  Gly Glu Arg Leu Thr  Val Asp Glu Ala Val  Arg Lys Gly
    3875                 3880                 3885

Leu Val  Gly Pro Glu Leu His  Asp Arg Leu Leu Ser  Ala Glu Arg
    3890                 3895                 3900

Ala Val  Thr Gly Tyr Arg Asp  Pro Tyr Thr Glu Gln  Thr Ile Ser
    3905                 3910                 3915

Leu Phe  Gln Ala Met Lys Lys  Glu Leu Ile Pro Thr  Glu Glu Ala
    3920                 3925                 3930

Leu Arg  Leu Leu Asp Ala Gln  Leu Ala Thr Gly Gly  Ile Val Asp
    3935                 3940                 3945

Pro Arg  Leu Gly Phe His Leu  Pro Leu Glu Val Ala  Tyr Gln Arg
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    3950                3955                3960

Gly Tyr  Leu Asn Lys Asp Thr  His Asp Gln Leu Ser  Glu Pro Ser
    3965                3970                3975

Glu Val  Arg Ser Tyr Val Asp  Pro Ser Thr Asp Glu  Arg Leu Ser
    3980                3985                3990

Tyr Thr  Gln Leu Leu Arg Arg  Cys Arg Arg Asp Asp  Gly Thr Gly
    3995                4000                4005

Gln Leu  Leu Leu Pro Leu Ser  Asp Ala Arg Lys Leu  Thr Phe Arg
    4010                4015                4020

Gly Leu  Arg Lys Gln Ile Thr  Met Glu Glu Leu Val  Arg Ser Gln
    4025                4030                4035

Val Met  Asp Glu Ala Thr Ala  Leu Gln Leu Arg Glu  Gly Leu Thr
    4040                4045                4050

Ser Ile  Glu Glu Val Thr Lys  Asn Leu Gln Lys Phe  Leu Glu Gly
    4055                4060                4065

Thr Ser  Cys Ile Ala Gly Val  Phe Val Asp Ala Thr  Lys Glu Arg
    4070                4075                4080

Leu Ser  Val Tyr Gln Ala Met  Lys Lys Gly Ile Ile  Arg Pro Gly
    4085                4090                4095

Thr Ala  Phe Glu Leu Leu Glu  Ala Gln Ala Ala Thr  Gly Tyr Val
    4100                4105                4110

Ile Asp  Pro Ile Lys Gly Leu  Lys Leu Thr Val Glu  Glu Ala Val
    4115                4120                4125

Arg Met  Gly Ile Val Gly Pro  Glu Phe Lys Asp Lys  Leu Leu Ser
    4130                4135                4140

Ala Glu  Arg Ala Val Thr Gly  Tyr Lys Asp Pro Tyr  Ser Gly Lys
    4145                4150                4155

Leu Ile  Ser Leu Phe Gln Ala  Met Lys Lys Gly Leu  Ile Leu Lys
    4160                4165                4170

Asp His  Gly Ile Arg Leu Leu  Glu Ala Gln Ile Ala  Thr Gly Gly
    4175                4180                4185

Ile Ile  Asp Pro Glu Glu Ser  His Arg Leu Pro Val  Glu Val Ala
    4190                4195                4200

Tyr Lys  Arg Gly Leu Phe Asp  Glu Glu Met Asn Glu  Ile Leu Thr
    4205                4210                4215

Asp Pro  Ser Asp Asp Thr Lys  Gly Phe Phe Asp Pro  Asn Thr Glu
    4220                4225                4230

Glu Asn  Leu Thr Tyr Leu Gln  Leu Met Glu Arg Cys  Ile Thr Asp
    4235                4240                4245

Pro Gln  Thr Gly Leu Cys Leu  Leu Pro Leu Lys Glu  Lys Lys Arg
    4250                4255                4260

Glu Arg  Lys Thr Ser Ser Lys  Ser Ser Val Arg Lys  Arg Arg Val
    4265                4270                4275

Val Ile  Val Asp Pro Glu Thr  Gly Lys Glu Met Ser  Val Tyr Glu
    4280                4285                4290

Ala Tyr  Arg Lys Gly Leu Ile  Asp His Gln Thr Tyr  Leu Glu Leu
    4295                4300                4305

Ser Glu  Gln Glu Cys Glu Trp  Glu Glu Ile Thr Ile  Ser Ser Ser
    4310                4315                4320

Asp Gly  Val Val Lys Ser Met  Ile Ile Asp Arg Arg  Ser Gly Arg
    4325                4330                4335
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Gln Tyr  Asp Ile Asp Asp Ala  Ile Ala Lys Asn Leu  Ile Asp Arg
    4340                 4345                 4350

Ser Ala  Leu Asp Gln Tyr Arg  Ala Gly Thr Leu Ser  Ile Thr Glu
    4355                 4360                 4365

Phe Ala  Asp Met Leu Ser Gly  Asn Ala Gly Gly Phe  Arg Ser Arg
    4370                 4375                 4380

Ser Ser  Ser Val Gly Ser Ser  Ser Ser Tyr Pro Ile  Ser Pro Ala
    4385                 4390                 4395

Val Ser  Arg Thr Gln Leu Ala  Ser Trp Ser Asp Pro  Thr Glu Glu
    4400                 4405                 4410

Thr Gly  Pro Val Ala Gly Ile  Leu Asp Thr Glu Thr  Leu Glu Lys
    4415                 4420                 4425

Val Ser  Ile Thr Glu Ala Met  His Arg Asn Leu Val  Asp Asn Ile
    4430                 4435                 4440

Thr Gly  Gln Arg Leu Leu Glu  Ala Gln Ala Cys Thr  Gly Gly Ile
    4445                 4450                 4455

Ile Asp  Pro Ser Thr Gly Glu  Arg Phe Pro Val Thr  Asp Ala Val
    4460                 4465                 4470

Asn Lys  Gly Leu Val Asp Lys  Ile Met Val Asp Arg  Ile Asn Leu
    4475                 4480                 4485

Ala Gln  Lys Ala Phe Cys Gly  Phe Glu Asp Pro Arg  Thr Lys Thr
    4490                 4495                 4500

Lys Met  Ser Ala Ala Gln Ala  Leu Lys Lys Gly Trp  Leu Tyr Tyr
    4505                 4510                 4515

Glu Ala  Gly Gln Arg Phe Leu  Glu Val Gln Tyr Leu  Thr Gly Gly
    4520                 4525                 4530

Leu Ile  Glu Pro Asp Thr Pro  Gly Arg Val Pro Leu  Asp Glu Ala
    4535                 4540                 4545

Leu Gln  Arg Gly Thr Val Asp  Ala Arg Thr Ala Gln  Lys Leu Arg
    4550                 4555                 4560

Asp Val  Gly Ala Tyr Ser Lys  Tyr Leu Thr Cys Pro  Lys Thr Lys
    4565                 4570                 4575

Leu Lys  Ile Ser Tyr Lys Asp  Ala Leu Asp Arg Ser  Met Val Glu
    4580                 4585                 4590

Glu Gly  Thr Gly Leu Arg Leu  Leu Glu Ala Ala Ala  Gln Ser Thr
    4595                 4600                 4605

Lys Gly  Tyr Tyr Ser Pro Tyr  Ser Val Ser Gly Ser  Gly Ser Thr
    4610                 4615                 4620

Ala Gly  Ser Arg Thr Gly Ser  Arg Thr Gly Ser Arg  Ala Gly Ser
    4625                 4630                 4635

Arg Arg  Gly Ser Phe Asp Ala  Thr Gly Ser Gly Phe  Ser Met Thr
    4640                 4645                 4650

Phe Ser  Ser Ser Ser Tyr Ser  Ser Ser Gly Tyr Gly  Arg Arg Tyr
    4655                 4660                 4665

Ala Ser  Gly Ser Ser Ala Ser  Leu Gly Gly Pro Glu  Ser Ala Val
    4670                 4675                 4680

Ala
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<210> SEQ ID NO 2
<211> LENGTH: 344
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 2

Met Arg Ser His His His His His His His His His His Arg Ser Gly
1 5 10 15

Thr Gly Asp Asp Asp Asp Lys Ala Met Ala Asp Ile Gly Ser Glu Phe
20 25 30

Glu Leu Arg Arg Gln Ala Cys Gly Phe Arg Ser Arg Ser Ser Ser Val
35 40 45

Gly Ser Ser Ser Ser Tyr Pro Ile Ser Pro Ala Val Ser Arg Thr Gln
50 55 60

Leu Ala Ser Trp Ser Asp Pro Thr Glu Glu Thr Gly Pro Val Ala Gly
65 70 75 80

Ile Leu Asp Thr Glu Thr Leu Glu Lys Val Ser Ile Thr Glu Ala Met
85 90 95

His Arg Asn Leu Val Asp Asn Ile Thr Gly Gln Arg Leu Leu Glu Ala
100 105 110

Gln Ala Cys Thr Gly Gly Ile Ile Asp Pro Ser Thr Gly Glu Arg Phe
115 120 125

Pro Val Thr Asp Ala Val Asn Lys Gly Leu Val Asp Lys Ile Met Val
130 135 140

Asp Arg Ile Asn Leu Ala Gln Lys Ala Phe Cys Gly Phe Glu Asp Pro
145 150 155 160

Arg Thr Lys Thr Lys Met Ser Ala Ala Gln Ala Leu Lys Lys Gly Trp
165 170 175

Leu Tyr Tyr Glu Ala Gly Gln Arg Phe Leu Glu Val Gln Tyr Leu Thr
180 185 190

Gly Gly Leu Ile Glu Pro Asp Thr Pro Gly Arg Val Pro Leu Asp Glu
195 200 205

Ala Leu Gln Arg Gly Thr Val Asp Ala Arg Thr Ala Gln Lys Leu Arg
210 215 220

Asp Val Gly Ala Tyr Ser Lys Tyr Leu Thr Cys Pro Lys Thr Lys Leu
225 230 235 240

Lys Ile Ser Tyr Lys Asp Ala Leu Asp Arg Ser Met Val Glu Glu Gly
245 250 255

Thr Gly Leu Arg Leu Leu Glu Ala Ala Ala Gln Ser Thr Lys Gly Tyr
260 265 270

Tyr Ser Pro Tyr Ser Val Ser Gly Ser Gly Ser Thr Ala Gly Ser Arg
275 280 285

Thr Gly Ser Arg Thr Gly Ser Arg Ala Gly Ser Arg Arg Gly Ser Phe
290 295 300

Asp Ala Thr Gly Ser Gly Phe Ser Met Thr Phe Ser Ser Ser Ser Tyr
305 310 315 320

Ser Ser Ser Gly Tyr Gly Arg Arg Tyr Ala Ser Gly Ser Ser Ser Leu
325 330 335

Gly Gly Pro Glu Ser Ala Val Ala
340

<210> SEQ ID NO 3
<211> LENGTH: 540
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 3

Met Ser Pro Ile Leu Gly Tyr Trp Lys Ile Lys Gly Leu Val Gln Pro
1 5 10 15

Thr Arg Leu Leu Leu Glu Tyr Leu Glu Glu Lys Tyr Glu Glu His Leu
20 25 30

Tyr Glu Arg Asp Glu Gly Asp Lys Trp Arg Asn Lys Lys Phe Glu Leu
35 40 45

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

Leu Thr Gln Ser Met Ala Ile Ile Arg Tyr Ile Ala Asp Lys His Asn
65 70 75 80

Met Leu Gly Gly Cys Pro Lys Glu Arg Ala Glu Ile Ser Met Leu Glu
85 90 95

Gly Ala Val Leu Asp Ile Arg Tyr Gly Val Ser Arg Ile Ala Tyr Ser
100 105 110

Lys Asp Phe Glu Thr Leu Lys Val Asp Phe Leu Ser Lys Leu Pro Glu
115 120 125

Met Leu Lys Met Phe Glu Asp Arg Leu Cys His Lys Thr Tyr Leu Asn
130 135 140

Gly Asp His Val Thr His Pro Asp Phe Met Leu Tyr Asp Ala Leu Asp
145 150 155 160

Val Val Leu Tyr Met Asp Pro Met Cys Leu Asp Ala Phe Pro Lys Leu
165 170 175

Val Cys Phe Lys Lys Arg Ile Glu Ala Ile Pro Gln Ile Asp Lys Tyr
180 185 190

Leu Lys Ser Ser Lys Tyr Ile Ala Trp Pro Leu Gln Gly Trp Gln Ala
195 200 205

Thr Phe Gly Gly Gly Asp His Pro Pro Lys Ser Asp Leu Val Pro Arg
210 215 220

Gly Ser Glu Phe Glu Leu Arg Arg Gln Ala Cys Gly Phe Arg Ser Arg
225 230 235 240

Ser Ser Ser Val Gly Ser Ser Ser Ser Tyr Pro Ile Ser Pro Ala Val
245 250 255

Ser Arg Thr Gln Leu Ala Ser Trp Ser Asp Pro Thr Glu Glu Thr Gly
260 265 270

Pro Val Ala Gly Ile Leu Asp Thr Glu Thr Leu Glu Lys Val Ser Ile
275 280 285

Thr Glu Ala Met His Arg Asn Leu Val Asp Asn Ile Thr Gly Gln Arg
290 295 300

Leu Leu Glu Ala Gln Ala Cys Thr Gly Gly Ile Ile Asp Pro Ser Thr
305 310 315 320

Gly Glu Arg Phe Pro Val Thr Asp Ala Val Asn Lys Gly Leu Val Asp
325 330 335

Lys Ile Met Val Asp Arg Ile Asn Leu Ala Gln Lys Ala Phe Cys Gly
340 345 350

Phe Glu Asp Pro Arg Thr Lys Thr Lys Met Ser Ala Ala Gln Ala Leu
355 360 365

Lys Lys Gly Trp Leu Tyr Tyr Glu Ala Gly Gln Arg Phe Leu Glu Val

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    370                 375                 380

Gln Tyr Leu Thr Gly Gly Leu Ile Glu Pro Asp Thr Pro Gly Arg Val
385                 390                 395                 400

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

Gln Lys Leu Arg Asp Val Gly Ala Tyr Ser Lys Tyr Leu Thr Cys Pro
            420                 425                 430

Lys Thr Lys Leu Lys Ile Ser Tyr Lys Asp Ala Leu Asp Arg Ser Met
        435                 440                 445

Val Glu Glu Gly Thr Gly Leu Arg Leu Leu Glu Ala Ala Ala Gln Ser
    450                 455                 460

Thr Lys Gly Tyr Tyr Ser Pro Tyr Ser Val Ser Gly Ser Gly Ser Thr
465                 470                 475                 480

Ala Gly Ser Arg Thr Gly Ser Arg Thr Gly Ser Arg Ala Gly Ser Arg
                485                 490                 495

Arg Gly Ser Phe Asp Ala Thr Gly Ser Gly Phe Ser Met Thr Phe Ser
            500                 505                 510

Ser Ser Ser Tyr Ser Ser Ser Gly Tyr Gly Arg Arg Tyr Ala Ser Gly
        515                 520                 525

Ser Ser Ser Leu Gly Gly Pro Glu Ser Ala Val Ala
    530                 535                 540


<210> SEQ ID NO 4
<211> LENGTH: 1398
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 4

atgaacttcg ggctcagctt gattttcctt gccctcattt taaaaggtgt ccagtgtgag     60

gtgcagctgg tggagtctgg gggagacttg gtgaagcctg gagggtccct gaaactctcc    120

tgtgcagcct ctggattcac tttcagtagg tatggcatgt cttgggttcg ccagactcca    180

gacaagaggc tggagtgggt cgcaaccatt agtattggtg gtacttacac ctactatcca    240

gacagtatga aggggcgatt caccatctcc agagacaatg ccaagaacac cctgtacctg    300

caaatgagca gtctgaagtc tgaggacaca gccatgtatt actgtgcaag acgggggtat    360

ggtaactact cttactatgg tatggactac tggggtcaag gaacctcagt caccgtctcc    420

tcagccaaaa cgacaccccc atctgtctat ccactggccc ctggatctgc tgcccaaact    480

aactccatgg tgaccctggg atgcctggtc aagggctatt tccctgagcc agtgacagtg    540

acctggaact ctggatccct gtccagcggt gtgcacacct tcccagctgt cctgcagtct    600

gacctctaca ctctgagcag ctcagtgact gtcccctcca gcacctggcc cagcgagacc    660

gtcacctgca acgttgccca cccggccagc agcaccaagg tggacaagaa aattgtgccc    720

agggattgtg gttgtaagcc ttgcatatgt acagtcccag aagtatcatc tgtcttcatc    780

ttcccccaa agcccaagga tgtgctcacc attactctga ctcctaaggt cacgtgtgtt    840

gtggtagaca tcagcaagga tgatcccgag gtccagttca gctggtttgt agatgatgtg    900

gaggtgcaca cagctcagac gcaaccccgg gaggagcagt tcaacagcac tttccgctca    960

gtcagtgaac ttcccatcat gcaccaggac tggctcaatg gcaaggagtt caaatgcagg   1020
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gtcaacagtg cagctttccc tgcccccatc gagaaaacca tctccaaaac caaaggcaga 1080

ccgaaggctc cacaggtgta caccattcca cctcccaagg agcagatggc caaggataaa 1140

gtcagtctga cctgcatgat aacagacttc ttccctgaag acattactgt ggagtggcag 1200

tggaatgggc agccagcgga gaactacaag aacactcagc ccatcatgga cacagatggc 1260

tcttacttcg tctacagcaa gctcaatgtg cagaagagca actgggaggc aggaaatact 1320

ttcacctgct ctgtgttaca tgagggcctg cacaaccacc atactgagaa gagcctctcc 1380

cactctcctg gtaaatga 1398

<210> SEQ ID NO 5
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 5

atgaacttcg ggctcagctt gattttcctt gccctcattt taaaaggtgt ccagtgt 57

<210> SEQ ID NO 6
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 6

gaggtgcagc tggtggagtc tgggggagac ttggtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt 90

<210> SEQ ID NO 7
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 7

aggtatggca tgtct 15

<210> SEQ ID NO 8
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 8

tgggttcgcc agactccaga caagaggctg gagtgggtcg ca 42

<210> SEQ ID NO 9
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 9

accattagta ttggtggtac ttacacctac tatccagaca gtatgaaggg g 51

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<210> SEQ ID NO 10
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 10

cgattcacca tctccagaga caatgccaag aacaccctgt acctgcaaat gagcagtctg 60

aagtctgagg acacagccat gtattactgt gcaaga 96

<210> SEQ ID NO 11
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 11

cgggggtatg gtaactactc ttactatggt atggactac 39

<210> SEQ ID NO 12
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 12

tggggtcaag gaacctcagt caccgtctcc tca 33

<210> SEQ ID NO 13
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 13

gaggtgcagc tggtggagtc tgggggagac ttggtgaagc ctggagggtc cctgaaactc 60

tcctgtgcag cctctggatt cactttcagt aggtatggca tgtcttgggt tcgccagact 120

ccagacaaga ggctggagtg ggtcgcaacc attagtattg gtggtactta cacctactat 180

ccagacagta tgaaggggcg attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgtgc aagacggggg 300

tatggtaact actcttacta tggtatggac tactggggtc aaggaacctc agtcaccgtc 360

tcctca 366

<210> SEQ ID NO 14
<211> LENGTH: 972
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 14

gccaaaacga cacccccatc tgtctatcca ctggcccctg gatctgctgc ccaaactaac 60

tccatggtga ccctgggatg cctggtcaag ggctatttcc ctgagccagt gacagtgacc 120

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tggaactctg gatccctgtc cagcggtgtg cacaccttcc cagctgtcct gcagtctgac 180

ctctacactc tgagcagctc agtgactgtc ccctccagca cctggcccag cgagaccgtc 240

acctgcaacg ttgcccaccc ggccagcagc accaaggtgg acaagaaaat tgtgcccagg 300

gattgtggtt gtaagccttg catatgtaca gtcccagaag tatcatctgt cttcatcttc 360

cccccaaagc ccaaggatgt gctcaccatt actctgactc ctaaggtcac gtgtgttgtg 420

gtagacatca gcaaggatga tcccgaggtc cagttcagct ggtttgtaga tgatgtggag 480

gtgcacacag ctcagacgca accccgggag gagcagttca acagcacttt ccgctcagtc 540

agtgaacttc ccatcatgca ccaggactgg ctcaatggca aggagttcaa atgcagggtc 600

aacagtgcag ctttccctgc ccccatcgag aaaaccatct ccaaaaccaa aggcagaccg 660

aaggctccac aggtgtacac cattccacct cccaaggagc agatggccaa ggataaagtc 720

agtctgacct gcatgataac agacttcttc cctgaagaca ttactgtgga gtggcagtgg 780

aatgggcagc cagcggagaa ctacaagaac actcagccca tcatggacac agatggctct 840

tacttcgtct acagcaagct caatgtgcag aagagcaact gggaggcagg aaatactttc 900

acctgctctg tgttacatga gggcctgcac aaccaccata ctgagaagag cctctcccac 960

tctcctggta aa 972

<210> SEQ ID NO 15
<211> LENGTH: 201
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 15

Met Asn Phe Gly Leu Ser Leu Ile Phe Leu Ala Leu Ile Leu Lys Gly
1 5 10 15

Val Gln Cys Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Lys
20 25 30

Pro Gly Gly Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe
35 40 45

Ser Arg Tyr Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu
50 55 60

Glu Trp Val Ala Thr Ile Ser Ile Gly Gly Thr Tyr Thr Tyr Tyr Pro
65 70 75 80

Asp Ser Met Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn
85 90 95

Thr Leu Tyr Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met
100 105 110

Tyr Tyr Cys Ala Arg Arg Gly Tyr Gly Asn Tyr Ser Tyr Tyr Gly Met
115 120 125

Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser Ala Lys Thr
130 135 140

Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala Ala Gln Thr
145 150 155 160

Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr Phe Pro Glu
165 170 175

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

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Thr Phe Pro Ala Val Leu Gln Ser Asp
195 200

<210> SEQ ID NO 16
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 16

Met Asn Phe Gly Leu Ser Leu Ile Phe Leu Ala Leu Ile Leu Lys Gly
1 5 10 15

Val Gln Cys

<210> SEQ ID NO 17
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 17

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

Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
20 25 30

<210> SEQ ID NO 18
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 18

Arg Tyr Gly Met Ser
1 5

<210> SEQ ID NO 19
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 19

Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val Ala
1 5 10

<210> SEQ ID NO 20
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 20

Thr Ile Ser Ile Gly Gly Thr Tyr Thr Tyr Tyr Pro Asp Ser Met Lys
1 5 10 15

Gly

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<210> SEQ ID NO 21
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 21

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

Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys Ala Arg
20 25 30

<210> SEQ ID NO 22
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 22

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

<210> SEQ ID NO 23
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 23

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> SEQ ID NO 24
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 24

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

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

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ile Gly Gly Thr Tyr Thr Tyr Tyr Pro Asp Ser Met
50 55 60

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

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

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

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

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<210> SEQ ID NO 25
<211> LENGTH: 324
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 25

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Ser Ala
1 5 10 15

Ala Gln Thr Asn Ser Met Val Thr Leu Gly Cys Leu Val Lys Gly Tyr
20 25 30

Phe Pro Glu Pro Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
35 40 45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu Tyr Thr Leu
50 55 60

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Glu Thr Val
65 70 75 80

Thr Cys Asn Val Ala His Pro Ala Ser Ser Thr Lys Val Asp Lys Lys
85 90 95

Ile Val Pro Arg Asp Cys Gly Cys Lys Pro Cys Ile Cys Thr Val Pro
100 105 110

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

Thr Ile Thr Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Ile Ser
130 135 140

Lys Asp Asp Pro Glu Val Gln Phe Ser Trp Phe Val Asp Asp Val Glu
145 150 155 160

Val His Thr Ala Gln Thr Gln Pro Arg Glu Glu Gln Phe Asn Ser Thr
165 170 175

Phe Arg Ser Val Ser Glu Leu Pro Ile Met His Gln Asp Trp Leu Asn
180 185 190

Gly Lys Glu Phe Lys Cys Arg Val Asn Ser Ala Ala Phe Pro Ala Pro
195 200 205

Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Arg Pro Lys Ala Pro Gln
210 215 220

Val Tyr Thr Ile Pro Pro Pro Lys Glu Gln Met Ala Lys Asp Lys Val
225 230 235 240

Ser Leu Thr Cys Met Ile Thr Asp Phe Phe Pro Glu Asp Ile Thr Val
245 250 255

Glu Trp Gln Trp Asn Gly Gln Pro Ala Glu Asn Tyr Lys Asn Thr Gln
260 265 270

Pro Ile Met Asp Thr Asp Gly Ser Tyr Phe Val Tyr Ser Lys Leu Asn
275 280 285

Val Gln Lys Ser Asn Trp Glu Ala Gly Asn Thr Phe Thr Cys Ser Val
290 295 300

Leu His Glu Gly Leu His Asn His His Thr Glu Lys Ser Leu Ser His
305 310 315 320

Ser Pro Gly Lys

<210> SEQ ID NO 26
<211> LENGTH: 720
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 26

atgaggttct ctgctcagct tctggggctg cttgtgctct ggatccctgg atccactgca 60

gatattgtga tgacgcaggc tgcattctcc aatccagtca ctcttggaac atcagcttcc 120

atctcctgca ggtctagtaa gagtctccta catagtaatg gcatcactta tttgtattgg 180

tatctgcaga agccaggcca gtctcctcag ctcctgattt atcagatgtc caaccttgcc 240

tcaggagtcc cagacaggtt cagtagcagt gggtcaggaa ctgatttcac actgagaatc 300

agcagagtgg aggctgagga tgtgggtgtt tattactgtg ctcaaaatct agaacttccg 360

ctcacgttcg gtgctgggac caagctggag ctgaaacggg ctgatgctgc accaactgta 420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttag 720

<210> SEQ ID NO 27
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 27

atgaggttct ctgctcagct tctggggctg cttgtgctct ggatccctgg atccactgca 60

<210> SEQ ID NO 28
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 28

gatattgtga tgacgcaggc tgcattctcc aatccagtca ctcttggaac atcagcttcc 60

atctcctgc 69

<210> SEQ ID NO 29
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 29

aggtctagta agagtctcct acatagtaat ggcatcactt atttgtat 48

<210> SEQ ID NO 30
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 30

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tggtatctgc agaagccagg ccagtctcct cagctcctga tttat 45

<210> SEQ ID NO 31
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 31

cagatgtcca accttgcctc a 21

<210> SEQ ID NO 32
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 32

ggagtcccag acaggttcag tagcagtggg tcaggaactg atttcacact gagaatcagc 60

agagtggagg ctgaggatgt gggtgtttat tactgt 96

<210> SEQ ID NO 33
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 33

gctcaaaatc tagaacttcc gctcacg 27

<210> SEQ ID NO 34
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 34

ttcggtgctg ggaccaagct ggagctgaaa 30

<210> SEQ ID NO 35
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 35

gatattgtga tgacgcaggc tgcattctcc aatccagtca ctcttggaac atcagcttcc 60

atctcctgca ggtctagtaa gagtctccta catagtaatg gcatcactta tttgtattgg 120

tatctgcaga agccaggcca gtctcctcag ctcctgattt atcagatgtc caaccttgcc 180

tcaggagtcc cagacaggtt cagtagcagt gggtcaggaa ctgatttcac actgagaatc 240

agcagagtgg aggctgagga tgtgggtgtt tattactgtg ctcaaaatct agaacttccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaa 336

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<210> SEQ ID NO 36
<211> LENGTH: 382
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 36

ctgtgctcaa aatctagaac ttccgctcac gttcggtgct gggaccaagc tggagctgaa 60

acgggctgat gctgcaccaa ctgtatccat cttcccacca tccagtgagc agttaacatc 120

tggaggtgcc tcagtcgtgt gcttcttgaa caacttctac cccaaagaca tcaatgtcaa 180

gtggaagatt gatggcagtg aacgacaaaa tggcgtcctg aacagttgga ctgatcagga 240

cagcaaagac agcacctaca gcatgagcag caccctcacg ttgaccaagg acgagtatga 300

acgacataac agctatacct gtgaggccac tcacaagaca tcaacttcac ccattgtcaa 360

gagcttcaac aggaatgagt gt 382

<210> SEQ ID NO 37
<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 37

Met Arg Phe Ser Ala Gln Leu Leu Gly Leu Leu Val Leu Trp Ile Pro
1 5 10 15

Gly Ser Thr Ala Asp Ile Val Met Thr Gln Ala Ala Phe Ser Asn Pro
20 25 30

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

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

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Gln Met Ser Asn Leu Ala
65 70 75 80

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

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

Cys Ala Gln Asn Leu Glu Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys
115 120 125

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

Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe
145 150 155 160

Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp
165 170 175

Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp
180 185 190

Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys
195 200 205

Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys
210 215 220

Thr Ser Thr Ser Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys

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225 230 235

<210> SEQ ID NO 38
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 38

Met Arg Phe Ser Ala Gln Leu Leu Gly Leu Leu Val Leu Trp Ile Pro
1 5 10 15

Gly Ser Thr Ala
20

<210> SEQ ID NO 39
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 39

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

Thr Ser Ala Ser Ile Ser Cys
20

<210> SEQ ID NO 40
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 40

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

<210> SEQ ID NO 41
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 41

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 42
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 42

Gln Met Ser Asn Leu Ala Ser
1 5

<210> SEQ ID NO 43
<211> LENGTH: 32

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

<400> SEQUENCE: 43

Gly Val Pro Asp Arg Phe Ser Ser Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
20 25 30

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

<400> SEQUENCE: 44

Ala Gln Asn Leu Glu Leu Pro Leu Thr
1 5

<210> SEQ ID NO 45
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 45

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
1 5 10

<210> SEQ ID NO 46
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 46

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

Thr Ser Ala Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

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

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

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

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

Leu Glu Leu Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> SEQ ID NO 47
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 47

Arg Ala Asp Ala Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu
1 5 10 15

Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe
20 25 30

Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg
35 40 45

Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser
50 55 60

Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu
65 70 75 80

Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser
85 90 95

Pro Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
100 105

<210> SEQ ID NO 48
<211> LENGTH: 1410
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 48

atggcttggg tgtggacctt gctattcctg atggcagctg cccaaagtat ccaagcacag 60

atccagttgg tgcagtctgg acctgagctg aagaagcctg gagagacagt caagatctcc 120

tgcaaggctt ctggttatac cttcacagac tattcaatgc actgggtgaa gcaggctcca 180

ggaaagggtt taaagtggat gggctggata aacactgaga ctggtgagcc aacatatgca 240

gatgacttca agggacggtt tgccttctct ttggaaacct ctgccagcac tgcctatttg 300

cagatcaaca acctcaaaaa tgaggacacg gctacatatt tctgtgcccc cggagggttt 360

gcttactggg gccaagggac tctggtcact gtctctgcag ccaaaacaac acccccatca 420

gtctatccac tggcccctgg gtgtggagat acaactggtt cctccgtgac tctgggatgc 480

ctggtcaagg gctacttccc tgagtcagtg actgtgactt ggaactctgg atccctgtcc 540

agcagtgtgc acaccttccc agctctcctg cagtctggac tctacactat gagcagctca 600

gtgactgtcc cctccagcac ctggccaagt cagaccgtca cctgcagcgt tgctcaccca 660

gccagcagca ccacggtgga caaaaaactt gagcccagcg ggcccatttc aacaatcaac 720

ccctgtcctc catgcaagga gtgtcacaaa tgcccagctc ctaacctcga gggtggacca 780

tccgtcttca tcttccctcc aaatatcaag gatgtactca tgatctccct gacacccaag 840

gtcacgtgtg tggtggtgga tgtgagcgag gatgacccag acgtccagat cagctggttt 900

gtgaacaacg tggaagtaca cacagctcag acacaaaccc atagagagga ttacaacagt 960

actatccggg tggtcagcac cctccccatc cagcaccagg actggatgag tggcaaggag 1020

ttcaaatgca aggtcaacaa caaagacctc ccatcaccca tcgagagaac catctcaaaa 1080

attaaagggc tagtcagagc tccacaagta tacatcttgc cgccaccagc agagcagttg 1140

tccaggaaag atgtcagtct cacttgcctg gtcgtgggct tcaaccctgg agacatcagt 1200

gtggagtgga ccagcaatgg gcatacagag gagaactaca aggacaccgc accagtcctg 1260

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gactctgacg gttcttactt catatatagc aagctcaata tgaaaacaag caagtgggag 1320

aaaacagatt ccttctcatg caacgtgaga cacgagggtc tgaaaaatta ctacctgaag 1380

aagaccatct cccggtctcc gggtaaatga 1410

<210> SEQ ID NO 49
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 49

atggcttggg tgtggacctt gctattcctg atggcagctg cccaaagtat ccaagca 57

<210> SEQ ID NO 50
<211> LENGTH: 90
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 50

cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggtta taccttcaca 90

<210> SEQ ID NO 51
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 51

gactattcaa tgcac 15

<210> SEQ ID NO 52
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 52

tgggtgaagc aggctccagg aaagggttta aagtggatgg gc 42

<210> SEQ ID NO 53
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 53

tggataaaca ctgagactgg tgagccaaca tatgcagatg acttcaaggg a 51

<210> SEQ ID NO 54
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

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<400> SEQUENCE: 54

cggtttgcct tctctttgga aacctctgcc agcactgcct atttgcagat caacaacctc 60

aaaaatgagg acacggctac atatttctgt gccccc 96

<210> SEQ ID NO 55
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 55

ggagggtttg cttac 15

<210> SEQ ID NO 56
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 56

tggggccaag ggactctggt cactgtctct gca 33

<210> SEQ ID NO 57
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 57

cagatccagt tggtgcagtc tggacctgag ctgaagaagc ctggagagac agtcaagatc 60

tcctgcaagg cttctggtta taccttcaca gactattcaa tgcactgggt gaagcaggct 120

ccaggaaagg gtttaaagtg gatgggctgg ataaacactg agactggtga gccaacatat 180

gcagatgact tcaagggacg gtttgccttc tctttggaaa cctctgccag cactgcctat 240

ttgcagatca acaacctcaa aaatgaggac acggctacat atttctgtgc ccccggaggg 300

tttgcttact ggggccaagg gactctggtc actgtctctg ca 342

<210> SEQ ID NO 58
<211> LENGTH: 1008
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 58

gccaaaacaa caccccatc agtctatcca ctggcccctg ggtgtggaga tacaactggt 60

tcctccgtga ctctgggatg cctggtcaag ggctacttcc ctgagtcagt gactgtgact 120

tggaactctg gatccctgtc cagcagtgtg cacaccttcc cagctctcct gcagtctgga 180

ctctacacta tgagcagctc agtgactgtc ccctccagca cctggccaag tcagaccgtc 240

acctgcagcg ttgctcaccc agccagcagc accacggtgg acaaaaaact tgagcccagc 300

gggcccattt caacaatcaa cccctgtcct ccatgcaagg agtgtcacaa atgcccagct 360

cctaacctcg agggtggacc atccgtcttc atcttccctc caaatatcaa ggatgtactc 420

-continued

atgatctccc tgacacccaa ggtcacgtgt gtggtggtgg atgtgagcga ggatgaccca 480

gacgtccaga tcagctggtt tgtgaacaac gtggaagtac acacagctca gacacaaacc 540

catagagagg attacaacag tactatccgg gtggtcagca ccctccccat ccagcaccag 600

gactggatga gtggcaagga gttcaaatgc aaggtcaaca acaaagacct cccatcaccc 660

atcgagagaa ccatctcaaa aattaaaggg ctagtcagag ctccacaagt atacatcttg 720

ccgccaccag cagagcagtt gtccaggaaa gatgtcagtc tcacttgcct ggtcgtgggc 780

ttcaaccctg gagacatcag tgtggagtgg accagcaatg ggcatacaga ggagaactac 840

aaggacaccg caccagtcct ggactctgac ggttcttact tcatatatag caagctcaat 900

atgaaaacaa gcaagtggga gaaaacagat tccttctcat gcaacgtgag acacgagggt 960

ctgaaaaatt actacctgaa gaagaccatc tcccggtctc cgggtaaa 1008

<210> SEQ ID NO 59
<211> LENGTH: 469
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 59

Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1 5 10 15

Ile Gln Ala Gln Ile Gln Leu Val Gln Ser Gly Pro Glu Leu Lys Lys
20 25 30

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

Thr Asp Tyr Ser Met His Trp Val Lys Gln Ala Pro Gly Lys Gly Leu
50 55 60

Lys Trp Met Gly Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala
65 70 75 80

Asp Asp Phe Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser
85 90 95

Thr Ala Tyr Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr
100 105 110

Tyr Phe Cys Ala Pro Gly Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu
115 120 125

Val Thr Val Ser Ala Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu
130 135 140

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

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

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

Gly Leu Tyr Thr Met Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp
195 200 205

Pro Ser Gln Thr Val Thr Cys Ser Val Ala His Pro Ala Ser Ser Thr
210 215 220

Thr Val Asp Lys Lys Leu Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn
225 230 235 240

-continued

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Pro Cys Pro Pro Cys Lys Glu Cys His Lys Cys Pro Ala Pro Asn Leu
                245                 250                 255

Glu Gly Gly Pro Ser Val Phe Ile Phe Pro Pro Asn Ile Lys Asp Val
            260                 265                 270

Leu Met Ile Ser Leu Thr Pro Lys Val Thr Cys Val Val Val Asp Val
        275                 280                 285

Ser Glu Asp Asp Pro Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val
    290                 295                 300

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

Thr Ile Arg Val Val Ser Thr Leu Pro Ile Gln His Gln Asp Trp Met
                325                 330                 335

Ser Gly Lys Glu Phe Lys Cys Lys Val Asn Asn Lys Asp Leu Pro Ser
            340                 345                 350

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

Gln Val Tyr Ile Leu Pro Pro Pro Ala Glu Gln Leu Ser Arg Lys Asp
    370                 375                 380

Val Ser Leu Thr Cys Leu Val Val Gly Phe Asn Pro Gly Asp Ile Ser
385                 390                 395                 400

Val Glu Trp Thr Ser Asn Gly His Thr Glu Glu Asn Tyr Lys Asp Thr
                405                 410                 415

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

Asn Met Lys Thr Ser Lys Trp Glu Lys Thr Asp Ser Phe Ser Cys Asn
        435                 440                 445

Val Arg His Glu Gly Leu Lys Asn Tyr Tyr Leu Lys Lys Thr Ile Ser
    450                 455                 460

Arg Ser Pro Gly Lys
465


<210> SEQ ID NO 60
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 60

Met Ala Trp Val Trp Thr Leu Leu Phe Leu Met Ala Ala Ala Gln Ser
1               5                   10                  15

Ile Gln Ala


<210> SEQ ID NO 61
<211> LENGTH: 30
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 61

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

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

-continued

<210> SEQ ID NO 62
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 62

Asp Tyr Ser Met His
1 5

<210> SEQ ID NO 63
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 63

Trp Val Lys Gln Ala Pro Gly Lys Gly Leu Lys Trp Met Gly
1 5 10

<210> SEQ ID NO 64
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 64

Trp Ile Asn Thr Glu Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 65
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 65

Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr Leu Gln
1 5 10 15

Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys Ala Pro
20 25 30

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

<400> SEQUENCE: 66

Gly Gly Phe Ala Tyr
1 5

<210> SEQ ID NO 67
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

-continued

<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 67

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala
1 5 10

<210> SEQ ID NO 68
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 68

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

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

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

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

Lys Gly Arg Phe Ala Phe Ser Leu Glu Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Asn Asn Leu Lys Asn Glu Asp Thr Ala Thr Tyr Phe Cys
85 90 95

Ala Pro Gly Gly Phe Ala Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
100 105 110

Ser Ala

<210> SEQ ID NO 69
<211> LENGTH: 336
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 69

Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro Gly Cys Gly
1 5 10 15

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

Phe Pro Glu Ser Val Thr Val Thr Trp Asn Ser Gly Ser Leu Ser Ser
35 40 45

Ser Val His Thr Phe Pro Ala Leu Leu Gln Ser Gly Leu Tyr Thr Met
50 55 60

Ser Ser Ser Val Thr Val Pro Ser Ser Thr Trp Pro Ser Gln Thr Val
65 70 75 80

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

Leu Glu Pro Ser Gly Pro Ile Ser Thr Ile Asn Pro Cys Pro Pro Cys
100 105 110

Lys Glu Cys His Lys Cys Pro Ala Pro Asn Leu Glu Gly Gly Pro Ser
115 120 125

Val Phe Ile Phe Pro Pro Asn Ile Lys Asp Val Leu Met Ile Ser Leu
130 135 140

-continued

Thr Pro Lys Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro
145 150 155 160

Asp Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala
165 170 175

Gln Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Ile Arg Val Val
180 185 190

Ser Thr Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe
195 200 205

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

Ile Ser Lys Ile Lys Gly Leu Val Arg Ala Pro Gln Val Tyr Ile Leu
225 230 235 240

Pro Pro Pro Ala Glu Gln Leu Ser Arg Lys Asp Val Ser Leu Thr Cys
245 250 255

Leu Val Val Gly Phe Asn Pro Gly Asp Ile Ser Val Glu Trp Thr Ser
260 265 270

Asn Gly His Thr Glu Glu Asn Tyr Lys Asp Thr Ala Pro Val Leu Asp
275 280 285

Ser Asp Gly Ser Tyr Phe Ile Tyr Ser Lys Leu Asn Met Lys Thr Ser
290 295 300

Lys Trp Glu Lys Thr Asp Ser Phe Ser Cys Asn Val Arg His Glu Gly
305 310 315 320

Leu Lys Asn Tyr Tyr Leu Lys Lys Thr Ile Ser Arg Ser Pro Gly Lys
325 330 335

<210> SEQ ID NO 70
<211> LENGTH: 720
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 70

atgaggtgcc tagctgagtt cctggggctg cttgtgctct ggatccctgg agccattggg 60

gatattgtga tgactcaggc tgcaccctct gtacctgtca ctcctggaga gtcagtatcc 120

atctcctgca ggtctagtaa gagtctcctg catagtaatg gcaacactta cttgtattgg 180

ttcctgcaga ggccaggcca gtctcctcag ctcctgatat atcggatgtc caaccttgcc 240

tcaggagtcc cagacaggtt cagtggcagt gggtcaggaa ctgctttcac actgagaatc 300

agtagagtgg aggctgagga tgtgggtgtt tattactgta tgcaacatct agaatatccg 360

ctcacgttcg gtgctgggac caagctggag ctgaaacggg ctgatgctgc accaactgta 420

tccatcttcc caccatccag tgagcagtta acatctggag gtgcctcagt cgtgtgcttc 480

ttgaacaact tctaccccaa agacatcaat gtcaagtgga agattgatgg cagtgaacga 540

caaaatggcg tcctgaacag ttggactgat caggacagca aagacagcac ctacagcatg 600

agcagcaccc tcacgttgac caaggacgag tatgaacgac ataacagcta tacctgtgag 660

gccactcaca agacatcaac ttcacccatt gtcaagagct tcaacaggaa tgagtgttag 720

<210> SEQ ID NO 71
<211> LENGTH: 60
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 71

atgaggtgcc tagctgagtt cctggggctg cttgtgctct ggatccctgg agccattggg 60

<210> SEQ ID NO 72
<211> LENGTH: 69
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 72

gatattgtga tgactcaggc tgcaccctct gtacctgtca ctcctggaga gtcagtatcc 60

atctcctgc 69

<210> SEQ ID NO 73
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 73

aggtctagta agagtctcct gcatagtaat ggcaacactt acttgtat 48

<210> SEQ ID NO 74
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 74

tggttcctgc agaggccagg ccagtctcct cagctcctga tatat 45

<210> SEQ ID NO 75
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 75

cggatgtcca accttgcctc a 21

<210> SEQ ID NO 76
<211> LENGTH: 96
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 76

ggagtcccag acaggttcag tggcagtggg tcaggaactg ctttcacact gagaatcagt 60

agagtggagg ctgaggatgt gggtgtttat tactgt 96

<210> SEQ ID NO 77
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 77

atgcaacatc tagaatatcc gctcacg 27

<210> SEQ ID NO 78
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 78

ttcggtgctg ggaccaagct ggagctgaaa 30

<210> SEQ ID NO 79
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 79

gatattgtga tgactcaggc tgcaccctct gtacctgtca ctcctggaga gtcagtatcc 60

atctcctgca ggtctagtaa gagtctcctg catagtaatg gcaacactta cttgtattgg 120

ttcctgcaga ggccaggcca gtctcctcag ctcctgatat atcggatgtc caaccttgcc 180

tcaggagtcc cagacaggtt cagtggcagt gggtcaggaa ctgctttcac actgagaatc 240

agtagagtgg aggctgagga tgtgggtgtt tattactgta tgcaacatct agaatatccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> SEQ ID NO 80
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polynucleotide

<400> SEQUENCE: 80

cgggctgatg ctgcaccaac tgtatccatc ttcccaccat ccagtgagca gttaacatct 60

ggaggtgcct cagtcgtgtg cttcttgaac aacttctacc ccaaagacat caatgtcaag 120

tggaagattg atggcagtga acgacaaaat ggcgtcctga acagttggac tgatcaggac 180

agcaaagaca gcacctacag catgagcagc accctcacgt tgaccaagga cgagtatgaa 240

cgacataaca gctatacctg tgaggccact cacaagacat caacttcacc cattgtcaag 300

agcttcaaca ggaatgagtg t 321

<210> SEQ ID NO 81
<211> LENGTH: 239
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 81

Met Arg Cys Leu Ala Glu Phe Leu Gly Leu Leu Val Leu Trp Ile Pro
1 5 10 15

-continued

```
Gly Ala Ile Gly Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Pro
            20                  25                  30

Val Thr Pro Gly Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser
        35                  40                  45

Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg
    50                  55                  60

Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Arg Met Ser Asn Leu Ala
65                  70                  75                  80

Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe
                85                  90                  95

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

Cys Met Gln His Leu Glu Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys
        115                 120                 125

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

Pro Ser Ser Glu Gln Leu Thr Ser Gly Gly Ala Ser Val Val Cys Phe
145                 150                 155                 160

Leu Asn Asn Phe Tyr Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp
                165                 170                 175

Gly Ser Glu Arg Gln Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp
            180                 185                 190

Ser Lys Asp Ser Thr Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys
        195                 200                 205

Asp Glu Tyr Glu Arg His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys
    210                 215                 220

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


<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 82

Met Arg Cys Leu Ala Glu Phe Leu Gly Leu Leu Val Leu Trp Ile Pro
1               5                   10                  15

Gly Ala Ile Gly
            20


<210> SEQ ID NO 83
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 83

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

Glu Ser Val Ser Ile Ser Cys
            20


<210> SEQ ID NO 84
```

-continued

<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 84

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

<210> SEQ ID NO 85
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 85

Trp Phe Leu Gln Arg Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr
1 5 10 15

<210> SEQ ID NO 86
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 86

Arg Met Ser Asn Leu Ala Ser
1 5

<210> SEQ ID NO 87
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 87

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Ala Phe Thr
1 5 10 15

Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys
20 25 30

<210> SEQ ID NO 88
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 88

Met Gln His Leu Glu Tyr Pro Leu Thr
1 5

<210> SEQ ID NO 89
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 89

-continued

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
1 5 10

<210> SEQ ID NO 90
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 90

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

Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30

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

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

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

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

Leu Glu Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> SEQ ID NO 91
<211> LENGTH: 106
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide

<400> SEQUENCE: 91

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

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

Pro Lys Asp Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln
35 40 45

Asn Gly Val Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr
50 55 60

Tyr Ser Met Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg
65 70 75 80

His Asn Ser Tyr Thr Cys Glu Ala Thr His Lys Thr Ser Thr Ser Pro
85 90 95

Ile Val Lys Ser Phe Asn Arg Asn Glu Cys
100 105

<210> SEQ ID NO 92
<211> LENGTH: 364
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Ser Ser Ser Asp Gly Val Val Lys Ser Met Ile Ile Asp Arg Arg Ser

-continued

```
1               5                   10                  15

Gly Arg Gln Tyr Asp Ile Asp Asp Ala Ile Ala Lys Asn Leu Ile Asp
            20                  25                  30

Arg Ser Ala Leu Asp Gln Tyr Arg Ala Gly Thr Leu Ser Ile Thr Glu
        35                  40                  45

Phe Ala Asp Met Leu Ser Gly Asn Ala Gly Gly Phe Arg Ser Arg Ser
    50                  55                  60

Ser Ser Val Gly Ser Ser Ser Ser Tyr Pro Ile Ser Pro Ala Val Ser
65                  70                  75                  80

Arg Thr Gln Leu Ala Ser Trp Ser Asp Pro Thr Glu Glu Thr Gly Pro
                85                  90                  95

Val Ala Gly Ile Leu Asp Thr Glu Thr Leu Glu Lys Val Ser Ile Thr
            100                 105                 110

Glu Ala Met His Arg Asn Leu Val Asp Asn Ile Thr Gly Gln Arg Leu
        115                 120                 125

Leu Glu Ala Gln Ala Cys Thr Gly Gly Ile Ile Asp Pro Ser Thr Gly
    130                 135                 140

Glu Arg Phe Pro Val Thr Asp Ala Val Asn Lys Gly Leu Val Asp Lys
145                 150                 155                 160

Ile Met Val Asp Arg Ile Asn Leu Ala Gln Lys Ala Phe Cys Gly Phe
                165                 170                 175

Glu Asp Pro Arg Thr Lys Thr Lys Met Ser Ala Ala Gln Ala Leu Lys
            180                 185                 190

Lys Gly Trp Leu Tyr Tyr Glu Ala Gly Gln Arg Phe Leu Glu Val Gln
        195                 200                 205

Tyr Leu Thr Gly Gly Leu Ile Glu Pro Asp Thr Pro Gly Arg Val Pro
    210                 215                 220

Leu Asp Glu Ala Leu Gln Arg Gly Thr Val Asp Ala Arg Thr Ala Gln
225                 230                 235                 240

Lys Leu Arg Asp Val Gly Ala Tyr Ser Lys Tyr Leu Thr Cys Pro Lys
                245                 250                 255

Thr Lys Leu Lys Ile Ser Tyr Lys Asp Ala Leu Asp Arg Ser Met Val
            260                 265                 270

Glu Glu Gly Thr Gly Leu Arg Leu Leu Glu Ala Ala Ala Gln Ser Thr
        275                 280                 285

Lys Gly Tyr Tyr Ser Pro Tyr Ser Val Ser Gly Ser Gly Ser Thr Ala
    290                 295                 300

Gly Ser Arg Thr Gly Ser Arg Thr Gly Ser Arg Ala Gly Ser Arg Arg
305                 310                 315                 320

Gly Ser Phe Asp Ala Thr Gly Ser Gly Phe Ser Met Thr Phe Ser Ser
                325                 330                 335

Ser Ser Tyr Ser Ser Ser Gly Tyr Gly Arg Arg Tyr Ala Ser Gly Ser
            340                 345                 350

Ser Ala Ser Leu Gly Gly Pro Glu Ser Ala Val Ala
        355                 360


<210> SEQ ID NO 93
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic Polypeptide
```

-continued

<400> SEQUENCE: 93

Gly Gly Gly Ser
1

What is claimed is:

1. An antibody or antigen binding fragment that specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 92.

2. The antibody or antigen binding fragment of claim **1**, wherein the antibody specifically binds an amino acid sequence set forth as: SEQ ID NO: 92.

3. An antibody or antigen binding fragment that specifically binds to a cell-surface exposed plectin-1, wherein the antibody or antigen binding fragment comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 24 or SEQ ID NO: 68.

4. The antibody or antigen binding fragment of claim **3** further comprising a light chain variable region having a sequence set forth as: SEQ ID NO: 46 or SEQ ID NO: 90.

5. The antibody of claim **3** or **4**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 24 and a light chain variable region having a sequence set forth as: SEQ ID NO: 46.

6. The antibody of claim **3** or **4**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 68 and a light chain variable region having a sequence set forth as: SEQ ID NO: 90.

7. The antibody of any one of claims **1** to **6**, wherein the antibody specifically binds an amino acid sequence having at least 85% identity to SEQ ID NO: 92.

8. The antibody of any one of claims **1** to **7**, wherein the antibody specifically binds an amino acid sequence set forth as SEQ ID NO: 92.

9. An antibody or antigen binding fragment that specifically binds to cell-surface exposed plectin-1, wherein the antibody or antigen binding fragment comprises variable heavy chain region comprising a complementarity determining region 3 (CDRH3) having a sequence set forth as: SEQ ID NO: 22 or SEQ ID NO: 66.

10. The antibody or antigen binding fragment of claim **5** further comprising a light chain variable region comprising a complementarity determining region 3 (CDRL3) having a sequence set forth as: SEQ ID NO: 44 or SEQ ID NO: 88.

11. An antibody that comprises a heavy chain variable region having a sequence set that shares at least 85% identity with SEQ ID NO: 15 and a light chain variable region that shares at least 85% identity with SEQ ID NO: 37.

12. An antibody that comprises a heavy chain variable region having a sequence set that shares at least 85% identity with SEQ ID NO: 59 and a light chain variable region that shares at least 85% identity with SEQ ID NO: 81.

13. The antibody of any one of the preceding claims, wherein the antibody is coupled to a targeted agent.

14. The antibody of claim **13**, wherein the targeted agent is a detectable moiety.

15. The antibody of claim **14**, wherein the detectable moiety is selected from the group consisting of a radioactive isotope, a magnetic compound, an x-ray absorber, a chemical compound, a biological tag, and a fluorescent molecule.

16. The antibody of claim **13**, wherein the targeted agent is a therapeutic agent.

17. The antibody of claim **16**, wherein the therapeutic agent is a cytotoxic moiety or an immunomodulatory moiety.

18. The antibody of any one of claims **13** to **17**, wherein the antibody is coupled to the targeted agent via a linker.

19. The antibody of claim **18**, wherein the linker is a flexible amino acid sequence.

20. The antibody of claim **18**, wherein the linker is a photolinker.

21. The antibody of any one of claims **13** to **20**, wherein the targeted agent comprises a physiologically inert nanoparticle.

22. The antibody of claim **21**, wherein the nanoparticle is magnetic, fluorescent, or radioactive.

23. The antibody of any one of claims **13** to **22**, wherein the targeted agent comprises a fluorochrome.

24. An antibody, or antigen binding fragment, that specifically binds to cell-surface exposed plectin-1 antigen and that comprises six complementarity determining regions (CDRs): CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3,

wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 18, CDRH2 comprises a sequence as set forth in SEQ ID NO: 20, CDRH3 comprises a sequence as set forth in SEQ ID NO: 22, CDRL1 comprises a sequence as set forth in SEQ ID NO: 40, CDRL2 comprises a sequence as set forth in SEQ ID NO: 42, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 44; or

wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 62, CDRH2 comprises a sequence as set forth in SEQ ID NO: 64, CDRH3 comprises a sequence as set forth in SEQ ID NO: 66, CDRL1 comprises a sequence as set forth in SEQ ID NO: 84, CDRL2 comprises a sequence as set forth in SEQ ID NO: 86, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 88.

25. The antibody, or antigen binding fragment, of claim **24**, wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 18, CDRH2 comprises a sequence as set forth in SEQ ID NO: 20, CDRH3 comprises a sequence as set forth in SEQ ID NO: 22, CDRL1 comprises a sequence as set forth in SEQ ID NO: 40, CDRL2 comprises a sequence as set forth in SEQ ID NO: 42, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 44.

26. The antibody, or antigen binding fragment, of claim **25**, comprising the heavy chain variable domain sequence of SEQ ID NO: 24.

27. The antibody, or antigen binding fragment, of claim **25** or **26**, comprising the light chain variable domain sequence of SEQ ID NO: 46.

28. The antibody, or antigen binding fragment, of any one of claims **25** to **27**, comprising the heavy chain variable domain sequence of SEQ ID NO: 24 and the light chain variable domain sequence of SEQ ID NO: 46.

29. The antibody, or antigen binding fragment, of claim **24**, wherein CDRH1 comprises a sequence as set forth in

SEQ ID NO: 62, CDRH2 comprises a sequence as set forth in SEQ ID NO: 64, CDRH3 comprises a sequence as set forth in SEQ ID NO: 66, CDRL1 comprises a sequence as set forth in SEQ ID NO: 84, CDRL2 comprises a sequence as set forth in SEQ ID NO: 86, and CDRL3 comprises a sequence as set forth in SEQ ID NO: 88.

30. The antibody, or antigen binding fragment, of claim **29**, comprising the heavy chain variable domain sequence of SEQ ID NO: 68.

31. The antibody, or antigen binding fragment, of claim **29** or **30**, comprising the light chain variable domain sequence of SEQ ID NO: 90.

32. The antibody, or antigen binding fragment, of any one of claims **29** to **31**, comprising the heavy chain variable domain sequence of SEQ ID NO: 68 and the light chain variable domain sequence of SEQ ID NO: 90.

33. The antibody, or antigen binding fragment, of any one of claims **1** to **32**, wherein the antibody or antigen binding fragment, is a monoclonal antibody, a humanized antibody, a diabody, a chimeric antibody, a Fab fragment, a F(ab')2 fragment, affibody, or an Fv fragment.

34. The antibody, or antigen binding fragment, of any one of claims **1** to **33**, wherein the antibody or antigen binding fragment, comprises a heavy chain constant domain having a sequence as set forth in SEQ ID NO: 15 or SEQ ID NO: 59.

35. The antibody, or antigen binding fragment, of any one of claims **1** to **34**, wherein the antibody or antigen binding fragment comprises a heavy chain constant domain selected from the group consisting of IgG, IgG1, IgG2, IgG2A, IgG2B, IgG2C, IgG3, IgG4, IgA1, IgA2, IgD, IgM, and IgE constant domains.

36. The antibody, or antigen binding fragment, of any one of claims **1** to **35**, wherein the antibody or antigen binding fragment is conjugated to an agent selected from the group consisting of a fluorescent agent, a luminescent agent, an enzymatic agent and a radioactive agent.

37. An antibody, or antigen binding fragment, that competes or cross-competes for binding to an amino acid sequence set forth as: SEQ ID NO: 92 with an antibody, or antigen binding fragment of any one of claims **1** to **36**.

38. The antibody or antigen binding fragment of claim **37**, wherein the antibody or antigen binding fragment competes or cross-competes with an equilibrium dissociation constant, Kd, of less than 10^{-6} M between the antibody or antigen binding fragment, and its antigen.

39. A composition comprising the antibody of any one of claims **1** to **38**, optionally further comprising a pharmaceutically acceptable excipient.

40. An isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRH1, CDRH2, and CDRH3, wherein CDRH3 comprises a sequence as set forth in SEQ ID NO: 22.

41. The isolated nucleic acid of claim **40**, wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 18.

42. The isolated nucleic acid of claim **40** or **41**, wherein CDRH2 comprises a sequence as set forth in SEQ ID NO: 20.

43. An isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRL1, CDRL2, and CDRL3, wherein CDRL3 comprises a sequence as set forth in SEQ ID NO: 44.

44. The isolated nucleic acid of claim **43**, wherein CDRL1 comprises a sequence as set forth in SEQ ID NO: 40.

45. The isolated nucleic acid of claim **43** or **44**, wherein CDRL2 comprises a sequence as set forth in SEQ ID NO: 42.

46. An isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRH1, CDRH2, and CDRH3, wherein CDRH3 comprises a sequence as set forth in SEQ ID NO: 66.

47. The isolated nucleic acid of claim **46**, wherein CDRH1 comprises a sequence as set forth in SEQ ID NO: 62.

48. The isolated nucleic acid of claim **46** or **47**, wherein CDRH2 comprises a sequence as set forth in SEQ ID NO: 64.

49. An isolated nucleic acid encoding a protein comprising three complementarity determining regions (CDRs): CDRL1, CDRL2, and CDRL3, wherein CDRL3 comprises a sequence as set forth in SEQ ID NO: 88.

50. The isolated nucleic acid of claim **49**, wherein CDRL1 comprises a sequence as set forth in SEQ ID NO: 84.

51. The isolated nucleic acid of claim **49** or **50**, wherein CDRL2 comprises a sequence as set forth in SEQ ID NO: 86.

52. An isolated nucleic acid comprising a sequence as set forth in a sequence selected from the group consisting of SEQ ID NO: 15, 24, 37, 46, 59, 68, 81, or 90.

53. An isolated cell comprising an isolated nucleic acid of any one of claims **40** to **52**.

54. The isolated cell of claim **53**, wherein the cell is a bacterial cell, a yeast cell, a mammalian cell, or an insect cell.

55. The isolated cell of claim **53** or **54**, wherein the cell is a hybridoma cell.

56. A method for targeting an agent to a cancer cell in a subject, the method comprising administering to the subject a composition comprising an antibody as described in any one of claims **1** to **38**, or the composition of claim **39**, coupled to a targeted agent, wherein the antibody binds to plectin-1 on the surface of the cancer cell in the subject.

57. The method of claim **56**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 24 or SEQ ID NO: 68.

58. The method of claim **57** further comprising a light chain variable region having a sequence set forth as: SEQ ID NO: 46 or SEQ ID NO: 90.

59. The method of any one of claims **56** to **58**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 24 and a light chain variable region having a sequence set forth as: SEQ ID NO: 46.

60. The method of any one of claims **56** to **58**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 68 and a light chain variable region having a sequence set forth as: SEQ ID NO: 90.

61. The method of any one of claims **56** to **60**, wherein the targeted agent is a detectable moiety.

62. The method of claim **61**, wherein the detectable moiety is selected from the group consisting of a radioactive isotope, a magnetic compound, an x-ray absorber, a chemical compound, a biological tag, and a fluorescent molecule.

63. The method of any one of claims **56** to **60**, wherein the targeted agent is a therapeutic agent.

64. The method of claim **63**, wherein the therapeutic agent is a cytotoxic moiety or an immunomodulatory moiety.

65. The method of any one of claims **56** to **64**, wherein the antibody is coupled to the targeted agent via a linker.

66. The method of claim **65**, wherein the linker is a flexible amino acid sequence.

67. The method of claim **65**, wherein the linker is a photolinker.

68. The method of any one of claims **56** to **67**, wherein the targeted agent comprises a physiologically inert nanoparticle.

69. The method of claim **68**, wherein the nanoparticle is magnetic, fluorescent, or radioactive.

70. The method of any one of claims **56** to **69**, wherein the targeted agent comprises a fluorochrome.

71. The method of any one of claims **56** to **70**, wherein the antibody or composition is administered at a dose in a range of 1 ng/kg and 100 mg/kg.

72. The method of any one of claims **56** to **71**, wherein the cancer cell is an ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell.

73. The method of claim **72**, wherein the cancer cell is a pancreatic ductal adenocarcinoma cell.

74. The method of any one of claims **56** to **73**, wherein the subject is a mammal, optionally a human.

75. A method for treating cancer, the method comprising administering to a subject having cancer an effective amount of an antibody of any one of claims **1** to **38**, or an effective amount of the composition of claim **39**.

76. The method of claim **75**, wherein the antibody is coupled to a targeted agent, and wherein the antibody binds to plectin-1 on the surface of the cancer cell in the subject.

77. The method of claim **75** or **76**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 24 or SEQ ID NO: 68.

78. The method of any one of claims **75** to **77**, wherein the antibody further comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 46 or SEQ ID NO: 90.

79. The method of claim **75** or **76**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 24 and a light chain variable region having a sequence set forth as: SEQ ID NO: 46.

80. The method of any one of claims **75** to **77**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 68 and a light chain variable region having a sequence set forth as: SEQ ID NO: 90.

81. The method of any one of claims **76** to **80**, wherein the targeted agent is a detectable moiety.

82. The method of claim **81**, wherein the detectable moiety is selected from the group consisting of a radioactive isotope, a magnetic compound, an x-ray absorber, a chemical compound, a biological tag, and a fluorescent molecule.

83. The method of any one of claims **76** to **82**, wherein the targeted agent is a therapeutic agent.

84. The method of claim **83**, wherein the therapeutic agent is a cytotoxic moiety or an immunomodulatory moiety.

85. The method of any one of claims **76** to **84**, wherein the antibody is coupled to the targeted agent via a linker.

86. The method of claim **85**, wherein the linker is a flexible amino acid sequence.

87. The method of claim **85**, wherein the linker is a photolinker.

88. The method of any one of claims **76** to **87**, wherein the targeted agent comprises a physiologically inert nanoparticle.

89. The method of claim **88**, wherein the nanoparticle is magnetic, fluorescent, or radioactive.

90. The method of any one of claims **76** to **89**, wherein the targeted agent comprises a fluorochrome.

91. The method of any one of claims **75** to **90**, wherein the antibody or composition is administered at a dose in a range of 1 ng/kg and 100 mg/kg.

92. The method of any one of claims **75** to **91**, wherein the cancer cell is an ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell.

93. The method of claim **92**, wherein the cancer cell is a pancreatic ductal adenocarcinoma cell.

94. The method of any one of claims **75** to **93**, wherein the subject is a mammal, optionally a human.

95. A method for detecting a cancer cell, the method comprising administering to a subject having cancer an effective amount of the antibody of any one of claims **1** to **38** or an effective amount of the composition of claim **39**.

96. The method of claim **95**, wherein the antibody is coupled to a targeted agent, and wherein the antibody binds to plectin-1 on the surface of the cancer cell in the subject.

97. The method of claim **95** or **96**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO: 24 or SEQ ID NO: 68.

98. The method of any one of claims **95** to **97**, wherein the antibody further comprises a light chain variable region having a sequence set forth as: SEQ ID NO: 46 or SEQ ID NO: 90.

99. The method of claim **95** or **96**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 24 and a light chain variable region having a sequence set forth as: SEQ ID NO: 46.

100. The method of any one of claims **95** to **97**, wherein the antibody comprises a heavy chain variable region having a sequence set forth as: SEQ ID NO 68 and a light chain variable region having a sequence set forth as: SEQ ID NO: 90.

101. The method of any one of claims **96** to **100**, wherein the targeted agent is a detectable moiety.

102. The method of claim **101**, wherein the detectable moiety is selected from the group consisting of a radioactive isotope, a magnetic compound, an x-ray absorber, a chemical compound, a biological tag, and a fluorescent molecule.

103. The method of any one of claims **96** to **102**, wherein the antibody is coupled to the targeted agent via a linker.

104. The method of claim **103**, wherein the linker is a flexible amino acid sequence.

105. The method of claim **103**, wherein the linker is a photolinker.

106. The method of any one of claims **96** to **105**, wherein the targeted agent comprises a physiologically inert nanoparticle.

107. The method of claim **106**, wherein the nanoparticle is magnetic, fluorescent, or radioactive.

108. The method of any one of claims **96** to **107**, wherein the targeted agent comprises a fluorochrome.

109. The method of any one of claims **95** to **108**, wherein the antibody or composition is administered at a dose in a range of 1 ng/kg and 100 mg/kg.

110. The method of any one of claims **95** to **109**, wherein the cancer cell is an ovarian cancer cell, esophageal cancer cell, head and neck squamous cell carcinoma cancer cell, or pancreatic cancer cell.

111. The method of claim **110**, wherein the cancer cell is a pancreatic ductal adenocarcinoma cell.

112. The method of any one of claims **95** to **111**, wherein the subject is a mammal, optionally a human.

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